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REVIEW

Effects of early life stress on cognitive and affective function: an integrated review of human literature

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Abstract
Rationale The investigation of putative effects of early life stress (ELS) in humans on later behavior and neurobiology is a fast developing field. While epidemiological and neurobiological studies paint a somber picture of negative outcomes, relatively little attention has been devoted to integrating the breadth of findings concerning possible cognitive and emotional deficits associated with ELS. Emerging findings from longitudinal studies examining developmental trajectories of the brain in healthy samples may provide a new framework to understand mechanisms underlying ELS sequelae.
Objective The goal of this review was twofold. The first was to summarize findings from longitudinal data on normative brain development. The second was to utilize this framework of normative brain development to interpret changes in developmental trajectories associated with deficits in cognitive and affective function following ELS.
Results Five principles of normative brain development were identified and used to discuss behavioral and neural sequelae of ELS. Early adversity was found to be associated with deficits in a range of cognitive (cognitive performance, memory, and executive functioning) and affective (reward processing, processing of social and affective stimuli, and emotion regulation) functions.
Conclusion Three general conclusions emerge: (1) higher-order, complex cognitive and affective functions associated with brain regions undergoing protracted postnatal development are particularly vulnerable to the deleterious effects of ELS; (2) the amygdala is particularly sensitive to early ELS; and (3) several deficits, particularly those in the affective domain, appear to persist years after ELS has ceased and may increase risk for later psychopathology.

Keywords Early life stress · Brain · Child abuse · Cognitive function · Emotion regulation

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Introduction

When a person is challenged in their emotional or physical well-being to an extent that exceeds their ability to cope, stress ensues (Gunnar and Quevedo 2007). Early life stress (ELS) is the exposure to a single or multiple events during childhood that exceeds the child's coping resources and leads to prolonged phases of stress. Commonly studied early childhood stressors include physical, sexual, emotional and verbal abuse, neglect, social deprivation, disaster, and household dysfunctions, including witnessing of violence, criminal activity, parental separation, parental death or illness, poverty, and substance abuse (Brown et al. 2009).

Due to the array of stressors subsumed by the term ELS, obtaining a clear estimate of how many children experience ELS remains challenging. In 2007, 3.5 million (22.5%) children came to the attention of child protective services in the USA alone. The rate of abuse and neglect, not considering household dysfunction, reached 10.6% in 2007 (U.S. Department of Health and Human Services 2009). Due to low rates of disclosure, these figures likely underestimate the incidence of childhood trauma (Finklehor 1994; Pereda et al. 2009).

ELS can be studied behaviorally and biologically. While the acute activation of the body's stress response systems is considered an adaptive mechanism that mobilizes resources to

increase chances of survival, high or chronic levels of stress may disturb brain development and affect mental health (Anda et al. 2006; De Bellis et al. 1999a, b; Lupien et al. 2009; Maniglio 2009; Pirkola et al. 2005; Spataro et al. 2004). Although epidemiological and neurobiological studies provide convincing evidence for the negative consequences of ELS (De Bellis 2005; Grassi-Oliveira et al. 2008; Teicher et al. 2003; Weber and Reynolds 2004), relatively little attention has been devoted to evaluating putative cognitive and emotional outcomes of ELS. Such knowledge could prove pivotal in tailoring early intervention and preventing long-term sequelae. In this review, we adopt a developmental approach in which we summarize recent findings on normative brain development in childhood and adolescence to assist later discussion on the disruptions of developmental trajectories of the brain following ELS.

Goals

The objective of this review was to review and integrate changes in the neurobiological pathways associated with cognitive and emotional functioning following ELS within the framework of recent longitudinal studies of normal human brain development. Priority was given to studies examining structural or functional sequelae of early adversity in conjunction with cognitive or emotional correlates. While ELS may affect an array of functions, due to space constraints, we have focused on behavioral phenotypes most widely investigated in both the psychological and neuroscientific literature, so that inferences about primary pathways of early neurobiological disruptions affecting later well-being could be advanced. In the first section, recent findings of longitudinal studies in healthy samples are reviewed to identify overarching principles of normative brain development. Mechanisms potentially disrupting the trajectory of brain development in those with a history of ELS are also discussed. In the second section, we specifically focus on structural and functional changes associated with deficits in cognitive function (cognitive performance, memory, and executive functioning) and affective functions (reward processing, processing of social and affective stimuli, and emotion regulation). In each section, behavioral, neuroimaging, and psychophysiological data are integrated, and selected animal findings are discussed (see other contributions in this issue for more comprehensive reviews of the animal literature on ELS). The review ends with a discussion of future directions in research on ELS.

Early life stress and psychopathology

The recent National Comorbidity Survey highlighted that childhood adverse experiences explain nearly 32% of psychiatric disorders and an even higher percentage (44%) of disorders with childhood onset (Green et al. 2010). Various forms of early adversity account for about 67% of the population-attributable risk for suicide (Dube et al. 2001). Exposure to multiple episodes of ELS can significantly increase the risk of mental illness and somatic disturbances (Anda et al. 1999, 2006, 2007; Chapman et al. 2004; Cutrona et al. 2005; Dong et al. 2004; Edwards et al. 2003; Pirkola et al. 2005). Notably, adults with more than six adverse childhood events had a higher likelihood of dying 20 years earlier than those without such histories (Anda et al. 2009; Brown et al. 2009). Others have emphasized the need for more differentiated research methods in order to investigate how common *clusters* of co-occurring ELS experiences are related to psychopathology (Green et al. 2010; Wright et al. 2009).

Developmental timing

The sequelae of ELS often depend on the type of adversity, the number of exposures, and, in particular, the age at the time of occurrence. For example, adults who were sexually abused in childhood after the age of 12 were ten times more likely to develop severe symptoms of posttraumatic stress disorder (PTSD) compared to those who experienced sexual abuse prior to the age of 12 (Schoedl et al. 2010). Teicher and colleagues (2006a, b) conducted extensive studies on "sensitive periods" emphasizing that the timing of ELS may especially affect those brain regions undergoing specific growth spurts at the time. For example, among females, experience of sexual abuse between ages 3 and 5 (and marginally between 11 and 13 years) was related to smaller hippocampal volume. Conversely, sexual abuse occurring between ages 9–10 and 11–14 years was linked to dysfunctions in the corpus callosum and prefrontal cortex (PFC), respectively (Andersen et al. 2008). Based on these and other data, it was concluded that brain regions with extended postnatal development are particularly vulnerable to long-term effects of stress (Teicher et al. 2003).

