

PREFRONTAL CORTEX DEVELOPMENT FOLLOWING VARIATIONS IN
EARLY LIFE EXPERIENCE: COGNITIVE AND NEURAL CORRELATES

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Dedication

“Isn’t it splendid to think of all the things there are to find out about? It just makes me feel glad to be alive - it’s such an interesting world.” –Anne of Green Gables

This thesis is dedicated to my parents, who answered millions of questions while still encouraging me to be curious, and to Mark and Theo, who continue to encourage me to explore. I love you all so dearly. Let’s go on an adventure together...

“The clearest way into the Universe is through a forest wilderness.” –John Muir

Abstract

Human brain development is not linear. Prefrontal cortex, typically considered a “late-developing” brain region, undergoes its most rapid development over the first years of life. Early and extended sensitivity of prefrontal cortical circuits to the environment allows maximum potential for infants to benefit from positive experiences, but can become a risk factor if the environment is non-optimal. The goal of the current studies was to characterize the dynamic influence of early experience on the development of prefrontal cortex structure, function, and dependent behaviors across developmental. We examined concurrent and long-term correlates of early risk in two different populations of children: children born moderate-to-late preterm (PT; 32-36 weeks gestation) and children adopted from orphanage care prior to five years of age (post-institutionalized or PI children). In Study 1 we characterized the structure of higher-level, prefrontal-dependent cognitive skills in 9-month-old infants and described the behavioral correlates of exposure to early biological risk (moderate-to-late PT birth) and of normative variations in the familial environment. In Study 2 we examined prefrontal cortex development in adolescents born moderate-to-late PT using structural and functional neuroimaging measures. In Study 3 we documented impacts of early deprivation on the connectivity of frontal-lobe systems in adolescents adopted from early orphanage care. Across studies, we found evidence that early adversity shapes both concurrent and long-term prefrontal cortex development. In healthy, moderate-to-late preterm infants, lower gestational age at birth was associated with poorer performance on five of six early executive function tasks (Study 1a), perhaps driven by underlying differences in early

attention shifting skills (Study 1b). Adolescents born moderate-to-late PT had reduced prefrontal cortex volume and altered prefrontal functional activity during an executive function task in comparison to full-term controls (Study 2), suggesting developmental continuity in atypical prefrontal cortex development following moderate-to-late PT birth. Impacts of early orphanage rearing on prefrontal systems were also not fully ameliorated by adolescence. PI youth had reduced cortical white matter volume and poorer white matter microstructural integrity across the brain, including in fronto-limbic and fronto-striatal tracts. These findings highlight the plasticity and vulnerability of prefrontal circuits during the first years of life.

Table of Contents

LIST OF TABLES.....	viii
LIST OF FIGURES.....	x
GENERAL INTRODUCTION.....	1
CHAPTER 1	
<i>Infant Prefrontal Cortex Development and Sensitivity to Early Environmental Experience</i>	
Outline.....	9
Acknowledgments.....	11
Introduction.....	12
Frontal Lobe Contributions to Infant Cognition.....	15
Neurobiological Development of PFC.....	19
Neuroimaging Measures of Early PFC Development.....	26
Defining Early Experience.....	37
Early Adverse Experiences and PFC Development.....	44
Potential Mechanisms for PFC Impacts.....	66
General Discussion.....	79
CHAPTER 2: Study 1a	
<i>Early Executive Function Development in Infants born Moderate-to-Late Preterm</i>	
Outline.....	91
Acknowledgments.....	93
Introduction.....	94
Methods.....	99
Results.....	109
Discussion.....	115
CHAPTER 3: Study 1b	
<i>Development of Early Executive Function Skills in Infancy: Biological and Environmental Contributions</i>	
Outline.....	122

Acknowledgments.....	124
Introduction.....	125
Methods.....	136
Results.....	147
Discussion.....	159
CHAPTER 4: Study 2	
<i>Long-Term Alterations in Prefrontal Structural and Functional Brain Development in Adolescents Born Moderately Preterm</i>	
Outline.....	167
Acknowledgments.....	169
Introduction.....	170
Methods.....	174
Results.....	183
Discussion.....	205
CHAPTER 5: Study 3	
<i>Non-linear Impacts of Early Adversity on White Matter Organization at Adolescence</i>	
Outline.....	214
Acknowledgments.....	216
Introduction.....	217
Methods.....	223
Results.....	238
Discussion.....	258
GENERAL DISCUSSION.....	269
BIBLIOGRAPHY.....	282
APPENDIX for Study 1a	
Supplemental Methods.....	318
APPENDIX for Study 3	
Supplemental Methods.....	332
Supplemental Results.....	337

List of Tables

CHAPTER 2: Study 1a

Early Executive Function Development in Infants born Moderate-to-Late Preterm

Table 2.1. Demographic characteristics.....	102
Table 2.2. Perinatal characteristics.....	103

CHAPTER 3: Study 1b

Development of Early Executive Function Skills in Infancy: Biological and Environmental Contributions

Table 3.1. Demographic characteristics.....	138
Table 3.2. Correlations of measures used in factor analysis in FT participants.....	148
Table 3.3. Principal axis factor analysis in FT participants: 5-factor solution	151
Table 3.4. Principal axis factor analysis in FT participants: 1-factor solution	152

