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Microstructural Abnormalities In Striatial And Medial-Temporal Tracts In Children With A History Of Early Severe Deprivation: A Diffusion Tensor Imaging Study

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MICROSTRUCTURAL ABNORMALITIES IN STRIATAL AND MEDIAL-TEMPORAL TRACTS IN CHILDREN WITH A HISTORY OF EARLY SEVERE DEPRIVATION: A DIFFUSION TENSOR IMAGING STUDY

by

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DEDICATION

I would like to dedicate this work to orphaned children around the world and to the adoptive parents who are waiting for their children to come home.

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CHAPTER 1 MICROSTRUCTURAL ABNORMALITIES IN STRIATIAL AND MEDIAL-TEMPORAL TRACTS IN CHILDREN WITH A HISTORY OF EARLY SEVERE DEPRIVATION: A DIFFUSION TENSOR IMAGING STUDY

Exposure to adverse caregiving environments in early childhood can have a negative impact on the architecture of the brain and is linked to a host of problems in both animal and human offspring, including poor health, delayed physical growth, and a heighted rate of developmental, and behavioral problems (Cirulli, et al., 2009; Durry et al., 2010; Fox, Levitt, & Nelson, 2010; Greenough, Black, & Wallace, 1987; Rutter & the ERA study team, 1998). Although the exact mechanisms underlying these detrimental changes are not fully understood, evidence is accumulating that these deleterious brain changes occur in part via complex epigenetic processes in early life (Fox, et al., 2010; Gottlieb, 2003; Greenough, et al., 1987; Shonkoff & Phillips, 2000).

Decades of animal research have shown that early occurring, extreme sensory deprivation results in permanent brain damage and a loss of function (Cirulli, et al., 2009). For example, research on visual development in kittens has shown early, varied visual experiences must occur for the visual cortex to develop normally. If the eyes of a one-month-old kitten are occluded and deprived of light (“expectable” visual stimulation) for specified periods of time after birth, the kitten will become functionally blind, even after normal visual input is restored (Crair, Gillespie, & Stryker, 1998; Wiesel & Hubel, 1965). This blindness is thought to stem from a failure of the brain to form or maintain synaptic connections between the eyes and the striatal cortex. More generally, research with rats and other animals has shown that variations in the quality of the early rearing environment can alter growth of neural pathways in the brain. For instance, the brains of animals reared in “enriched” environments (e.g., socially and physically stimulating cages) have denser synaptic connections than the brains of animals reared in isolation (Greenough & Black, 1992).

Greenough and colleagues (Greenough, et al., 1987; Greenough & Black, 1992) have described two types of brain development that provide a useful theoretical framework for understanding this body of research: *experience-expectant* versus *experience-dependent* brain development. Experience-expectant brain growth refers to the rapidly developing organization of the young brain, which depends on input from ordinary, expectable (“species-typical”) experiences in early life. Most members of a species are exposed to “expectable” environmental stimulation during specific periods of development, which affects developing sensory and motor systems. A key process involved in the storage of experience-expectant information is the inherent proliferation of synaptic connections between neurons, followed by a paring back process based on the environmental experiences to which one is exposed. Therefore, exposure to typical rearing environments is vital and determines what connections are made and which ones survive the pruning process in early ontogeny. Experience-expectant brain growth is thought to be a primary mechanism underlying sensitive or critical periods.

In contrast, experience-dependent brain growth consists of additional growth, including the refinement of established brain structures, stemming from specific learning experiences that vary widely across individuals and cultures, such as reading, writing, weaving a rug, or playing a violin (Fogel, 2011; Greenough & Black, 1992). Due to the varied manner and timing in which this information can be availed, there are no specific restrictions on one’s ability to acquire this information. The mechanism crucial to this process is the ability to form new synaptic connections when the need to incorporate new information arises (Greenough, et al., 1987).

For human offspring, exposure to appropriate environmental stimulation in early life plays a crucial role in brain development (Kundsen, 2004). The neurological framework within which all future neural and synaptic development occurs begins in the prenatal period and continues during early childhood and beyond (Fox et al., 2010; Shonkoff & Phillips, 2000). Infants' brains are prepared to "expect" specific environmental stimuli for normal growth. Neural connections are formed in response to these species-typical environmental experiences, while the actual exposure to the stimuli allows for organization and specification of these pathways (Perry, 2006).

Fortunately, the majority of human infants receive an appropriate level of stimulation in their typical caregiving environments to support experience-expectant brain growth (e.g., opportunities to hear language and other sounds, to see and touch objects, to be held and comforted when distressed, to move and explore the environment, etc.; Fogel, 2011).

When human infants are exposed to adverse caregiving environments, such as those characterized by extreme social deprivation, sensory deprivation, neglect, or abuse, the developing brain can be altered (Perry, 2006). For instance, adverse caregiving experiences are associated with a delayed rate of myelination and a failure to create appropriate synaptic connections, including appropriate pruning of connections that are foundational to species-typical development (Fox et al., 2010; Shonkoff & Phillips, 2000). Moreover, Gunnar and colleagues demonstrated that early, deprived institutional rearing disrupts the brain's ability to manage stress. In longitudinal research, these investigators showed that children who had spent their first 8 months (or longer) in Romanian institutions had higher concentrations of salivary cortisol than age-mates who had been adopted shortly after birth, and these findings held up to 6½ years after the time of adoption (Gunnar et al., 2001; Gunnar & Cheatham, 2003).

Institutional Deprivation as a “Natural Experiment”

Studies of infants placed in institutional settings (orphanages) who are later adopted and exposed to ordinary family rearing are important “natural experiments” that confirm the importance of a generally stimulating physical and social environment for human brain development and multiple domains of functional development (Fogel, 2011). Institutional settings are often characterized by extreme social, sensory, and nutritional deprivation. In many institutions, the number of children needing care far exceeds the number of available caregivers; child-caregiver ratios range from 8 to 35 children per caregiver (McMullan & Fisher, as cited in Ames, 1997). Moreover, the over-burdened caregivers in such institutions typically are not assigned to care for individual infants, or even specific groups of children (Ames, 1997). Thus, not only do children raised in institutions have only limited social contact with a caregiver, they also lack consistency in caregivers over time (Ames, 1997; Nelson, et al, 2007; Rutter, & the ERA study team, 1998).

When social contact occurs, caregivers typically provide little or no personalized caregiving. As a result, they are likely to be unresponsive or insensitive to the specific needs of individual infants. To maximize efficiency in meeting the physical needs of the large number of children in their care, caregivers often follow rigid, highly structured routines (Nelson, et al., 2007. For instance, based on their observations in Romanian orphanages Rutter and his colleagues (1998) reported that infants and toddlers are often propped so they could bottle-feed themselves and are cleaned in an impersonal manner, such as by being hosed off. Researchers visiting these settings also noted that caregivers spent very little time communicating directly to, or playing with the infants and children (Rutter & the ERA study team, 1998).

The rearing environment in many institutions also provides limited cognitive stimulation, opportunities for exploration of the environment, or for independent locomotion. Rutter and his research group (1998) noted that in many institutions, few toys were available, and children were often confined to cots. Even when children in the same room were awake, very little social interaction occurred among them: As many as five minutes would pass without a sound (Ames, 1997, Rutter& the ERA study team, 1998).

Not surprisingly, delays in physical growth, malnourishment, and illness among children raised in institutions are commonly reported (Ames, 1997; Mason & Norad, 2005). In several reports of the physical outcomes of children reared in Eastern European institutions, children's average height, weight, and head circumference at the time of adoption fell one and a half to two standard deviations below the means established for non-institutionalized children from both their country of origin and their country of adoption (Judge, 2003; Rutter & the ERA study team, 1998). Moreover, based on data collected for children raised in institutions in Eastern Europe or China, children reared in institutions reportedly lost one month of linear growth for every three months they were institutionalized (Johnson, 2000). In addition, 79% of children reared in Romanian orphanages had at least one medical problem at the time of adoption. The most common medical diagnoses were intestinal parasites, hepatitis B, and anemia (Ames, 1997). Given these multiple experiences of deprivation and associated heath challenges, it is not surprising that institutionalized children also exhibit a heightened rate of developmental and psychosocial delays and difficulties relative to that observed in age-matched, non-institutionalized peers (Ames, 1997; Jacobs, et al., 2010; Nelson et al, 2007; Rutter, O'Connor, & the ERA study team, 2004; Zeanah, et al., 2009).

Thus, as an "experiment in nature", the study of children reared in an environment characterized by extreme social, emotional, and nutritional deprivation provides unique insights into the impact of environment on the plasticity of the brain and early developmental processes. When these children are suddenly removed from a deprived environment and placed in an enriched adoptive family environment, it is possible to evaluate more clearly the impact of environment on the process and timing of brain development and associated developmental outcomes (Ames, 1997).

Within the internationally adopted population, researchers have observed both consistent and specific areas of deficits, as well as areas of improvement for many children, in multiple areas of cognitive and psychosocial functioning (Ames, 1997, Jacobs, et al., 2010; Nelson et al, 2007; Rutter, O'Connor, & the ERA study team, 2004; Zeanah, et al., 2009). As detailed in the sections below, these results generally support the notion of a sensitive period for early development, and are consistent with an experience-expectant mechanism (Rutter et al., 2004). Interestingly, findings from neurological studies also support the notion of a sensitive period, and an underlying experience expectant mechanism for brain growth. For instance, children reared in institutions who were adopted earlier have fewer abnormalities in white-matter structural integrity than their later-adopted counterparts (Kumar et al., 2013).

Notably, neurological studies also provide evidence supporting the experience-dependent mechanism. Behen and colleagues (Kumar et al., 2013) found that time spent in the enriched environment was directly linked to increased efficiency of the white matter pathways in specific areas of the brain; the arcuate fasciculi and cingulum. Therefore, it appears that both experience-expectant and experience-dependent mechanisms of brain growth are impacted by early deprivation (Kumar, et al., 2013; Shonkoff & Phillips, 2000). Further studies evaluating the correlation between structural and functional imaging changes associated with early deprivation, and the daily functional outcomes correlated with them are needed. Such studies will further expound on the role of experience on the functioning of adopted children who were reared in institutional settings,

Developmental and Psychological Sequelae of Deprivation

For over a half a century, researchers have demonstrated a variety of developmental delays and difficulties in children raised in institutions, compared to non-institutionalized children raised in a family environment (Ames, 1997; Nelson, et al, 2007; Rutter & the ERA study team, 1998; Spitz, 1945). The majority of the research over the last few decades has focused on outcomes for children from Eastern European institutions due the extreme deprivation experienced by these children, but for some groups of researchers this region has not been the sole focus (Rutter & the ERA study team, 1998; van IJendoorn, Luijk, & Juffer, 2008)

Cognitive development. At the time of adoption, the majority of children reared in Romanian institutions are extremely impaired on multiple measures of cognitive development (Ames, et al., 1997; Rutter & the ERA study team, 1998). For instance, 74% of children scored in the mentally retarded range immediately after being placed in their adopted home and nearly 60% of these children were classified as being moderately or severely impaired (Rutter & the ERA study team, 1998). Many children also displayed multiple delays in other areas of their development. In addition to deficits in IQ, 78% of children reared in Eastern European institutions also were delayed in their fine and gross motor abilities, social skills, and language development. One study showed that at the time of adoption, all institutionally reared children in their sample were delayed in a least two areas of development (Ames, 1997). Moreover, the cognitive deficits observed at the time of adoption appear to be a direct result of institutionalization. For instance, Romanian children who were adopted internationally as newborns, and thus not institutionalized, on average, had similar cognitive scores on age-referenced assessments as their same age non-institutionalized, non-adopted peers (Rutter & the ERA study team, 1998).

It is important to note that institutional deprivation and its associated developmental deficits are not unique to children reared in Eastern European institutions, despite the fact that this region has received substantial attention from researchers. Investigations into the developmental functioning of children institutionalized in several other regions of the world (i.e., Russia, Asia, & South America) have found 75% to 100% of adoptees had significant delays in two or more areas of development at the time of adoption (Ames, 1997; Jacobs, Miller & Tirella, 2010; Judge, 2003; Meese, 2005). Moreover, a recent meta-analysis found that the standard scores of children raised in orphanages in 19 different countries were 20 points lower on a measure of developmental/intellectual function than those of their same-aged, family-raised peers (84.4 vs. 104.2). Interestingly, the three countries in which institutionalized children had the lowest cognitive scores were located in Africa, not Eastern Europe (van IJzendoorn, Luijk, & Juffer, 2008). As such, it will be important to expand the scope of this body of research beyond Eastern Europe to further our understanding of the impact of variations in institutional deprivation.

Critically, a growing body of research is showing that many of the developmental delays observed at the time of adoption ameliorate after the child is placed in an enriched environment, either through adoption or placement into foster care families, (e.g., Beckett, et al. 2006; Chugani, et al., 2001; Jacobs et al., 2010; Kreppner et al, 2007; Rutter & the ERA study team, 1998; Rutter, O'Connor, & the ERA study team, 2004). By age 6 only 14% of children raised in Romanian orphanages had a full-scale IQ (FSIQ) score below 80 (Rutter, Kreppner, & O'Connor, 2001). Moreover, when compared to their own level of functioning at the time of adoption, both early and late adopted children show substantial improvements in cognitive functioning. A meta-analysis found that institutionally reared children who were adopted had significantly higher IQ scores than their peers and siblings who remained institutionalized; however, they did not differ in IQ from age-matched peers in their adoptive environment (van IJzendoorn, Juffer, & Poelhuis, 2005).

Emotional and behavioral functioning. Cognitive development is not the only aspect of functioning impacted by early institutionalization. Many children who were reared in institutions also exhibit emotional and/or behavioral problems (Ames, et al., 1997; Jacobs, et al., 2010; Lee et al., 2010).

Some behavior problems are uniquely related to children's history of deprivation; specifically, lack of access to responsive caregivers and inconsistent access to food. Initially following adoption, for instance, many children engaged in institution-specific behaviors such as hoarding food, refusing to eat solid food, and lying in bed quietly, in the morning or after a nap, until retrieved by a caregiver. Many adopted children who were reared in institutions also showed indiscriminately friendly behavior to unfamiliar people. In addition, stereotypical behaviors, such as rocking or visual fixation on hand movements, were present at adoption in 84% of Romanian adoptees. These stereotypical behaviors are believed to result from attempts by institutionalized children to engage in self-soothing and/or to create self-stimulation in an otherwise deprived environment (Ames, et al., 1997).

Children reared in institutions also display higher rate of non-deprivation specific emotional and behavioral problems than same-aged non-institutionalized peers. In one review, 61% of institutionalized children evidenced an emotional or behavioral problem (Zeanah, et al., 2009. In another review, over half of international adoptees evidenced problem behaviors at the time of adoption; with 34% of children having two or more behavioral problems (Jacobs et al., 2010). There are inconsistent finding on the exact natures of these problems. Some researchers have found higher rates of internalizing problems at institutionalized children, compared to institutionalized children placed in family-based foster care (Zeanah, et al., 2009) or institutionalized children who were adopted before four months of age (Ames, et al., 1997). Other researchers found significantly higher rate of both internalizing and externalizing behavior problems for institutionalized children than children who were adopted internationally (Lee et al., 2010).

Once institutionalized children are placed in an enriched family environment the overall rate of their emotional and behavioral problems tends to decrease (Ames, et al., 1997; Behen, et al., 2008; Rutter, Kreppner, and O'Connor, 2001; Kreppner, et al, 2001). There is also a subset of children for whom these difficulties never ameliorated. Eleven percent of children continue to display pervasive behavior problems (Gunnar, et al, 2007) and 20 to 36% continued to exhibit at least one emotional or behavioral problem after adoption (Ames, et al., 1997; Behen, et al., 2008; Rutter, et al., 2001).

It is important to understand internationally adopted children's behavior in the contact of normative development; some level of behavior problems is normative among young children and adolescents. In early childhood, particularly among children placed or adopted into new families, children often present with increased behavioral problems, regardless of prior institutional experience (Rutter et al., 2001). Additionally adolescence is a time of increased emotional and behavior problems for all individuals.

Studies that followed the development of international adoptees longitudinally showed that most of these children were free from any behavioral problems by early to middle childhood (Rutter et al, 2001; Gunnar, Van Dulmen, & The International Adoption Project Team, 2007; Jacobs, et al., 2010; Rojewski, Shapiro, & Shapiro, 2000), but in middle childhood to early adolescence there is a resurgence of both internalizing and externalizing problems above the rate experienced in their non-adopted peers (Culvert, et al., 2008; Merz & McCall, 2010; Wiik, et al., 2011).

In contrast to the significant "catch-up" finding often reported for measures of intellectual functioning, emotional problems remain more entrenched despite the enriched environment. Furthermore, some difficulties intensified following placement in the adoptive home. One study found that internalizing problems of institutionalized children decreased following adoption, but externalizing problems increased (Ames, et al., 1997). Another study, found that children were 1.1 times more likely than never-adopted children to display either externalizing or internalizing problems for each year in the adoptive home (Rutter et al., 2007). Moreover, it has been consistently found that adoptees are significant more likely to exhibit specific types of problems; possibly due to their deprivation-specific rearing environments. These children were more likely to have difficulties with forming attachments to caregivers, peer relationships, attention and concentration, hyperactivity, oppositional behavior (ODD), and quasi-autism symptoms (Ames, et al., 1997; Jacob, et al., 2010; McLaughlin, et al., 2010; Rutter, et al., 2001; van Londen, Juffer & van IJzendoorn, 2007).

The largest body of research on the stability of behavioral problems among internationally adopted children who had been reared in institutions has focused on the persistence of problems with hyperactivity, attention, and concentration (Jacobs et al., 2010; Kreppner et al., 2001; Loman, et al., 2013; McLaughlin, et al., 2010). These phenomena have been labeled the Inattentive/Overactive (I/O) phenotype. Parents and teachers both have reported higher rates of I/O symptoms in adoptees than in age-matched typically developing peers (Kreppner, et al., 2001, 2007; McLaughlin et al., 2010; Stevens et al, 2008). One study found that 28% of formerly institutionalized preschoolers had a significant number of ADHD symptoms (Jacobs, et al., 2010), while another reported 20.7% (Zeanah et al., 2009). Furthermore, the presentation of I/O symptoms at age four did not diminish in this population over time, even when children were placed in an enriched caregiving environment (Kreppner, et al., 2001, 2007; McLaughlin et al., 2010; Stevens et al, 2008, Wiik, et al., 2011). In one study, relative continuity in the presentation of I/O symptoms has been reported from early childhood up to age 11 (Stevens et al., 2008). Even after controlling for cognitive functioning, which is correlated with behavioral measures of executive functioning in children, institutionalized children's performance on measures of executive functioning was deficient compared to children raised in their biological family (Hostinar, et al., 2013; Loman, et al, 2013). Interestingly, one study showed a specific deficit in sustained attention, rather than a patter of more general executive dysfunction (Loman, et al., 2013).

Factors Associated with Heterogeneous Outcomes

As previously discussed, despite exposure to an enriched environment, there is a subgroup of internationally adopted children reared in institutions, for whom initially observed cognitive and/or emotional difficulties persist (Ames, et al., 1997; Jacobs et al., 2010; Rutter, et al., 2001; Stevens et al., 2008; van Londen, Juffer & van IJzendoorn, 2007). Length of institutionalization and country of adoption are two factors that have reliably predicted differential outcomes in this population (Behen et al, 2008; Nelson et al., 2007).

Length of institutionalization. The association between a history of institutional rearing and cognitive impairment seems to be dose-related, such that the rate of impairment increases as a function of the time spent institutionalized (Ames, et al., 1997; Behen, et al., 2008; Rutter & the ERA study team, 1998; Rutter, et al., 2001). Remaining in an institutional setting rather than being placed in family-based foster care led to a decrease of 0.59 Developmental Quotient (DQ) points or 0.85 Full Scale Intellectual Quotient (IQ) points per month (Nelson et al, 2007). Furthermore there is evidence of a sensitive period, such that children institutionalized for more than the first six months of their life had persistently lower IQs than those adopted prior to six months of age (Kreppner et al, 2007; Rutter & the ERA study team, 1998; Beckett, et al, 2006). Specifically, children adopted between 6 and 24 months of age had a higher rate of impairment than children adopted before 6 months, and children adopted after 24 months of age showed persisting intellectual deficits (Beckett et al., 2006).

The effects of institutionalization during this sensitive period remain years after the child is removed from the socially deprived environment. At age 11 children who were adopted from Romania before 6 months of age show age-typical cognitive development, with average FSIQ scores of 110.86. In contrast, children adopted after six months of age demonstrated significantly poorer performance on cognitive testing. Those children adopted between 6 and 24 months averaged FSIQ scores of 85.7, while those adopted after 24 months averaged FSIQ scores of 82.83 (Beckett, et al., 2006). Interesting, a small subset of Romanian children who were adopted after six months, but had no history of institutionalization, performed similarly to those adopted before six months or British children adopted within the UK (Rutter, & the ERA study team, 1998). This finding provides additional evidence that being raised in a deprived environment during the first six months of life is directly related to later deficits in cognitive functioning.

The long-term dose-related effect of early institutionalization is not specific to intellectual functioning. Effects on other areas of functioning, such as academic performance, stress reactivity, or the presence of behavior problems, have also been documented. However, the specific “cut-off” denoting the boundaries of a sensitive period varies, depending on the investigative team and the specific dependent variable in question.

Support for a dose-related hypothesis was also found for the presence of emotional and behavior problems. In longitudinal research, the more time children spent institutionalized prior to being adopted, the more likely it was that these children displayed emotional and behavioral problems post adoption (Ames, et al., 1997; Beckett, et al, 2007; Jacobs, et al., 2010; Kreppner, et al, 2007; Stevens, et al., 2008). Several investigators have reported that children adopted after six months of age exhibited more difficulties with attention and concentration than children adopted prior to six months (Beckett et al., 2007; Kreppner et al., 2007), and were more likely to be classified as exhibiting an I/O phenotype. The six-month cut-point was not supported for identifying differential rates of externalizing or internalizing problems (Beckett, et al., 2007; Kreppner et al, 2007). One study’s findings suggest a later sensitivity period of 18 months, after which time internationally adopted children were found to be an increased risk for both internalizing and externalizing problems, as well as attention problems (Merz & McCall, 2010). Gunnar et al. (2007) postulated the latest sensitive period of prior to 24 months of age for attention problems only (19% vs. 42%). Similarly, in other studies, outcomes for children adopted before 24 months of age showed a linear relationship between length of deprivation and I/O symptoms (Kreppner, et al., 2007;

Stevens et al., 2008). Rutter and colleagues (Rutter et al., 2001) provided further evidence for a dose-related hypothesis. Among children with a history of early institutional rearing, quasi-autism symptoms were more prevalent as age at adoption increased (Rutter, et al., 2001). Loman and colleges (2013), however, found no direct relationship between length of institutionalization and behavioral problems after controlling for cognitive functioning.

