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EARLY DEPRIVATION, ATYPICAL BRAIN DEVELOPMENT, AND INTERNALIZING SYMPTOMS IN LATE CHILDHOOD

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Abstract—Children exposed to extreme early-life neglect such as in institutional rearing are at heightened risk for developing depression and anxiety disorders, and internalizing problems more broadly. These outcomes are believed to be due to alterations in the development of neural circuitry that supports emotion regulation. The specific neurodevelopmental changes that contribute to these difficulties are largely unknown. This study examined whether microstructural alterations in white matter pathways predicted long-term risk for internalizing problems in institutionally reared children. Data from 69 children were drawn from the Bucharest Early Intervention Project, a randomized clinical trial of foster care for institutionally reared children. White matter was assessed using diffusion tensor imaging (DTI) when children were between 8 and 10 years of age. Internalizing symptoms were assessed at the time of the MRI scan, and once children reached 12–14 years of age. Results indicated that neglect-associated alterations in the external capsule and corpus callosum partially explained links between institutional rearing status and internalizing symptoms in middle childhood and early adolescence. Findings shed light on neural mechanisms contributing to increased risk for emotional difficulties among children reared in adverse conditions and have implications for prevention and intervention.

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Key words: institutional rearing, white matter, DTI, depression, anxiety, late childhood.

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Abbreviations: AD, axial diffusivity; ANOVAs, analyses of variances; BEIP, bucharest early intervention project; CAUG, care as usual group; DTI, diffusion tensor imaging; EPI, echo planar imaging; FA, fractional anisotropy; FCG, foster care group; HBQ, health behavior questionnaire; MD, mean diffusivity; NIG, never institutionalized group; RD, radial diffusivity; TBSS, tract based spatial statistics.

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INTRODUCTION

Institutional rearing is a common practice for abandoned children, with an estimated eight million children currently living in institutions around the world (Committee on the Rights of the Child, United Nation's Children's Fund, 2004; UNICEF, 2010). It is well established that institutional rearing increases risk for a number of psychiatric problems. Disorders associated with poor emotion regulation and elevated internalizing symptoms, such as anxiety and depression, are highly prevalent (Smyke et al., 2007; Ghera et al., 2009; Bos et al., 2011). Growing evidence suggests that early experienced-based alterations in brain development may contribute to increased emotional dysregulation in severely neglected children (Simsek et al., 2008; Zeanah et al., 2009; Wiik et al., 2011). However, the specific neurodevelopmental alterations that contribute to these symptoms have yet to be elucidated.

Due to high child to caregiver ratios, limited caregiver responsiveness, and an absence of typical emotional and cognitive stimulation, institutionally reared children are deprived of basic early experiences that drive typical brain development. These adverse experiences occur at a critical point in brain development and interfere with normative neurodevelopmental maturation in key circuitry. Findings from animal work demonstrate that early adverse rearing conditions are associated with alterations in synaptogenesis, neuronal differentiation, and synaptic pruning, especially in circuitry involved in stress regulation, reward response and motivation (as reviewed in Cirulli et al., 2003; Pryce et al., 2005; Stevens et al., 2009; Lutz and Turecki, 2014).

Consistent with animal models, findings from human neuroimaging studies show long-term alterations in neural pathways that support higher level emotional functioning in children reared in adverse contexts. For example, children exposed to severe early-life neglect show alterations in limbic (Chugani et al., 2001; Mehta et al., 2009a; Tottenham et al., 2010, 2011; Gee et al., 2013; Hanson et al., 2014) and fronto-striatal (Behen et al., 2009; Mehta et al., 2009b) circuitry. These neurodevelopmental alterations have been discussed as potential mechanisms underlying risk for increased anxiety, poorer emotion regulation, and reduced sensitivity to reward stimuli, which may contribute to risk for depression and anxiety disorders.

Beyond these functional and structural changes in key cortical and subcortical neural regions, developmental differences in myelination patterns and neural

connectivity in pathways that support emotion regulation may also contribute to risk for emotional difficulties in institutionally reared children. Specific neglect-associated alterations in white matter fiber tracts have recently been investigated using diffusion tensor imaging (DTI). DTI provides estimates of microstructural changes in white matter pathways throughout the brain, allowing for a more nuanced understanding of white matter differences, when compared with traditional volumetric methods.