CHAPTER 4: Study 2

Long-Term Alterations in Prefrontal Structural and Functional Brain Development in Adolescents Born Moderately Preterm

Table 4.1. Demographic characteristics.....	176
Table 4.2. Perinatal characteristics.....	177
Table 4.3. Attention control effects for all participants.....	189
Table 4.4. Inhibitory control effects for all participants.....	191
Table 4.5. Group differences in inhibitory control effects.....	195
Table 4.6. Group differences in global activity (task > fixation)	198
Supplemental Table 4.1. Group differences in global activity (congruent-go > fixation)	200
Supplemental Table 4.2. Group differences in global activity (incongruent-go > fixation)	201
Supplemental Table 4.3. Group differences in global activity (no-go > fixation)	203

CHAPTER 5: Study 3

<i>Non-linear Impacts of Early Adversity on White Matter Organization at Adolescence</i>	
Table 5.1. Demographic characteristics.....	228
Table 5.2. Adoption history of post-institutionalized youth.....	230
Supplemental Table 5.1. Comparison of age and sex adjusted white matter scalar metrics in controls and PI children (12-direction and 56-direction DTI data)	244
Supplemental Table 5.2. Comparison of age and sex adjusted white matter scalar metrics in controls, PI-EA, and PI-LA children (12-direction DTI data)	251
Supplemental Table 5.3. Associations between age and sex adjusted white matter scalar metrics and age at adoption (prior to 24 months of age), in tracts that differed by group (12-direction DTI data).....	256
APPENDIX for Study 1a	
Appendix Table 1. Example scoring rubric for three-step problem in problem solving task.....	329
APPENDIX for Study 3	
Appendix Table 1. Demographics of youth with 56-direction DTI data.....	334
Appendix Table 2. Adoption history of post-institutionalized youth with 56-direction DTI data.....	336
Appendix Table 3. Comparison of age and sex adjusted white matter scalar metrics in Controls and PI children, corrected for individual differences in white matter volume, in tracts that differed by group (12-direction and 56-direction DTI data)	348
Appendix Table 4. Comparison of age and sex adjusted white matter scalar metrics in Controls, PI-EA, and PI-LA children, corrected for individual differences in white matter volume, in tracts that differed by group (12-direction and 56-direction DTI data)	353

List of Figures

CHAPTER 1

Infant Prefrontal Cortex Development and Sensitivity to Early Environmental Experience

Figure 1.1. Summary of the approximate timeline of neurobiological processes in the human brain across prenatal and early postnatal development.....	22
Figure 1.2. Spatial distribution of cortical thickness, inferred myelination (via myelin water fraction – MWF), and default mode network in neonates, infants, and toddlers (left hemisphere)	34

CHAPTER 2: Study 1a

Early Executive Function Development in Infants born Moderate-to-Late Preterm

Figure 2.1. Novelty preference scores by group and gestational age.....	113
Figure 2.2. A not B performance and gestational age.....	114

CHAPTER 3: Study 1b

Development of Early Executive Function Skills in Infancy: Biological and Environmental Contributions

Figure 3.1. Degree of prematurity and relation to attention shifting composite scores.....	155
Figure 3.2. SES predicts infant attention shifting and encoding.....	158

CHAPTER 4: Study 2

Long-Term Alterations in Prefrontal Structural and Functional Brain Development in Adolescents Born Moderately Preterm

Figure 4.1. Group differences in prefrontal cortex gray matter volume.....	184
Figure 4.2. Activation for attentional control contrast for all participants.....	188
Figure 4.3. Activation for sustained attention contrast for all participants....	190
Figure 4.4. Greater activation for PT adolescents in motor regions.....	194
Figure 4.5. Greater activation for FT adolescents across frontal-parietal regulatory regions.....	197

CHAPTER 5: Study 3

Non-linear Impacts of Early Adversity on White Matter Organization at Adolescence

Figure 5.1. Group differences in cortical white matter volume, adjusted for age, sex, and total intracranial volume.....	239
Figure 5.2. TBSS group differences in FA and RD.....	241
Figure 5.3. TBSS group differences in AD and MD.....	242

APPENDIX for Study 3

Appendix Figure 1. TBSS adoption group differences in FA.....	340
Appendix Figure 2. TBSS adoption group differences in RD.....	342
Appendix Figure 3. TBSS adoption group differences in AD.....	343
Appendix Figure 4. TBSS adoption group differences in MD.....	344

GENERAL INTRODUCTION

Early Experiences Shape Development

Human brain development is remarkably sensitive to early life experiences. Ideally young children are raised in the context of a relationship with a responsive caregiver, within an environment that supports the development of foundational perceptual, motor, cognitive, and socioemotional skills. In this case, early neuroplasticity tunes the brain to best match the unique features of the environment. Unfortunately, many children are exposed to early risk factors that can derail normative trajectories of brain development. In a large, representative sample of United States adults a recent study documented that 64% of adults reported being exposed to at least one adverse early childhood experience (ACE; abuse, neglect, major household dysfunction; see Anda et al., 2006). Higher levels of exposure to ACEs predicted both poorer mental and physical health years later (Anda et al., 2006). Follow-up studies have demonstrated that the negative impact of ACEs on health begin much earlier in development, including during the early childhood years (Kerker et al., 2015), suggesting that exposure to early adversity sets the stage for both concurrent and long-term disparities in mental health and well-being. However, these large, population-based studies have been somewhat atheoretical in describing the pathways through which early experiences “get under the skin” (Hertzman & Boyce, 2010) and influence long-term developmental trajectories.