The influence of length of exposure to deprivation does not apply universally to all indices of adoptees' future outcomes, however. Age at adoption did not impact the rate of catch-up for physical indicators, such as height or weight (Rutter & the ERA study team, 1998). However, Rutter (2006) reported that a longer amount of time of institutional rearing and poor cognitive functioning were correlated with below-average head circumference, suggesting that early lack of stimulation damaged the brain. Furthermore, age of adoption was not related to an increased risk for all types of behavioral problems (Kreppner, et al., 2001; Rojewski, et al, 2000). For instance, in one study, the rate of conduct disorder did not differ among children adopted before or after six months of age (Kreppner, et al, 2001).

Country of origin. While the duration of deprivation associated with institutional rearing can partially explain children's heterogeneous outcomes for cognitive and social-emotional difficulties, it is not the only explanatory factor. The country in which children were institutionalized also accounts for some of this variance. For instance, several studies of international adoptees have reported fewer cognitive, emotional and behavioral problems in individuals adopted from specific regions of the world (Gunnar et al, 2007; Dalen, 2002; Dalen et al., 2008; Odenstad et al., 2008; Lindblad, et al. 2009).

Generally speaking, children adopted from Asian countries (e.g., Korea or China) have better cognitive and behavioral outcomes than children adopted from Eastern Europe/ Russia (Gunnar et al, 2007; Dalen et al., 2008; Odenstad et al., 2008; Lindblad, et al. 2009), or South American countries (e.g., Colombia; Dalen, 2002). In turn, children adopted from any of these countries have better outcomes (on average) than children adopted from African countries (IJzendoorn, et al., 2008). However, findings vary with the specific outcome in question. For example, in one survey, children adopted from Eastern Europe and the Middle East/Africa had the highest risk for attention deficit hyperactivity disorder (Lindblad, Weitoft, & Hjern, 2010).

Although the explanation for these cross-country differences is not fully understood, variations in the quality of institutional environments in different countries may reflect country-specific differences in financial resources and infrastructure, cultural norms/beliefs, and/or national policies regarding institutionalized children (IJzendoorn, et al., 2008; Johnson, 2000; Kim & Carrol, 1975; Warren et al., 2001).

Country of origin is not consistently found to predict cognitive or emotional/behavioral outcomes. Several researchers found country of origin was not significant associated with differences in level of behavioral or intellectual functioning among international adoptees (Jacobs et al., 2010; Juffer & Rosenboom, 1997). One possible reason for these inconsistent results may be due to within-country differences in the quality of rearing environments. Methodological differences among studies may also contribute to the inconsistent findings in this literature. Many researchers include a heterogeneous group of institutionalized children in their study samples, including children who were institutionalized continuously from birth, children who spent some time with their biological parents, and/or children who were in foster care for variable periods of time prior to adoption (Jacobs et al, 2010; Gunnar et al., 2007; Lindbald et al., 2009). The differences in exposure to frank, institution-related deprivation within samples of adopted children from the same countries may also explain the inconsistency of findings in the literature. For instance, Loman (2009) reported that country of origin was unrelated to adopted children's language outcomes, when the length of time spent in the orphanage was covaried.

Impact of Early Institutional Rearing on Brain Development: Functional and Structural Outcomes

Most studies of the effect of early institutional rearing on post-adoption child outcomes have focused on children's performance on age-referenced neuropsychological tests, or indices of observable behavior (e.g., parent or teacher reports of children's behavior problems, such as the Inattentive/Overactive phenotype). More recently, there has been a shift towards attempting to understanding how early deprivation may alter biological and neurological systems. This is an important shift because it promises to further our understanding of how early deprivation may directly impact brain development. Although behavioral measures may provide an indirect look at how differences in early environment may affect brain development, they do not directly measure brain structure or function. Moreover, current behavioral measures may not have the required sensitivity or specificity to fully capture indirect effects of early experience on brain development. Thus, they may underestimate the presence of deprivation-related deficits on brain architecture or functioning (Kundsen, 2004). In the following sections, recent findings from studies using direct measures of brain structure and function in this population will be described.

Electroencephalography. Electroencephalographic (EEG) data on children with a history of early deprivation have revealed differences in brain activity related to length of institutionalization (Marshall, Fox, & the BEIP Core Group, 2004; Marshall et al, 2008; McLaughlin et al., 2010; Tarullo, Garvin, & Gunnar, 2011). Specifically, children who were placed in family-based foster care before 24 months of age had higher alpha power at 48 months than children who were placed in foster care later in life or children who remained in an institution. An increase in alpha as children grow older is a developmentally typical result of brain maturation (Marshall, et al., 2008; Vanderwert et al., 2010). More substantial differences are found when infants and toddlers with a history of early institutionalization are compared to those who had never been institutionalized. Regarding absolute power, Marshall et al. (2004) reported that children with a history of early deprivation had lower alpha and beta at the frontal and temporal sites, as well as higher theta at occipital sites, compared to non-institutionalized children. Furthermore, the early deprivation group had higher theta and lower alpha relative power than the normal control group at frontal, occipital and parietal sites (Marshall, et al., 2004).

McLaughlin et al. (2010) showed that specific EEG patterns (theta, alpha, and beta levels) were consistently associated with a diagnosis of attention deficit hyperactivity disorder (ADHD). For instance, relative power in the temporal region for theta and the frontal region for alpha was associated with hyperactivity, whereas theta relative power for the frontal, temporal, and parietal regions and alpha relative power for the frontal and parietal regions were associated with impulsivity. In addition, theta levels for the temporal region were associated with inattention, and theta levels in the frontal and temporal regions were associated with anxiety (McLaughlin, et al., 2010). These specific EEG patterns associated with ADHD are consistent with the overall results found in samples of children exposed to early deprivation (Marshall et al., 2004; 2008). These studies provided suggestive evidence that the behavioral and emotional problems associated with early deprivation might be linked to specific patterns of brain activity. Several recent studies have found a direct correlation between performance on behavioral measures and specific EEG findings. Post-institutionalized children showed poor sustained attention and lower amplitudes for frontal central regions (Loman, et al., 2013). Interestingly, although internationally adopted children consistently had lower amplitudes on tasks measuring impulsivity, there are mixed finding for behavioral outcome measures; indicating these children may or may not be more behaviorally impulsive than children reared with their biological parents (Loman, et al., 2013; McDermott, Westerlund, Zeanah, Nelson, & Fox, 2012).

Magnetic resonance imaging. Children exposed to early deprivation have a reduced head circumference compared to typically developing children (Judge, 2003; Rutter & the ERA study team, 1998; Rutter, 2006). Head circumference is often correlated with children's diminished cognitive performance (Rutter, 2006), yet the impact smaller head circumference may have on specific structures within these children brains has not been well researched. Consistent with institutionalized children's reduced head circumference, Romanian adoptees have been shown to have less brain matter volume than age-matched typically developing, non-adopted children.

Specifically, these adopted children had 15% less gray matter and 18% less white matter (Rutter & the ERA study team, 1998). However, when post-institutionalized adopted children were compared to never-institutionalized, never-adopted comparison children not all areas of the brain had volumetric differences. Similarly, in another study of post-institutionalized adopted children from Romania, the adopted children had reduced volume in the hippocampus, but not in the corpus callosum. The reduced volume in the hippocampus was due to reduced gray and white matter volume (Meta et al, 2009).

Furthermore, Bauer et al. (2009) showed that children adopted from institutions in Eastern Europe and China had less volume in the superior-posterior lobe of their cerebellum compared to never-institutionalized control children. Specifically, children exposed to early deprivation had less volume in the left hemisphere, compared to the right, whereas the comparison children had similar volume for the left and right superior-posterior cerebellum. There were no differences for the other regions of the cerebellum (Bauer, et al., 2009).

Meta et al. (2009) also showed that, when adjusting for total brain matter volume, the amygdala of Romanian adoptees was 33.5% larger than that of the comparison children. This overall difference was largely driven by the Romanian adoptees' significantly enlarged right hemisphere amygdala (Meta et al., 2009). Interestingly, although only right amygdala adjusted size accounted for the differences between Romanian adoptees and comparison children, within the Romanian adoptee group the left amygdala adjusted volume was the only area correlated with length of institutionalization. Children with lower adjusted left amygdala volume had lengthier periods of institutionalization (Meta et al., 2009). Somewhat different results were reported in a sample of children adopted from Eastern Europe and Asia. In that study, larger amygdala adjusted volume was found only for late-adopted post-institutionalized children. It is important to note that there was a confound between time of adoption and country of origin in this research: More late-adopted children in this sample were from Eastern Europe, while more early-adopted children were from Asia (Tottenham, et al., 2009).

Advanced imaging techniques. Advances in technology have allowed researchers to expand investigation of the effects of early institutional rearing beyond pure volume measures. Positron emission tomography (PET) and magnetic resonance diffusion tensor imaging (MR-DTI) studies have each been used to identify structural and functional brain abnormalities in this population (Behen et al., 2009, 2011; Chugani, et al, 2001; Eluvathingal, et al., 2006; Govindan, et al., 2009).

PET imaging data from post-institutionalized adopted children showed decreased glucose metabolism in the orbital frontal cortex, prefrontal infralimbic cortex, lateral temporal cortex, medial temporal structures (including the amygdala and hippocampus), and brain stem, relative to non-institutionalized control children. These brain regions are interconnected and play a role in emotional and stress responses (Chugani, et al., 2001). There is evidence that these regions of the brain are altered in response to prolonged exposure to stress (Kaufman et al., 2000) such as that stemming from exposure to extreme social and sensory deprivation in the institutionalized setting.

Studies using MR-DT imaging revealed that adopted children with a history of institutionalization also had reduced white matter connectivity in the right uncinate fasciculus, compared to the left. However the only difference in connectivity between previously institutionalized adoptees and non-institutionalized controls was in the left uncinate fasciculus (Eluvathingal, et al., 2006). These results were replicated and expanded on in two later studies. Post-institutionalized adopted children were shown to have decreased bilaterally connectivity for the uncinate fasciculus (Govindan et al., 2009). In a recent study, decreased connectivity, as well as decreased integrity of white matter tracts, was found for the right arcuate fascicule, uncinate fasciculus and cingulum (Kumar, et al., 2013). Interestingly, the locations of the abnormalities reported by Chugani and his research group (2001) all originate or terminate in the uncinate fasciculus. Although less thoroughly documented, differences in the frontal-striatal circuit for adopted children with a history of early deprivation and non-adopted, non-institutionalized controls have also been found (Behen, et al., 2009).

Relationships Between the Brain and Behavior.

The structural and functional changes in the brain observed in post institutionalized children from Asia and Eastern Europe, relative to non-institutionalized children, are present in areas associated with the cognitive and emotional difficulties observed in these children, which were reported earlier (Bauer, et al., 2009, Behen, et al., 2009; Chugani et al., 2001; Eluvathingal et al., 2006; Kumar et al., 2012). Much of this research has focused on aspects of cognitive functioning. In research by Bauer et al., (2009), the left-superior-posterior cerebellum volume mediated performance on memory tasks. Institutionalized children, who on average had lower superior-posterior cerebellum volume, performed worse on memory tasks. Moreover, Kumar et al. (2013) showed that for the children with more white matter connectivity from arcuate fasciculus also had more proficient language skills, regardless of group classification (internationally adopted or comparison children; Kumar, et al., 2013). Additionally, children with a history of institutionalization, who on average had poorer connectivity for the arcuate fasciculus, also exhibited poorer language skills.

It is important to note that, volume differences in volume are not always associated with was not related to For example, performance on motor tasks, despite the fact that institutionalized children had lower scores on tasks of motor functioning than non-institutionalized children, was not related to cerebellum volume differences (Bauer, et al., 2009).

Functional and structural brain abnormalities in children exposed to early deprivation tend to be located in the same areas associated with emotion and behavior, although few studies have directed examined that relationship. Abnormalities have been found for areas of the limbic system (amygdala and hippocampus), which is linked to emotion regulation, and for the striatal-frontal pathway, which has been linked to problems with attention and concentration (Behen, et al., 2009; Chugani et al., 2001; Kumar et al., 2013; Meta et al, 2009; Silk et al., 2009; Tottenham et al., 2009).

Several studies have attempted to correlate abnormalities in the brain to differences in behavior. White matter connectivity between the caudate in both left and right hemispheres was found to predict externalizing behavioral problems (Behen, et al., 2009). Decreased connectivity for the right cingulum was also related to externalizing problems (Kumar et al., 2013). Larger amygdala size was associated with more symptoms of anxiety and increased parental report of internalizing problems in both post-institutionalized adopted children and non-institutionalized comparison children.

Consistent with the finding of overall larger amygdala size in post-institutionalized adoptees, these children also had higher rates of internalizing problems and anxiety (Tottenham et al., 2009).

The Relationship Between Striatal and Medial-Temporal Pathways and Behavior

Adopted children with a history of early institutional rearing and associated deprivation are consistently found to have cognitive and behavioral problems. Additionally, these children have consistently exhibiting both functional and structural brain abnormalities when compared to non-institutionalized, non-adopted children (Behen, et al., 2009, 2011; Chugani et al., 2001; Eluvathingal, et al., 2006; Govindan et al., 2009; Tottenham, et al., 2009). Few studies have directly compared the relationship between functional or structural abnormalities and cognitive or behavioral outcomes in children with early deprivation, despite their consistent co-occurrence. Prior research in samples of post-institutionalized children has shown that these children have brain abnormalities in areas of the brain associated with emotions, and executive functions (Behen, et al., 2009; Chugani et al., 2001; Eluvathingal, et al., 2006; Govindan et al., 2009; Kumar, et al., 2012; Tottenham, et al., 2009; Hornak et al., 2003; Gallagher & Chiba, 1996; Silk, et al, 2009).

Specifically, internationally adopted children show abnormalities on striatal-frontal structures (Behen et al., 2009; Marshall et al., 2008; Veenstra et al., 2011). Abnormalities on these same striatal-frontal structures are linked to the diagnosis of Attention Deficit Hyperactivity Disorder in non-institutionalized children (Durston, 2003; Konrad, & Eickhoff, 2010; Silk et al., 2009).

Moreover, both emotion and executive functions is associated with medial-temporal connectivity. The medial-temporal to orbitofrontal circuitry has been linked to emotional difficulties, such as depression and anxiety in human and animal studies (Adhikari, Topiwala & Gordon, 2010; Hornak et al., 2003; Gallagher & Chiba, 1996), Abnormalities in this pathway are also related to other psychological problems, such as autism (Bachevalier, 2002). Medial temporal to anterior temporal circuitry has been associated with sustained attention (Castellanos & Proa, 2010), while broad disruption of the medial temporal region (e.g., epilepsy) is associated with frontal lobe dysfunctions (executive dysfunction; Stretton & Thompson, 2012).

Magnetic Resonance Diffusion Tensor Imaging

Magnetic resonance diffusion tensor imaging (MR-DTI) was utilized in this study as it promises to be an effective measure for evaluating the impact of early institutional rearing on brain development. MR-DTI is a noninvasive approach used to measure white matter diffusion characteristics, as well as the structural integrity of white matter. In DTI, neuroanatomy is inferred based on the movement of water. The development of MR-DTI was a crucial technological advancement in understanding the structure of the human brain. MR-DTI offers an advantage over conventional MR images in that MR imaging is not able to provide a visual representation of the anatomy of white matter tracts. Prior to MR-DTI the only way to obtain this data was with postmortem histology (Mori & Zhang, 2006). Due to obvious ethical restraints, histology is not a feasible option for human studies on the impact of deprivation throughout a child’s development.

DTI is a technique that measures the diffusion of water in the brain, specific to dispersal and directionality. Two indexes were calculated based on diffusion: *Apparent*

Diffusion Coefficient (ADC) refers to the magnitude of diffusion in each voxel. Higher ADC scores indicate free water dispersion, whereas lower scores imply restriction of movement, likely due to structure in the surrounding tissue (e.g., white-matter; Le Bihan, 1995).

Anisotropy (FA) measures the direction of the water diffusion in each voxel (Beaulieu, 2002). When the movement of water is in a circular pattern it is called *isotropic diffusion*, which can be represented numerically by zero on a scale of zero to one. *Anisotropic* diffusion occurs when the water forms an ellipse (i.e., is elongated along one axis). When movement occurs along one axis (anisotropy), it suggests the present of fibers traveling in the direction of the elongated portion of the ellipse (Mori & Zang, 2006).

The diffusion process of water molecules is constrained by the structure of the axon fiber. Thus FA is high in regions where there are a number of white-matter pathways. High rates of FA could be an indication of the presence of several different features: high density of fibers, high levels of myelination and/or a crossing of fibers pathways (Beaulieu, 2002; Mori & Zang, 2006).

Decreased FA could reflect different types of neurological damage. The first is loss or lack of myelination (Jito et al., 2008). Decreased FA can also be due to edema of the tissue or damage resulting in the presence of gliosis (e.g., stroke, multiple sclerosis), or loss of axons. Lastly, decreased FA can be a result of newly developing axons, axonal spin formation, or the brains natural architecture (increased fiber crossing; Madler et al., 2008). When there are no apparent signs of neurological pathology, abnormalities in FA are likely due to processes associated with a history of deprivation.

It is important to note that MRI-based imaging techniques have several limitations associated with constraints on resolution and contrast. These constraints stem from the fact that this methodology is still in its early stages of development. One additional practical limitation directly relates to the outcomes of this study. MRI techniques are based on the movement of water molecules throughout structures in the brain and therefore do not provide any direct measurement of the brain's structure. Therefore, the results in this analysis were based on indirect data of biological events in the brain (Mori, & Zhang, 2006).

Magnetic Resonance Diffusion Tensor Imaging Findings for Early Deprivation

The use of MR-DT Imaging in studies on children with a history of early institutional rearing has shown increased cortical-striatal connectivity for post-internationally adopted children, as compared to non-deprived non-adopted children (Figure 1; Behen et al., 2009).

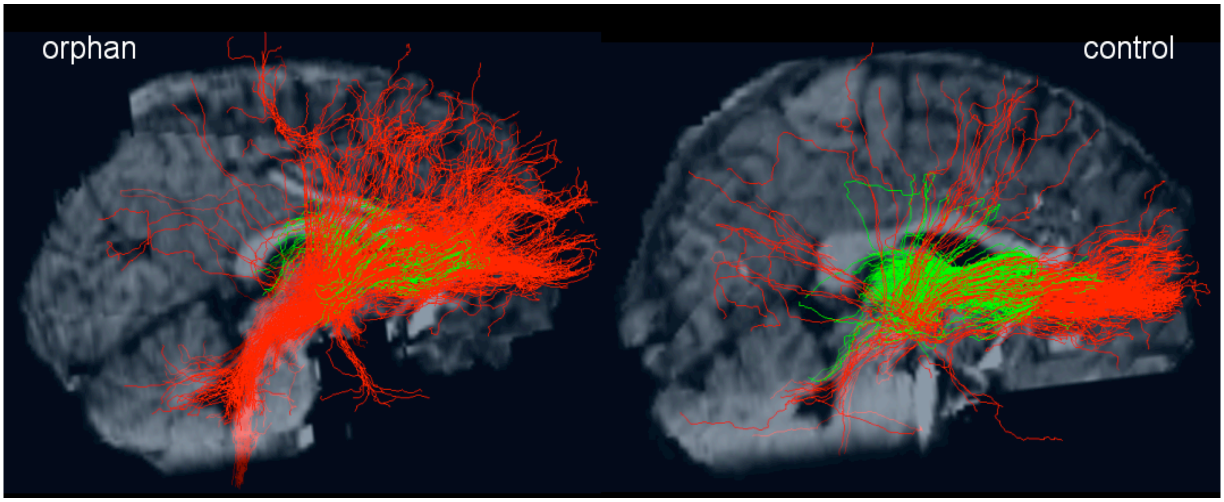

Figure 1. Distribution of probabilistic fiber tracts originating from a region in the right caudate in an IA child (left) and a control subject (right)

Interestingly, a more recent small-scale pilot investigation including 12 children with a history of early institutional rearing found that not all children with histories of early deprivation show a pattern of increased cortical-striatal connectivity. Two specific patterns for fiber connectivity were identified in post-institutionalized children for striatal-cortical connectivity; both patterns identified in the sample of internationally adopted children differed from the pattern found in the non-adopted comparison children (Figure 2). One post-institutionalized group showed a pattern of diffuse connectivity. The *diffuse group* was characterized by significantly higher connectivity in the left, but not right, hemisphere compared to that observed in non-institutionalized, non-adopted children. The other configuration in the post-institutionalized sample was characterized by severely decreased left-hemispheric connectivity. Thus, the *low connectivity group* had significantly less connectivity in the left, but not right, hemisphere compared to comparison children.

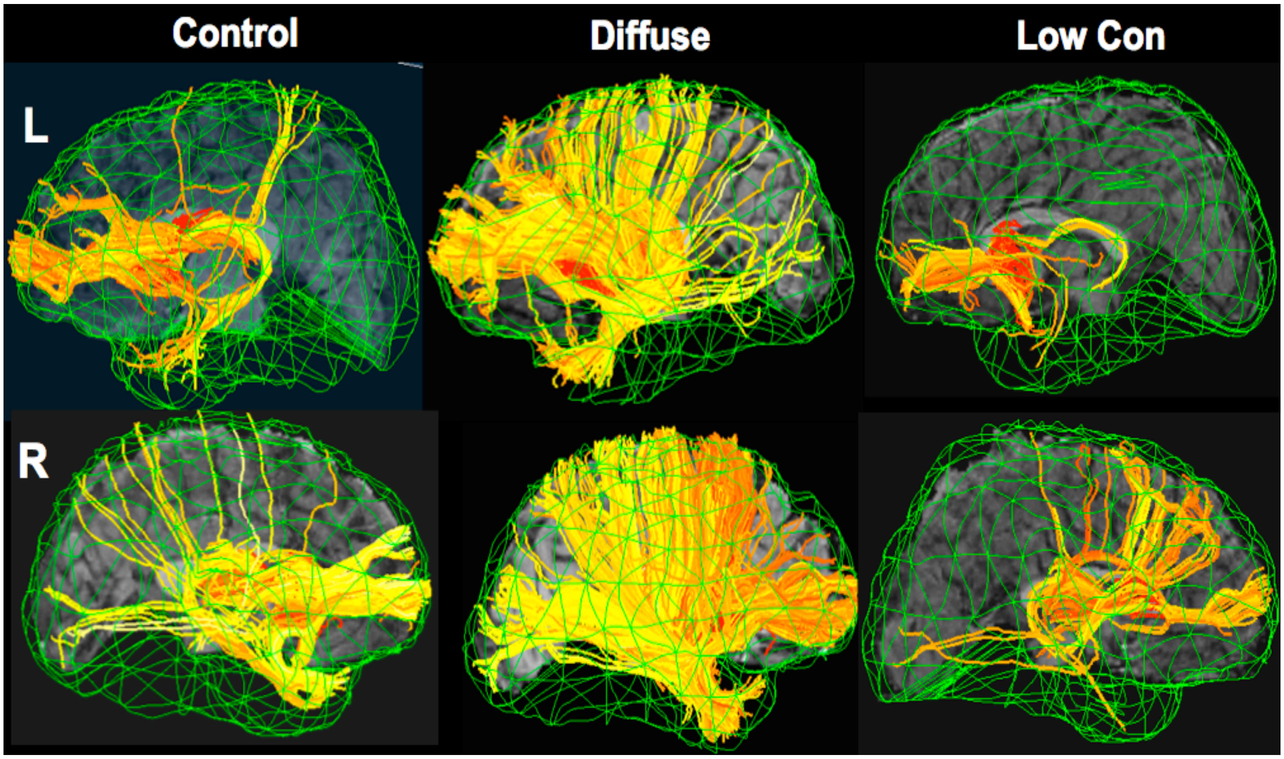

Figure 2. Distribution of probabilistic fiber tracts originating from a region in the striatum in a control subject (left) and two IA children; diffuse connectivity group (center) and low connectivity group (right).