While research has emphasized the outcomes of ELS on mental health, less attention has been devoted to explaining the link between cognitive and emotional sequelae of ELS and brain development. Before summarizing findings on normative brain development in childhood and adolescence, we would like to emphasize several key points relevant to understanding the limitation of the following discussion. First, neuroimaging research commonly focuses on changes in regional brain volume or cortical thickness. It should be kept in mind that while these volumetric changes are important means to identify possible abnormalities, little is known about the specific mechanisms underlying these changes. Disruptions in neurogenesis, myelination, and synaptic

pruning are often invoked to explain structural changes, but modest empirical support exists for these claims (Gogtay and Thompson 2010). Furthermore, while delineating structural abnormalities in single regions is an important first step for investigating cognitive and affective deficits following ELS, our limited understanding of the effects of ELS on functional connectivity and development of neural circuits remains an important challenge for the future. Lastly, throughout the review, and consistent with recent publications, we refer to primary, lower-order functions vs. complex, higher-order functions (Gogtay and Thompson 2010; Marsh et al. 2008). This differentiation should not imply that primary brain functions are deemed as less critical, especially as they become increasingly involved in complex computations during maturation. Instead, we emphasize that regional brain development mirrors the immediate needs of each developmental stage which, in turn, may help to explain the diversity in outcomes depending on the timing of ELS.

Brain development in healthy children and adolescents

Brain development is an exceedingly complex process as the organism needs to respond to the challenges and demands of the environment (Teicher et al. 2006b). In this section, we highlight five principles of brain development derived from recent findings in healthy longitudinal and cross-sectional samples, which represent the framework along which ELS acts.

Principle 1: Human brain development is largely a nonlinear process (Giedd et al. 1999; Gogtay and Thompson 2010; Shaw et al. 2008)

While the developmental trajectory of grey matter (GM) volume follows an inverted U-shape, white matter (WM) volume increases steadily throughout childhood and adolescence and is likely to reflect improved connectivity and integration of disparate neural circuits (Gerber and Peterson 2009; Giedd et al. 1999). More specifically, different brain regions have been shown to develop along three main patterns of maturation. *Cubic* developmental trajectories are characterized by an early increase in GM cortical thickness followed by a decrease in adolescence and stabilization in adulthood. This applies, for example, to lateral frontal, lateral temporal, parietal, and occipital cortex (Shaw et al. 2008). Cortical thickness in the insula and anterior cingulate follows a *quadratic* developmental course, increasing over childhood, decreasing in adolescence, but demonstrating no phase of stabilization within first three decades of life. Finally, a *linear* developmental trajectory corresponding to increased cortical thickness with age is characteristic of a large number of brain regions (e.g., posterior orbitofrontal, frontal operculum, portions of piriform cortex, subgenual cingulate areas; Shaw et al. 2008). With various brain regions undergoing different patterns of maturation, neural consequences of ELS depend on the developmental stage at which the stress occurred (Teicher et al. 2003). Stress may therefore have a greater impact in childhood and adolescence as the brain experiences critical changes compared to adulthood (e.g., cubic developmental trajectory).

Principle 2: Higher-order association cortices develop only after lower-order sensorimotor cortices have matured in structure and function (Gogtay et al. 2004; Gogtay and Thompson 2010; Shaw et al. 2008)

During the process of development, essential structures, such as sensorimotor cortex and occipital poles, develop first. The remainder of the cortex matures in a back-to-front direction (parietal to frontal). This ensures the child's early availability of primary motor and sensory function including vision, taste, and smell followed by areas involving spatial orientation, speech, language, and attention. Higher-order structures that contain complex, association sites develop very late in the brain's trajectory. Among the last areas to develop are frontal lobe structures [e.g., dorsolateral PFC (DLPFC)] involved in executive functioning, attention, motor coordination as well as heteromodal association regions (e.g., superior temporal cortex). Association areas mature after basic earlier-developing sensory regions, whose function they integrate (Gogtay et al. 2004; Gogtay and Thompson 2010; Shaw et al. 2008). It can thus be hypothesized that complex functions in higher-order structures are more susceptible to the effects of ELS due to protracted periods of postnatal development.

Principle 3: Ontogeny recapitulates phylogeny (Gogtay et al. 2004; Gogtay and Thompson 2010; Lenroot et al. 2009; Shaw et al. 2008)

The brain regions latest to mature in development—including the DLPFC, orbitofrontal cortex (OFC), temporal lobes, and superior parietal lobes—are the most recent areas from an evolutionary point of view (Lenroot et al. 2009). Again, these evolutionarily "young" structures are linked to higher-order, complex skills, such as decision-making, executive functioning, and inhibition (Gogtay et al. 2004; Gogtay and Thompson 2010; Shaw et al. 2008), and are at greater risk of impairment following ELS.

Principle 4: Brain development is guided by genes but sculpted by the environment (Lenroot and Giedd 2008; Lenroot et al. 2009; Peper et al. 2009; Schmitt et al. 2008)

While early experiences have pivotal effects on brain developmental, recent twin studies in healthy samples also identified substantial genetic influences. For example, a large research study using magnetic resonance imaging (MRI) data from 308 twins, 64 siblings of twins, and 228 singletons with no twin siblings found that a single factor accounted for up to 60% of genetic variance in cortical thickness (Schmitt et al. 2008). Genetic effects were largest for frontal lobes while their influence gradually declined from temporal to parietal lobes with the occipital lobe showing the smallest degree of heritability (Schmitt et al. 2008). Moreover, later-maturing brain regions (e.g., DLPFC, superior parietal cortex, temporal cortex, language-associated regions) involved in complex cognitive processes (e.g., executive function, language) become more heritable with increasing age (Lenroot and Giedd 2008; Lenroot et al. 2009). As heritability varies with age, brain regions that develop *earlier* during development show stronger genetic influences earlier in life, while *later* developing brain regions are under greater genetic influences later in life (Lenroot et al. 2009). The effects of ELS on brain development may therefore be potentiated or buffered, depending on the strength and timing of genetic influences on specific brain regions.