Across the fields of neuroscience, epidemiology and public health, clinical psychology, and developmental psychology, multiple lines of research have investigated mechanisms through which early adversity shapes development. Converging evidence

suggests that the development of the brain's prefrontal cortex may be particularly sensitive to early variations in the environment. The frontal lobe undergoes the greatest expansion over the trajectory of an individual's brain maturation, representing approximately one-third of neocortex by adulthood (Fuster, 2002). Prefrontal cortex supports critical abilities, some perhaps specific to humans (Saxe, 2006), including the aptitude for complex social interactions (Saxe, 2006) and the capacity for higher-level executive function (EF) skills that allow for sequencing actions in a goal-directed fashion (Fuster, 2002). Both animal models of early life stress (e.g. Ovtcharoff & Braun, 2001) and studies of infants and toddlers growing up in adverse environments (e.g. Hanson et al., 2013) have demonstrated that impacts of early adversity on frontal lobe development can be detected within the first year of life. Long-term changes in frontal lobe structure, function, and dependent behaviors are associated with diverse early risk factors including exposure to childhood poverty (Lawson, Duda, Avants, Wu, & Farah, 2013), disruptions of parent-infant caregiver relationships (Hanson et al., 2010), nutritional deficiencies (e.g. see review in Georgieff, 2007), prenatal drug exposure (Mayes, Molfese, Key, & Hunter, 2005), and preterm birth (Nosarti et al., 2008).

Development of Prefrontal Cortex: Infancy - Adolescence

There are likely multiple mechanisms via which variations in the early environment impact trajectories of prefrontal cortex development. However, there is increasing recognition that the sensitivity of prefrontal cortex to early environments may reflect its rapid rate of growth during infancy (see Chapter 1 for comprehensive review), including dramatic changes in gray matter volume, white matter connectivity, and

functional organization. Advances in infant neuroimaging have demonstrated that prefrontal cortex is not “functionally silent” during early infancy. Instead, this rapidly developing brain region is implicated in a variety of cognitive and socioemotional processes (Grossmann, 2013), including early complex attention, memory, and inhibition skills that represent the foundations of EF in the first year of life (Hendry, Jones, & Charman, 2016).

The rapid rate of development of infant prefrontal cortex is widely underappreciated in the broader scientific community, including within the developmental psychology literature, largely because prefrontal cortex has been characterized as a “late developing” brain region. Longitudinal and cross-sectional neuroimaging studies have demonstrated that prefrontal cortex undergoes extended structural development into the adolescent years (Asato, Terwilliger, Woo, & Luna, 2010; Giedd, 2004; Nagy, Westerberg, & Klingberg, 2004; Sowell, Thompson, Holmes, Jernigan, & Toga, 1999; Sowell, Thompson, Tessner, & Toga, 2001). Macrostructural changes observed in gray matter density and white matter organization across adolescence likely reflect a longer time course for the overproduction of synapses, along with a slower rate of synapse elimination, relative to other regions of the brain (Kolb et al., 2012). Rapid development during infancy combined with refinement through late adolescence implies there may be multiple windows in development during which prefrontal cortex is maximally sensitive to the environment. Long-term plasticity in prefrontal circuits allows for later, positive environments to potentially ameliorate risks induced by early adverse experiences. Characterization of the long-term impact of

variations in early life experience on prefrontal cortex development thus requires an integration of these perspectives.

Delineating the impacts of early life experience on development has proved to be challenging for developmental psychologists, as defining both “early” and “experience” is difficult (see Chapter 1). In this dissertation, “early” is considered to reflect development across approximately the first two years of life, as post-mortem studies suggest that basic brain structure and connectivity are well-established during this age range (Huttenlocher & Dabholkar, 1997) and altered trajectories of brain development underlying developmental disorders can already be measured (e.g. Hazlett et al., 2011). “Experience” is even more ambiguous, requiring characterization of both the timing and nature of the early environment, which is a topic of extended discussion in Chapter 1. There are two major conceptual approaches to examining the impacts of early experience on prefrontal development: examination of the effects of early experience as temporally close to its occurrence as feasible (i.e. concurrent impacts), or examination of the enduring and/or emerging effects of early experience through long-term follow-up studies.

Framework of Dissertation

The goal of this dissertation is to combine these conceptual approaches to describe the dynamic influence of early experience on prefrontal cortex development across developmental time. We utilized measures of prefrontal cortex development that spanned multiple levels of analysis, including behavioral measures of EF (Studies 1a, 1b, 2), neuroimaging measures of prefrontal cortex volume and organization (Studies 2, 3),

and functional neuroimaging during a prefrontal-dependent task (Study 2). We examined the impacts of multiple types of early adverse experiences (i.e. preterm birth and early deprivation) to illustrate that changes in prefrontal cortex structure, function, and dependent behaviors may represent a final, common pathway through which variations in the environment shape early brain development.