When the calculated probability score was normalized to the total cortical probability score to determine the connectivity ratio, the normalized connectivity ratio in the left hemisphere was significantly lower for post-institutionalized children in both the diffuse and low connectivity groups, compared to the connectivity observed for comparison children. Furthermore, in the right hemisphere, the normalized connectivity score was significantly lower for post-institutionalized children in the diffuse group as compared to comparison children (Veenstra, et al, 2011).

These findings indicate early deprivation has an impact on the connectivity of brain regions, possibly via the synaptic pruning process, such that some children undergo very limited pruning, while others undergo excessive pruning. However, it is also possible that the low connectivity group underwent limited pruning while also forming limited cortical-striatal connections as a result of a lack of exposure to expected stimuli during the appropriate period of time (Fox et al., 2010; Kundsen, 2004; Shonkoff & Phillips, 2000).

The Current Study

The primary goal of the current study is to expand and extend prior research by further investigating the impact of early institutional rearing on the structure of the brain and associated behavioral outcomes. First, data are evaluated for striatal subgroups (i.e., diffuse connectivity and limited connectivity) and medial-temporal subgroups in a sample of children with a history of early institutional rearing. Furthermore, striatal-frontal, striatal-dorsolateral-prefrontal, and medial-temporal-orbitofrontal, medial-temporal-anterior-temporal and medial-temporal-frontal tracts for children with a history of early institutional rearing are evaluated for differences from those observed in a matched sample of non-institutionalized children.

The frontal lobe is an area that is associated with the ability to sustain attention and engage in effortful control, and is known to play a role in attention deficit hyperactivity disorder (Durston, 2003; Konrad & Eickhoff, 2010; Silk et al, 2009). As children with a history of early institutional rearing exhibit a higher rate of attentional and other behavior problems, the striatal and medial-temporal connections in this sample are evaluated to determine whether the pattern of connectivity between these tracts relate to differences in parent reported behavior problems, parent reported executive dysfunction or, children’s performance on executive functioning measures.

Medial temporal structures, such as the amygdala and hippocampus, and the orbitofrontal area are known to play a role in the experience, comprehension, and regulation of emotions (Adhikari, Topiwala & Gordon, 2010; Hornak et al., 2003; Gallagher & Chiba, 1996). There is also emerging evidence for the role of the medial-temporal and anterior temporal areas in executive functions (Castellanos & Proal, 2012; Stretton & Thompson, 2011). The purpose of focusing on the medial temporal connectivity is to determine if the pattern of connectivity for medial-temporal tracts relate to differences in parent observed behaviors; specifically psychosocial difficulties such as internalizing problems (anxiety, depression) and externalizing problems (aggression) that have been previously observed in adoptees (Ames, et al., 1997; Behen, et al., 2008; Rutter, Kreppner, and O'Connor, 2001), as well as parent report and children's performance on executive functioning measures.

If there are structural differences in brain connectivity related to differences in observed behavior, it is important to determine what role, if any, deprivation-specific and adoption-specific variables play in these differences. Based on the experience-expectant literature, it is expected that children who remained in institutions for a longer amount of time would display differences in these brain structures, as well as more behavioral difficulties. However, given that these children were adopted into enriched family environments and many likely have shown substantial functional improvements post adoption, I expect that experience-dependent learning may also account for some of the variance in the group differences, possibly through the creation of new synaptic connections. In this case, deprivation-specific variables would not influence connectivity, but length of time in adoptive home would.

Aims and Hypotheses

This present study has six specific aims, as detailed below.

Aim 1. The first aim is to assess differences in striatal-frontal, and medial-temporal to orbitofrontal/frontal/anterior-temporal connectivity within the internationally adopted orphan sample using MR-DTI derived metrics (normalized probability score). This aim is an attempt to expand on the findings of a small-scale pilot study conducted previously (Veenstra, et al., 2011).

***Hypothesis 1a*.** Specifically, for the striatum, I expected to identify two subgroups among children with a history of early institutional rearing based on the probability score for the whole cortex: one with diffuse connectivity, and a second with low left-hemispheric connectivity (Veenstra, et al., 2011).

Hypothesis 1b. As was the case for my hypotheses for the striatum, I also expected that two subgroups would emerge for medial temporal connectivity based on the probability score for the whole cortex; one with diffuse connectivity and a second with low connectivity (Veenstra et al, 2011).

Given the paucity of literature on this topic, I did not predict the specific nature of the connectivity differences (i.e., whole brain versus hemispheric differences) for medial-temporal connectivity.

Aim 2. The second aim was to determine whether white matter connectivity and integrity, as measured by FA, ACD and NPR, differed between the groups identified in Aim 1 for children with a history of early institutionalized rearing and/or the group of comparison children without a history of early institutionalization or adoption for striatal to frontal/dorsolateral-prefrontal tracts, and medial-temporal to orbitofrontal/frontal/ anterior-temporal tracts.

***Hypothesis 2a*.** I predicted that striatum groupings for adopted children with a history of early institutional rearing would differ on measures of frontal-striatal and dorsolateral-prefrontal-striatal connectivity. I also predicted that striatum groups would differ from non-adopted, non-institutionalized comparison children. Specifically, within the post-institutionalized adopted group, I expected that a group characterized by whole brain striatal-cortical-diffuse connectivity would also show increased connectivity on specific striatal tracts, whereas a group characterized by low striatal-cortical connectivity would show decreased connectivity on specific striatal tracts. Also, consistent with prior findings (Veenstra et al, 2011), I expected that IA groups would show significantly lower white matter connectivity ratios than children in the comparison group, as measured by NPR.

***Hypothesis 2b*.** I hypothesized that post-institutionalized, adopted children would differ from the non-adopted, non-institutionalized children on measures of medial-temporal connectivity (FA, ADC, NPR). Consistent with prior findings (Veenstra et al., 2011), I predicted that, a group characterized by whole brain medial-temporal cortical-diffuse connectivity would show increased connectivity on specific medial-temporal tracts, whereas a group characterized by low connectivity would show decreased connectivity on specific medial-temporal tracts. However, I predicted that the sample of IA children would show significantly lower NPR's for medial-temporal tracts compared to children in the comparison group.

Aim 3. The third aim of the study was to associate MR-DTI metrics with children's psychosocial outcomes. Specifically, IA groups and comparison children's connectivity for specific striatal and medial-temporal tracts were evaluated for associations with parental reports of behavior problems.

Hypothesis 3a I expected that the comparison children and post-institutionalized, adopted children (grouped based on striatal/medial temporal-cortical connectivity) would differ on parental report of behavioral problems on the BASC/BASC-2. As behavioral problems have been found to be associated with abnormal white-matter connectivity (Behen, et al., 2009, 2011), children in the post-institutionalized subgroups and comparison children were predicted to differ in the number of symptoms reported for internalizing, externalizing, and behavioral symptoms index. The low-connectivity striatal group was predicted to display more externalizing problems (Behen, et al., 2011). No predications specific predictions were made for the pattern of cortical connectivity for other types of behavioral problems.

Hypothesis 3b. I also predicted that the striatal and medial-temporal groups of post-institutionalized children and comparison children would differ on rates of the I/O phenotype. Given the inconsistency in the literature on patterns of white-matter connectivity for non-deprived children with ADHD (Konrad, & Eickhoff, 2010), no specific predictions for structural differences in the IA sample were made.

Hypothesis 3c. I hypothesized that the groups of IA children identified based on striatal-cortical and medial-temporal cortical connectivity would differ on measures of executive function (Metacognition and Behavioral Regulation) as measured via parent report on the BRIEF (Gioia et al, 2000). BRIEF data was not collected for comparison children and therefore they were not included in this hypothesis.

***Hypothesis 3d*.** Specific striatal and medial-temporal tracts that were identified to significantly differ in aim two between the groups identified in aim one were investigated for potential differences on parental ratings measures.

Aim 4. The fourth aim of the study was to determine whether differences observed in the striatal and medial-temporal tracts in the groups identified in aim one for IA children and comparison children, were associated with behavioral measures of sustained attention, and impulsivity (Gordon Diagnostic Systems – Vigilance; Hits and False Alarms, respectively)

***Hypothesis 4a*.** I expected that the proposed groups of children in the post-institutionalized, adopted sample and the comparison children would be associated with differences on behavioral measures of vigilance and impulsivity. No specific predictions for structural differences in the IA sample were being made as the inconsistencies in the prior evidence do not offer suggestions as to which pattern would be associated with impairments in the areas of attention and concentration, and impulsivity (Konrad, & Eickhoff, 2010).

***Hypothesis 4b*.** Specific striatal and medial-temporal tracts that were identified to significantly differ by group in hypothesis two were investigated for potential differences on behavioral performance measures.

Aim 5. The fifth aim of this study was to determine whether the consistently reported prior findings for parent-reported behavioral measures (Gunnar et al, 2007; Dalen, 2002; Dalen et al., 2008; Odenstad et al., 2008; Lindblad, et al. 2009) could be identified in this sample.

***Hypothesis 5a*.** I predicted that children within the adoptive sample would show significantly more behavioral problems than would be expected for children their age, based on published age norms. I also expected that these rates would be consistent with rates previously found in international adopted samples.

***Hypothesis 5b*.** I hypothesized that children were adopted earlier (18 or 24 months) exhibited fewer behavioral and executive function problems, as measured by the BASC and BRIEF (Ames, et al., 1997; Beckett, et al, 2007; Jacobs, et al., 2010; Kreppner, et al, 2007; Stevens, et al., 2008).

***Hypothesis 5c*.** I predicted that children adopted from different countries would differ in the rate of behavioral problems as measured by the BASC (Gunnar et al, 2007; Dalen, 2002; Dalen et al., 2008; Odenstad et al., 2008; Lindblad, et al. 2009). Specifically, I expected that children from Eastern European countries would have higher rates of internalizing, externalizing, and behavioral symptoms than those from South/East Asia.

***Hypothesis 5d*.** I hypothesized that children with more time in the adopted home would exhibit more behavioral problems (internalizing and externalizing) on the BASC, then children who have spent less time in the adoptive home. I also expected that behavioral symptoms would not be related to time in the adoptive home (Rutter et al., 2007).

Aim 6. The sixth aim was to evaluate whether different patterns of brain connectivity were associated with orphanage-specific variables (i.e., country of adoption, duration in orphanage) or an adoption-specific variable (i.e., time in adoptive home) among children with a history of early institutional rearing.

***Hypothesis 6a*.** There is extensive evidence linking duration of institutionalization to emotional and behavioral outcomes (Ames, et al., 1997; Beckett, et al, 2007; Jacobs, et al., 2010; Kreppner, et al, 2007; Stevens, et al., 2008). As such, I expected that children's age at the time of adoption would be associated with group classification. Given that there are no prior imaging findings from which to base the direction of this hypothesis, I made no specific prediction as to which pattern would be related to early or late adoption.

***Hypothesis 6b*.** Given prior literature showing that IA children from similar countries of origin show similar behavior patterns (Gunnar et al, 2007; Dalen, 2002; Dalen et al., 2008; Odenstad et al., 2008; Lindblad, et al. 2009), I hypothesized that children adopted from similar regions would show similar patterns of white matter connectivity, as determined by their group classification.

***Hypothesis 6c*.** I also expected that the amount of time children spent in their adoptive home would be associated with cortical based group classification. This is based on the research evidence that time in the adoptive home was specifically related to structural outcomes beyond length of institutionalization (Behen, et al., 2009). There were no prior imaging findings from which to base the direction of this hypothesis. As such, I made no specific prediction as to which pattern would be related to the amount of time in the adoptive home.

CHAPTER 2

Method

Participants

Analyses in this study were based on neuroimaging and behavioral data collected for a cohort of 30 internationally adopted children, and 12 comparison children who participated in a larger ongoing study conducted by Behen and colleagues (Structural and functional neural correlates of early postnatal deprivation; 5K08MH079176-05). All adopted children were foreign-born and had been placed in an institutional setting within several days following their birth, or subsequent to a more extended hospital stay following birth. These children's biological parent(s) spent no time with them as caregiver. Furthermore, all children were adopted into homes in the United States where English was spoken as the primary language. Most of the children with a history of early institutional rearing were adopted into families with a residence in the Great Lakes area.

At the time of their evaluation, children in the post-institutionalized, adopted group were between 6 and 16 years of age (*M* = 10.64 years; *SD* 2.22) and slightly more than half were female (53.3%). Most children were right-hand dominant (73.3%). The children were adopted from orphanages in Eastern Europe (i.e., Bulgaria *n* = 1; Romania *n* = 5; Russia; *n* = 19), East Asia (i.e., China; *n* = 3), and South America (i.e., Guatemala *n* = 2). These children spent an average of 19.98 months (*SD* = 10.76 months) residing in an institution, although the time institutionalized varied greatly among individual children in the sample (range = 3 - 42 months).

At the time they were tested, most children had spent more time living with their adoptive family than they had spent living in an institution. The average length of time children had resided in their adoptive homes was 9 years (*SD* = 2.19 years), with a range from 5.5 and 14 years. Despite the number of years in their adoptive home, a large proportion of these children continue to be classified as underweight, with a mean Body Mass Index (BMI) of 18.6 (*SD* = 2.53), range = 14.1 - 23.2.

Children's adoptive parents varied in years of completed education. All adoptive parents graduated from high school (range 12-22 years), and many mothers (*n* = 30: *M* = 17.47; *SD* = 2.21) and fathers (*n* = 25: *M* = 16.68; *SD* = 2.56) earning a college or advanced degree.

Children in the not-institutionalized, not-adopted comparison group were all born in the United States and had resided with their biological parents in the Great Lakes area since the time of their birth. At the time of evaluation, these children ranged in age from 7.75 to 17.92 years (*M* = 12.60; *SD* = 3.11). As was the case with the adopted group, the majority of children in the comparison group were right handed (91.7%) and more than half were female (66.7%).

Inclusion and exclusion criteria. There are a number of factors (e.g., prenatal drug exposure, premature birth) that are known to have a neurobiological impact, and therefore could confound our results. As such, children with evidence of known confounding factors were excluded from the larger study.

To be eligible to participate, the post-institutionalized children in the international adoption group had to have been placed in an institutional setting following birth, with no care provided by a biological parent. Due to age-requirements specific to the larger study, post-institutionalized adopted children were between the ages of 6 and 17, whereas there were no specific age-requirements for comparison children in the larger study.

Children in the international adoption group were excluded from the study if there was evidence of any of the following known confounding factors including; premature birth (i.e., delivery before 37 gestational weeks); evidence of pre/peri-natal difficulties; past or present major medical illnesses, such as epilepsy; history of, or suspicion of, prenatal drug and/or alcohol exposure, as documented via parental report; or significant evidence of prenatal alcohol exposure based on a brief neurological examination at the time of testing in the current study. The neurological examination was conducted as an additional screener for prenatal alcohol exposure due to the scant prenatal information often provided to adoptive parents. Children with a “high” phenotypic suggestion of alcohol exposure, based on Miller et al.’s (2006; cut-off of 12) criteria, were also excluded from the study.

It is important to note that, within this population, not all adopted parents were provided with accurate or complete medical histories of their children, particularly information related to the prenatal environment and/or the birth of their child. As such, it is possible that some children who should have been excluded from this study based on their pre-adoptive histories were included in this study. To compensate for this, a neurological exam was performed at the same visit in which the testing took place. One child who was identified based on imaging data to have significant neurological structural abnormalities was excluded from the study. An additional four children were excluded due to poor image quality.

Children in the comparison group were eligible to participate if they were raised from birth by their biological parent(s) and were between the ages of 6 and 18 years at the time of the evaluation. Exclusion criteria for children in the comparison group were the following: parent report of prenatal drug or alcohol exposure, premature birth, a history of developmental delay, learning problems, or a diagnosis of a serious medical or mental health problem. Furthermore children whose parents endorsed present concerns of significant emotional or behavioral problems on the Behavioral Assessment Scales for Children (BASC or BASC-2; Reynolds & Kamphaus, 2004) were excluded from the study.

Procedures

Recruitment. Families raising adopted children with a history of early institutional rearing (international adoptees) were recruited through announcements and informational presentations presented to local and national adoption support groups for internationally adopted children and their parents. Families of comparison children were recruited through fliers posted throughout the campus of a large urban children's hospital. Parents of children who participated in the study also referred families from their social network or adoption support groups.

Parents interested in their child participating in the study were screened by phone to determine if their child met the study's inclusion and exclusion criteria. Additionally, parents of comparison children were mailed the Behavioral Assessment Scales for Children (BASC & BASC-2; Reynolds & Kamphaus, 2004), to be returned before their eligibility was determined. If children qualified for the study, they were scheduled for two appointments.

The present study uses data from two separate visits. At the first visit, prior to any study procedures, trained research staff reviewed information about the study, as detailed on the informed consent form, and HIPAA polices with the family. After reviewing these materials and addressing any questions or concerns, the parent(s) signed the consent form, and children aged 7 or older provided assent. Children over age 13 signed the assent form if they chose to continue with the study. Children between 7 and 12 years of age provided verbal assent, indicating their willingness to participate. Families were provided with copies of the informed consent and assent forms, and the hospital's HIPAA policy.

Following the informed consent procedures, all children participated in a neuropsychological evaluation, and were evaluated for height and weight. Children's weight was calculated using a standard electronic digital column medical scale, and their height was measured using a wall-attached stadiometer. Height and weight were used to calculate the children's body mass index (BMI). BMI was evaluated as a potential covariate in the present study. Children in the adopted group also received a brief (10-minute) neurologic screen conducted by a neurologist, which was used to confirm children's eligibility to participate in the study, as described above.

The neuropsychological evaluation lasted between four and five hours. Children were administered a battery of standardized measures of intellectual functioning, verbal and visual memory, expressive language, receptive language, executive functioning, academic achievement, and manual dexterity. In the present study, children's age-referenced scores from the third and forth version of the Wechsler Intelligence Scales for Children and the Wechsler Adult Intelligence Scales forth edition (WISC-III, Wechsler 1991; WISC-IV, Wechsler 2003; WAIS; Wechsler, 2008) and the vigilance portion of the Gordon Diagnostic System (Gordon & Mettelman, 1988) were evaluated. The WISC/WAIS was the first test administered. The vigilance portion of the Gordon Diagnostic System (Gordon & Mettelman, 1988) was administered approximately half way though testing. Per the test instructions, procedures from the Gordon Diagnostic System were given following a break, and thus where this test fell in the order of administration was contingent on when the child's break occurred.

While their children were participating in the neuropsychological evaluation, adoptive parent completed a battery of questionnaires regarding their child's current behavioral and psychosocial functioning and provided basic information about the children's medical history, health, and familial demographic information (Appendix A).

In this study, the following data were evaluated: parental reports of children's behavioral problems, as measured by the Behavioral Assessment Scales for Children (BASC & BASC-2; Reynolds & Kamphaus, 2004), orphanage-specific information (age at the time of adoption, country of origin), and demographic information. Additionally, parental reports of children's executive functioning, as measured by the Behavioral Rating Inventory of Executive Functioning (BRIEF; Gioia et al, 2000), were evaluated only for the internationally adoptee sample, as this information was not provided by the parents of comparison children, per the approved study protocol.

The second visit typically took place within one to two weeks after the first visit and lasted about one hour. During this visit, children underwent a functional MRI (fMRI), T1 weighted Magnetization Preparation Rapid Acquisition Gradient Echo (MP-RAGE) scan and Magnetic Resonance-Diffusion Tensor imaging (MR-DTI).

Prior to beginning the fMRI, the child underwent a training task to learn the task that was to be performed during the fMRI. In the present study, 55 direction MR-DTI data were used to provide information on the microstructure of the children’s white matter. The variables evaluated in this study from the MR-DTI evaluation included Normalized Probability Scores, Normalized Probability Ratio (NPR), Apparent Diffusion Coefficient (ADC) and Fractional Anisotropy (FA). ADC and FA were calculated based on the images acquired with MR-DTI, as was the normalized probability score and ratio (see below for more details).

Measures and Instruments

Intellectual functioning. Two composite indexes from the Wechsler Intelligence Scales for Children and Wechsler Adult Intelligence Scale (WISC-IV; Wechsler 2003; WAIS; 2008) were used as indicators of children’s current measured intellectual functioning. The WISC-III, WISC-IV, and WAIS are widely used standardized measure of cognitive functioning that has consistently demonstrated good reliability and validity in a variety of populations (Sattler & Dumont, 2004).

The Verbal Comprehension Index (VCI) assesses verbal knowledge and understanding obtained through formal and informal education, as well as the capacity for application of verbal skills to new situations. The VCI is comprised of three subtests: Similarities, Vocabulary, and Comprehension, all of which were administered to adoptees. Comparison children were administered only the Similarities and Vocabulary subtests. For these children, a prorated VCI score was calculated, based on instructions from the WISC-IV and WAIS manual.

The Perceptual Reasoning Index (PRI) of the WISC-III and WISC-IV measures children’s ability to interpret and organize visually perceived material, as well as their capacity to generate and test hypotheses related to problem situations. The PRI is based on children’s scores on three subtests: Block Design, Picture Concepts, and Matrix Reasoning. All three subtests were administered to adoptees to calculate their PRI, whereas the non-adopted comparison children were administered only two of the three subtests: Block Design and Picture Concepts. PRI scores were calculated based on instructions in the WISC-IV and WAIS manual. PRI scores based on either two or three subtests are highly reliable and are valid measures of perceptual reasoning (Sattler & Dumont, 2004; Wechsler, 2003; Wechsler, 2008).

WISC scores were classified into categories based level of performance: Borderline (70-79), Low Average (80-89), Average (90-109), High Average (110-119), Superior (120-129; Wechsler, 2003).

Attention and concentration. The Vigilance subtest from the Gordon Diagnostic System was used to assess sustained attention and impulsivity. The Vigilance Hits score was used to measure sustained attention, while the Vigilance False Alarms score was used to measure impulsivity (Gordon & Mettelman, 1988). The vigilance task required the child to push a button to indicate when a specific number combination flashed on the screen. The child’s Vigilance Hits score was calculated using the total number of times the child correctly identified the *one, nine* combination. The Vigilance False Alarms score was the sum total times that the child incorrectly indicated they have observed the 1-9 combination when it was not presented.

The raw scores for each measure were converted to *T*-scores, which corrects for age (population mean = 50, *SD* = 10). These scores were categorized as normal (>25th percentile), borderline (6-25th percentile), and abnormal (<5th percentile; Gordon & Mettelman, 1988). The two vigilance subtests evaluated in this study are widely used measures with good reliability and validity (Dickerson Mayes, Calhoun, & Crowell, 2001).