Principle 5: Trajectories of brain development differ for females and males (Gerber and Peterson 2009; Lenroot et al. 2007; Lenroot and Giedd 2010; Marsh et al. 2008)

Gender differences can be found in overall brain volume, with males having a proportionally larger (between 9% and 12%) mean cerebral volume despite reaching GM peak volume 1–3 years later than females (Gerber and Peterson 2009; Lenroot and Giedd 2010). However, not all studies found gender differences in total brain volume, especially when controlling for intracranial volume (Peper et al. 2009). Gender-specific differences in brain regions occur primarily in areas containing sex steroid receptors (e.g., hypothalamus) or regions with strong connections to areas with high sex steroid receptor density (e.g., amygdala, parts of the nucleus of the stria terminalis; Lenroot and Giedd 2010). As developmental trajectories differ for males and females, ELS occurring at the same time may lead to diverse, sex-specific outcomes.

Interim summary: normative brain development

Findings from healthy samples suggest that a given brain region may be affected by ELS differently at different times, depending on its pattern of growth. Moreover, high-order cortices and complex functions develop after lower-order cortices and primary functions have matured. Genetic and sex influences jointly contribute to individual differences in brain development. The following section will review the specific mechanisms by which ELS can impact brain development.

Early life stress and brain development

Since the early 1990s, a large body of neurobiological and neuroendocrine studies has highlighted the impact of chronic stress on brain development. The most accepted explanation for alterations in brain structures postulates that ELS interferes with the critical waves of neurogenesis, synaptic overproduction, and pruning of synapses and receptors (Teicher et al. 2006a, b). As the loss in GM often exceeds what can be explained by aberrant increases in synaptic pruning, an expansion in WM through an increase in myelination in intra-cortical axons may also contribute to the apparent loss of GM (for review, see Paus et al. 2008). Due to limited resolution of current MRIs, the cellular processes underlying such structural changes, however, remain impenetrable with in vivo neuroimaging techniques (Gogtay and Thompson 2010).

Mechanisms of stress

From a biological point of view, encountering a stressful situation activates the sympathetic nervous system and hypothalamic—pituitary adrenal (HPA) axis (for a review on HPA dysfunction, see Yehuda et al. in this issue; Gunnar and Quevedo 2007; Heim and Nemeroff 2001, Lupien et al. 2009). While the acute activation of stress response systems is considered an adaptive mechanism that mobilizes resources to increase chances of survival, high or chronic levels of stress can lead to aberrant reactivity of the HPA axis (Glaser 2000; Gunnar and Quevedo 2007). When faced with a stressor, corticotrophin-releasing hormone and arginine vasopressin travel to the anterior pituitary where they stimulate the release of adrenocorticotropic hormone, which in turn interacts with receptors on the cortex of the adrenal gland (Gunnar and Quevedo 2007; Heim and Nemeroff 2001; Lupien et al. 2009). This cascade releases glucocorticoids throughout the brain and body which then bind to mineralocorticoid and glucocorticoid receptors. Most importantly, glucocorticoids acting via glucocorticoid receptors can impair neural plasticity (Gunnar and Quevedo 2007). This explains why brain regions with a particularly high density of glucocorticoid receptors and characterized by prolonged phases of postnatal development (e.g., PFC, hippocampus) are more susceptible to disturbances (Teicher

et al. 2003; Tottenham and Sheridan 2010). Exactly how ELS affects cognitive functioning and emotional well-being via specific neurobiological pathways, however, remains poorly understood. The following sections review how particular cognitive and affective functions may be impacted by disruptions in brain development following ELS.

ELS and cognitive functioning

Global cognitive performance

Impaired intellectual ability, worse academic performance, and a greater need for individualized education programs have been noted in children who experienced ELS, including early institutionalization, neglect, or various forms of maltreatment (Cohen et al. 2008; De Bellis et al. 2009; Johnson et al. 2010; Loman et al. 2009; Nelson et al. 2007; van den Dries et al. 2010). Smaller intracranial volume, reduced hemispheric integration, and a smaller corpus callosum are some of the neural correlates of impaired global cognitive functioning following ELS (Noble et al. 2005; Schiffer et al. 1995; Teicher et al. 2004).

Intellectual performance

A recent study by De Bellis and colleagues (2009) used a battery of standardized tests to investigate neurocognitive functioning in neglected children with and without PTSD compared to non-traumatized controls. Regardless of their PTSD diagnosis, neglected children scored significantly lower on intelligence quotient (IQ) than controls. Even when differences in IQ were statistically controlled, significant differences between neglected and non-neglected children were found in a range of cognitive functions including language, memory/learning, and attention/executive functioning (De Bellis et al. 2009).

Similar results emerged from a study of orphans. Children who spent the first part of life in institutionalized care showed decreased intellectual performance, language difficulties, poorer cognitive abilities, and impaired psychomotor development compared to never institutionalized children (Cohen et al. 2008; Loman et al. 2009; Rutter and O'Connor 2004; van den Dries et al. 2010). The time spent in an institution was positively related to the extent of cognitive deficits (Loman et al. 2009; Noble et al. 2005; Rutter and O'Connor 2004). Confirming prior studies (e.g., Perez and Widom 1994), greater severity of abuse was linked to lower IQ (De Bellis et al. 2009).

Interestingly, foster care at 10 months or older resulted in significant gains in cognitive functioning, commonly referred to as "catch-up" (Nelson et al. 2007). Findings are consistent with other studies describing a significant increase in cognitive functioning 6 months post-adoption (Cohen et al. 2008; van den Dries et al. 2010). Despite some functional gains, institutionalized children often still lag behind children raised by their biological parents even after years of quality care (Rutter and O'Connor 2004). It should be noted that most studies assessing IQ in abused or neglected children do not control for heritability factors. Accordingly, parents who abuse or neglect their children might be more likely to score lower on intelligence measures, which can introduce interpretative biases.

Cerebral volume

Several studies on ELS uncovered a relationship between amount of GM and IQ, with earlier onset and longer duration of abuse being correlated with decreased cerebral volumes (De Bellis et al. 2002b; Noble et al. 2005). As evident from research in healthy samples, cortical GM follows an inverted U-shaped developmental trajectory undergoing change from childhood to late adolescence (Principle 1; Gerber and Peterson. 2009; Gogtay and Thompson 2010). GM peaks earliest in primary sensorimotor areas and latest in association areas of the frontal cortex (e.g., DLPFC peaking at 10.5 years) and temporal cortex [e.g., superior temporal gyrus (STG) peaking at 14.9 years; Gerber and Peterson 2009; Gogtay et al. 2004; Shaw et al. 2008]. Although the deprivation in institutionalized children takes place at an early age, complex association areas continue to mature once lower-order sensorimotor regions are developed (Principle 2; Gogtay and Thompson 2010). The protracted development of GM association areas (DLPFC, STG) poses an increased risk of impairment and is likely to contribute to deficits in cognitive performance.