Study populations.

Children born preterm. Preterm birth (PT; birth before 37 weeks gestation) is a public health problem in the United States and across the globe. Although medical care advances have remarkably improved outcomes for children born PT, many studies have documented long-term differences in prefrontal cortex development in children born early (see Nosarti, 2010 for review). Even in the absence of major medical complications, brain development in PT infants that occurs outside of the womb appears to be fundamentally different from that of their full-term peers (Moeskops et al., 2015). Across three studies (Studies 1a, 1b, 2), we characterized the development of prefrontal cortex dependent behaviors, structure, and function in children born moderate-to-late PT (32-36 weeks gestation). Infants born only moderate-to-late PT represent approximately 8% of all births in the United States (and 80% of all PT births; Hamilton, Martin, Osterman, Curtin, & Matthews, 2015). Although moderate-to-late PT infants are much healthier than their very PT (<32 weeks gestation) peers at birth, they are still at risk for altered prefrontal cortex development, as rapid brain growth extends over the final weeks of term pregnancy (Hüppi et al., 1998). As such, infants born moderate-to-late PT may experience an early biological risk factor (i.e. a process that initiates PT birth) in

combination with early exposure to the biologically-unexpected postnatal environment.

Children exposed to early deprivation. The impact of early adversity has been widely studied in children exposed to maltreatment (see recent reviews in Bick & Nelson, 2016; Hart & Rubia, 2012) and children growing up in poverty (see recent reviews in Hackman, Farah, & Meaney, 2010; Hackman, Gallop, Evans, & Farah, 2015).

Unfortunately, most children exposed to *early* forms of adversity also experience adversity *later* in development. In contrast, children adopted internationally from orphanage care (post-institutionalized or PI children) experience adversity limited to an early period in life: time spent in the orphanage. Following adoption, PI children exit the depriving environment and are generally raised in middle-to-high socioeconomic status families. In Study 3, we characterized the long-term impacts of early deprivation on prefrontal cortex structure and connectivity in PI children adopted from orphanage care prior to age 5, who had been living with their adoptive families in the United States for an average of 12 years. Despite growing recognition of its potentially devastating impact on infant development, orphanage care is still the primary method of non-parental care for children in many European and Asian countries (UNICEF, 2012). Deprivation of normative aspects of the environment in the orphanage context, including nutritional deficiencies, reduced cognitive stimulation, and the lack of a consistent caregiver relationship, all represent converging risks for the early development of prefrontal cortex that may lead to deficits that continue to persist following years of living in a more positive environment.

Selection of study populations. Children born PT and children reared in

orphanage care during early childhood have experienced different forms of early biological and/or environmental risks that may converge to impact both concurrent and long-term trajectories of prefrontal cortex development (see Chapter 1 for additional discussion). These two types of adverse experiences differ greatly in terms of the timing of risk factors (prenatal/early post-natal vs. risk across early childhood), the contextual dimensions of the experience (excess environmental stimulation for an under-developed brain vs. deprivation of necessary environmental stimulation), and possibly in characteristics of later environments (e.g. influences of parenting, familial income, experiences evoked by the child, etc.). Despite a downward trend in PT birth rates (Hamilton et al., 2015) and increasing recognition world-wide that foster-care and/or guardian care is more beneficial for children's well-being than orphanage rearing (UNICEF, 2012), these forms of early adversity remaining disappointingly common and are broadly representative of the types of adverse experiences encountered by children growing up in the United States and worldwide.

Outline of dissertation. In light of recent advances in infant neuroimaging research, we first provide a position paper (Chapter 1) advocating that prefrontal cortex should be conceptualized as a “rapidly changing”, rather than only “late-developing”, region of the brain. We review prefrontal cortex development across multiple levels (neurobiology to behavior) and expand our discussion of the impact of environmental variation on prefrontal cortex development to include mechanisms of change. We then present three studies characterizing the impact of early experience on prefrontal cortex across different levels of measurement and different developmental time scales. In Study

1 we characterize the structure of higher-level, prefrontal-dependent cognitive skills in 9-month-old infants (Study 1b). We describe the behavioral correlates of exposure to early biological risk (moderate-to-late PT birth; Study 1a and 1b) and of normative variations in the familial environment (Study 1b), demonstrating that meaningful differences in frontal-lobe dependent behaviors can be measured within the first year of life. In Study 2 we provide evidence that disruptions in prefrontal cortex development in children born moderate-to-late PT persist into adolescence using structural and functional neuroimaging measures. In Study 3 we document impacts of a different type of early adverse experience (orphanage rearing) and describe its long-term impact on the connectivity of frontal-lobe systems in adolescents; these results indicate that the impact of severe early adversity extends beyond frontal lobe systems and may lead to alterations in how the brain adapts to later environments. We conclude by integrating the results of our work with the broader literature, providing suggestions for future directions, and highlighting the translational importance of this work for improving the well-being of young children.