Behavioral functioning. The Behavioral Assessment Scales for Children (BASC & BASC-2; Reynolds & Kamphaus, 2004) is a parent-report measure of children's internalizing and externalizing problems, and behavioral symptoms. This measure is standardized for use with children aged 2 to 21 years. Scoring of the BASC yields four composite scales, and three of these were used in the present study: Internalizing Problems, Externalizing Problems, and the Behavioral Symptoms Index. These three composite scales are made up of several subscales. The Externalizing Problems composite was derived from children's scores on three subscales (hyperactivity, aggression, and conduct problems). The composite scale labeled Internalizing Problems was derived from children's scores on three subscales: anxiety, depression and somatization. The Behavioral Symptoms Index was derived from children's scores on the atypicality, withdrawal, and attention problems subscales. The raw scores were converted to age-referenced *T*-scores (population mean = 50, *SD* = 10). Per BASC instructions: *T*-scores below 60 were categorized as within normal limits, *T*-scores between 60 and 69 were categorized as at-risk, *T*-scores of 70 or more were categorized as clinically significant (Reynolds & Kamphaus, 2004).

In addition, within the early social deprivation research literature two BASC subscales (attention problems and hyperactivity) are often combined to create a scale labeled as the Inattentive/Overactive phenotype. Averaging the *T*-scores for the attention problem and hyperactivity subscales created this variable. I/O phenotype scores were categorized using BASC categories: *T*-scores below 60 were categorized as within normal limits, *T*-scores between 60 and 69 were categorized as at-risk, *T*-scores of 70 or more were categorized as clinically significant (Reynolds & Kamphaus, 2004). The attention problem and hyperactivity subscales have demonstrated good reliability and validity (Reynolds & Kamphaus, 2004) and these scales have frequently been used in prior research on internationally adopted children to identify the I/O phenotype (i.e., Behen, 2009).

Demographic questionnaire. In this questionnaire, parents were asked to provide basic demographic information (e.g., years of maternal and paternal education, current age and sex of child), as well as information regarding the presence of possible psychological or medical problems that would exclude their child from the study (Appendix A). Only parents of adopted children were asked to report on their child's age at the time of adoption as well as the country from which their child was adopted. Demographic variables evaluated as potential covariates in this study include children's age and sex, and parents' level of education.

Executive functioning. The Behavioral Rating Inventory of Executive Functioning (BRIEF; Gioia et al, 2000) is a widely utilized parent-report measure used to assess executive functioning in children aged 5 to 18 years. The BRIEF was completed only by parents of children in the internationally adoption group. Therefore, the BRIEF was analyzed only for this subsample of children in this study. The parent was asked to rate the extent to which a list of specific behaviors described their child's current functioning, using a 4-point Likert-type scale. The BRIEF yields eight clinical scales and two validity indexes. The clinical scales were combined to create two composite indexes. Behavioral Regulation was based on scores from the following subscales: Inhibit, Shift, Emotion Control. Metacognition was based on scores from the following subscales: Initiate, Working Memory, Plan/Organize, Organization of Material, and Monitor. All parental ratings were determined to be valid as neither of the validity indexes were elevated for any study participant.

The raw scores from the BRIEF were converted to age-referenced *T*-scores (population mean = 50, *SD* = 10). *T*-scores falling below 65 are classified as within normal limits, whereas *T*-scores of 65 or higher are classified as clinically significantly (Gioia et al, 2000). These indices each have demonstrated good reliability and validity (Gioia, et al, 2000; Mahone et al, 2002).

Child anthropometric measurements. Children were weighed on a standard electronic digital column medical scale and their height was measured using a wall-attached stadiometer. Height and weight were used to calculate the children's body mass index based on an age and gender normed formula (Center for Disease Control and Prevention).

MR image acquisition. All imaging studies were performed in accordance with guidelines stipulated by the Ethics Committee of Wayne State University. MRI studies were performed on the same GE 3 Tesla Signa unit (GE Medical Systems, Milwaukee, WI). High-resolution T1-weighted images were obtained using a spoiled gradient-echo

(SPGR) sequence generating 124 contiguous 1.5 mm sections of the head by using a 35/5/1 (TR/TE/NEX) pulse sequence, flip angle of 35 degrees, matrix size of 256x256, and a field-of-view (FOV) of 240 mm. These images were performed in the coronal plane and the imaging time for this sequence was about 8 min. In addition, diffusion-weighted dual spin-echo single shot echo-planar MR images were acquired using the following parameters: 6000/110/1 (TR/TE/NEX), FOV of 240mm, 128x128 data matrix reconstructed to a 256x256 image matrix with a slice thickness of 3mm covering the whole brain. It was shown that the dual spin-echo sequence minimizes artifacts due to eddy currents (Reese et al., 2003). The DTI sequence consisted initially of an image volume with no diffusion weighting (B0; $b = 0$ s/mm^2) followed by the acquisition of image volumes in 55 gradient directions with a b-value of 1000 s/mm^2. The complete MR scan session took about 20 minutes.

Image analysis. Removal of the skull and non-brain tissue was conduced using Freesurfer (Segonne, et al., 2004). In order to combine information from DTI and T1-weighted images in native space, an integrative framework was used (Lin et al., 2010; Muzik et al., 2007; Zou et. al. 2006). Using this software, regions of interest (ROIs) representing the bilateral head of caudate, and the amygdala and hippocampus regions were defined based on high-resolution T1-weighted image volumes. These 3D ROIs were then transformed into DTI space and subsequently used as seed regions for probabilistic tractography in native space. Finally, sets of finite elements representing the whole hemisphere, the dorso-lateral prefrontal cortex (DLPF), the frontal pole (FP), the temporal pole (TP), and orbitofrontal cortex were defined in both hemispheres and used as target regions for probabilistic fiber tracking.

Probabilistic fiber tracking was performed using a Bayesian framework developed by Friman et al. (2006). In this model, the local probability density function (PDF) was determined at each step location based on the PDF of the neighboring eight image voxels, weighted by the distance from the current position. The so obtained local PDF was subsequently multiplied with a prior distribution, giving preference for continuation in the previous-step direction (zero probability for turns > 90 degrees), and evaluated at 2562 predefined unit length vectors obtained by a fourfold tessalation of an icosahedron. Starting from a seed point, random samples are drawn from the posterior distribution and fiber paths were created which terminate when the local fractional anisotropy (FA) decreases below a pre-selected value (0.15 in this study). It should be noted that this model assumes only one fiber direction in each voxel (single-fiber model) and any deviation from this model (such as fiber crossing/convergence) was translated into uncertainty in the posterior distribution. This uncertainty leads locally to an increased probability of randomly sampled fibers to diverge into multiple directions, thus allowing a certain portion of fiber paths to cross low-anisotropy areas, hence realizing minor fiber tracks.

In order to quantitatively assess connectivity between a given source and target region, the average probability p_i (equation 1) was calculated for each individual fiber path i of length N_i connecting the source and target region, where p_{ij} was the randomly sampled probability of voxel j (j = 1,..N_i) determined from the local PDF calculated earlier. In this context the index j refers to voxels along path i and not to the step length used to sample from the local PDF (which is smaller). The obtained value of p_i can be interpreted as the average probability along the path with index i, independent of the path length. Because the number of fiber paths that connected a seed and target region was only a subset of all created fibers (M > N), all path probabilities p_i were subsequently normalized to the sampling space (total number of fiber paths k = 1,…, M) as p_i’ (equation 2). Finally, the normalized probability score of connection between two regions A and B (termed P_{A-B}) was calculated as the sum of p_i’ values from all fiber paths l (l = 1,.. L < M) connecting the source and target regions (equation 3).

$$p_i = \sqrt[N_i]{\prod_{j=1}^{N_i} p_{ij}} \qquad p_i' = \frac{p_i}{\sum_{k=1}^{M} p_k} \qquad P_{A\rightarrow B} = \sum_{l=1}^{L} p_i'$$

Equations 1-3

The diffusion-tensor was calculated from DTI data (B0, 55 gradient directions) on a pixel-by-pixel basis using the Stejskal-Tanner equation (Stejskal and Tanner, 1965) yielding the diffusion tensor D_{ij}. Once D_{ij} was determined, it was diagonalized in order to obtain the local PDF. The previously created cortical elements (10mm depth) were then used as seed and target regions and fiber tracts were created as described above. For each seed point within a cortical element, 100 paths were created, yielding a minimum of 10,000 paths originating from each cortical element.

The normalized probability score (P_{A-B}) was calculated for each seed region for all cortical elements. A cortical pattern was created based on this data. This was then transformed into a two-dimensional cortical fiber distribution map using a Mercator projection. The normalized probability score between the seed and target regions in each hemisphere was calculated by summing all elements comprising the target regions. This created for each subject a normalized probability score between the head of the caudate and the ipsilateral hemisphere, frontal pole, or dorsolateral prefrontal cortex for each hemisphere, as well as a normalized probability score between the hippocampus-amygdala and the ipsilateral hemisphere, frontal pole, temporal pole, or orbitofrontal cortex for each hemisphere.

Analysis Plan

Analyses in this study followed a multi-step plan. First, univariate analyses were conducted on all study variables to evaluate their distributional properties. Second, bivariate analyses were carried out to evaluate whether demographic variables (e.g., child age or sex, or parental education) or the child anthropometric variable (body mass index; BMI) were related to our variables of interest. Demographic and child anthropometric variables that were correlated with the test variables were analyzed as covariates in relevant analyses using Quade's Analysis of Covariance tests (Quade, 1967) when data met test assumptions.

The first aim of the present study was to identify subgroups of children in the international adoption group who differed in the degree of connectivity separately for the striatum and medial-temporal region as determined by the probability score. To accomplish this, a hierarchical cluster analysis ("furthest neighbors") was conducted to determine the number of groups present and to classify the children into subgroups.

The second aim was to evaluate whether white-matter tracts differed between children in the international adoptee subgroups and the comparison group. Nonparametric tests were used for these analyses due to violations of normality. To address this aim, Kruskal-Wallis and Quade's Analysis of Covariance tests were carried out for the frontal-striatal tract using the FA, ADC, and the NPR as the test variables. The grouping variable was the three subgroups that emerged for the adoptee sample and the comparison sample. Kruskal-Wallis and Quade's Analysis of Covariance tests were also run for the medial-temporal region to contralateral target regions (frontal pole, temporal pole, and orbitofrontal). The grouping variable was the two subgroups that emerged for the adoptee sample and the comparison sample. When significant differences were identified, post-hoc analysis (multiple Mann-Whitney tests; pairwise Quade's Analysis of Covariance tests) were run to identify the specific groups that differed.

To address the third and fourth aims of the study, Welch ANOVA's were run for each hypothesis, except hypothesis three part D and four part B The goal of these analyses was to determine whether the predictor variables (post-institutionalized subgroups and comparison children) for the striatal or medial-temporal tracts predict the dependent variables (parental report of behavioral symptom as measured by BRIEF and BASC/BASC-2 scores). As described above, classification of children into subgroups was based on the Probability Score.

The lack of normal data precluded planned analyses to address part D of Aim three and part B of Aim four. Therefore these were assessed indirectly through conducting Kruskal-Wallis and Quade's Analysis of Covariance tests only for striatal and medial-temporal tracts shown significantly differ by group in prior analyses. FA, ADC, and the NPR for significantly different tracts by group were used as the test variables. The grouping variable was the classification systems for *T*-scores for the Gordon, BRIEF and BASC. When significant differences were identified, post-hoc analysis (multiple Mann-Whitney tests; pairwise Quade's Analysis of Covariance tests) were run to identify the specific groups that differed.

To address part A of Aim five, a chi-square test of goodness-of-fit was performed to determine whether the proportion of children with behavioral problems fit with typical rates found in early social deprivation samples.

To address parts B of Aim 5, Kruskal-Wallis tests were carried out, where the test variables were the parental report of child behavior problems (BASC/BASC-2) and executive dysfunction (BRIEF). Grouping variables were age at time of adoption and duration of stay in adoptive home.

Hypotheses associated with part C of Aim 5 and part A of Aim 6 were not analyzed. The grouping variable for these hypotheses were children's region of adoption. The majority of the children in this sample were from Eastern European countries (*n* = 25). There were too few children from other regions (East Asia; *n* = 3; South America *n* = 2) for this hypothesis to be reliably explored.

To address parts D of Aim five, Kruskal-Wallis tests were carried out, where the test variable was the duration of time in the adoptive home. The grouping variables were based on the classification systems for *T*-scores from the Gordon Diagnostic System, BRIEF, and BASC.

To address parts B and C of aim Six, Kruskal-Wallis tests (for striatal groups) and Mann-Whitney U tests (for medial-temporal groups) were conducted. Test variables were orphanage-specific (i.e., duration in orphanage) or adoption-specific variables (i.e., time in adoptive home). The grouping variables were the subgroups that emerged for the adoptee sample.

All data analyses were run using SPSS 21 (IBM Corp. 2012). The conventional level of *alpha* $\leq .05$ was used in determining statistical significance, except for follow-up analysis to Kruskal-Wallis tests, where a Bonferroni correction was applied.

CHAPTER 3

RESULTS

Data Screening

Prior to evaluating the study's aims, the data were cleaned and analyzed for their suitability for the planned analyses using standard data cleaning procedures. Missing Value Analyses were conducted using the Missing Values Analysis procedure in SPSS 21 (IBM Corp. 2012). In the internationally adopted (IA) group, missing data were less than 5% for all variables except for children's BMI and fathers' education. These variables were determined to be missing from cases at random, Little's MCAR: χ^2 (19, N = 30) = 12.14, p = .88, For the comparison group, missing data were less than 5% for all variables except Vigilance Hits and False Alarms, Little's MCAR: χ^2 (11, N = 12) = 12.15, p = .35. Mean substitution was used to address missing data for the comparison group (Hits M = 54.7; False Alarm M = 52.3). Univariate outliers were identified by converting the data for each variable to z-scores separately for the IA group and comparison group. Based on the sample size in this study, 2.57, and -2.57 were used as the cut-off for outliers. For the IA group, there were two univariate outliers on the variable Vigilance False Alarm, whereas the BASC Somatization and Atypical Behavior subscales each had one outlier. No outlier was present in the comparison group for neuropsychological or demographic data. All univariate outliers were Winsorized.

For the IA group, age at the time of study and time in the adoptive home were highly correlated, r (28) = .908, p < .001; thus only age at the time of testing was evaluated in subsequent analyses, except when duration of time in the adopted home was the variable of interest. Parent report and neuropsychological variables were normally distributed; however, tests for homogeneity of variances between the comparison and IA group were significant for Vigilance Hits, *Levene F* (1, 39) = 13.22, *p* = .001; Vigilance False Alarms, *Levene F* (1, 39) = 26.50 *p* < .001; and BASC Behavioral Symptoms Index, *Levene F* (1, 39) = 4.41 *p* = .04. These variables were not included in subsequent analyses that required homogeneity of variance.

When data were grouped using hierarchal cluster analysis, within-group outliers were identified for the medial-temporal groups. One group had one outlier each for the normalized probability ratio for the left frontal pole (FP), right FP, left orbitofrontal region (OF) and FA for the left temporal pole (TP). The other group had one outlier each for the left OF normalized probability ratio (NPR) and left OF apparent diffusion coefficient (ADC). No univariate outliers were detected for striatal groups. One univariate outlier was present in the comparison group for the probability variable for the right dorsolateral-prefrontal region (DLPF). All univariate outliers were Winsorized.

Following transformations, these data were not normally distributed; however, without transformation of the variables the distributional shapes between groups were similar. Tests for homogeneity of variances for the IA striatal subgroup and the comparison group were significant for left caudate to DLPF ADC, *Levene F* (4, 37) = 6.11, *p* = .001; and left caudate to FP NPR, *Levene F* (4, 37) = 5.59, *p* = .001. Tests for homogeneity of variances for IA medial-temporal group and the comparison group were significant for right amygdala/hippocampus to OF FA, *Levene F* (3, 38) = 3.05, *p* = .04; left amygdala/hippocampus to FP ADC, *Levene F* (3, 38) = 16.64, *p* < .001; right medial amygdala/hippocampus to FP ADC, *Levene F* (3, 38) = 8.48, *p* = < .001; right amygdala/hippocampus to OF ADC, *Levene F* (3, 38) = 7.44, *p* < .01; left amygdala/hippocampus to OF NPR, *Levene F* (3, 38) = 7.36, *p* = .001; and right amygdala/hippocampus to OF NPR, *Levene F* (3, 38) = 3.52, *p* = .02. These variables were not included in subsequent analyses that required homogeneity of variance.

Preliminary Analyses

Univariate analysis. The mean cognitive performance of children in the IA group, as measured by WISC verbal and nonverbal reasoning indices, fell in the Average range. In contrast, the mean cognitive performance for children in the comparison group fell in the High Average range (Table 1).

Table 1: *Mean Scores for Parent Ratings and Neuropsychological Tests*

	Adopted *n* = 30		Comparison *n* = 12	
	M	*SD*	*M*	*SD*
WISC[a] (standard scores)				
Verbal Comprehension	97.90	13.86	114.75	7.66
Perceptual Reasoning	97.93	14.35	112.58	11.61
BRIEF[b] (*T*-score)				
Behavioral Regulation	63.07	15.38	--	--
Meta-Cognition	63.73	13.10	--	--
BASC[c] (*T*-score)				
Internalizing	57.34	14.39	42.83	8.06
Externalizing	63.14	11.29	43.67	8.33
Behavioral Symptoms	63.93	14.67	41.67	7.38
Inattentive/Overactive Phenotype [d]	63.91	12.32	43.00	7.03
GDS[e] Vigilance (*T*-scores)				
Hits	45.52	13.02	56.01	2.32
False Alarms	36.76	20.52	52.67	4.05

[a] WISC = Wechsler Intelligence Scale for Children. [b] BRIEF = Behavior Rating Inventory of Executive Functioning. [c] BASC = Behavior Assessment System for Children [d] The inattentive/Overactive phenotype is derived from the average of the BASC inattention and hyperactivity subscale *T*-scores. [e] GDS = Gordon Diagnostic System.

For children in the IA group, the average scores from parental ratings of children's executive functioning and performance on a measure of sustained attention fell within normal limits for age. However, their mean performance on a measure of impulsivity was in the borderline range. As a group, the performance of the comparison children on measures of sustained attention and impulse control fell within normal limits (Table 1). As would be expected based on the study's exclusion criteria, parents of children in the comparison group reported no significant behavioral or emotional concerns. In contrast, parents of the IA children, as a group, reported scores that fell in the At-Risk range on all behavior scales, except for internalizing scores, which fell within normal limits for age (Table 1).

Bivariate analyses. Correlations between demographics, adoption specific data, parent ratings of emotional/behavioral and executive functioning, and children's performance on cognitive and executive functioning measures were carried out for the IA and comparison children. Correlations involving adoption specific variables (e.g., BRIEF) were carried out using data from the children in the IA group only, as these data were not collected form children in the comparison group.

Results of the correlational analyses revealed one significant association between maternal level of education and Gordon Diagnostic Systems (GDS) Vigilance Hits. This is an IA group only variable. Paradoxically, as maternal education increased, children's performance on the measure of sustained attention declined (Table 2). None of the other demographic characteristics for the IA sample, including age, gender, or dominant handedness, were significantly correlated with cognitive, executive, or behavioral/ emotional functioning. Therefore, these demographic variables were not evaluated further as potential covariates in the subsequent analyses of parent ratings of emotional/behavioral and executive functioning or children's performance on cognitive and executive functioning measures.

Table 2*: Summary of Intercorrelations Between Adoptions Specific Demographic Characteristics and Parent Ratings, and Neuropsychological Test Scores*

	Pearson Correlation Coefficient					
	Age	Sex	Duration in Institution	Maternal Education	Paternal Education	BMI [f]
WISC [a]						
Verbal Comprehension	.13	.00	.15	.02	-.01	.16
Perceptual Reasoning	.31	.15	.06	-.06	.04	.31
BRIEF [b]						
Behavioral Regulation	-.10	-.25	.30	.13	-.10	.04
Meta-Cognition	.24	-.23	.32	.16	-.08	.14
BASC [c]						
Internalizing	-.08	.22	.20	-.02	-.00	-.07
Externalizing	-.00	-.06	.20	-.13	.19	.02
Behavioral Symptoms	.06	-.11	.17	-.03	.09	-.19
I/O Phenotype [d]	.13	.06	.4	-.03	.05	-.08
GDS Vigilance [e]						
Hits	.13	.14	.05	-.50**	.02	.01
False Alarms	.14	.22	.09	-.21	.02	.25

Note. Duration of Institution, Region, Maternal and Paternal Education, BMI, and BRIEF data were only collected for internationally adopted children, thus these correlations only reflect the relationship between these variables for internationally adopted children.

[a] WISC = Wechsler Intelligence Scale for Children. [b] BRIEF = Behavior Rating Inventory of Executive Functioning. [c] BASC = Behavior Assessment System for Children [d] I/O = Overactive/Inattentive; The inattentive/Overactive phenotype is derived from the average of the BASC inattention and hyperactivity subscale *T*-scores. [e] GDS = Gordon Diagnostic System. [f] BMI = Body Mass Index.

$p < .05$; ** $p < .01$

Demographic and adoption specific data were also assessed for their intercorrelations with MR-DTI metrics (FA, ADC, and NPS) for the caudate to FP/DLPF tracks and amygdala/hippocampus to FP/TP/OF tracts for IA and comparison children. Correlations run on adoption specific variables (e.g., BRIEF) were based on data from children in the IA group only; these data were not collected form children in the comparison group.

Age was significantly and positively correlated with FA and ADC for the right caudate to FP tract, NPR for the left caudate to FP tract, FA and ADC for the right caudate to DLPF tract, ADC for the right amygdala/hippocampus to FP tract, and ADC for the right amygdala/hippocampus to TP tract. As DTI metrics for these tracts increased, so did age. Age was significantly and negatively correlated with NPR for the right caudate to DLPF and right amygdala/hippocampus to FP tracts, such that as these DTI metrics increased, age decreased. Length of time spent institutionalized was significantly positively correlated with NPR for the left caudate to FP tract, and FA for the left amygdala/hippocampus to OF tract. Children who spent more time institutionalized had higher scores on the listed DTI-metrics for these tracts. Maternal education was significantly and negatively correlated with FA for the left caudate to FP tract and significantly and positively correlated with ADC for the right amygdala/hippocampus to TP tract. Lastly, BMI was significantly and positively correlated with ADC for the right amygdala/hippocampus to TP tract (Table 3), such that as children’s BMI increased so did their ADC score for the right medial-temporal-TP tract. Based on these results age, duration of institutionalization, maternal education, and BMI were analyzed further as potential covariates.