Interhemispheric integration and corpus callosum

As the largest WM structure in the brain, the corpus callosum is composed of myelinated axons allowing an interhemispheric integration of diverse cognitive, motor, and sensory processes. In healthy samples, increased growth patterns were found for the anterior part of the corpus callosum between ages 3 and 6, assisting in vigilance and planning of new actions (Thompson et al. 2000). As language and associative memory functions become more prevalent, a sharp increase in posterior corpus callosum growth was noted around puberty (6–13 years). An attenuated but continuous growth pattern was found thereafter, ceasing at about 29 years of age (Pujol et al. 1993; Thompson et al. 2000). It should be noted that this trajectory reflects the corpus callosum's substantial role in connecting various brain regions which are likely to affect

various aspects of cognitive functioning at different stages throughout development.

In both non-human and human research, exposure to ELS has been associated with decreases in corpus callosum size. In a study by Sánchez and colleagues (1998), primates separated from their mother from 2 to 12 months of age were later characterized by a reduced volume of the corpus callosum, loss of WM in prefrontal and parietal regions, and impairments in recognition memory and reversal learning. In line with these preclinical data, reduced hemispheric integration and a smaller-sized corpus callosum, particularly in the medial and posterior regions, have been described in adults maltreated as children (Navalta et al. 2006; Schiffer et al. 1995), with the corpus callosum in neglected children being 17% smaller than in controls, and 11% smaller than in non-abused psychiatric children (Teicher et al. 2004). These findings have been strengthened by diffusion tensor imaging techniques, which have uncovered reduced fractional anisotropy in medial and posterior regions of the corpus callosum in maltreated children with PTSD (Jackowski et al. 2008) and in the genu of the corpus callosum in nonclinical adults with a history of ELS (Paul et al. 2008).

Despite these initial findings, additional studies are needed to investigate with greater precision the functional outcomes associated with a reduction in corpus callosum size. At this stage, one can conclude that the separate growth spurts of the anterior and posterior regions of the corpus callosum appear to subserve specific functions. The anterior corpus callosum develops and assists with functions needed earlier in life (e.g., vigilance, approach behavior), while other functions coinciding with posterior growth become more relevant later in development (e.g., language, associative memory). Generally, with the corpus callosum developing until the third decade of life, it can be suggested that this structure supports various higher-order functions vulnerable to effects of ELS (Principles 1 and 2).

Memory

Exposure to stress can have numerous effects on mnemonic function including stress-induced potentiation of emotional memory (associated with increased amygdala activation) as well as disruption of neutral memory (Payne et al. 2007). In cases of ELS, multiple studies have found significant impairments in verbal, visual, and global memory function in adulthood (Bos et al. 2009; Bremner et al. 2003a, b; De Bellis et al. 2010; Navalta et al. 2006; Tomoda et al. 2010). For sexual abuse and mixed maltreatment, the extent of memory deficit appears to be moderated by the chronicity of the abuse, the number of incidents, and the relationship to the perpetrator (Anda et al. 2006; Navalta et al. 2006). For example, for those who reported four or more adverse life events, impairments in childhood memory was increased by 4.4-fold (Anda et al. 2006). The number of age periods affected by such memory gaps gradually increased with the number of adverse ELS experiences (Anda et al. 2006).

Memory and the hippocampus

While postnatal neuronal proliferation in the hippocampus begins at a very early age, it has been shown to continue into adulthood (Gogtay et al. 2006). The hippocampus is a heterogeneous structure, with subregions responsible for different functions and developing along different growth trajectories. In healthy samples, the anterior portion of the hippocampus—which projects to the amygdala, PFC and HPA axis and plays a role in anxiety-related behavior, associative memory, and emotional processing—shows volume reduction with increasing age. Conversely, posterior regions (particularly, the CA3 region)—which play a significant role in spatial learning and contextual memory—gradually increase over time (Gogtay et al. 2006).

In adults who experienced ELS, reduced volume of the hippocampus is a common finding (see meta-analyses by Karl et al. 2006; Woon and Hedges 2008; Woon et al. 2010). Animal studies confirm the relationship between ELS (e.g., maternal separation) and reduced hippocampal volume in late life, suggesting permanent impairments in hippocampus-dependent learning and memory (Karten et al. 2005). Morphometric changes may be due to elevated levels of glucocorticoids in the glucocorticoid receptor-rich hippocampus. Accordingly, cortisol secreted as a result of ELS would bind to these receptors and negatively impact neurogenesis, resulting in cell loss (Sapolsky 1996).

However, not all studies have found reduced hippocampal volume following ELS. Numerous studies have failed to demonstrate volumetric reductions in younger individuals with ELS (Carrion et al. 2001; De Bellis et al. 2002b; De Bellis et al. 2010; Teicher et al. 2003; see meta-analyses by Karl et al. 2006; Woon and Hedges 2008; Woon et al. 2010). Moreover, some studies failed to demonstrate a link between abnormal hippocampal volume and deficits in memory functioning following maltreatment (Pederson et al. 2004; Stein et al. 1997). In the next sections, we briefly explore the potential explanations for these divergent findings.

Prolonged exposure to stress

Some have argued that prolonged periods of cortisol secretion and HPA hyper-activation are needed for long-term hippocampal atrophies to be manifested at the level of resolution of current MRI technology (Carrion et al. 2007).

This would imply that hippocampal volume loss may be detectable only years after trauma onset, thus explaining why imaging studies have described hippocampal volume decreases in adults but not in children. Preliminary support for this hypothesis stems from a longitudinal study of traumatized children in which markers of stress (PTSD symptoms, cortisol levels) predicted reduced hippocampal volume from baseline to follow-up 12–18 months later (Carrion et al. 2007). However, it should be noted that this study used a very small sample of children (n=15) with PTSD and a short time interval between initial and follow-up assessment.