CHAPTER 1

Rapid Infant Prefrontal Cortex Development and Sensitivity to Early Environmental Experience

Outline

Over the last fifteen years, the emerging field of developmental cognitive neuroscience has described the relatively late maturation of prefrontal cortex in children and the relation between gradual structural changes and children's protracted development of prefrontal-dependent skills. This widespread recognition by the broader scientific community of the extended maturation of prefrontal cortex has led to the overwhelming perception of prefrontal cortex as a "late developing" region of the brain. However, despite its supposedly protracted development, multiple lines of research have converged to suggest that prefrontal cortex development may be particularly susceptible to individual differences in children's early environments. Diverse experiences that produce measurable, long-term changes in frontal lobe structure, function, and/or dependent behaviors include childhood poverty, disruptions of parent-infant caregiver relationships, preterm birth, and even normative variations in the prenatal environment. Recent studies demonstrate that the impacts of early adverse environments on prefrontal cortex are present very early in development: within the first year of life. We review new neuroimaging evidence demonstrating that prefrontal cortex should be characterized as a "rapidly developing" region of the brain, discuss the converging impacts of early adversity on prefrontal circuits, and present potential mechanisms via which adverse

environments shape both concurrent and long-term measures of prefrontal cortex development. Given that environmentally-induced disparities are present in prefrontal cortex development within the first year of life, we argue that translational work in intervention and/or prevention science should focus on intervening early in development to take advantages of this early period of rapid prefrontal development and heightened plasticity.

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Rapid Infant Prefrontal Cortex Development and Sensitivity to Early Environmental Experience

Human brain development is not a linear process. Widespread recognition of the extended maturation of prefrontal cortex in human children has led to the overwhelming perception of prefrontal cortex as a “late developing” region of the brain. Mapping the protracted trajectory of prefrontal cortex development has been central to explanations of age-related changes in children’s cognitive development. Rapid improvements in children’s ability to regulate their behavior and emotions in a goal-directed fashion, commonly referred to as executive function (EF) skills (Fuster, 2002), likely rely on the maturation of prefrontal cortex (e.g. see Best & Miller, 2010). Slow refinement of prefrontal circuits necessary for decision-making and cognitive control is presumed to underlie the vulnerability of adolescents to making risky choices (Casey et al., 2011). Early individual differences in prefrontal-dependent behaviors also show predictive power over the lifespan; EF skills at preschool-age are predictive of long-term measures of well-being, including academic achievement, social competence, stress resilience, externalizing disorders, divorce rates, and adult body mass index (Ayduk et al., 2000; Casey et al., 2011; Eigsti et al., 2006; Mischel, Shoda, & Peake, 1988; Mischel, Shoda, & Rodriguez, 1989; Schlam, Wilson, Shoda, Mischel, & Ayduk, 2013; Shoda, Mischel, & Peake, 1990).

The characterization of frontal lobe as late developing has been useful in conveying to the general public one reason why children and adolescents think and behave differently from adults, and has even generated important dialogue regarding the

application of developmental science to the field of law (Steinberg, 2009). It has also resulted in an unintended and unfortunate cost: a perception of prefrontal cortex as structurally and functionally undeveloped in young infants and toddlers. Neuroimaging techniques have advanced remarkably over the last 10 years and prefrontal cortex development can now be investigated in extremely young infants. These new studies purport that prefrontal cortex development advances most rapidly within the first two years of life, and that frontal lobe regions organize and direct cortical development in intriguing ways.

If prefrontal cortex development is uniquely precocious during early infancy, this has important implications for how children's early environments shape the development of frontal circuits important for complex cognitive skills. Animal models and human studies suggest that development of frontal lobe structure, function, and behaviors are permanently shaped by, and may be uniquely susceptible to, early adverse experiences. Fortunately, there is growing awareness across the scientific community, government organizations, private corporations, and the general public that children are not 'just resilient': adverse early experiences can lead to a myriad of harmful outcomes at both the individual and societal level. The extensive media coverage of the ACE (Adverse Childhood Experiences) Study has been particularly instrumental in demonstrating the importance of early experiences for health-related outcomes in adulthood (e.g. Anda et al., 2006). Vulnerable young children are exposed to adverse environments in high numbers; even in highly industrialized countries like the United States, one in five children live in poverty (Jiang, Ekono, & Skinner, 2016). Funding for research to reduce

disparities associated with early adversity is on the up-swing; in 2016 the United States allocated an additional \$1.5 billion dollars (\$10.1 billion total) to support Head Start, a program targeted toward promoting school readiness in young children from low-income families. Understanding the mechanisms via which experiences shape the development of prefrontal cortex is critical to the design of intervention programs that effectively ameliorate the impact of adversity early in life when the brain remains most malleable. Unfortunately, because the rapid development of infant prefrontal cortex has been underappreciated, our field lacks a comprehensive understanding of how experiences impact prefrontal development during the earliest years of life.