Table 3: *Summary of Intercorrelations Between Adoptions Specific Demographics and MR-DTI Measures for Left and Right Hemisphere Striatal and Medial-Temporal Tracts.*

	Spearman R Correlation Coefficient					
	Age	Sex	Duration in Institution	Maternal Education	Paternal Education	BMI [f]
Caudate to FP [a]						
FA						
Right	.32*	.15	.11	-.05	.04	.24
Left	.21	.14	.08	-.38*	-.09	.05
ADC						
Right	.46**	.04	.24	-.14	-.05	-.01
Left	.13	.15	.19	-.09	-.19	.27
NPR						
Right	.17	-.16	.27	-.06	-.05	.29
Left	.46**	.10	.42*	-.11	-.27	-.06
Caudate to DLPF [b]						
FA						
Right	.40*	.21	.19	-.36	-.15	.29
Left	.10	.07	.09	-.46*	.09	-.24
ADC						
Right	.30	-.09	.14	.10	-.31	-.06
Left	-.21	.12	-.02.	-.16	.26	.00
NPR						
Right	-.39*	.26	-.36	.02	.02	-.32
Left	-.41**	.05	-.28	-.24	-.01	-.07
A/H [c] to FP [a]						
FA						
Right	.26	-.21	.33	-.17	-.11	.14
Left	-.10	-.22	-.15	-.22	-.10	-.25
ADC						
Right	.32*	-.18	.30	.12	-.20	.47*
Left	.06	-.17	.17	-.22	-.01	-.05
NPR						
Right	.36*	-.12	.28	.12	-.10	.37
Left	.24	.00	.20	-.11	-.08	-.03
A/H [c] to TP [d]						
FA						
Right	.15	.09	.15	-.23	.21	.06
Left	-.16	.01	-.18	-.25	.17	.06
ADC						
Right	.40*	-.05	.02	-.37*	-.12	.16
Left	.14	-.06	.10	.01	.08	.32

	Age	Sex	Duration in Institution	Maternal Education	Paternal Education	BMI
NPR						
Right	.00	.07	.11	-.16	-.10	-.31
NPR	.10	-.10	.27	-.08	-.19	-.32
A/H ^{c} to OF ^{e}						
FA						
Right	.10	-.22	.04	.19	.13	-.12
Left	.16	-.05	.50*	.16	-.02	-.01
ADC						
Right	.00	-.20	.00	.09	.02	.10
Left	.06	-.19	.29	.10	.01	-.02
NPR						
Right	.16	.05	.30	.19	.17	-.01
Left	.01	-.10	.33	.19	-.01	-.01

Note. Duration of Institution, Region, Maternal and Paternal Education, BMI, and BRIEF data were only collected for internationally adopted children, thus these correlations only reflect the relationship between these variables for internationally adopted children. FA = Fractional Anisotropy, ADC = Apparent Diffusion Coefficient, NPR = Normalized Probability Ratio

[a] FP = Frontal Pole; [b] DLPF = Dorsolateral Prefrontal Cortex; [c] A/H = Amygdala/ Hippocampus, [d] TP = Temporal Pole, [e] OF = Orbitofrontal, [f] BMI = Body Mass Index.

$p < .05$; ** $p < .01$

Variables were retained in the analyses as covariates when they met assumptions for use in Quade's Analysis of Covariance. Homogeneity of variance was met for all demographic and adoption specific variables for Internalizing Problems, Externalizing Problems, Behavioral Symptoms, Meta-Cognition, Behavioral Regulation, and Vigilance Hits. The test of homogeneity of variance for false alarm categories were significant for age, *Levene F* (2, 38) = 4.05 p = .03, thus age was not analyzed as a covariate for tracts differences for false alarm categories.

The relationship between cognitive functioning and parent ratings of emotional/behavioral and executive functioning and children's performance on cognitive and executive functioning measures was investigated in the adoption sample only. Performance on verbal reasoning tasks (VCI) for the IA group was significantly correlated with performance on visual-spatial reasoning tasks (PRI). Perceptual reasoning performance was significantly correlated with Externalizing Problems, Internalizing Problems, Behavioral Symptoms, I/O Phenotype, Behavioral Regulation, Vigilance Hits, and Vigilance False Alarms (Table 4).

Table 4: *Summary of Intercorrelations Between Cognitive Performance, and Parent Ratings and Neuropsychological Test Scores for the Adopted Group*

	Spearman R Correlation Coefficient	
	WISC Verbal Comprehension	WISC Perceptual Reasoning
WISC		
Verbal Comprehension	--	0.46**
Perceptual Reasoning	0.46**	--
BRIEF[a]		
Behavioral Regulation	-0.10	-0.36*
Meta-Cognition	-0.02	-0.34
BASC[b]		
Internalizing	-0.25	-0.60**
Externalizing	-0.09	-0.42**
Behavioral Symptoms	-0.17	-0.52**
I/O Phenotype[c]	-0.11	-0.49**
GDS[d] Vigilance		
Hits	0.01	0.39*
False Alarms	0.31	0.43*

Note. WISC = Wechsler Intelligence Scale for Children
[a] BRIEF = Behavior Rating Inventory of Executive Functioning. [b] BASC = Behavior Assessment System for Children [c] I/O = Overactive/Inattentive; The Inattentive/Overactive phenotype is derived from the average of the BASC inattention and hyperactivity subscale *T*-scores. [d] GDS = Gordon Diagnostic System.
* $p < .05$; ** $p < .01$.

The higher an IA child scored on nonverbal reasoning tasks, the better they performed on tasks of sustained attention and the fewer impulsive errors they made. Additionally, as IA children's performance on visual-spatial reasoning tasks improved, their parents reported fewer externalizing and internalizing problems, fewer behavioral symptoms, less inattention and/or hyperactivity, and better behavioral regulation. Performance on the Verbal Comprehension Index was not significantly correlated with scores on any executive performance tests or parent ratings (Table 4).

Parents of IA children rated them as having significantly more internalizing and externalizing problems than parents of comparison children (Table 5).

Table 5: *Differences Between Groups on Sample Characteristics, Parent Ratings, and Neuropsychological Test Scores.*

	Mean Rank			
	Adopted	Not Adopted	*U*	*z*
Age at testing	19.03	26.36	106.00	-1.74
Gender	20.70	23.50	156.00	-0.78
Handedness	22.60	18.75	147.00	-1.29
WISC				
Verbal Comprehension	17.25	32.13	52.50	-3.56***
Perceptual Reasoning	18.08	30.04	77.50	-2.86**
BASC ^{a}				
Internalizing	24.71	12.04	66.50	-3.08**
Externalizing	26.03	8.83	28.50	-4.19***
I/O Phenotype ^{b}	25.88	9.21	32.50	-4.06***

^{a} BASC = Behavior Assessment System for Children ^{b} I/O = Overactive/Inattentive; The inattentive/Overactive phenotype is derived from the average of the BASC inattention and hyperactivity subscale *T*-scores.
* $p < .05$; ** $p < .01$ ***$p < .001$

Aim 1 Results: Findings from Hierarchical Cluster Analysis

The first aim was to assess differences in cortical-striatal and cortical medial-temporal white-matter connectivity within the IA sample using a MR-DTI derived metric (normalized probability score).

Striatum. A cluster analysis was run based on the probability scores for connectivity between the right caudate and the whole cortex and the left caudate and the whole cortex for the 30 IA children. The hierarchical cluster analysis, using furthest neighbors, produced three clusters (Table 6).

Table 6: *Clusters based on Cortical-Striatal Probability Score*

	Left Caudate		Right Caudate	
	M	*SD*	*M*	*SD*
Adopted				
Group 1	.347	.045	.326	.054
Group 2	.162	.052	.383	.042
Group 3	.156	.061	.247	.048
Comparison				
Group 4	.243	.102	.325	.096

As shown in Figure 3, the first cluster was characterized by high connectivity in the *left* hemisphere (Group 1 “*Diffuse Left Striatal Connectivity;*” *n* = 7). The second cluster was characterized by high connectivity in the *right* hemisphere and low connectivity in the *left* hemisphere (Group 2 “*Mixed Striatal Connectivity;*” *n* = 9). The third cluster was characterized by low connectivity in the *left* and *right* hemispheres (Group 3 “*Low Striatal Connectivity;*” *n* = 12). Two children from the IA group, whose pattern of connectivity was characterized by more diffuse right connectivity (*M* = .448) did not fit into one of the three clusters and were excluded from further analysis based on the striatal groups.

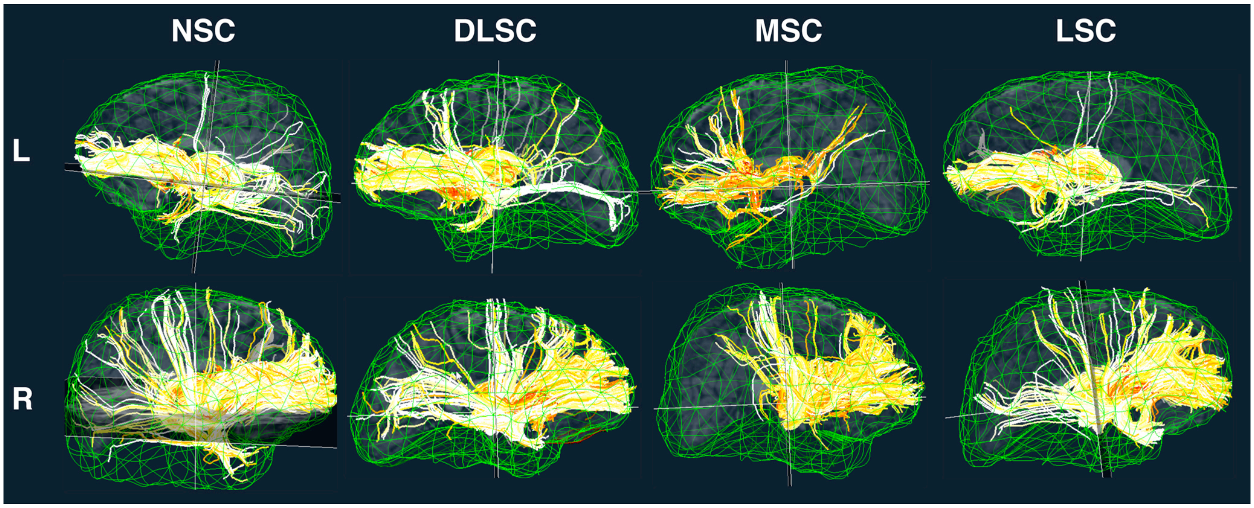

Figure 3. Distribution of probabilistic fiber tracts originating from the caudate in a comparison child (left) and children from the IA group; a diffuse left connectivity child (central left), a child from the mixed connectivity group (central right), and a child from the low connectivity group.

Medial-Temporal. A cluster analysis was run based on the probability data for connectivity between the hippocampus and amygdala and the whole cortex for the left and right hemispheres for the 30 IA children. A hierarchical cluster analysis using furthest neighbors produced two clusters (Table 7).

Table 7: *Clusters based on Medial-Temporal Probability Score*

	Left Hippocampus - Amygdala		Right Hippocampus-Amygdala	
	M	*SD*	*M*	*SD*
Adopted				
Group A	.684	.049	.727	.040
Group B	.602	.077	.669	.076
Comparison				
Group C	.617	.089	.678	.079

The first cluster, as shown in Figure 4 was characterized by high connectivity in *both* hemispheres (Group A "*Diffuse Medial-Temporal Connectivity;*" *n* = 17). The second cluster was characterized by no divergent connectivity (Group B "*Comparatively Normal Medial-Temporal Connectivity;*" *n* = 11). Two children in the IA group did not fit into either of the two clusters and were excluded from further analyses utilizing the medial-temporal groups. These two children showed patterns of higher diffuse connectivity in the left hemisphere (M = .879).

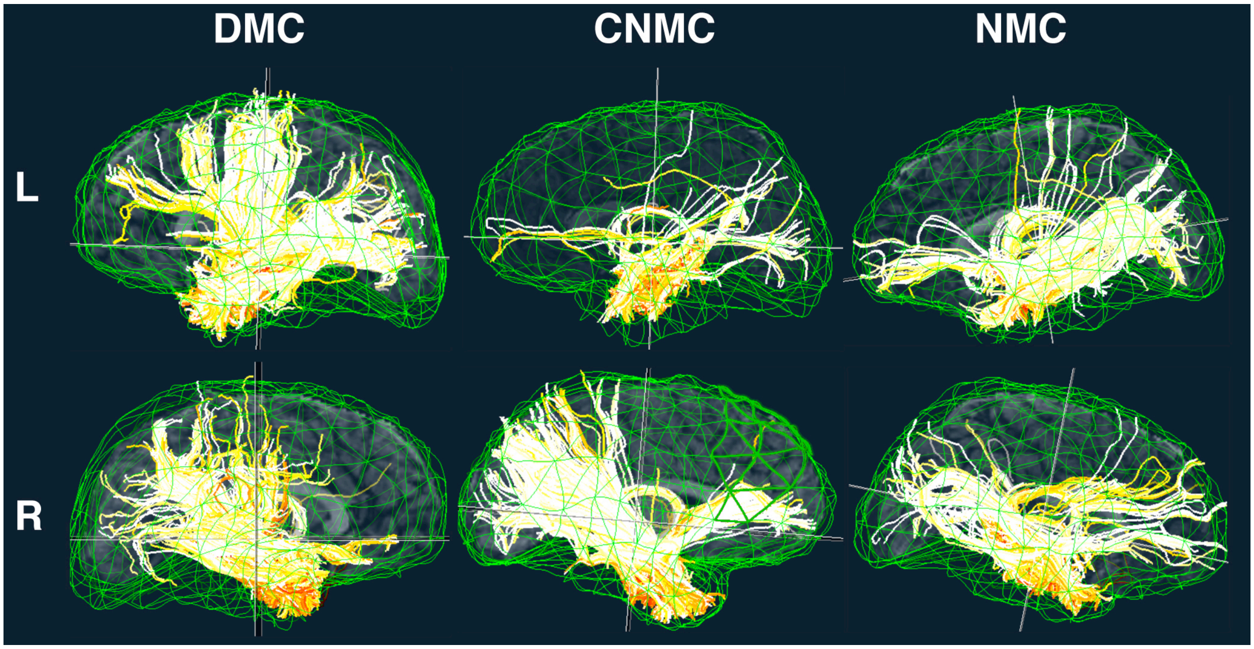

Figure 4. Distribution of probabilistic fiber tracts originating from the amygdala and hippocampus in a child from the IA diffuse connectivity group (left), an IA child from the comparably normal connectivity group (center) and a comparison child (right).

Aim 2 Results: Between Group Differences on Specific Striatal and Medial-Temporal Tracts

The second aim was to determine whether MR-DTI measures indicative of white matter connectivity and integrity differed between the groups for specific striatal and medial-temporal tracts in IA children with a history of early institutionalized rearing and/or the group of comparison children without a history of early institutionalization or adoption. The specific MR-DIT metrics used were: Fractional Anisotropy (FA), Apparent Diffusion Coefficient (ADC), and Normalized Probability Ratio (NPR).

Striatum. Kruskal-Wallis tests and Quade's Analysis of Covariate tests were conducted to evaluate for differences between groups in FA, ADC, and NPR for specific striatal pathways to the frontal pole (FP) and dorsolateral prefrontal cortex (DLPF). The three groups derived from striatal connectivity (DLSC, MSC, LSC), and the comparison group (NSC) were evaluated for mean rank changes or mean rank residual changes in FA, ADC, and NPR for tracts from the head of the caudate to the FP and DLPF for the right and left hemispheres.

There was a significant difference by group in FA between the right caudate and FP after controlling for the effect of age, *F* (2, 36) = 2.97, *p* = .04. There was no significant difference by group on FA for the right caudate and DLPF after controlling for age, *F* (3, 36) = 1.29, *p* = .29. There also was no significant effect by connectivity group after controlling for maternal education for the left caudate and FP, *F* (2, 25) = 1.85, *p* = .18, nor for the left caudate and DLPF, *F* (2, 25) = .57, *p* = .57. When this analysis was rerun without controlling for maternal education, there were no significant differences by group on FA for the left caudate and FP, χ^2 (3, *N* = 40) = 5.56, *p* = .13, or the left caudate and DLPF, χ^2 (3, *N* = 40) = 2.14, *p* = .54.

Multiple Quade's Analysis of Covariance tests were conducted to analyze for pair-wise differences between the groups for FA in the right caudate to FP pathway. None of the pair-wise comparisons between striatal groups differed significantly based on a Bonferroni correction, *p* > .008: DLSC and MSC, *F* (1, 14) = 2.87, *p* = .11; DLSC and LSC, *F* (1, 17) = 8.26, *p* = .01, DLSC and NSC, *F* (1, 17) = 1.99, *p* = .18; MSC and

LSC, *F* (1, 19) = 2.99, *p* = .10; MSC and NSC, *F* (1, 19) = .00, *p* = .99; LSC and NSM, *F* (1, 22) = 2.15, *p* = .16

There was a significant difference by group in the ADC score between the left caudate and FP, χ² (3, *N* = 40) = 12.84, p< .01. The right caudate and FP were not significantly different by group after controlling for age, *F* (3, 36) = 1.34, *p* = .28. There was no significant difference by group on the ADC score between the right caudate and DLPF, χ² (3, *N* = 40) = 4.35, *p* = .23.

Follow up Mann-Whitney U tests were conducted to analyze for pair-wise differences between the groups for ADC in the left striatal-frontal pathway. For the left caudate tract, mean rank ADC in the DLSC group was significantly higher than mean the rank ADC score for the MSC group, *U* (1) = 4.00*, z* = -2.91, *p* = .004. None of the other comparisons between the groups differed significantly (Bonferroni *p* > .008): DLSC and LSC, *U* (1) = 14.00*, z* = -2.36, *p* = .02; DLSC and NSC, *U* (1) = 36.00*, z* = -.51, *p* = .61; MSC and LSC, *U* (1) = 86.00*, z* = -.92, *p* = .36; MSC and NSC, *U* (1) = 65.00*, z* = -2.42, *p* = .02; LSC and NSM, *U* (1) = 34.00*, z* = -2.19, *p* = .03.

There were no significant differences by group on the NPR between the right caudate and FP, χ² (3, *N* = 40) = 2.71, *p* = .44. There also was no significant effect of group on NPS after controlling for age for the right caudate and DLPF, *F* (3, 36) = .61, *p* = .61, or the left caudate and DLPF, *F* (3, 36) = 2.79, *p* = .06.

Medial-temporal. Kruskal-Wallis and Quade’s Analysis of Covariance tests were conducted to evaluate for differences between groups in FA, ADC, and NPR for specific medial-temporal tracts to the FP, temporal pole (TP), and orbitofrontal (OF) regions. The two groups derived from medial-temporal connectivity (DMC, CNMC) and the comparison group (NMC) were evaluated for mean rank changes or mean rank residual changes in FA, ADC, and NPR for tracts from the amygdala/hippocampus to the FP and DLPF for the right and left hemispheres.

There were significant differences by group in FA between the left hippocampus/ amygdala and FP, χ^2 (2, $N = 40$) = 6.52, $p = .04$, and left amygdala/hippocampus and TP, χ^2 (2, $N = 40$) = 6.56, $p = .04$. The left amygdala/hippocampus and OF region did not differ by groups on FA after controlling for duration of institutionalization, F (1, 26) = 2.78, $p = .11$, nor did is differ when not controlling for duration, left hippocampus/ amygdala and OF region, χ^2 (3, $N = 40$) = 2.03, $p = .36$. There were no significant differences by group on FA for the right amygdala/hippocampus connection to the FP, χ^2 (2, $N = 40$) = 1.07, $p = .59$, or TP, χ^2 (2, $N = 40$) = .49, $p = .78$.

Multiple Mann-Whitney U tests were conducted to analyze for pair-wise differences (Bonferroni correction, $p < .017$). For the left amygdala/hippocampus to TP tract mean rank FA was not significantly different between DMC and CNMC, U (1) = 57.00, $z = -1.71$, $p = .09$, or DMC and NMC, U (1) = 74.00, $z = -1.24$, $p = .23$. The CNMC and NMC groups, U (1) = 27.00, $z = -2.40$, $p = .016$, however did significantly differ, where mean rank FA was higher for the NMC group than the CNMC group. For the left amygdala/hippocampus to FP tract mean rank FA in the NMC group is not significantly different form the CNMC, U (1) = 30.00, $z = -2.24$, $p = .02$, or DMC groups, U (1) = 53.00, $z = -2.19$, $p = .03$. Additionally, the two IA groups did not differ, U (1) = 74.00, $z = -.56$, $p = .57$.

There were no significant differences by group on mean rank ADC scores between the right amygdala/hippocampus and TP after controlling for age and maternal education, F (1, 26) = .01, p = .92, but there was an effect of group on the ADC score when only controlling for age, F (1, 37) = 3.77, p = .03. There were no significant between group difference in mean rank ADC score between the left amygdala/ hippocampus and OF, χ^2 (2, N = 40) = 1.03, p = .60, or left amygdala/hippocampus TP, χ^2 (2, N = 40) = 5.70, p = .06.

Multiple Quade's Analysis of Covariance tests were conducted to analyze for pair-wise differences between the groups for ADC in the right amygdala/hippocampus to TP pathway. ADC was significantly different between the CNMC and NMC groups, F (1, 21) = 7.40, p = .013, based on a Bonferroni correction, p > .017, where the NMC group had a higher ADC than then CNMC group. The pair-wise comparisons between the other groups were not significantly different: DMC and CNMC groups, F (1, 26) = .40, p = .54, and the DMC and NMC groups, F (1, 27) = 4.98, p = .03.

There was a significant differences by group for the NPR between the right amygdala/hippocampus and TP, χ^2 (2, N = 40) = 6.25, p = .04. There were no significant differences by group for on the NPR between the left amygdala/hippocampus and FP, χ^2 (2, N = 40) = 2.50, p = .29, or left amygdala/hippocampus, TP, χ^2 (2, N = 40) = 4.57, p = .10. There also was not a significant effect of group on NPR after controlling for age for the right amygdala/hippocampus and FP tract, F (1, 37) = .33, p = .72

Multiple Mann-Whitney U tests were conducted to analyze for pair-wise differences between the groups for NPR in the right amygdala/hippocampus to TP tract. For this tract the mean rank NPR group was not significantly different from the NMC group's NPR for right hippocampus/amygdala to TP, U (1) = 33.00, z = -2.03, p < .04, nor was it different from the DMC group, U (1) = 44.00, z = -2.33, p = .02, Furthermore, the DMC and CNMC groups also were not significantly different on the NPR for this tract, ($p < .017$), U (1) = 43.00, $z = -2.11$, $p = .04$, based on the Bonferroni correction.

Aim 3 Results: Relationship between Connectivity Groups and Parent Ratings of Child Behavior

The third aim of this study was to evaluate whether MR-DTI data were associated with children's psychosocial outcomes. Specifically, parental reports of behavior problems were evaluated for any associations with connectivity and integrity of the striatal and medial-temporal tracts in the post institutionalized groups and comparison group.

Internalizing. Striatal IA groups (DLSC, MSC, LSC) and the comparison group (NSC) were analyzed for differences in parent reported internalizing symptoms. For striatal subgroups a one-way ANOVA of parent ratings on internalizing problems revealed a statistically significant main effect, *Welch's F* (3, 16.37) = 6.14, $p < .01$, indicating that striatal subgroups differed on parental ratings of internalizing problems. Post hoc comparisons using Games-Howell post hoc procedures were conducted to determine if specific groups significantly differed. The comparison group (NSC) significantly differed from the DLSC & MSC groups, such that parents in the NSC group reported fewer internalizing symptoms, on average, than parents in the DLSC and MSC groups. However, parent ratings of internalizing symptoms in the NSC group were not significantly different from parent rating of internalizing symptoms in the LSC group. None of the IA groups differed significantly (Table 8).