Preexisting vulnerability

Could reduced hippocampal volume be a risk-factor for stress-related pathology rather a consequence of ELS? It is currently a matter of debate whether smaller hippocampi may be a risk factor for stress hypersensitivity. Non-human primate research illustrates that naturally occurring hippocampal volume differences predicted adrenocorticotropic cortisol levels following a restraining stressor (Lyons et al. 2007). Along similar lines, in a monozygotic twin study, Gilbertson and colleagues (2002) found that *non-traumatized* twin siblings of those who developed PTSD following combat exposure had smaller hippocampi. Although not directly related to ELS, these finding strengthens the argument that small hippocampi may be a risk factor for impaired regulation of the HPA axis and a vulnerability factor to stress-related psychopathology.

Impact on other neurobiological systems

Most recently, Tottenham and Sheridan (2010) argued that hippocampal development lags behind the developmental trajectory of the amygdala. In a study of the Israeli Defense forces, 50 healthy recruits were studied upon their entry to the military and 18 months after serving as combat paramedics during which they were exposed to high levels of stress (Admon et al. 2009). The authors found that pre-exposure amygdalar, but not hippocampal, reactivity predicted a greater increase in stress symptoms over time. Moreover, hippocampal alteration in response to stress-related pictures following the stress exposure was predicted by higher amygdala pre-stress reactivity (Admon et al. 2009). Although this military-related stress experience does not resemble ELS, it could be speculated that amygdala hyperreactivity precedes volumetric changes in the hippocampus following stress exposure (Tottenham and Sheridan 2010). This, in turn, could explain why research fails to detect changes in hippocampal volume in children. Similar to the argument of prolonged stress exposure, ELS may lead to hippocampal atrophy only in later life.

Comorbidity

Hippocampal size may also be associated with psychiatric illness or substance abuse. Unfortunately, studies examining memory performance or hippocampal volume often fail to control for psychiatric illness, such as PTSD (Stein et al. 1997) or borderline personality disorder (Driessen et al. 2000). Only a few studies have controlled for the presence of clinical disorders, or used nonclinical samples in order to attribute reductions in hippocampal volume to ELS (De Bellis et al. 2009; Vythilingam et al. 2002). Some studies did not find volumetric differences even when controlling for common psychopathology such as PTSD (e.g., Pederson et al. 2004).

Genetic factors

Finally, animal studies have demonstrated that at least 54% of hippocampal size variance is attributable to genetics (Lyons et al. 2001). In humans, several genetic markers have been associated with smaller hippocampi (Principle 4). For example, Met carriers of the BDNF polymorphism were found to exhibit smaller hippocampal volumes in the presence of stress, trait depression and neuroticism (Joffe et al. 2009). Depressed adults exposed to ELS carrying the short allele of the serotonin transporter gene also displayed smaller hippocampal volumes than adults who had only one risk factor (ELS or short allele; Frodl et al. 2010). Notably, among healthy controls, emotional neglect and 5HTTLPR allele jointly explained 57% of variance in hippocampal WM, while neither variable alone explained significant variance (Frodl et al. 2010).

In sum, based on data reviewed above, it is clear that longitudinal studies controlling for comorbidity and investigating genetic influences will be required to disentangle how ELS contributes to long-term structural changes in the hippocampus. Most importantly, more research is needed to explain how changes in different subregions of the hippocampus relate to specific impairments in memory function.

Executive functioning

Global deficits in executive functioning following ELS are frequently reported (Bos et al. 2009; Colvert et al. 2008; Pollak et al. 2010). Executive functions (e.g., inhibitory control, cognitive flexibility, sustained attention) are subserved by a network of brain regions including various PFC and striatal regions (Leh et al. 2010). Accordingly, the development of executive functions is thought to coincide with growth spurts in the maturation of the frontal cortex occurring between birth and 2 years, 7–9 years, during adolescence, and continue into the third decade of life

(Jurado and Rosselli 2007; Marsh et al. 2008, Shaw et al. 2008). Two developmental characteristics make the PFC particularly vulnerable to stress effects. First, PFC circuits progress in a back-to-front direction and are marked by long developmental trajectories supporting higher-order functions (Principle 2; Gogtay et al. 2004). Second, the PFC has a high density of glucocorticoid receptors and dopaminergic (DA) projections that are stress-susceptible (Brake et al. 2000).

Frontostriatal circuits and inhibitory control

A recent study by Mueller and colleagues (2010) explored the perturbations in cognitive control and their underlying neural correlates in ELS. In a functional MRI (fMRI) study, adolescents were asked to inhibit a prepotent response (*Go*) and initiate a non-prepotent alternative (*Change*). Individuals with ELS not only displayed longer reaction times on the *Change* trials but also demonstrated greater activations in regions involved in cognitive control, in particular, the inferior frontal cortex (cognitive inhibitory control) and striatum (response control). Greater activation only occurred during the *Change* trials compared to *Go* trials, thus suggesting a specific impairment in inhibitory control rather than simple motor function (Mueller et al. 2010). Interestingly, diminished inhibitory capacity was also found in a sample of high-functioning college women with sexual abuse histories (Navalta et al. 2006).

Inhibitory control is thought to improve with age due to increasing activity in the frontostriatal circuits; however, the development of these circuits may be affected by early stress experiences even in high-functioning abuse survivors (Marsh et al. 2008). Both studies revealed impairments to aspects of cognitive control and prefrontal–striatal networks that can also be found in psychopathologies related to ELS such as depression (Langenecker et al. 2007) and PTSD (Falconer et al. 2008).

Cerebellum and planning

Bauer and colleagues (2009) found an association between deficits in planning and a smaller right superior–posterior cerebellar lobe in early institutionalized children. In addition to motor learning, balance, and coordination, the cerebellum is also involved in affective and cognitive processes such as language, visual spatial learning, and working memory (Tiemeier et al. 2010). Of note, the cerebellum demonstrates one of the most drawn-out developmental time courses (Gogtay and Thompson 2010), with total volume peaking at about 12 years for females and 16 years for males (Tiemeier et al. 2010). Interestingly, this implies that the cerebellum peaks approximately 2 years later than cerebral volume (Gerber and Peterson 2009). It could be argued that the prolonged development of the cerebellum leaves it susceptible to long-term stress exposure and altered cytoarchitecture (Principle 2) and may therefore interfere with the later developing cognitive functions, e.g., planning (Bauer et al. 2009) or learning and working memory (Tiemeier et al. 2010) associated with the cerebellum.

