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# Duration of early adversity and structural brain development in post-institutionalized adolescents

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ABSTRACT

For children reared in institutions for orphaned or abandoned children, multiple aspects of the early environment deviate from species-typical experiences, which may lead to alterations in neurobehavioral development. Although the effects of early deprivation and early life stress have been studied extensively in animal models, less is known about implications for human brain development. This structural neuroimaging study examined the long-term neural correlates of early adverse rearing environments in a large sample of 12–14 year old children ($N = 110$) who were internationally adopted from institutional care as young children (median age at adoption = 12 months) relative to a same age, comparison group reared with their biological families in the United States. History of institutional rearing was associated with broad changes in cortical volume even after controlling for variability in head size. Results suggested that prefrontal cortex was especially susceptible to early adversity, with significant reductions in volume (driven primarily by differences in surface area rather than cortical thickness) in post-institutionalized youth. Hippocampal volumes showed an association with duration of institutional care, with later-adopted children showing the smallest volumes relative to non-adopted controls. Larger amygdala volumes were not detected in this sample of post-institutionalized children. These data suggest that this temporally discrete period of early deprivation is associated with persisting alterations in brain morphology even years after exposure. Furthermore, these alterations are not completely ameliorated by subsequent environmental enrichment by early adolescence.



## Introduction

Research in both animal and human populations has demonstrated that early, postnatal experiences can have a profound impact on later brain, cognitive, and socioemotional development (Greenough et al., 1987). The range of experiences known to produce measurable, long-lasting changes in brain structure and function is relatively diverse, encompassing global differences in the early environment such as poverty (Lawson et al., 2013), maltreatment (Hanson et al., 2010), and variations in the prenatal environment (Raznahan et al., 2012). In many cases, children who experience early adverse environments also experience ongoing adversity during major portions of childhood, thus making it difficult to relate the timing of experience to later indices of brain and behavioral functioning. Recently, researchers have begun examining brain development in children for whom periods of significant adversity are confined to the first years of life by studying children adopted or fostered from institutions (orphanages) into middle- and upper-middle class families.

Institutional rearing environments deviate from species-typical care in multiple ways, leading to potential alterations in both experience-expectant (i.e. functions that develop for all members of a species given a typical environment) and experience-dependent (i.e. functions that develop based on unique interactions between the individual and his/her environment) aspects of brain development (Greenough et al., 1987). The quality of institutional care varies widely, but may include poor and/or inadequate nutrition, exposure to infection due to unsanitary conditions, lack of cognitive and/or perceptual stimulation, high ratios of children to caregivers, and frequent staff turnover, disrupting the formation of infant–caregiver attachment relationships (Nelson, 2007). Furthermore, children currently residing in institutions show biological markers of chronic stress such as altered daily cortisol patterns (Carlson and Earls, 1997), suggesting that the orphanage care environment may alter aspects of brain development that are stress sensitive.

Most post-institutionalized (PI) children exhibit remarkable recovery following adoption into families. However, altered development of specific brain structures, including the limbic system and prefrontal cortex, is of interest given established long-term difficulties in this population with cognitive and socioemotional functions thought to depend on

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these regions of the brain (Bauer et al., 2010; Bos et al., 2009; Colvert et al., 2008; Hostinar et al., 2012; Rutter and O'Connor, 2004; Rutter, 1998). Although individual variability in neurodevelopmental outcomes exists, longer duration of institutional care is generally associated with poorer outcomes, including reduced physical catch-up growth (Rutter and O'Connor, 2004; Rutter, 1998; van Ijzendoorn and Juffer, 2006), poorer cognitive recovery (Rutter and O'Connor, 2004; Rutter, 1998), and increased risk of psychological disturbance (Rutter and O'Connor, 2004), suggesting a dose-dependent effect of duration of early life deprivation on neurobehavioral development.

### *Animal models of early adversity and brain development*

Several decades of research utilizing animal models have indicated that the prefrontal cortex, responsible for temporal sequencing of goal-directed behaviors, and the brain's limbic structures associated with forms of memory (i.e. hippocampus) and emotional processing (i.e. amygdala) are highly sensitive to stress, deprivation, and related forms of adversity. In adult rodents and nonhuman primates, repeated mild stress results in reduced dendritic branching, reduced length, and atrophy in both hippocampal and medial prefrontal neurons (e.g. Cook and Wellman, 2004; McEwen, 1999). In contrast, amygdala pyramidal and stellate neurons undergo increased dendritic arborization following stress (e.g. Vyas et al., 2002).