Table 8

Parent Report of Behavior and Executive Functioning Measures Grouped by Striatal Groups

	Striatal Groups									
	Group1 [c]		Group 2 [d]		Group 3 [e]		Group 4 [f]		Difference Statistic	
Outcome Measures	*(n)*	*Mean ± SD*	*(n)*	*Mean ± SD*	*(n)*	*Mean ± SD*	*(n)*	*Mean ± SD*	*F*	Games-Howell
BASC [a]										
Internalizing	7	64.29±15.54	9	56.44±10.45	12	55.00±16.67	12	42.83±8.06	4.60**	4 < 1; 4 < 2
Externalizing	7	68.57±9.27	9	62.33±12.39	12	60.67±11.83	12	43.67±8.32	10.33***	4 < 1; 4 < 2; 4 < 3
Inattentive/Overactive	7	65.86±11.20	9	65.55±13.33	12	61.95±13.35	12	43.00±7.03	9.83***	4 < 1; 4 < 2; 4 < 3
BRIEF [b]										
Meta-Cognition	7	62.43±10.47	9	68.78±12.33	12	61.42±15.67		--	0.87	
Behavioral Regulation	7	61.00±14.28	9	67.33±15.78	12	63.25±16.67		--	0.35	

[a] BASC = Behavior Assessment System for Children, [b] BRIEF = Behavior Rating Inventory of Executive Functioning, [c] Group 1 = Diffuse Left Striatal Connectivity [d] Group 2 = Mixed Striatal Connectivity, [e] Group 3 = Low Striatal Connectivity, [f] Group 4 = Normal Striatal Connectivity

* $p < .05$; ** $p < .01$, *** $p < .001$

Next, medial-temporal subgroups (DMC, CNMC) and the comparison group (NMC) were analyzed for differences in parent reports of internalizing symptoms. For medial-temporal groups, a one-way ANOVA of parent ratings of internalizing problems revealed a statistically significant main effect, *Welch's F* (2, 21.65) = 7.65, *p* = .003, indicating that medial-temporal groups differed on parental ratings of internalizing problems. Post hoc comparisons using Games-Howell post hoc procedures were conducted to determine if specific groups significantly differed. The comparison group (NMC) significantly differed from the two IA groups (DMC & CNMC). The IA groups were not significantly different (Table 9).

Externalizing. Striatal IA groups (DLSC, MSC, LSC) and the comparison group (NSC) were analyzed for differences in parent reported externalizing symptoms. For striatal groups the one-way ANOVA of parent ratings on externalizing problems revealed a statistically significant main effect, *Welch's F* (3, 17.75) = 13.37, *p* < .001, indicating that the striatal groups differed on parental ratings of externalizing problems. Post hoc comparisons using Games-Howell post hoc procedures were conducted to determine if specific pairs of groups significantly differed. The comparison group (NCS) was significantly different from the three IA groups (DLCS, MSC, & LSC), such that parents in the NSC group reported fewer externalizing symptoms, on average, than parents in DLSC MSC and LSC groups. None of the IA groups differed significantly from one another on parent reported externalizing problems (Table 8).

Next, medial-temporal IA groups (DMC, CNMC) and the comparison group (NMC) were analyzed for differences in parent reported externalizing symptoms. For medial-temporal groups a one-way ANOVA of parent ratings of externalizing problems revealed a statistically significant main effect, *Welch's F* (2, 22.88) = 17.42, *p* < .001, indicating that the medial-temporal groups differed on parental ratings of externalizing problems. Post hoc comparisons using Games-Howell post hoc procedures were conducted to determine if specific pairs of groups were significantly different from one another. The comparison group (NMC) significantly differed from the two IA groups (DMC & CNMC), such that parents in the NMC group reported fewer externalizing problems than parents of children in either IA group. The IA groups did not significantly differ from one another on parent reported externalizing problems (Table 9).

Inattentive/Overactive Phenotype. Striatal IA groups (DLSC, MSC, LSC) and the comparison group (NSC) were analyzed for differences in parent reported inattentive/overactive symptoms (I/O phenotype). For striatal groups the one-way ANOVA of parent ratings on the I/O phenotype revealed a statistically significant main effect, *Welch's F* (3, 16.60) = 14.30, *p* < .001, indicating that the striatal groups differed on parental ratings of I/O phenotype. Post hoc comparisons using Games-Howell post hoc procedures were conducted to determine if pairs of groups significantly differed between each other on parent reported I/O symptoms. The comparison group (NSC) significantly differed from the three IA groups (DLSC, MSC, & LSC), such that parents in the NSC group reported fewer I/O symptoms, on average, than the parents in DLSC MSC and LSC groups. None of the IA groups differed significantly from one another on parent reported I/O symptoms (Table 8).

Next, medial-temporal IA groups (DMC, CNMC) and the comparison group (NMC) were analyzed for differences in parent reported I/O symptoms. For medial-temporal groups the one-way ANOVA of parent ratings of the I/O phenotype revealed a statistically significant main effect, *Welch's F* (2, 21.58) = 23.75, *p* < .001, indicating that the medial-temporal groups differed on parental ratings for the I/O phenotype. Post hoc comparisons using Games-Howell post hoc procedures were conducted to determine pairwise between group differences. The comparison group (NMC) was significantly different from the two IA groups (DMC, CNMC), such that parents in the NMC group reported fewer externalizing problems, on average, than parents of children in either IA group. None of the IA groups differed significantly from one another on parent reported I/O symptoms (Table 9).

Meta-Cognition. Striatal derived IA groups (DLSC, MSC, LSC) were analyzed for differences in parent reported Meta-Cognition. Results of the one-way ANOVA of parent ratings of meta-cognition revealed no statistically significant main effect, *Welch's F* (2, 16.05) = .87, *p* = .44. These results indicated that parent ratings of meta-cognition are similar for the three striatal derived IA groups (Table 8).

Medial-temporal derived IA groups (DMC, CNMC) were analyzed for differences in parent reported Meta-Cognition. Results of the one-way ANOVA of parent ratings of Meta-Cognition revealed no statistically significant main effect, *Welch's F* (1, 21.42) = .03, *p* = .87. These results indicated that parental ratings of meta-cognition were not different between the two medial-temporal IA groups (Table 9).

Behavioral Regulation. Striatal derived IA groups (DLSC, MSC, LSC) were analyzed for differences in parent reported Behavioral Regulation. Results of the one-way ANOVA of parent ratings of Behavioral Regulation revealed no statistically significant main effect, *Welch's F* (2, 15.30) = .35, *p* = 71. These results indicated that striatal groups derived for IA children were not significantly different from one another on parental ratings of Behavioral Regulation (Table 8).

Table 9

Parent Report of Behavior and Executive Functioning Measures Grouped by Medial Temporal Groups

	Medial Temporal Groups							
	Group A[c]		Group B[d]		Group C[e]		Difference Statistic	
Outcome Measures	*(n)*	*Mean* ± *SD*	*(n)*	*Mean* ± *SD*	*(n)*	*Mean* ± *SD*	*F*	Games-Howell
BASC[a]								
Internalizing	17	57.88±16.33	10	56.20±11.77	12	42.83±8.06	7.65***	C < A; C < B
Externalizing	17	65.59±13.05	10	62.20±9.01	12	43.67±8.27	17.42**	C < A; C < B
Inattentive/ Overactive	17	64.38±13.19	10	64.40±10.34	12	43.00±7.03	23.75***	C < A; C < B
BRIEF[b]								
Meta-Cognition	17	64.76±13.47	11	63.91±13.54		--	1.12	
Behavioral Regulation	17	66.65±16.01	11	60.64±13.74		--	0.03	

[a] BASC = Behavior Assessment System for Children, [b] BRIEF = Behavior Rating Inventory of Executive Functioning, [c] Group A = Diffuse Medial-Temporal Connectivity [d] Group B = Comparatively Normal Medial-Temporal Connectivity, [e] Group C = Normal Medial-Temporal Connectivity

* $p < .05$; ** $p < .01$, *** $p < .001$

Next, medial-temporal derived IA groups (DMC, CNMC) were analyzed for differences in parent reported Behavioral Regulation. Results of the one-way ANOVA of parent ratings of Behavioral Regulation revealed no statistically significant main effect, *Welch's F* (1, 23.81) =1 .12, p = .30. These results indicated that parental ratings of Behavioral Regulation in the medial-temporal IA groups were not significantly different from one another (Table 9).

Parent Ratings and Striatal and Medial-Temporal Tracts

These analyses were only conducted only for the striatal and medial-temporal tract that significantly differed between cluster-derived groups in the prior analyses.

Internalizing. Kruskal-Wallis and Quade's Analysis of Covariate tests were conducted to evaluate for group differences in median change connectivity scores (FA, ADC, NPR) based on level of internalizing problem (Normal, n = 12; IA Normal, n = 19; Not Normal, n = 10). The At-Risk (n = 3) and Clinically Significant (n = 7) were combined to create the "Not Normal" group.

FA was significantly different based on level of internalizing problem for the left amygdala/hippocampus to FP, χ^2 (2, N = 41) = 7.22, p = .03, but not for the left amygdala/hippocampus to TP, χ^2 (2, N = 41) = 2.89, p = .29. NPS also was not significantly different between groups for level of internalizing problem in the right amygdala/hippocampus to TP tract, χ^2 (2, N = 41) = .42, p = .81, nor was ADC different in the left caudate to FP tract based on level of internalizing problem, χ^2 (2, N = 41) = 4.02, p = .13. After controlling for age there was a significant effect on internalizing problem for ADC in the right amygdala/hippocampus to TP tract F (2, 38) = 4.14, p = .02, but not for FA in the right caudate to FP tract, F (2, 38) = 0.46, p = .63.

Mann-Whitney U tests were conducted to evaluate for pair-wise differences between the groups. For the left amygdala/hippocampus to FP tract mean rank FA was not significantly different for the Not Normal group as compared to the IA Normal, *U* (1) = 64.00, *z* = -1.44, *p* = .15, and Normal group, *U* (1) = 41.00, *z* = -1.26, *p* = .21. The Normal group was, however, different from the IA Normal group, *U* (1) = 52.00*, z* = -2.54, *p* = .011, based on the Bonferroni correction (*p* < .017). Additionally, multiple Quade's Analysis of Covariance tests were conducted to analyze for pair-wise differences between the groups for ADC in the right amygdala/hippocampus to TP pathway when controlling for age. ADC was significantly different between the Normal and Not Normal, *F* (1, 21) = 12.51, *p* = .002. The pair-wise comparisons between the IA Normal and Not Normal groups *F* (1, 26) = 2.46, *p* = .13, and Normal and IA Normal groups, *F* (1, 30) = 3.06, *p* = .09, however, were not significantly different based on a Bonferroni correction, *p* > .017.

Externalizing. Kruskal-Wallis and Quade's Analysis of Covariate tests were conducted to evaluate for differences in median change connectivity scores (FA, ADC, NPR) based on level of externalizing problem (Normal, *n* = 12; IA Normal, *n* = 10; At-Risk, *n* = 12; Clinically Significant, *n* = 7).

Controlling for the effect of age, there was a significant effect on externalizing problem on ADC in the right amygdala/hippocampus to TP tract, *F* (3, 36) = 6.02, *p* = .006, but not on FA for the right caudate to FP, *F* (3, 37) = .24, *p* = .87. Level of externalizing problem did not significantly differ on NPS in the right amygdala/hippocampus to TP tract, χ^2 (3, *N* = 41) = 1.79, *p* = .62. Level of externalizing problems were not significantly different on FA for the left amygdala/hippocampus to

TP, χ^2 (3, N = 41) = 7.59, p = .06, or left amygdala/ hippocampus to FP tract, χ^2 (2, N = 41) = 6.02, p = .11. The ADC in the left caudate to FP tract, χ^2 (3, N = 41) = 6.54, p = .08, was also not significantly different.

Multiple Quade's Analysis of Covariance tests were conducted to analyze for pair-wise differences between the groups for ADC in the right amygdala/hippocampus to TP pathway when controlling for age. Except for the Normal and Clinically Significant groups, F (1, 16) = 9.50, p = .007, none of the groups differed significantly based on a Bonferroni correction, p > .008: Normal and IA Normal, F (1, 19) = .83, p = .37; Normal and At-Risk, F (1, 22) = 8.05, p = .01; IA Normal and At-Risk, F (1, 19) = 2.31, p = .14; IA Normal and Clinically Significant, F (1, 13) = 3.87, p = .07; At-Risk and Clinically Significant, F (1, 16) = 1.05, p = .32.

Behavioral Symptoms. Kruskal-Wallis and Quade's Analysis of Covariates tests were conducted to evaluate for differences in median change connectivity scores (FA, ADC, NPR) based on level of behavioral problem (Normal, n = 12; IA Normal, n = 12; At-Risk, n = 7, Clinically Significant, n = 10).

After controlling for the effect of age, there was a significant effect of level of behavioral symptom by ADC in the right amygdala/hippocampus to FP tract, F (3, 37) = 3.64, p = .02. FA was significantly different based on level of behavioral symptom for the left amygdala/hippocampus to FP tract, χ^2 (3, N = 41) = 8.02, p = .05, but not for the left amygdala/hippocampus to TP tract, χ^2 (3, N = 41) = 3.26, p = .35. There also was not a significant difference in level of behavioral symptom on ADC in the left caudate to FP tract, χ^2 (3, N = 41) = 5.18, p = .15, or NPS in the right amygdala/hippocampus to TP tract, χ^2 (2, N = 41) = 1.30 p = .73. After controlling for the effect of age, there was not a significant effect on behavioral symptom by FA in the right caudate to FP tract, *F* (3, 37) = .41, *p* = .74.

Multiple Quade's Analysis of Covariance tests were conducted to analyze for pair-wise differences between the groups for ADC in the right amygdala/hippocampus to TP pathway when controlling for age. Except for the Normal and Clinically Significant groups, *F* (1, 19) = 9.26, *p* = .007, ADC was not significantly different between the groups based on level of Behavioral Symptoms (Bonferroni correction, *p* > .008): Normal and IA Normal, *F* (1, 21) = 2.58, *p* = .10; Normal and At Risk, *F* (1, 17) = 5.02, *p* = .04; IA Normal and At-Risk, *F* (1, 16) = .88, *p* = .36; IA Normal and Clinically Significant, *F* (1, 18) = 2.13, *p* = .16; At-Risk and Clinically Significant, *F* (1, 16) = .88, *p* = .36. Multiple Mann-Whitney U tests were conducted to analyze for pair-wise differences in FA for the left amygdala/hippocampus to FP based on groups derived from level of Behavioral Symptoms. FA was not significantly different between the groups based on level of Behavioral Symptoms (Bonferroni correction, *p* > .008): Normal and IA Normal, *U* (1) = 42.00, *z* = -1.74, *p* = .08; Normal and At Risk, *U* (1) = 14.00, *z* = -2.43, *p* = .02, Normal and Clinically Significant, *U* (1) = 37.00, *z* = -1.52, *p* = .12, IA Normal and At-Risk, *U* (1) = 24.50, *z* = -1.54, *p* = .12; IA Normal and Clinically Significant *U* (1) = 59.50, *z* = -.03, *p* = .97; At-Risk and Clinically Significant, *U* (1) = 17.50, *z* = -1.75, *p* = .08.

I/O Phenotype. Kruskal-Wallis and Quade's Analysis of Covariate tests were conducted to evaluate for differences in median change connectivity scores (FA, ADC, NPR) based on I/O Phenotype group (Normal, *n* = 12; IA Normal, *n* = 5; At-Risk *n* = 8; Clinically Significant, *n* = 15).

There was no significant difference in FA based on level of I/O phenotype significantly for the left amygdala/hippocampus to FP tract, χ^2 (2, *N* = 41) = 7.20, *p* = .07 or the left amygdala/hippocampus to TP tract, χ^2 (3, *N* = 41) = 5.51, *p* = .14. There also was not a significant effect of level of I/O phenotype on ADC in the left caudate to FP tract, χ^2 (3, *N* = 41) = 6.11, *p* = .11, or for NPS in the right amygdala/hippocampus to TP tract, χ^2 (3, *N* = 41) = .63, *p* = .89. After controlling age there was no significant effect of I/O phenotype level on FA in the right caudate to FP tract, *F* (3, 37) = .22, *p* = .88. The relationship between level of I/O phenotype and ADC for the left amygdala/hippocampus to TP after controlling for age could was not reported due to heterogeneity of variance, *Levene F* (3, 37) = 3.41 *p* = .02.

Meta-Cognition. Mann Whitney U and Quade's Analysis of Covariate tests were conducted to evaluate for differences in median change connectivity scores among IA children based on level of Meta-Cognition (IA Normal, *n* = 14; Clinically Significant, *n* = 16) for connectivity scores (FA, ADC, NPR).

Children who were categorized as Normal and Clinically Significant on Meta-Cognition were not significantly different on any connectivity measures for the evaluated medial-temporal or striatal tracts. Specifically, level of Meta-Cognition was not significantly different on FA for the left amygdala/hippocampus to FP tract, *U* (1) = 83.00, *z* = -1.22, *p* = .22, or the left amygdala/hippocampus to TP tract, *U* (1) = 93.50, *z* = -.77, *p* = .44. There also was no significant effect of level of Meta-Cognition on ADC in the left caudate to FP tract, *U* (1) = 73.00, *z* = -1.62, *p* = .11, or on NPR in the right amygdala/ hippocampus to TP tract, *U* (1) = 101.00, *z* = -.46, *p* = .65. After controlling for age, there was no significant effect of level of Meta-Cognition on FA in the right caudate to FP tract, *F* (2, 28) = .60, *p* = .45.

Behavioral Regulation. Mann Whitney U and Quade's Analysis of Covariate tests were conducted to evaluate for differences in median change connectivity scores was conducted to evaluate differences among IA children based on level of Behavioral Regulation (IA Normal, *n* = 14; Clinically Significant, *n* = 16) on connectivity scores (FA, ADC, NPR).

Children who were categorized as Normal and Clinically Significant on Behavioral Regulation did not significantly differ on connectivity measures for any evaluated medial-temporal or striatal tracts. Analyses showed that level of Behavioral Regulation was not significantly different on FA for the left amygdala/hippocampus to FP tract, *U* (1) = 88.00, *z* = -1.01, *p* = .31, or the left amygdala/hippocampus to TP tracts, *U* (1) = 106.50, *z* = -.23, *p* = .82. There also was no significant effect of level of Behavioral Regulation on ADC in the left caudate to FP, *U* (1) = 83.00, *z* = -1.21, *p* = .23, or on NPR in the right amygdala/hippocampus to TP tract, *U* (1) = 106.00, *z* = -.25, *p* = .80. After controlling for the age, there was no significant effect on level of Behavioral Regulation on FA in the right caudate to FP tract, *F* (2, 28) = .19, *p* = .67.

Aim 4 Results: Children's Executive Functioning Performance for Striatal and Medial-Temporal Tracts

The fourth aim of the study was to determine whether differences in the striatal and medial-temporal tracts in the proposed IA groups and comparison group were associated with behavioral measures of sustained attention (Gordon Diagnostic Systems; Vigilance Hits) and impulsivity (Gordon Diagnostic Systems; Vigilance False

Alarm). Analyses used connectivity scores only for striatal and medial temporal tracts that significantly differed based on the cluster-derived groups.

Sustained Attention. Kruskal-Wallis and Quade's Analysis of Covariance tests were conducted to evaluate the relationship between performance on Vigilance Hits (Normal, $n = 12$; IA Normal, $n = 22$; Not Normal, $n = 7$) and connectivity scores (FA, ADC, NPR) for all children in this study. Few children performed in the Borderline ($n = 4$) or Abnormal ($n = 3$) range, thus these two categories were collapsed into a single "Not Normal" category.

After controlling for the effect of age, there was a significant effect of level of performance on Vigilance Hits on FA in the right caudate to FP tract, $F\ (2, 38) = 4.28$, $p = .02$, and on ADC in the right amygdala/hippocampus to TP tract, $F\ (1, 38) = 4.74$, $p = .02$. There was no significant effect of level of performance on Vigilance Hits on NPS in the right amygdala/hippocampus to TP tract, $\chi^2\ (2, N = 41) = 2.05$, $p = .36$. Performance level on Vigilance Hits was not significantly different on FA for the left amygdala/hippocampus to FP tract, $\chi^2\ (2, N = 41) = 5.95$, $p = .051$, or the left amygdala/hippocampus to TP tracts, $\chi^2\ (2, N = 41) = 3.39$, $p = .18$. There also was no significant effect of level of sustained attention on ADC in the left caudate to FP tract, $\chi^2\ (2, N = 41) = 4.56$, $p = .10$.

Multiple Quade's Analysis of Covariance tests were conducted to analyze for pair-wise differences between the groups for ADC in the right amygdala/hippocampus to TP pathway and FA for the right caudate to FP pathway when controlling for age. Except for the Normal and Not Normal groups, $F\ (1, 17) = 15.50$, $p = .001$, ADC was not significantly different between the groups based on level of Vigilance Hits performance

(Bonferroni correction, *p* > .017): Normal and IA Normal, *F* (1, 32) = 3.57, *p* = .07; IA Normal and Not Normal, *F* (1, 27) = 2.46, *p* = .13. Except for the IA Normal and Not Normal groups, *F* (1, 27) = 9.79, *p* = .004, FA was not significantly different between the groups based on level of Vigilance Hits performance: Normal and IA Normal, *F* (1, 32) = .59, *p* = .45; Normal and Not Normal, *F* (1, 17) = 3.67, *p* = .07.

Impulsivity. Kruskal-Wallis and Quade's Analysis of Covariance tests were conducted to evaluate the relationship between performance on Vigilance False Alarm (Normal, *n* = 12; IA Normal, *n* = 14; Not Normal, *n* = 15) and connectivity scores (FA, ADC, NPR) for all children in this study. Few children performed in the Borderline (*n* = 3) range, thus it was collapsed into the Abnormal (*n* = 12) range category to create a single "Not Normal" category. Analyses that used age as a covariate were not run for this variable as these they did not meet test assumptions for use in Quade's Analysis of Covariance.

Performance level for Vigilance False Alarm was not significantly different on FA for the left amygdala/hippocampus to FP tract, χ^2 (2, *N* = 41) = 5.92, *p* = .052, or the left amygdala/ hippocampus to TP tract, χ^2 (2, *N* = 41) = 2.31, *p* = .32. There also was no significant effect for level of impulsivity on ADC in the left caudate to FP tract, χ^2 (2, *N* = 41) = 3.91, *p* = .14, or NPS in the right amygdala/hippocampus to TP tract, χ^2 (2, *N* = 41) = .58, *p* = .74.

Aim 5 Results: Parent Reports of Child Behavior and Adoption-Specific Variables

The fifth aim of this study was to determine whether the consistently reported findings for child behavior problems prior in IA samples could be identified in this sample, and whether adoption-specific variables, such as age at adoption, duration in adoptive home, and country of origin, were associated with parent reports of behavior problems.