In the current review we summarize new neuroimaging research along with studies of prefrontal neurobiological development and infant prefrontal-dependent behaviors to argue that prefrontal cortex should be characterized as a “rapidly maturing” brain region. We restrict our discussion of development to approximately the first two years of life, as postmortem studies suggest that basic brain structure and connectivity is present by this age (e.g. Huttenlocher & Dabholkar, 1997) and deviations in brain development associated with developmental disorders can already be detected (e.g. Hazlett et al., 2011). Next, we provide evidence that multiple, diverse early risk factors converge to impact long-term frontal lobe development. We begin this section with a discussion of conceptual approaches to defining experience, and then provide three examples (maltreatment, poverty, and preterm birth) of how early adversity impacts prefrontal cortex development. Although it is unlikely that one mechanism specifically explains how early experience becomes biologically instantiated in later frontal lobe

development, we review multiple processes by which prefrontal cortex development may be impacted by the early environment. We conclude our review by integrating our current understanding of infant prefrontal cortex development and sensitivity to early environments, along with a discussion of future directions and challenges in this field.

Frontal Lobe Contributions to Infant Cognition

Commonalities in behavior of adult prefrontal lesion patients and young infants and toddlers are often used as evidence of the relative immaturity or “functional silence” of prefrontal cortex early in life (see Zelazo & Müller, 2002 for review of this argument). However, one of the first developmental neuroimaging studies demonstrated that metabolic activity in frontal lobe changes dramatically over the first year of life (Chugani & Phelps, 1986). To date, there has been a dramatic convergence of evidence from behavioral studies and the application of neuroimaging techniques to the study of cognition in young infants and toddlers to suggest that frontal lobe functioning is actively changing, even early in infancy. In this section, we briefly highlight examples of diverse infant cognitive and socioemotional processes supported by early prefrontal cortex development. For more comprehensive reviews, see Grossmann (2015) or Hendry, Jones, and Charman (2016).

Early Executive Function (EF) Skills

Both infant behavioral, infant neuroimaging, and non-human primate lesion studies convincingly demonstrate that infant prefrontal cortex supports early EF development. For example, young infants’ failure to pass Piaget’s classic A not B task, a widely-accepted measure of early inhibitory control and working memory abilities, is

presumed to reflect the developmental immaturity of infant prefrontal cortex (Diamond, 1990b). In this task infants are asked to retrieve a hidden object from one of two locations. Dramatic age-related improvements occur on this task between 7-12 months, as infants become able to tolerate longer delays before searching (Diamond, 1990b). The dependence of flexible searching behavior on prefrontal circuits has been demonstrated in non-human primates, where dorsolateral prefrontal cortex lesions selectively disrupt task performance (Diamond, 1990a). Frontal lobe function is also implicated in human infants; age-related improvements in performance are correlated with changes in frontal electroencephalographic (EEG) activity (Bell & Fox, 1992, 1997; Cuevas, Bell, Marcovitch, & Calkins, 2012) and measures of frontal lobe activation using functional near-infrared spectroscopy (fNIRS; Baird et al., 2002). Even younger infants can exhibit behaviors reflecting some knowledge of the true hiding location of the object if subtle task features are manipulated (e.g. measuring looking direction rather than reaching; see review in Luciana, 2003). Taken together, these brain-behavior relationships indicate that infant prefrontal cortex is functional earlier in development than previously recognized, and likely underlies early forms of EF skills.

Longitudinal studies have also convincingly demonstrated that infant measures of complex attention, memory, and inhibition skills are predictive of EF measures in later childhood. For example, individual differences in infant measures reflecting the ability to both sustain and flexibly shift attention are predictive of EF during childhood and adolescence (Cuevas & Bell, 2014; Johansson, Marciszko, Gredebäck, Nyström, & Bohlin, 2015; Papageorgiou et al., 2014; Sigman, Cohen, & Beckwith, 1997; Sigman,

Cohen, Beckwith, Asarnow, & Parmelee, 1991), both in typically developing infants and in at-risk populations (Hitzert, Van Braeckel, Bos, Hunnius, & Geuze, 2014; Rose, Feldman, Jankowski, & Van Rossem, 2012). These predictive relationships typically remain even after controlling for general intellectual ability (e.g. IQ) and/or processing speed. Complementary findings in the behavioral literature also suggest that normative variations in dopaminergic genes with receptors in prefrontal and fronto-striatal brain regions are related to individual differences in a variety of infant and toddler cognitive behaviors, including diverse forms of attention (Holmboe et al., 2010; Markant, Cicchetti, Hetzel, & Thomas, 2014a, 2014b; Voelker, Sheese, Rothbart, & Posner, 2009). Although frontal lobe function cannot be directly inferred from these behavioral studies, they provide striking evidence of developmental continuity in complex cognitive skills, emerging prior to 12 months of age, that likely involve prefrontal circuitry (Hendry et al., 2016).

Diverse Cognitive and Socioemotional Functions

In addition to its role in early EF, recent functional neuroimaging studies indicate that infant prefrontal cortex is functionally active across a variety of cognitive and socioemotional tasks, even when activation would not be predicted from the adult neuroimaging literature (Grossmann, 2013a; Johnson, 2011). For example, 2-month-old infants selectively recruit the left inferior frontal gyrus when processing face, but not object, stimuli, although this brain region does not show face-selective activity in adults (Tzourio-Mazoyer et al., 2002). Frontal activation has also been reported in infants during sensory processing, speech and language processing, early forms of attention and

novelty preference, and later emerging inhibitory control and working memory abilities (e.g. Dehaene-Lambertz & Dehaene, 1994; Grossmann, 2013; Nakano, Watanabe, Homae, & Taga, 2009; see Dehaene-Lambertz & Spelke, 2015 for recent review of speech and language processing literature). Why frontal lobe is implicated in so many behaviors in young infants is unclear. Classic frontal-lobe functions such as working memory may be implicated in cross-task activation (e.g. holding the previous sensory stimulus in mind to judge whether it is novel or familiar) or the frontal lobe may support more general, top-down learning processes in young infants (Dehaene-Lambertz & Spelke, 2015).