Interim summary: cognitive functioning

A substantial number of studies have demonstrated that ELS can be associated with global cognitive difficulties, including decreased intellectual performance, academic success, language abilities, and aspects of executive functioning (e.g., inhibitory control, planning). These higher-order functions are subserved by association sites (PFC, STG) and regions that undergo protracted development (corpus callosum, cerebellum), which could explain the increased risk for global impairment as a consequence of ELS (Principles 2 and 3). Findings of memory deficits and hippocampal volume reductions have been more inconsistent, particularly, as hippocampal volume reduction has been found in adults but not in children.

ELS and affective functioning

Reward processing

The ability to evaluate and learn from rewarding outcomes and respond to reward-predicting cues is vital to survival and contributes to adaptive, goal-directed decision-making (Ernst and Paulus 2005). Key components of the reward circuit, including basal ganglia regions involving the ventral (e.g., nucleus accumbens) and dorsal (e.g., caudate) striatum, amygdala, and OFC, undergo significant changes throughout childhood and adolescence (Forbes and Dahl 2005; Giedd et al. 1999). Some basal ganglia structures (e.g., caudate) and the amygdala are also subject to volumetric sex differences, possibly suggesting differences in reward responsiveness (Principle 5; Lenroot and Giedd 2010).

The mesolimbic DA system, in particular, plays a crucial role in various aspects of reward processing including attributing incentive salience to reward-related stimuli ("wanting"; Berridge 2007). DA cell bodies in the ventral tegmental area project heavily to the nucleus accumbens, and both midbrain and striatal DA cells fire in response to both reward-predicting cues and unpredictable rewards. Blunted mesolimbic DA transmission has been postulated in depression, particularly in the presence of anhedonia, low energy, loss of libido, and apathy (Dunlop and Nemeroff 2007; Hasler et al. 2008; Pizzagalli et al. 2009a, b). Of major relevance to this review, animal studies have shown that chronic stressors and early adverse rearing

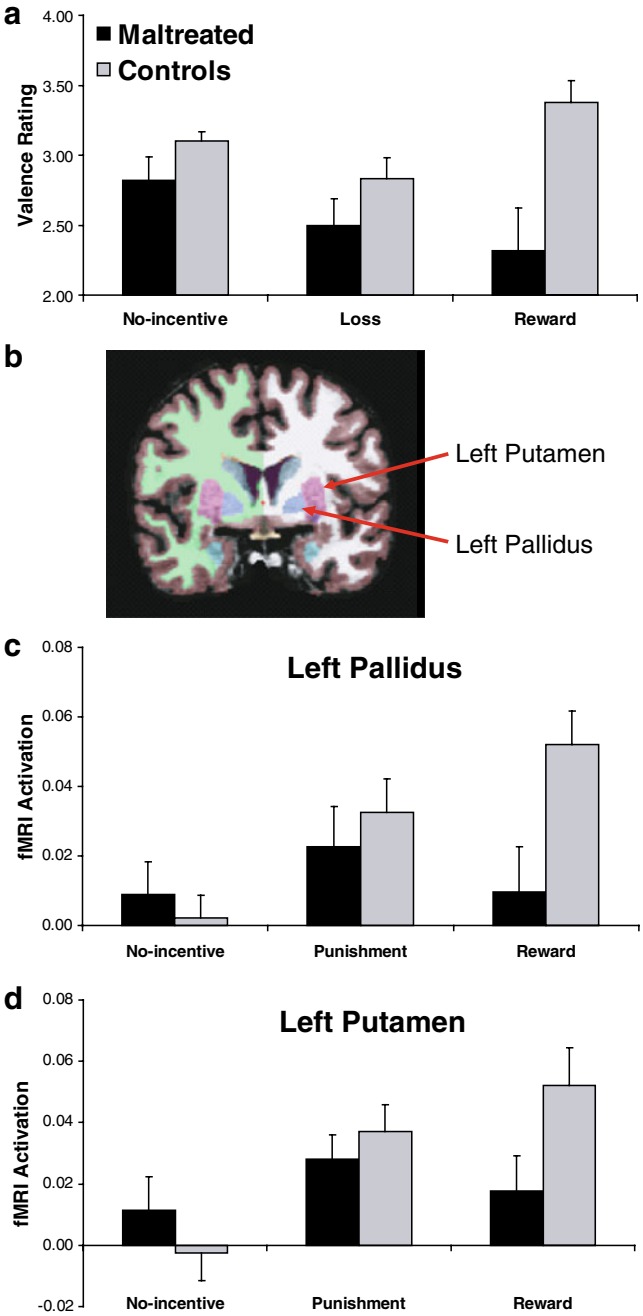

Fig. 1 Affective and neural dysfunction during a monetary incentive delay task in a longitudinal sample of young adults (mean age 24.58, SD 0.88) exposed to childhood adversities. Eight of the maltreated participants have been studied since infancy (mean age at enrollment 8.88 months), and five have been studied since young adulthood (mean age at enrollment 20.60 years). Relative to healthy controls (n=31), maltreated individuals (n=13) reported reduced positive affect (**a**) and were characterized by reduced activation in the left pallidus and left putamen during the anticipation of a potential reward (monetary gains; **b**–**d**). Highlighting the specificity of these findings, groups did not differ in their affective ratings or neural responses while anticipating a potential loss (monetary penalty) or no-incentive outcome (no monetary changes; for all variables, the *Group*×*Condition* interaction was significant.) Functional MRI signals were extracted from structurally defined basal ganglia regions including the putamen and pallidus (see *panel b*). Reprinted from Biol Psychiatry, 66/3, Dillon DG, Holmes AJ, Birk JL, Brooks N, Lyons-Ruth K, Pizzagalli DA, Childhood adversity is associated with left basal ganglia dysfunction during reward anticipation in adulthood, 206–213, Copyright (2009), with permission from Elsevier

environments lead to anhedonia-like behavior (including reduced motivation to pursue reward) and dysfunction in mesolimbic DA pathways in adulthood (Anisman and Matheson 2005; Matthews and Robbins 2003; Pryce et al. 2004; Strekalova et al. 2004). In light of these preclinical data, two recent studies have probed putative dysfunction in reward-related brain activation in adults exposed to ELS.

In a study with a longitudinal component, Dillon and colleagues (2009) found that, relative to non-abused individuals, maltreated subjects were characterized by decreased anticipatory reward-related activity in the left pallidus and putamen, two key regions in the basal ganglia that have been implicated in the processing of reward-predicting cues (Fig. 1). Maltreated subjects, who reported more symptoms of anhedonia than non-abused subjects, also rated reward cues as less positive. Based on prior data, we speculated that the abnormal pallidus activity might weaken the ability of reward-predicting cues to elicit goal-directed behavior.