Rate of behavior problems. A *chi-square* test of goodness-of-fit was performed to determine whether the proportion of IA children in this sample who were rated by their parents as having behavioral/emotional problems were greater than the rate expected based on the normative sample. Based on published age norms two percent of children were expected to fall in to the “Clinically Significant” category (*T*-score: >69) and 14 percent of children were expected to fall in the “At-Risk” category (*T*-score: 60-69). The number of IA children in each internalizing problems category was significantly different from rates expected in a normative sample, χ^2 (2, n = 29) = 336.29, $p < .001$. Similarly, the number of IA children in each externalizing category was significantly different from the rate expected in a normative sample, χ^2 (2, n = 29) = 131.42, $p < .001$. Lastly, the number of IA children in each category for behavioral symptoms was significantly different from the rate expected in a normative sample, χ^2 (2, n = 29) = 109.04, $p < .001$. Overall a higher percentage of IA children were classified in the Clinically Significant and At-Risk categories and a lower percentage of IA children were classified in the Normal category than might be expected based on published age norms for this instrument.

A *chi-square* test of goodness-of-fit was performed to determine whether the proportion of children in the IA sample who were rated by their parents as having the I/O phenotype or behavioral/emotional problems was consistent with rates reported in previous studies of IA children. The number of children categorized as having the I/O phenotype was consistent with reports in prior research, χ^2 (1, n = 29) = 0.188, p = .83

(Jacobs et al. 2010; Zeanath et al., 2009). Although 43.5% of parents in the current study reported that their child exhibited at least one emotional or behavioral problem, the rate of problems did not significant differ from the slightly lower rates reported in prior studies, χ^2 (1, N=29) = 4.31, $p = .06$ (Ames et al., 1997; Behen et al., 2008; Rutter et al., 2001).

Age at adoption. A Kruskal-Wallis test was conducted to evaluate the relationship between median changes in BRIEF and BASC scores based on age at the time of adoption (<18 months, 18 to 24 months, ≥25 months). Age categorizations were based on sensitivity periods suggested in prior studies on IA children (Gunner et al, 2007; Kreppner, et al., 2007; Merz & McCall, 2010; Stevens et al., 2008;). Age at adoption was not significantly associated with differences in behavioral regulation, meta-cognition, externalizing problems, or internalizing problems (Table 10).

Table 10: *Kruskal-Wallis Analysis Identifying Differences in Emotional/Behavioral Problems and Executive Functioning from Age at Adoption*

	Mean Rank			
	Age Groups (months)			χ^2
	<18	18-24	> 24	
BASC[a]				
Internalizing	15.42	11.31	18.00	2.54
Externalizing	14.12	15.94	15.50	0.27
I/O Phenotype[a]	14.27	14.25	16.94	0.57
BRIEF[a]				
Behavioral Regulation	15.15	13.63	17.67	0.93
Meta-Cognition	14.46	14.88	17.56	0.71

[a] BASC = Behavior Assessment System for Children [b] I/O = Overactive/Inattentive;
[c] BRIEF = Behavior Rating Inventory of Executive Functioning
* p < .05; ** p < .01

Duration in adoptive home. Contrary to predictions, children's length of time in the adopted home was not related to differences in the level of behavioral problems (Normal, At-Risk, Clinically Significant) for either internalizing, χ^2 (2, *n* = 29) = 1.43, *p* = .49, or externalizing problems, χ^2 (2, *n* = 29) = 0.18, *p* = .91. Similarly and consistent with expectations, level of behavioral symptoms were not related to time in the adoptive home, χ^2 (2, *n* = 29) = 1.05, *p* = .59.

Country of Origin. The majority of the children in this study were from (Eastern Europe). Due to restricted sample sizes for other regions (i.e., East Asia and South America), potential differences in emotional/behavioral problem or subgroup categorization based on the child's region of origin could not be analyzed.

Aim 6 Results: Adoption Specific Variables and Their Association with Striatal and Medial-Temporal Groups

The sixth aim was to evaluate whether different patterns of white-matter connectivity, based on MR-DTI metrics were associated with orphanage- and adoption-specific variables (i.e., age at adoption, duration in adoptive home) among IA children.

Age at Adoption. A Kruskal-Wallis test was conducted to evaluate differences among children based on striatal groups (DLSC, MSC, & LSC) and median change in age at adoption. Striatal groups were not associated with differences in age at adoption, χ^2 (2, *n* = 28) = 1.06, *p* = .58. Similarly the Mann-Whitney U test was used to assess for differences in age at adoption among children based on medial-temporal groups (DMC & CNMC). Age at time of adoption also was not significantly different for medial-temporal groups, *U* (1) = 88.50, *z* = -0.24, *p* = .82.

Duration in Adoptive Home. A Mann-Whitney U test was conducted to assess for differences among children based on medial-temporal subgroups (DMC & CNMC) and duration in adoptive home. Median change in duration in adoptive home for medial-temporal group was significant, *U* (1) = 49.00, *z* = -2.09 *p* = .05. Children in the DMC group (*M* = 97.97, *SD* = 4.35) had spent significantly less time in their adoptive home than children in CNMC group (*M* = 123.05, *SD* = 32.52). Of note median changes based on age at time of study in the medial-temporal groups (DMC & CNMC) median change was not significant, *U* (1) = 54.00, *z* = -1.86 *p* = .07. A Kruskal-Wallis test was conducted to evaluate differences among children based on striatal groups (DLSC, MSC, & LSC) and time in adoptive home. Striatal groups were not related to differences in duration in the adoptive home, χ^2 (2*, n* = 28) = 3.54, *p* = .17.

CHAPTER 4

DISCUSSION

The results of this study suggest that exposure to adverse caregiving environments in early childhood does indeed have a negative impact on both the architecture of the brain and behavior. Additionally, the results of this study suggest that the architecture of the brain can be modified later in life by exposure to an enriched environment. Importantly these results demonstrate the advantage of inter-individual comparison over whole group analysis within a heterogeneous population. Specific results for each study hypothesis are discussed below, organized by study aim.

Cortical Connectivity

The first aim of this study was to expand on the findings of an earlier small-scale pilot study (Veenstra, et al., 2011) that suggest heterogeneous striatal-cortical connectivity within a sample of children exposed to early social deprivation and to determine whether heterogeneous connectivity patterns are also evident in medial-temporal-cortical connectivity.

Striatal. As predicted internationally adopted (IA) children showed distinct within group patterns of cortical-striatal connectivity that also differed from that observed for the comparison children. The two predicted patterns of diffuse and low left-hemispheric cortical-striatal connectivity (Veenstra, et al., 2011) were not fully supported by the current study, as instead three specific patterns of cortical-striatal connectivity were found.

Instead of finding the one predicted group with diffuse cortical-striatal connectivity in both hemispheres (Veenstra, et al., 2011) the present study identified two clusters characterized by hemispheric specific diffuse cortical-striatal connectivity. One cluster is characterized by high cortical-striatal connectivity in only the left hemisphere (Diffuse Left Striatal Connectivity; DLSC), whereas the second cluster is characterized by high cortical-striatal connectivity in the right hemisphere (Mixed Striatal Connectivity; MSC).

Contrary to expectations, neither of the groups with low cortical-striatal connectivity is characterized purely by the predicted pattern of low left hemisphere cortical-striatal connectivity (Veenstra et al., 2011). Instead, one group is characterized by low cortical-striatal connectivity in the left and right hemisphere (Low Striatal Connectivity; LSC), whereas the other is characterized by low cortical-striatal connectivity in the left hemisphere, but also has high cortical-striatal connectivity in the right hemisphere (MSC).

These findings suggest that children who are exposed to early social deprivation followed by placement in a typical/enriched caregiving environment show different patterns of cortical-striatal white-matter connectivity than children reared by their biological parents in a typical/enriched environment. Furthermore, it indicates that exposure to early social deprivation followed by placement in a typical/enriched environment differentially impacts cortical-striatal white-matter connectivity.

The finding that all three IA groups exhibit different patterns of cortical-striatal connectivity from comparison children is consistent with the reliable finding of structural and functional brain abnormalities in the striatal region for this population, when compared to family reared children (Behen et al., 2009, 2011; Chugani, et al, 2001; Eluvathingal, et al., 2006; Govindan, et al., 2009). Furthermore, low white-matter cortical-striatal connectivity in the LSC and MSC groups supports the prior finding that

IA children, as a group, have less white matter than non-adopted developmentally typical controls (Rutter & the ERA study team, 1998). However, Rutter and colleges (1998) did not look for differential patterns within their sample, thus is it is possible their sample also included an unidentified group with higher rates of white matter than controls (e.g., DLSC group).

Results from the present analyses do not fully support the finding in the earlier pilot study (Veenstra, et al. 2011). One explanation is that the current study allowed for increased specificity in identification of different patterns of cortical-striatal connectivity by minimizing or eliminating several of the limitations from the pilot study. First, the IA group in the current study is more than double the size that that evaluated in the pilot study (*N* = 30 vs. *N* = 12), increasing the probability of capturing true patterns more accurately. Additionally, the pilot study relied on visual discrimination for identification of different cortical-striatal groups. In the current study the three distinct cortical-striatal groups are identified based on statistical analyses, reducing the potential for rater bias or failure to fully perceive differences based on visual evaluation.

Although the size of the current sample is larger than that in the pilot study, it is possible that the current sample is still not sufficiently large to capture all true patterns of cortical-striatal white-matter connectivity in the IA population. There is evidence of a potential fourth pattern of cortical-striatal connectivity. Two children from the IA group do not fit the pattern observed in any of the three statistically identified IA cortical-striatal groups. Instead these two children show a pattern characteristic of diffuse right hemisphere cortical-striatal connectivity, without low left hemisphere cortical-striatal connectivity. Increased sample size in future studies will help clarify whether these children represent a fourth subgroup or if their scores represent an anomalous pattern of connectivity.

Medial-Temporal. Two divergent patterns of medial-temporal white-matter connectivity were identified in the IA sample. One pattern is characterized by high connectivity to the left and right hemispheres (Diffuse Medial-Temporal Connectivity; DMC). Unexpectedly, the second cluster that emerged is characterized by a pattern similar to the non-adopted family reared children (Comparatively Normal Medial-Temporal Connectivity; CNMC). Contrary to predictions none of the IA children show a pattern of low cortical-medial-temporal connectivity.

The current study found support only for diffuse medial-temporal connectivity (DMC). Prior research findings are suggestive of a correlation between structure size and white matter connectivity, thus it is likely that a larger hippocampus or amygdala co-occurs with the observed pattern of increased connectivity. Notably, the current study found diffuse medial-temporal connectivity in both hemispheres, not just the right hemisphere, which has been linked to increased amygdala volume in IA children (Bauer et al., 2009).

Unexpectedly, the second IA group identified in this study (CNMC) does not differ from the comparison group (NMC), despite consistent prior findings for abnormalities in the medial-temporal regions in prior IA samples (Bauer et al., 2009; Chugani, et al., 2001; Meta et al, 2009). This finding suggests that either the amygdala and/or hippocampus in children in the current study are structurally intact, thus leading to intact white matter medial-temporal cortical connectivity, or some children are able to develop medial-temporal-cortical white-matter connectivity similar to that of family reared children, despite the presence of structural abnormalities. Structural abnormalities, such as these could lead to normal or aberrant medial-temporal-cortical connectivity, depending on the relationship between structure and function, which is not investigated as part of this study. It is important to note that the presence of similar normalized probability scores for medial-temporal-cortical connectivity in the CNMC and comparison children does not necessarily mean they have similar patterns of connectivity for medial-temporal tracts.

The current study also does not provide support for the predicted low cortical-medial-temporal white-matter connectivity group. This is surprising, as IA children have previously shown a pattern of reduced hippocampal volume (Meta et al. 2009) and decreased glucose metabolism in medial-temporal structures (Chaugni, et al., 2001), which theoretically should lead to reductions in white matter. This suggests that the IA children in this study either do not have reduced hippocampus volume or poor integrity of medial-temporal structures, or these factors are present in this IA sample, but are not predictive of the connectivity of the medial-temporal-cortical white matter pathways as measured by MR-DTI.

Moreover, examination of scores for the two IA children who do not fit into either of the two groups also contradicts the hypothesis for a low connectivity subgroup. Instead these two children show a pattern of higher diffuse connectivity in the left hemisphere. It is possible that these children are part of the DMC group, as they display a similar pattern of connectivity as children in that group, with a higher level of connectivity in the left hemisphere. These findings suggest further evaluation of these associations in a larger sample would be unlikely to identify a group with low cortical-medial-temporal connectivity.

On the other hand, further investigation into medial-temporal connectivity should be based on a larger sample. This would allow us to determine whether the two children with higher diffuse left hemisphere medial-temporal connectivity represent an additional subgroup, belong in the DMC group, or are outliers. Future research should also focus on evaluating the relationship between the medial-temporal structural abnormalities and specific patterns of medial-temporal-cortical connectivity to the two IA groups, using other imaging techniques (MRI and PET). Future research should also investigated if groups show amygdala or hippocampal structural abnormalities, and what, if any, structural abnormalities are associated with intact medial-temporal-cortical white-matter connectivity.

Group Differences in Specific White-Matter Tracts

The second aim of this study was to determine whether groups with different overall cortical connectivity also differ on specific brain pathways. White matter connectivity and tract integrity were assessed using three MR-DTI metrics, which are indirect measures of white-matter connectivity and integrity: fractional anisotropy (FA), apparent diffusion coefficient (ACD), and the normalized probability ratio (NPR).

Striatal. The hypothesis that FA and ADC would differ for all groups on each striatal tract was largely unsupported, with most striatal-frontal and striatal-dorsolateral-prefrontal tracts showing no FA or ADC differences between groups. For ADC, the hypothesis of between group differences is only supported for the left striatal-frontal tract. The magnitude of diffusion is significantly higher in the DLSC group when compared to the MSC group. Unexpectedly, these groups do not differ from the NSC or LSC groups. For FA, one tract did show an on overall group difference, but no specific between group differences. Furthermore, contrary to expectations based on the pilot study (Veenstra, et al., 2011), the IA groups (DLSC, MSC, & LSC) did not differ from the comparison group on the Normalized Probability Ratio (NPR) for any of the striatal tracts.

In sum, these results show that, despite differences in striatal-cortical connectivity, most striatal-frontal and striatal-dorsolateral prefrontal tracts have statistically similar patterns of FA, ADC, and NPR. Overall, striatal-cortical connectivity is related only to one specific difference, on one specific tract. Specifically, the IA group characterized by diffuse left striatal connectivity (DLSC) has a higher magnitude of diffusion in the left striatal-frontal tract than the IA group characterized by low left and high right cortical striatal connectivity (MSC). It is surprising that this difference was found for the left striatal-frontal tract, as a previous study on IA children indicated poor connectivity in the right, but not left striatal frontal tract (Behen, 2009). The discrepancy between the results from these two studies could reflect obscured tract based differences that result from evaluating for overall group differences in a heterogeneous IA sample.

Although there is little support for striatal group differences relating to tract-based differences, the one tract based finding is consistent with study’s predictions for the association between patterns of diffuse cortical connectivity and higher tract based ADC scores (Veenstra, et al., 2011). An overabundance of white matter whole brain connections from the left striatum (DLSC) is associated with poorer integrity of the left striatal-frontal tract, relative to that observed in a group of IA children who show a pattern of overabundance of white matter connections in the contralateral hemisphere, and restricted connectivity in the ipsalateral hemisphere (MSC). The difference in ADC scores for the DLSC and MSC groups provides support for one of the primary predictions of this study; namely, that there are significant white-matter integrity differences within the IA population that are observable for specific tracts and overall connectivity.

These findings suggest that early social deprivation's impact on overall striatal-cortical connectivity has the most pronounced effect on the left frontal-striatal tract. The impact of deprivation on white matter connectivity in this tract is not the same for all IA children, nor does it lead to aberrant patterns of connectivity in this tract in all IA children (i.e., right frontal-striatal tract for DLSC groups). When followed by later enrichment, early social deprivation therefore does not grossly impact all aspects of brain development, nor does it preclude children from developing statistically similar pathways as those observed for non-institutionalized comparison children. There appears to be some process (e.g., pruning, myelination) that impacts both overall cortical-striatal white-matter connectivity and the left striatal-frontal tract for DLSC and MSC. It is possible that, given the aberrant early life circumstances of children in the IA group, some aspect of these early experiences/environment for the MSC and DLSC children differed (experience-expectant) leading to measurable differences in both their cortical-striatal and left striatal-frontal connectivity. Similarly, some aspect of their white matter pathway development later in life could be due to exposure to specific experiences (experience-dependent) that directly resulted in improved integrity of the left striatal-frontal tract in MSC children. This would indicate that these enriching experiences were either not available to children in the DLSC group, or they were not able to benefit from enriched experiences in the same way as children from the MSC group.

Overall, the paucity of striatal tract between group differences, specifically the lack of many differences between the IA and comparison groups, is surprising. Many prior studies demonstrated functional and structural striatal differences secondary to early life stressors for both humans and animals, relative to those observed for controls (Behen, et al, 2009; Cirulli, et al., 2009; Mueller et al., 2009; Roceri et al., 2003). This may mean that, despite aberrant overall striatal connectivity in children exposed to early social deprivation, IA children have striatal-dorsolateral-prefrontal and striatal-frontal white-matter tracts that are similar to those found in family reared children. The between group differences in cortical-striatal connectivity are possibly due to connectivity with ancillary tracts or they may impact the integrity of striatal tracts not investigated as part of this study.

Medial-Temporal. It was predicted that FA and ACD would differ for specific striatal pathways (FP, TP, and OF) between all groups (IA groups and comparison group). Results from this study give moderate support for this hypothesis. Specific between group differences were observed on two tracts.

The NMC and CNMC groups differ on FA for the left medial-temporal to anterior-temporal tract and ADC for the right medial-temporal to anterior-temporal tract. Despite having similar medial-temporal cortical probability patterns, left medial-temporal to anterior-temporal directional diffusion is significantly higher in the NMC group than the

CNMC group. Thus, although these two groups initially appeared to be very similar, the NMC group has more fiber bundles traveling in the same direction for the left medial-temporal to anterior-temporal tract than the CNMC group.

Similarly, the NMC and CNMC differed on the ADC score for the right medial-temporal to anterior-temporal tract. This pathway shows an observable pattern of between group maturational changes which is consistent with expectations for this tract (Liauw, van Wezel-Meijler, Veen, van Buchem, & van der Grond, 2009), but this factor does not fully explain ADC scores differences for this tract. Contrary to expectations, ACD in the NMC group is higher than ADC for the CNMC group, indicating higher rates of diffusion in the NMC group than the CNMC group. Typically higher ACD reflects lower white mater density or structural disorganization (Le Bihan, 1995); however, it is also possible that the CNMC group has below typical diffusion rates for this tract. Additionally, it is possible that the higher FA in the left medial-temporal to anterior temporal white matter tract for the NMC group reflects typical development, while the lower FA for this tract, combined with low ADC on the right medial-temporal tract, is indicative of reorganization to the tract in the contralateral hemisphere (Bengoetxea et al., 2012).

Consistent with the above findings, the NPR score significantly differs by group for the right medial-temporal to anterior-temporal connectivity after controlling for age. However, follow up analyses did not reveal any specific between group differences. This finding does, however, suggest that there are differences between groups in the percentage of tracts that terminate in the anterior-temporal region.

Unexpectedly, the one group with atypical medial-temporal cortical connectivity (DMC) is not identified as having significantly different integrity or connectivity for any of the evaluated white matter tracts. Replication in a larger sample size may allow for identification of the DMC groups as driving the specific between group differences in NPR for the right medial-temporal to anterior-temporal tract, as well as for FA in the left medial-temporal to frontal tract. These findings suggest that the pattern of diffuse cortical connectivity reflects an aberrant process (e.g., lack of pruning) that does not impact the measured pathways or that the diffuse pattern of connectivity reflects additional connections created in other pathways due to non-typical environmental demands (Fox et al., 2010; Perry, 2006; Shonkoff & Phillips, 2000).

Relationship Between Connectivity Derived Groups and Behavior

As would be expected based on knowledge from previous studies (Ames, et al., 1997; Behen, et al., 2008; Kreppner, et al., 2001, 2007; McLaughlin et al., 2010; Rutter, et al., 2001; Stevens et al, 2008) parental ratings of externalizing problems, behavioral symptoms, and executive functioning (I/O Phenotype) for the comparison group significantly differed from those in the IA striatal (DLCS, MSC, LSC) and medial-temporal (DMC, CNMC) groups. Similarly, as hypothesized, parental ratings of internalizing problems for the comparison group significantly differed from the IA striatal and medial-temporal groups, excluding one unexpected non-significant finding. Parental ratings of internalizing problems for the comparison group (NSC) did not significantly differ from the LSC group (striatal). This finding suggests that within this sample, low striatal connectivity is associated with lower rates of parent reported internalizing problems. The IA groups did not differ significantly from one another on level of internalizing problems, externalizing problems, behavioral symptoms, or executive functioning (I/O Phenotype, Meta-Cognition, Behavioral Regulation).

It was predicted based on prior findings that children with diffuse striatal connectivity would have increased rates of externalizing problems (Behen, et al., 2009). However, the current study did not show different rates of externalizing problems for children with low, diffuse, or typical connectivity for either hemisphere. Children in each IA group had significantly more externalizing and behavioral problems than children in the comparison group. This indicates that any deviant pattern of striatal-cortical or medial-temporal cortical connectivity may be a risk factor for externalizing and behavioral problems.

IA children were, however, at a decreased risk for internalizing problems when they showed a pattern of low striatal cortical connectivity. This finding contrasts with the typical findings for other clinical populations (e.g., OCD, preterm birth), where lower rates of striatal-cortical white-matter integrity are related to higher rates of internalizing symptoms (Loe, Lee, E, & Feldman, 2013; Chen, Silk, Dally, Vance, 2013). This suggests that for internalizing symptoms there may be a unique process related to early social deprivation that results in lower rates of internalizing symptoms and striatal-cortical connectivity. For medial-temporal cortical connectivity, aberrant and typical patterns are both related to generally increased risk for internalizing problems. This finding fits with the known relationship between medial-temporal structures and internalizing problems (Adhikari, et al., 2010; Hornak et al., 2003; Gallagher & Chiba, 1996).

As expected, IA children have increased rates of the I/O phenotype compared to the comparison children and do not differ on parent ratings of executive functioning. This is consistent with prior research findings showing abnormal striatal-cortical and medial-temporal-cortical connectivity in children with ADHD (Durston, 2003; Konrad, & Eickhoff, 2010; Silk et al., 2009) and/or executive dysfunctions (Castellanos & Proa, 2010; Loe, et al., 2013; Stretton & Thompson, 2012).

It is surprising that children in the CNMC group did not show lower rates of emotional, behavioral or executive problems. This suggests that children in the CNMC group may have a different pattern of medial-temporal connectivity, despite having a similar overall probability of cortical connectivity as children in the comparison group. It is also possible that these children's elevated ratings are driven by their pattern of striatal connectivity, rather than medial-temporal connectivity.

Broad differences in cortical connectivity may not be the best means for identifying pathways related to specific behavioral problems. Cortical connectivity does not differentiate between location of tract termination, and thus may lack sufficient precision to reveal specific behavioral differences. Specific white matter pathways within these groups may be a more precise indicator of white matter differences that are associated with parent reported behavioral problems and performance on behavioral measures.