Infant prefrontal cortex is also highly sensitive to social stimuli during early development (see Grossmann, 2015 for recent review), perhaps even showing early functional specialization for detecting social signals (Jones, Venema, Lowy, Earl, & Webb, 2015). fNIRS studies indicate that infant prefrontal cortex is implicated in detecting and processing affect in human voices (Blasi et al., 2011), and in comprehending the communicative intent of adults through detection of both eye contact and sensitivity to the infant's own name in preverbal infants (Grossmann, Parise, & Friederici, 2010). Although some of these purportedly social functions of infant prefrontal cortex may reflect early EF skills such as sustained attention to relevant stimuli in the face of distraction, joint attention has been argued to be fundamentally social in nature (Grossmann, 2015), is known to relate to left dorsolateral prefrontal activity in infants (Caplan et al., 1993; Grossmann & Johnson, 2010) and may represent a uniquely human prefrontal-dependent skill (Saxe, 2006).

Functional Divisions of Infant PFC

The growing fNIRS literature examining prefrontal involvement in infant cognitive and socioemotional processing supports a broad division of frontal lobe into two gross anatomical regions with differing functional properties: a medial region primarily responsible for affective processing (Saito, Aoyama, et al., 2007; Saito, Kondo, et al., 2007), and a more lateral region primarily responsible for cognitive processes such as attention and memory (Baird et al., 2002; Nakano et al., 2009; Watanabe et al., 2013; Watanabe, Homae, Nakano, & Taga, 2008). This division generally coincides with organizational principles of prefrontal function from adult lesion studies and adult functional magnetic resonance imaging (fMRI) studies, suggesting a relatively continuous developmental organization of prefrontal cortical function (Grossmann, 2013a). Implications for the diverse roles of prefrontal cortex in infant cognition will be more extensively discussed later in this paper as a potential mechanism by which variations in early experience may impact long-term prefrontal development. However, it is evident that the popular conception of infant prefrontal cortex as remaining “functionally silent” should be definitively overturned.

Neurobiological Development of PFC

A role for infant prefrontal cortex across multiple cognitive and socioemotional processes suggests that important maturational changes occur in this brain region during the first years of life. A full review of embryonic and postnatal neurobiological brain development processes that support frontal lobe functional maturation is not possible here (see Markant & Thomas, 2013 for in-depth review). Instead, we briefly summarize major

pre- and postnatal neurobiological processes in human brain development, with special attention to unique temporal and organizational features of early prefrontal cortex development. See Figure 1.1 for a summary of the approximate timeline of neurobiological processes.

Neuroanatomical Definition

The frontal lobe is one of the cortical regions to undergo the greatest expansion within the trajectory of an individual's brain maturation, representing approximately one-third of an adult's neocortex (Fuster, 2002). The frontal lobe is defined as cortex that lies anterior to the central fissure (Goldman-Rakic & Porrino, 1985), or as the projection field of the dorsal medial thalamus (Goldman-Rakic & Porrino, 1985; Kolb et al., 2012).

Anatomical subdivisions in primates based on histology include dorsolateral, ventromedial (cingulate), and orbitofrontal regions (Stuss & Benson, 1986). Divisions are also characterized based on differing patterns of connectivity, with dorsolateral regions demonstrating increased connectivity with the basal ganglia (Fuster, 2002) and posterior parietal cortex (Petrides et al., 1984), while medial and orbital regions show increased connectivity with the hypothalamus and limbic structures (Fuster, 2002).

Ultimately, prefrontal cortex is purported to be the best connected of all cortical structures, receiving input from all other cortical regions (Fuster, 2002; Kolb et al., 2012) and may be central to coordinating the functioning of multiple, broad cortical networks (Vincent, Kahn, Snyder, Raichle, & Buckner, 2008).

The homology of prefrontal cortex anatomy and connectivity across mammalian species is well-established but remains somewhat controversial and is beyond the scope

of the current paper (see Fuster, 2002 for brief review). Much of our understanding of early human brain development is derived from studies of cortical development in primates, with the inference that processes proceed in a similar order in human fetuses and neonates, although on a different timescale due to differences in gestational length.