In a number of studies, internationally adopted children with histories of institutional rearing show reductions in integrity of fiber tracts involved in emotional processing and regulation, including lower fractional anisotropy (FA) and higher mean diffusivity (MD) in limbic and para-limbic (Eluvathingal et al., 2006; Govindan et al., 2010; Kumar et al., 2010; Hanson et al., 2013) and fronto-striatal (Behen et al., 2009; Kumar et al., 2014) circuitry, relative to non-neglected children. White matter microstructural changes have recently been investigated in the bucharest early intervention Project (BEIP), the first-ever randomized clinical trial of an early intervention for institutionally reared children. As part of the BEIP, children around two years of age were randomly assigned to receive ‘‘care as usual” in an institutional center or be removed from the institution and placed in high quality foster care (for more details on the study, see Zeanah et al., 2003; Nelson et al., 2014).

White matter microstructure was assessed at a follow up MRI scan when children in the BEIP reached 8–10 years of age. Irrespective of foster care status, all children with histories of institutional rearing showed lower FA, and higher MD and radial diffusivity (RD) of the body of the corpus callosum relative to family reared children. However, children who were removed from the institution and placed into foster care showed normalization of white matter tracts involved in limbic circuitry (higher axial diffusivity (AD) of the right fornix cres, lower MD and RD of the right cingulum of the cingulate gyrus), and fronto-striatal circuitry (higher FA and lower MD and RD of the left external capsule, higher FA of the right external capsule, lower AD of the right anterior corona radiata, lower MD and AD of the left superior corona radiata; Bick et al., 2015). These findings point to the long-term impact of early-life neglect on white matter development, and also suggest the potential for early intervention to support remediation in critical white matter pathways.

Despite substantial progress in understanding alterations in white matter microstructure associated with institutional rearing, there is significantly less known in terms of how disruptions in white matter microstructure may increase risk for psychiatric symptoms in neglected children. White matter tracts involved in circuitry that supports emotion and stress regulation may be particularly implicated in risk for internalizing symptoms. Candidate tracts may include those involved in fronto-limbic, limbic, and para-limbic connectivity, such as the cingulum (which contains fibers running from limbic regions such as the amygdala and parahippocampal gyrus to the frontal lobe), the uncinate fasciculus (which contains white matter fibers that connect limbic and paralimbic regions to the orbitofrontal cortex), and the fornix (which connects the hippocampus to the mammillary body, Dejerine, 1895; Klingler and Gloor, 1960; Crosby et al., 1962; Nieuwenhuys et al., 2008). Given implications in top down control of emotion regulation, reward sensitivity, and motivation (Pessiglione et al., 2006), alterations in fronto-striatal pathways may also increase risk for internalizing symptoms, particularly depression. Candidate tracts include anterior portions of the corona radiata, the anterior internal capsule, and the external capsule (Catani and Thiebaut de Schotten, 2012).

Corpus callosum reductions have been implicated in a number of internalizing disorders in children, including pediatric depression (Aghajani et al., 2013; Macmaster et al., 2013; Bessette et al., 2014), trauma-related disorders involving anxiety (i.e. intrusive thoughts, avoidance, and hyperarousal; De Bellis et al., 1999) and anxiety symptoms (Jackowski et al., 2008) in children exposed to early-life stress. The corpus callosum is the largest white matter tract in the brain and facilitates inter-hemispheric communication necessary for higher level emotional and cognitive abilities (Kitterle, 1995; Giedd et al., 1996). Structural alterations in this region have also been consistently observed in individuals exposed to early adverse rearing conditions, including conditions involving childhood maltreatment (De Bellis et al., 1999, 2002; De Bellis and Keshavan, 2003; Teicher et al., 2004; Jackowski et al., 2008; Paul et al., 2008; Huang et al., 2012) and institutional rearing (Mehta et al., 2009a). The genu and rostral portions of the corpus callosum contain projections to the ventral, lateral, and orbital regions of the prefrontal cortex and the mid-body contains projections to the anterior cingulate cortex (Georgy et al., 1993; Catani and Thiebaut de Schotten, 2012). Therefore, both of these subregions are considered to support processing and regulation of emotions. For this reason, alterations in the body and genu of the corpus callosum may be particularly implicated in risk for depression and anxiety symptoms.

A primary goal of this study was to examine whether neglect-induced alterations in selected limbic and fronto-striatal white matter tracts and the corpus callosum would be associated with concurrent and prospective risk for internalizing among institutionally reared children in the BEIP. We specifically hypothesized that white matter microstructural alterations in tracts involved the limbic, fronto-striatal, and corpus callosum pathways would mediate associations between early-life deprivation and risk for internalizing symptoms emergent in late childhood and pre-adolescence. We secondarily hypothesized that early intervention-based improvements in microstructural alterations would indirectly explain reduced risk for internalizing problems concurrently and prospectively.

EXPERIMENTAL PROCEDURES

Procedure

BEIP is a randomized clinical trial of foster care as an intervention for early institutionalization. At around two