Relationship Between Behavior and Specific Tracts

IA children whose parents report no significant Internalizing concerns have lower white matter integrity in their left medial-temporal to frontal tract than children who do not have a history of early social deprivation, but whose parents similarly note no significant anxiety concerns. Additionally, after controlling for maturation, children whose parents rate them as having At-Risk or Clinically Significant level anxiety problems have a lower magnitude of diffusion than do comparison children, whose parents rate them in the Normal range on anxiety. Level of Externalizing problem and Behavioral Symptoms are related to ADC scores for the right medial-temporal-anterior-temporal tract, after controlling for effects due to brain maturation. Specific between group differences revealed that magnitude of diffusion is higher in the Normal group than in the Clinically Significant group. However, level of Internalizing, Externalizing, and Behavioral Symptoms do not significantly differ for striatal tracts.

FA for the superior longitudinal fasciculus, which included connectivity to the frontal region, has been shown to increase as internalizing symptoms decrease in children who were born prematurely. Interestingly, this relationship applied only to the preterm children, whereas for comparison children, there was no relationship between FA and internalizing symptoms (Loe et al., 2013). This finding could explain why IA children rated as “normal” for level of internalizing symptoms have lower FA in the left medial-temporal to fontal tract than comparison children, whereas children who do not differ from comparison children in FA display elevated levels of internalizing symptoms. These findings suggest that children with structural abnormalities due to their history of early life trauma show a relationship between white matter integrity changes and risk of anxiety symptoms. Furthermore, it suggests that when there is a history of disruption early in life aberrant patterns of connectively (lower FA) actually lead to decreased risk of some pathological behaviors (i.e., anxiety symptoms).

ADC in the right medial-temporal to anterior temporal tract shows higher diffusion in comparison children than for children whose parents reported emotional and behavioral concerns (Internalizing, Externalizing and Behavioral Symptoms). This finding is initially counterintuitive, as it suggests “normal” children have poor white matter integrity in this tract. However, it is also possible that this finding reflects the developmentally typical process of pruning that begins in childhood and extends into midadolescence and leads to increased gray matter (Huttenlocher, & Dabholkar, 1997) as the weakest synapses are removed in a progressive process without disrupting function (Chechik, Meilijson, & Ruppin, 1999).

In addition, children in this sample had a lower rate of internalizing problems, relative to the rate of other types of problems. It is possible that the sample size in this study was too small to detect patterns of connectivity related to internalizing problems.

Additionally, only tracts that differed between groups were investigated for emotional and behavioral correlates. As a result, some tracts that were likely to reveal significant associations between connectivity and behavioral/emotional functioning were not evaluated for differences in this study. For example, ACD in the left and right orbitiofrontal regions is known to be related to level of internalizing symptoms (Govindan, et al., 2010). These tracts were measured, but not evaluated under the paradigm of the current study.

Relationship Between Executive Functioning and Specific Tracts

Parent ratings of executive functioning (I/O phenotype, Meta-Cognition, and Behavioral Regulation) were not related to any differences on the medial temporal or striatal tracts. It may be that parent rated measures are not as precise an indicator of executive dysfunction as standardized assessments of the child’s actual performance (e.g., Vigilance Hits and False Alarm).

Level of performance on Vigilance Hits significantly differed between groups on FA scores for the right striatal-frontal tract and ADC scores for the right medial-temporal-anterior-temporal tract, after controlling for brain maturation. Mean ADC scores are highest for children who performed in the normal range, whereas ADC scores for children whose performance is in the borderline or abnormal range are relatively lower. Additionally, FA is higher in the right striatal-frontal tract for IA children who showed intact sustained attention as compared to children who showed poor sustained attention. This suggests that intact sustained attention is associated with decreased myelination or less dense axonal packing for the right frontal-striatal tract and higher magnitude of diffusion for the right medial-temporal-anterior-temporal tract. This pattern of findings replicates those found in children with ADHD (Shaw, 2007). The current findings suggest that the pruning process is delayed for IA children who have poor sustained attention. This is similar to the pattern found in ADHD, where a delay occurs in the process of pruning, which is most pronounced for the frontal and temporal regions (Shaw, 2007).

Level of performance on Vigilance False Alarms did not significantly differ for striatal or medial-temporal tracts. These results indicate that ether none of the measured tracts are related to impulsivity, or possibly a larger sample size with less range restriction would be needed to identify the patterns of connectivity in pathways related to impulsivity for IA children. Additionally, although these children are often rated as having inattentive and overactive symptoms (Jacobs et al., 2010; Kreppner et al., 2001; Loman, et al., 2013; McLaughlin, et al., 2010), results from analyses using behavioral outcome measures do not give consistent support for the hypothesis that IA children are more behaviorally impulsive than children reared with their biological parents (Loman, et al., 2013; McDermott et al., 2012). It should be noted that is performance based measures and parent ratings are found to be incongruent when evaluating executive functioning (Thompson, & Nichols, 1992).

International Adoption Specific Factors

As predicted, children in this sample show rates of parent reported emotional/behavioral problems and I/O Phenotype that are consistent with the rates previously reported in studies of IA children (Ames et al., 1997; Behen et al., 2008; Jacobs et al. 2010; Rutter et al., 2001; Zeanath et al., 2009). These rates are also significantly higher than those reported for children in a normative comparison population (Reynolds & Kamphaus, 2004). This indicates that the children recruited in the present sample are similar in these characteristics to those reported in prior studies with IA children (Ames et al., 1997; Behen et al., 2008; Jacobs et al. 2010; Rutter et al., 2001; Zeanath et al., 2009), and thus it is likely that the emotional and behavioral tract based findings in the present study would generalize to the broader IA population.

This study did not replicate prior findings of a relationship between age of adoption or duration in adoptive home and behavioral, emotional, or executive functioning (Ames, et al., 1997; Beckett, et al, 2007; Jacobs, et al., 2010; Kreppner, et al, 2007; Stevens, et al., 2008). However, even within the body of literature on the effect of length of institutionalization, no consistent sensitivity period has been identified; although 6, 18, and 24 months of age have been suggested as potential cut-points for attention (Beckett et al., 2007; Gunnar et al., 2007; Kreppner et al., 2007; Merz & McCall, 2010), and 6 and 18 months have been suggested as potential cut-points for externalizing or internalizing problems (Beckett, et al., 2007; Hawk & McCall, 2010; Kreppner et al, 2007 Merz & McCall, 2010). It is possible that the current study found no differences based on duration variables because the IA children in this sample are generally cognitively intact. This restriction of range on general intelligence could have resulted in a nonsignificant relationship between duration in the adoptive home and behavior, similar to what is found in prior studies that control for the relationship between low cognitive functioning and behavior problems (Loman et al., 2013). However, this is unlikely the cause of the non-significant duration findings, as the present study consists of a generally cognitively intact IA sample. Notably IA children did show a relationship between nonverbal intellectual functioning and emotional, behavioral, and executive functioning despite being generally cognitively intact.

Length of duration in the adoptive home was found to be related to medial-temporal-cortical derived groups (DMC & CNMC). Specifically, children in the DMC group spent significantly less time in their adoptive home than children in CNMC group. Although the DMC and CNMC groups do not significantly differ in age at time of study, the association between group and age is approaching significance. In a larger sample this difference in connectivity might be associated with age, rather than length of time in an enriched environment. However, these findings are consistent with prior research (Kumar et al., 2013), and tentatively suggest that time in the adoptive home impacts patterns of medical-temporal connectivity. As the child spends more time in the adoptive home they show improvement in the organization of their synaptic connects until they have patterns similar to non-adopted, family reared children.

Theoretical Implications

This study replicates the findings from the pilot study for divergent patterns of cortical-striatal connectivity within the IA population and extends these findings to the medial-temporal tract. The divergent patterns of cortical connectivity in these tracts suggest that early experiences directly, yet differentially, impact children reared in deprived environments. This supports the notion of experience-expectant brain development, whereby early social deprivation disrupts the developmentally typical process of expansion of synaptic connections and/or the subsequent pruning process (Greenough, et al., 1987; Fox et al., 2010; Shonkoff & Phillips, 2000). The impact of early social deprivation on brain architecture leads to the patterns of diffuse and low striatal connectivity, and diffuse medial-temporal connectivity observed in this study.

Furthermore, the current findings are consistent with the notion of experience-dependent brain development, but only in medial-temporal connectivity. The CNMC group, who spent more time in their adoptive home, showed a rate of cortical connectivity that is similar to children reared in by their biological parents. The sustained exposure to a more enriched environment appears to have led to the creation of new synaptic connections or refinement of synaptic connections (Fogel, 2011; Greenough & Black, 1992; Perry, 2006).

As a whole, these data support the current focus on inter-individual imaging differences, rather than viewing the IA population as one homogeneous group. This focus on individual differences fits both with the tract-based differences found in this study and the heterogeneous behavioral outcomes consistently found for IA children (Ames, et al., 1997; Behen, et al., 2008; Gunnar, et al, 2007; Rutter, et al., 2001). However, cortical connectivity, as utilized in this study, does not appear to be a robust indicator of either specific tract based patterns or emotional, behavioral or executive functioning. Indeed, two of the three group based differences on tracts are due to decreased integrity of tracts for the CNMC group as compared to the comparison children. As there are no other observed causes for these differences (e.g., structural abnormalities or edema), this pattern of tract based deficiencies in the CNMC group is likely related to altered brain development specific to the right and left medial-temporal tracts due to the aversive early caregiving experience (Fox et al., 2010; Perry, 2006; Shonkoff & Phillips, 2000). It is also possible that the pattern of cortical connectivity in the CNMC group reflects an incomplete but changing neural network related to the enriched environment, suggestive of delayed rates of brain maturation (Chechik, Meilijson, & Ruppin, 1999; Huttenlocher, & Dabholkar, 1997; Shaw, 2007).

Although it would be more cumbersome, the evaluation of specific tract based differences may better elucidate the relationship between brain function and behavioral function. Group differences based on striatal and medial-temporal cortical connectivity for emotional/behavioral and executive outcomes are relatively nonexistent in this sample. Functional differences in this study appear to be the best indicator of divergent tract based difference and suggest a strong relationship between right medial-temporal integrity and risk for emotional, behavioral, and attention problems. This is not surprising, as the amygdala has been linked to both emotional processes and attention (Gallagher & Chiba, 1996). Interestingly, Eastern European IA children, who make up a large proportion of the current sample, show increased right amygdala volume (Meta, et al., 2009), suggesting that this structural difference may underlie the observed medial-temporal tract based differences in the current study. Inter-individual changes on internalizing symptoms are also evident for the left striatal-frontal tract, which is not a region traditionally associated with internalizing symptoms. Intriguingly, the left medial-temporal to anterior-temporal tract, which is a region where structural abnormalities are associated with internalizing symptoms (Tottenham et al., 2009), only differed between children who had normal level internalizing problems. Together, these findings suggest that the left and right hemisphere may be uniquely impacted by early deprivation, whereby aberrant left hemisphere patterns of connectivity lead to typical functional outcomes, while deviant right hemisphere integrity leads to atypical functioning. It is also possible that these differences reflect un-measured but co-occurring tract based differences (e.g., cross-modal plasticity, as discussed by Bengoetxwa, et al., 2012).

Although there are clear inter-individual differences in connectivity patterns for some tracts based on emotional, behavioral, and executive outcomes, the timing of exposure to deprivation does not distinguish between children based on level of risk, thus failing to provide direct support for a critical period in IA children’s emotional development. It is possible that a true critical period exists that was not captured in this sample, or that the critical period was not observed because it does not impact the tracts assessed in the current study. However, it is more likely that a more complex, dynamic developmental process exists, that combines early and later environmental and possibly genetic risk factors (Fox, et al., 2010; Gardner et al., 2009; Gottlieb, 2003; Greenough, et al., 1987; Makinodan, Rosen, Ito, & Corfas, 2012; Shonkoff & Phillips, 2000). Animal studies have suggested that early experiences impact myelination of specific brain pathways that increase the later risk for emotional/behavioral symptoms, but only for those animals exposed to a later environmental stressor (Gardner et al., 2009; Makindan, et al., 2012). Thus, failure to find tract-based differences in regions known to be associated with behavioral/emotional functioning could reflect this dynamic interchange between environment and risk. IA children therefore could have a pattern of white matter integrity that places them at an increased risk for a specific behavioral or emotional problem, but this behavior is not manifested because they have not been exposed to a prompting environmental stressor that would lead to the manifestation of this pathology.

Limitations

Although the overall sample size is moderate to large for an imaging study that also includes neuropsychological data, the clustering procedures used for IA children in the present study created relatively small groups and may have reduced power. Also as suggested earlier, based on outliers in cluster analyses, the size of the IA sample was likely not large enough to capture all true clusters. Furthermore, the results of this study could reflect spurious findings resulting from the inclusion of an unmatched comparison sample. This is unlikely, however, given that the comparison sample did not significantly differ from IA children on any demographic factors.

Moreover, it is possible that the failure to find the predicted differences on behavioral, emotional, or executive factors for IA groups or tracts may be due to limitations of parent report measures over direct measures of behavior. Some of these limitations include differences in parental expectations, biased perceptions of their child’s functioning, careless responding, impression management, idiosyncratic understanding of the items, and fatigue. The current study uses a multi-modal approach by including performance based executive functioning measures to compensate for the risks associated with parent report measures, but unfortunately no comparable measures were available for emotional or behavioral functioning.

Another limitation of the current study is that country of origin, which is an indirect measurement of exposure to species typical environmental experiences, could not be assessed. Based on general regional quality of institutions, children from Eastern Europe/Russia are at an increased risk for more severe social deprivation than children from Asia (Ames, 1997; IJzendoorn, et al., 2008; Johnson, 2000; Kim & Carrol, 1975; Warren et al., 2001). Likewise, there is some support for the notion that IA children from Eastern Asia have better behavioral outcomes than IA children from Eastern Europe/Russia (Gunner & VanDulmen, 2007; Lindblad, et al. 2009).

The children in this study resided in their adoptive homes for a minimum of five years at the time this study took place. Although this allowed the investigators to evaluate the more intractable behavioral, emotional, and executive symptoms in this population, it also decreases the likelihood of identifying change in brain structures that occur over time (experience-dependent).

Moreover, the IA children in this study are part of a community-recruited sample. Although this was not a randomly selected sample, it does not appear to be biased towards either increased or decreased pathology. Rates of IA children in this study with behavioral concerns are not different from the rates reported in other IA samples (Ames et al., 1997; Behen et al., 2008; Jacobs et al., 2010; Rutter et al., 2001; Zeanath et al., 2009), but they are higher than in a normative population (Reynolds & Kamphaus, 2004).

DTI represents a technological advancement that provides a sensitive measure of diffusion characteristics of cerebral white matter that does not require any invasive procedures (e.g., histology). It is an established tool for assessment of the structural integrity of white matter, but this approach is not without limitations. DTI is inherently low in spatial resolution, which limits its accuracy. Acquisition of images can impact the accuracy of the data when there are acquisition artifacts (e.g., geometric distortion). Accuracy of DTI is further bound to the quality of the image, with potation problems resulting from thermal and physiological noise, brain motion, and imaging artifacts. Relative to other methods, DTI has a lengthy scan time, thus increasing the risk of motion artifacts, particularly in children (Mori & Zhang, 2006). Although a stringent quality control process was used in this study to reduce the impact of image artifacts such as motion, it is possible that results are at least partially impacted by movement artifacts.

As a technique, tractography also has several technical limitations. DTI-metrics do not differentiate orientation of motion; therefore, specific directionality cannot be identified in any given axon. Also tractography averages cellular level anatomical information within the larger voxel volume. This method is limited in accuracy when there are crossing fibers, as the overall index is decreased and does not accurately reflect either set of fibers. Fifty-five direction data, rather than six direction data, is used in this study to reduce the loss of data in tenor calculations, however analyses still assume a homogeneous pixel, thus leading to some loss of data (Mori & Zhang, 2006).

The imaging procedures used in this study attempt to reduce bias and increase accuracy by using anatomical maps to identify ROI's (Lin et al., 2010; Muzik et al., 2007; Zou et. al. 2006), but the utility of this method may be limited in children who have grossly atypical brain structures. Finally, although these techniques are widely used it is a relative new method with limited information on the relationship between tractography methods and anatomical data (Schmahmann et al., 2007). Despite these limitations, it is important to note that results from the present study did identify abnormalities in tracts for the IA groups that are significantly different from controls. This finding is also consistent with expectations for regional abnormalities based on previous studies using disparate methods (e.g., EEG, MRI).

Future Directions

As discussed earlier, findings from this study contribute to a growing body of research providing strong evidence for the use of inter-individual differences in identifying the relationship between behavior, and functional and structural imaging, rather than viewing IA children as a homogeneous group. The general approach utilized in this study (cortical based differences), however, lacks the necessary precision. Future studies should focus on identifying within group behavioral differences based on patterns for specific tracts, while also determining whether these findings can be correlated with structural differences (e.g., amygdala size). Ideally such future studies would be longitudinal. This would allow for better evaluation of the impact of an enriched environment on change over time in brain structure and function, while also correlating these results to functional behavioral change.

Results from this current study also show that specific patterns of white matter integrity are related to emotional and behavioral symptoms, and sustained attention.

The addition of a comparison group with similar emotional, behavioral, or executive symptoms could help determine if diffusion abnormalities are associated more with history of early deprivation or are idiopathic signs of the psychological symptoms for all children. Additionally, future studies should include a larger group of IA children who have more diverse adoption specific demographic variables (e.g., country of origin, duration in adoptive home) to better evaluate the impact of these factors on the brain and behavior outcomes.

Furthermore, tract based differences identified in this study are associated with children's functioning and therefore merit further investigation. For example, there is a known relationship between the medial-temporal region and memory. It will be important that future studies use a multi-modal measurement approach of outcome data, when possible, as there are limitations to parent report and performance based measures.

Practical Implications

This study highlights the importance of rearing children in an enriched "species-typical" environment early in life, which supports experience-expectant brain development, as well the importance of continually exposing them to adequate environmental experiences throughout childhood and adolescence, which allows for experience-dependent learning. When children are exposed to an impoverished, atypical early rearing environment, there is an increased long-term risk for altered brain development and emotional, behavioral, and executive functioning problems, although it is still unclear what comprises a "good enough" environment, or what the specific sensitive periods are for this critical exposure. Early social deprivation is a clear example of an atypical adverse rearing environment with clear neurologic, cognitive, emotional, and behavioral sequelae. There are many less severe atypical early life experiences that could similarly impact brain development (e.g., neglect, lengthy hospitalizations). It will be important to extend these findings into other populations with less severe levels of social deprivation to understand at what point social environmental factors no longer meet the threshold for experience expectant learning.

On the other hand, there does appear to be direct benefit to being raised by a consistent caregiver in a family environment, even after being exposed to social deprivation (Beckett, et al. 2006; Chugani, et al., 2001; Jacobs et al., 2010; Kreppner et al, 2007; Rutter & the ERA study team, 1998; Rutter, O'Connor, & the ERA study team, 2004). When children are exposed to an enriched environment after a period of social deprivation, there is evidence of normalization of cortical connectivity (CNMC) over the duration of time spent in the enriched environment. In the present study, duration of time in the adoptive home was not related to improvements in behavioral outcome data. Thus, further research needs to be conducted to better understand the functional outcomes related to the normalization of cortical connective that results from experience dependent learning. Future research should attempt to identify what types of enriched environmental experiences (experience-dependent) increases the likelihood of normalization of white matter tracts that are associated with risk for emotional, behavioral, and attention problems secondary to early deprivation children.

Conclusion

This study demonstrated that children with histories of early social deprivation who are later adopted into enriched environments should be viewed as a heterogeneous group in analyses involving brain architecture. Within the IA group, different patterns of cortical connectivity were found for both the striatal and medial-temporal regions. These cortical based group differences were not as accurate an indicator of emotional, behavioral, or executive problems as were specific tracts. The use of inter-individual tract based differences offers a promising new methodological approach, one that could help investigators better understand the impact of early and later life experiences on brain architecture and behavior.

APPENDIX A

Parent Information Form

Child’s Name: ____

Child’s Birthdate: ____

Gender: Male Female

Handedness: Right Left Mixed

Child’s Weight: ____________lbs.

Child’s Height: ____________

Below are some questions about your child, please circle “Y” for yes and “N” for no.

Attends school regularly	Y	N
Premature	Y	N
Low birth weight	Y	N
Hearing Loss	Y	N
Epilepsy	Y	N
Psychiatric Diagnosis	Y	N

How many years of school had the child’s adoptive mother completed? ___________

How many years of school had the child’s adoptive father completed? ____________

For Parents of Adopted Children only:

Child’s age at adoptions: ______________

Country of adoption: _______________

For Office Use Only

Head Circumferences: ___________________________

Group: Control SLI non-SLI

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ABSTRACT

MICROSTRUCTURAL ABNORMALITIES IN STRIATIAL AND MEDIAL-TEMPORAL TRACTS IN CHILDREN WITH A HISTORY OF EARLY SEVERE DEPRIVATION: A DIFFUSION TENSOR IMAGING STUDY

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Major: Psychology (Clinical)

Degree: Doctor of Philosophy

The purpose of this study was to determine if early social deprivation led to different patterns of frontal and/or medial-temporal cortical connectivity in internationally adopted children and if these patterns of cortical connectivity were related to specific white matter tract or behavioral differences. Based on theories of brain development, it was expected that environmental factors would impact children's tract based differences and behavioral differences. A sample of 30 internationally adopted children and 12 comparison children participated in functional and structural imaging and a neuropsychological evaluation. For internationally adopted children frontal-cortical connectivity showed patterns of diffuse and low connectivity, whereas medial-temporal cortical connectivity showed patterns of diffuse and "normal" connectivity. Patterns of cortical connectivity were related several specific tract based differences and rates of internalizing problems. Tract based differences were the best indictor of emotional, behavioral, and executive functioning, with differed for the right medial-temporal to anterior- temporal, left medial-temporal to frontal, and left striatal-frontal tracts. Cortical

connectivity differences were associated with length of time in adoptive home, but only for the medial-temporal tract. The results of this study support the theories of experience-expectant and experiences dependent learning. The results of this study also support the use of inter-individual connectivity differences over whole group differences in understanding the impact of early deprivation on brain architecture and behavior. This approach should also be applied to other imaging methods and other populations with aberrant early life circumstances.

AUTOBIOGRAPHICAL STATEMENT

Amy Veenstra is currently in her six year of a clinical psychology program at Wayne State University. While her passion for psychology was not discovered until she entered University, she has long maintained an interest in the intricacies God created in human behavior and its associated biological unpinnings. As her passion for psychology has developed and matured, she has refined her area of interest from all of human behavior to a more manageable undertaking; specifically, the impact of complex medical conditions on children's psychosocial and developmental functioning. Amy is currently completing her pre-doctoral internship in pediatric psychology at The Children's Hospital of Michigan. Following graduation, she will move across the country and begin a post-doctoral position at Children's Hospital of Orange County working primarily with children diagnosed with seizure disorders.