Interestingly, decreased basal ganglia activity was found for the anticipatory but not the consummatory phase of reward processing. These findings were recently replicated in a study investigating Romanian adoptees who had experienced global early deprivation. Using a similar task, Mehta et al. (2010) also described reduced ventral striatal activation to reward-predicting cues in the deprived young adults (see also Guyer et al. 2006 for behavioral evidence of suboptimal reward-related decision-making in a gambling task).

Overall, these findings are consistent with theoretical arguments (Charney 2004) and initial empirical evidence (Vythilingam et al. 2009), suggesting that robust brain reward function is a key component of resiliency following trauma. The fact that reward dysfunction in the two fMRI studies was specific to the anticipatory component of the task is intriguing, based on (1) animal studies indicating that chronic and unpredictable stressors lead to a down-regulation of mesolimbic DA (Cabib and Puglisi-Allegra 1996), and (2) evidence implicating DA in incentive motivation (wanting; Berridge 2007). Both groups speculated that fMRI findings might reflect reduced phasic DA transmission in maltreated individuals. Recent findings showing that BOLD signal during a similar reward task correlated with an indirect measure of endogenous DA release (Schott et al. 2008) provide further evidence for this hypothesis. Critically, blunted responsiveness to reward-predicting cues might be associated with two opposite sequelae: (1) anhedonic behavior, which might increase the

risk for mood disorders, and (2) compensatory reward-seeking behavior, which might increase the risk of maladaptive behaviors including substance abuse. In this context, it is interesting to note that individuals with a history of ELS show more frequent, heavier, and earlier smoking behavior in adulthood compared to individuals without early adversity (Anda et al. 1999). Because nicotine is a potent modulator of the brain reward system (Kenny and Markou 2006), it is possible that substance use might be a self-medication attempt to ameliorate anhedonic symptoms.

Emotional perception

Emotion-modulated attentional biases

Maltreated and neglected infants and children show abnormalities in identifying and responding to facial expressions of negative valence (Cicchetti and Curtis 2005; Fries and Pollak 2004; Parker et al. 2005; Pollak et al. 2000). For example, event-related potential (ERP) studies have shown that, unlike children not exposed to physical maltreatment, those with such histories generated larger P3b amplitudes when presented with angry faces (or voices) compared to happy or fearful targets (Pollak et al. 2001; Shackman et al. 2007). Potentiated P3b was interpreted as indicating increased attentional resources devoted to angry cues in maltreated children (see also Pine et al. 2005 for similar behavioral evidence). Because children with maltreatment histories are more likely to witness anger and subsequent adversity, recruitment of more cognitive processes and selective attention to threat-related cues appears justified (see also Shackman et al. 2007). Fitting these interpretations, abused children have been found to require less visual information to detect anger in facial expressions, which might reflect their effort to identify potential threats as early as possible to minimize harm (Pollak and Kistler 2002). A number of studies have confirmed the presence of attentional bias in maltreated or institutionalized children of varying ages. The Bucharest Early Intervention Project, for example, showed that institutionalized children between 7 and 32 months of age exhibited greater N170 and smaller P250 amplitude to fearful expressions at both the midline and lateral electrode sites, suggesting potentiated encoding of threat-related faces (Parker et al. 2005; see also Cicchetti and Curtis 2005).

These behavioral and electrophysiological data have been complemented by neuroimaging findings. A large body of work has shown that recognizing and understanding emotions depends on the amygdala and its projections to occipitotemporal regions (e.g., fusiform gyrus), STG, thalamus, and OFC (Adolphs 2002). Individuals with a history of ELS show functional and structural abnormalities within these pathways. Accordingly, maltreated children with PTSD were found to have increased gray matter volume in the STG compared to non-maltreated children without PTSD (De Bellis 2005; De Bellis et al. 2002a). This is consistent with the recent finding of a 14% increase in GM volume of the left STG in a group of adults who experienced parental verbal abuse (Tomoda et al. 2010). The STG is a heteromodal structure critically implicated in receptive and non-verbal auditory processing and critically implicated in emotional perception (Adolphs 2002), which may be particularly vulnerable to effects of ELS due to its prolonged, cubic developmental trajectory (peak GM at about 15 years; Principles 1, 2, and 3; Gogtay et al. 2004; Gogtay and Thompson 2010; Shaw et al. 2008). An increase in GM volume might therefore reflect abuse-related increases in sensitivity to non-verbal stimuli, thus contributing to attentional bias in processing affective facial expressions.

Abused children show selective attention to and difficulty disengaging from threat-related cues, including facial and vocal expressions of anger and fear. The fact that these dysfunctions do not extend to happy facial expressions argues against global information processing deficits. Emerging neuroimaging data indicate that abnormalities might be linked to dysfunction in subcortical and cortical regions critically implicated in processing emotional and social cues, including the amygdala and STG (Tomoda et al. 2010; Tottenham et al. 2010). Although early and potentiated detection of anger may be an adaptive coping mechanism, it is important to emphasize that most of the children studied had been removed from their noxious environment. This suggests that while some of the previously described cognitive impairments following ELS are subject to a catch-up in functioning, emotion-associated deficits may prove less plastic.

Emotional regulation

Children exposed to severe ELS experience significant emotion regulation difficulties, which are thought to confer risks for later psychopathology (Lyons-Ruth 2008; Tottenham et al. 2010). Research in healthy controls has emphasized the role of the DLPFC and anterior cingulate cortex (ACC) in emotion regulation, and successful downregulation of negative affect has been associated with decreased amygdala activation (for review, see Ochsner and Gross 2005). Thus, emotional dysregulation in maltreated individuals might be associated with functional and structural abnormalities in frontocingulate and frontolimbic pathways.

The amygdala and emotional responsiveness

While the DLPFC and ACC mature in early adolescence (peak cortical thickness ~10.5 years), the amygdala is present in its basic cytoarchitecture and function at birth. It

develops rapidly thereafter, reaching its peak volume as early as age 4 in females (Shaw et al. 2008). Interestingly, the amygdala is not only functional at a very early age but also appears more reactive in childhood compared to adulthood. This early development may indicate a very early sensitive period in which ELS (e.g., early deprivation) can disrupt maturation (Tottenham et al. 2010). Overall, the amygdala is pivotal in learning and responding to social and emotional stimuli in the child's environment. Disruptions in its developmental trajectory are likely to alter thresholds to emotional information and contribute to psychopathology, particularly, anxiety (Tottenham and Sheridan 2010; Kim and Whalen 2009).