The majority of animal models investigating the impacts of early adversity employ varying amounts of maternal deprivation, although some now model maltreatment (e.g. see Lutz and Turecki, 2014; Teicher et al., 2006 for reviews). In most animal models of early adversity, conditions that elicit stress responses are conflated with deprivation of species-typical stimulation, with both aspects of adverse care potentially affecting the developing brain. Early deprivation of parental care is associated with long-term alterations in amygdala (Poeggel et al., 2003) and prefrontal microstructure in juvenile and adult animals (Braun et al., 2000; Ovtscharoff and Braun, 2001; Poeggel et al., 2003). Prefrontal microstructure effects are likely reflected at the volumetric level, given that maternal deprivation in non-human primates is associated with long-term changes in medial prefrontal cortex volume (Lyons et al., 2002; Spinelli et al., 2009). Interestingly, several studies have reported that the effects of early adverse care on hippocampal development are not observed until animals reach adolescence or adulthood (Andersen and Teicher, 2004; Huot et al., 2002; Karten et al., 2005; Poeggel et al., 2003), although this finding has been somewhat inconsistent (Law et al., 2009; Lyons et al., 2001; Sánchez et al., 1998; Spinelli et al., 2009). Taken together, this growing literature indicates that early adverse experiences alter neuronal microstructure and brain volume in regionally specific ways, perhaps through early disruption of normative neurodevelopmental processes that persists into adolescence and adulthood.

### *Preliminary studies of brain development in PI children*

A small number of studies have focused on brain development in children adopted or fostered from institutions, providing preliminary evidence that the effects of early adversity observed in animal models have comparable correlates in humans. Positron emission tomography (PET) studies have demonstrated that PI children show reduced glucose metabolism in limbic regions, including the amygdala and hippocampus (Chugani et al., 2001). However, the current literature on hippocampal and amygdala development following a history of early deprivation is contradictory, potentially due to differences in the ages and ethnic backgrounds of PI children tested in specific samples. PI children have been reported to show increased amygdala volume in comparison to non-adopted controls (Mehta et al., 2009; Tottenham et al., 2010), with greater alterations in later adoptees (Tottenham et al., 2010). However, several studies have failed to detect a difference in hippocampal volume in children with a history of institutional care after controlling for overall brain volume (Mehta et al., 2009; Sheridan et al., 2012; Tottenham et al., 2010).

Prefrontal cortex structure and connectivity are also altered following institutional rearing. Diffusion tensor imaging (DTI) studies indicate that PI children show reduced fractional anisotropy in the uncinate fasciculus (Eluvathingal et al., 2006; Govindan et al., 2010; Hanson et al., 2013), a white matter tract connecting limbic and frontal lobe regions, as well as more diffuse frontal–striatal projections (Behen et al., 2009) between middle childhood to late adolescence. Multiple studies have found evidence that global white matter volume is reduced in PI children (Eluvathingal et al., 2006; Mehta et al., 2009; Sheridan et al., 2012), that prefrontal white matter organization is disrupted (Behen et al., 2009; Eluvathingal et al., 2006; Govindan et al., 2010; Hanson et al., 2013), and that regions of prefrontal cortex show reduced cortical thickness (McLaughlin et al., 2013) in PI children. However, despite documented deficits within this population on prefrontal-dependent tasks, no study has reported whether organizational differences are accompanied by volumetric alterations in prefrontal cortex, as observed in animal models of early adversity.

### *Importance of brain development during childhood and adolescence*

The relationship between early (infantile) experience and brain development during childhood and adolescence is of particular interest for children removed from adversity early and placed in an enriched environment. Given the plasticity of the developing brain and the regionally specific continuation of neurodevelopmental processes including synaptic pruning and myelination (Huttenlocher and Dabholkar, 1997), it is possible that experience in the adoptive home may ameliorate the impacts of early adversity.

Although prefrontal cortex is widely considered to be a “late-developing” region of the brain, developmental changes in structure and function are evident early during the postnatal period, with dramatic increases in glucose metabolism (Chugani and Phelps, 1986) over the first year of life. Extended structural development continues throughout childhood and into adolescence in both the gray and white matter of the frontal lobes, with dorsolateral prefrontal cortex showing a particularly slow rate of structural maturation (Giedd, 2004; Sowell et al., 2001). In contrast, the brain's limbic structures mature relatively early in human development. Maximal growth of the hippocampus occurs during the prenatal and early postnatal periods (Pfluger et al., 1999), with slower growth during early childhood (Knickmeyer et al., 2008; Pfluger et al., 1999). The amygdala appears relatively well-developed by the eighth month of gestation in human fetuses (Ulfig et al., 2003), although rapid changes in its volumetric development continue during the early postnatal months in nonhuman primates (Payne et al., 2010). Although amygdala development appears to be earlier and more rapid in comparison to the hippocampus, structural MRI studies indicate that both regions show continued, subtle changes over childhood and into early adulthood, although these effects may be sex specific, differ by structural sub-regions within each structure, and may show increased individual variability following puberty (Giedd et al., 1996; Lange et al., 1997). The early and rapid development of limbic structures may place these regions at heightened vulnerability in the face of adverse early experiences (Tottenham and Sheridan, 2009). Additionally, differences in the continued rate of growth and maturation of limbic and prefrontal regions indicate that they may be differentially impacted by early childhood adversity when long-term effects are measured in adolescence.

### *Current study*

The present study aimed to investigate whether disruptions in structural brain development in limbic and prefrontal regions would be observed in PI youth during early adolescence, and to determine whether the magnitude of disruption scaled with duration of exposure to early