Providing initial evidence for some of these arguments, Tottenham and colleagues (2010) recently described in a sample of institutionalized but later adopted children morphometric differences in the limbic system accompanied by response inhibition impairments in the presence of negative distractors in an emotional go–nogo task. Compared to controls, previously institutionalized children showed greater amygdala volumes and made more false alarm errors when the nogo condition used negatively valenced faces. Moreover, reaction times of institutionalized children varied with slower responses to neutral stimuli in the context of positive valence and accelerated response to neutral stimuli in the context of negative faces. Behavioral and neurobiological evidence therefore suggests that late-adopted children may be more influenced by emotional contexts, contributing to their emotion regulation difficulties (Tottenham et al. 2010). One might argue that this outcome could be attributed to the previously reviewed difficulties in recognizing emotions (Pollak et al. 2000). However, the majority of errors made in Tottenham's sample (false alarm) suggest a *hypersensitivity* to emotional arousal rather than failure to identify the emotion (miss).

Interestingly, in contrast to global cognitive functions showing improvements after removal from the adverse environment (Nelson et al. 2007), the amygdala seems more resistant to environment change. It has been suggested that this pattern may contribute to the persistence of emotional problems displayed by children who were relieved of their adverse environment over 10 years ago (see Tottenham and Sheridan 2010 for a review).

Interim summary: affective functioning

ELS has been linked to impairments in reward processing and reduced activation in the basal ganglia regions. In addition, individuals with a history of ELS are often characterized by increased attention and potentiated encoding of negative or threatening faces and larger STG, suggesting increased sensitivity to non-verbal stimuli. Larger amygdala volumes and increased emotional reactivity to negative stimuli are likely to contribute to psychopathology commonly seen following ELS (e.g., anxiety). Overall, affective impairments remain evident long after the removal of the stressor. An important avenue for future research will be to directly test the speculation that affective deficits due to the early disruption of associated brain regions (e.g., amygdala) are more resistant to change than aspects of cognitive functioning. Moreover, as the amygdala continues to be a sexually dimorphic structure (earlier peak volume for females, larger total volume for males), future studies are needed to test whether ELS occurring at a given time may lead to gender-specific impairments and mental health problems (Principle 5, Lenroot and Giedd 2010).

Conclusion

In this review, we merged findings from two independent but complementary lines of research, namely, studies on normative brain development and disruptions to brain development, to understand mechanisms associated with cognitive and affective functioning following ELS. Using a developmental approach, we identified general principles of normative brain development that significantly add to our understanding of the sequelae of ELS. By integrating normative and ELS outcomes of brain development, we concluded that brain regions with prolonged developmental trajectories (e.g., PFC) are particularly vulnerable to ELS which may partially explain impairments in complex, higher-order functions (e.g., executive functioning). These dysfunctions could contribute to the progression of mental illness; for example, executive dysfunction may impair emotion regulation and foster rumination as seen in depression (Gotlib and Joormann 2010). Another interesting finding that requires attention is the extent of catch-up in cognitive and affective functioning following the relief of the stressor. While cognitive functions have shown some degree of recovery after relief from the stressful environment, deficits in affective functioning (e.g., emotion regulation) and associated brain regions (e.g., amygdala) appear more resistant. This may contribute to the higher rates of anxiety and mood disorders commonly seen in adults with ELS histories.

Finally, we would like to note that the structure of this review is guided by research developments in humans over the past two decades, often inspired by important findings in animal models. We acknowledge that discussing separate brain regions as contributing to specific emotional or cognitive deficits can appear simplistic. However, considering the plethora of studies investigating ELS using a vast range of designs, it was our objective to merge findings to highlight primary pathways of early neurobiological disruptions affecting later well-being. While past research

commonly focused on single brain–behavior associations, we support more recent approaches investigating functionally connected networks (Lu et al. 2009). Moreover, although we focused on behavioral phenotypes most often investigated in clinical and basic studies (e.g., memory, executive functioning, and affective processing), ELS can negatively impact a wide range of functions (e.g., language), and further research exploring additional phenotypes is warranted.

Future directions

Partially due to the relative recency of this line of work, there are several outstanding questions that remain unanswered and should be the topic of future studies. First, as developmental trajectories differ for males and females, studies will be needed to evaluate sex-specific outcomes of ELS occurring at particular developmental stages. This knowledge is critical since it might inform sex-specific prevention and intervention strategies. Second, initial evidence indicates that genetic influences on brain development might be region- and age-specific (Lenroot and Giedd 2008; Lenroot et al. 2009). Accordingly, studies are warranted to evaluate whether the effects of ELS on brain development may be moderated by the strength and timing of genetic influences on specific brain regions. Moreover, a stronger focus on potential *Gene×Environment* interactions might provide important clues about mechanisms and pathways associated with increased risk for psychopathology following ELS. Third, an important topic for future research will be to investigate whether permanent abnormalities of stress reactivity reviewed here may contribute to overall poor decision-making due to stress-related impairments in processing reward and punishment cues. In particular, adolescents and adults who have experienced ELS show increased odds of maladaptive behavior including eating disorders (Rayworth et al. 2004), substance abuse (Bailey and McCloskey 2005), alcohol dependence (Nelson et al. 2002), high-risk sexual behaviors or disorders (Maniglio 2009), dissociation (Wright et al. 2009), and self-harm or suicide (Dube et al. 2001; Paolucci et al. 2001). More recently, researchers have started to conceptualize these behaviors as maladaptive coping in an attempt to relieve or alleviate distress despite receiving negative feedback (Accident Compensation Corporation 2008). Future research should therefore focus on the relationship among harmful behavior, the affective and cognitive deficits discussed above (e.g., reward processing), and associated changes manifested in the brain (e.g., ACC, PFC, amygdala). This research is of particular practical importance, because it speaks to a vicious cycle that too often characterizes abuse. While abused children are generally at an increased risk of subsequent abuse (Maniglio 2009; Nelson et al. 2002), the number of maladaptive coping strategies is one of the strongest predictors of revictimization (Filipas and Ullman 2006)—a fact that may reflect a combination of impaired cognitive and affective functioning following ELS.

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