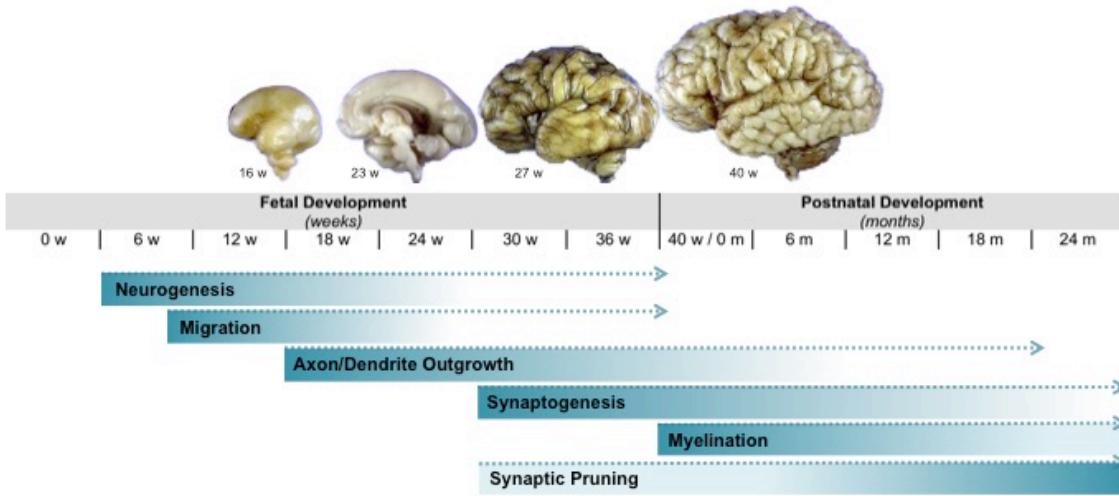


Figure 1.1 Summary of the approximate timeline of neurobiological processes in the human brain across prenatal and early postnatal development. Dashed lines represent periods of active development and darker colored shading represents periods of peak change. Fetal brains show rapid change in cortical complexity across the last trimester of pregnancy.

Adapted from de Graaf-Peters & Hadders-Algra, 2006; Anderson, 2003; and fetal brain images via metstat.med.utah.edu

Birth, Differentiation, and Migration of PFC Neurons

Brain development begins early in pregnancy with the formation of the neural plate shortly after conception. Over several days, the neural plate folds and elongates to form the neural tube. Along the anterior end of the neural tube neuronal and glial precursor cells rapidly proliferate in the subplate zone. The subplate zone subserving prefrontal cortex is proportionally larger than that of other regions of the brain (e.g. four times wider than the subplate of occipital cortex; Rakic, 1995). It also remains present in frontal cortex longer than in any other region of the brain, persisting up to 13 months in the gyral crowns of frontal cortex (vs. 6 months in other associative cortex areas; Pandit et al., 2013). The expansion in size and extended maturation of the frontal lobe subplate zone likely reflect the complex connectivity of prefrontal cortex, even in the infant brain (Rakic, 1995).

Neurons destined for prefrontal cortex are already developing by embryonic day 50-100 in non-human primates (Schwartz, Rakic, & Goldman-Rakic, 1991). Prefrontal neurons arrive at their final locations via migration from the subplate zone to cortex in a series of waves that results in the adult-like, six-layered neocortex. Migration occurs primarily along radial glia fibers, specialized glial cells that have long processes extending to the edge of cortex (Kriegstein & Gotz, 2003). Radial organization is prominent throughout the brain during the second trimester of gestation, but persists longer in ventral frontal areas than posterior brain regions (Takahashi, Folkerth, Galaburda, & Grant, 2012). Migratory pathways for prefrontal cortical neurons are also physically longer in distance than those of other cortical neurons, increasing the risk for

migration errors (Rakic, 1995). Despite these longer pathways, prefrontal neurons are among the first to arrive in cortex due to a general anterior to posterior progression of neurogenesis and migration, and are thus more likely to support intrinsic firing patterns in the developing brain (Cahalane et al., 2011; see review in Johnson, 2012).

As migration progresses, cells acquire specific fates and differentiate to take on their mature characteristics, including the development of rudimentary dendrites and axons (Pandit et al., 2014). Elongation of axons leads to the formation of major anatomical tracts during the second trimester of gestation (e.g. limbic and thalamocortical fibers; Huang et al., 2006). Importantly, the uncinate fasciculus, a large white matter tract connecting limbic regions to prefrontal cortex, is one of the few long-range association pathways that can be reliably detected in early fetal brains (Takahashi et al., 2012). Although this major frontal lobe tract develops early, within lobe pathways are instead present first in occipital and parietal cortex, emerging later in frontal regions (Takahashi et al., 2012). Across cerebral cortex, this initial series of neurobiological processes occurs primarily during the prenatal period, with cell migration ending by the first week of postnatal life; however, axon and dendritic growth proceeds well into the postnatal period as neurons begin to establish and refine connectivity patterns (see Markant & Thomas, 2013 for review).

Synaptogenesis and Synaptic Pruning in PFC

Synaptogenesis (formation of synapses) and synaptic pruning (elimination of synapses) begin prenatally but extend well into postnatal life, with differential rates of change across regions of the brain. Prenatal and postnatal connectivity is generally

established through exuberant development, which is then followed by a phase of selection and pruning of connections (Collin & van den Heuvel, 2013). Although this over production and subsequent pruning may seem inefficient, it allows for the individual organism's neural circuitry to be shaped by unique environmental experiences.

Unlike primary sensory regions which reach peak synaptic density in the first months of life, post-mortem studies indicate that human prefrontal cortex attains its maximum number of synapses after 15 months of age, with some prefrontal regions not reaching peak density until early childhood (Huttenlocher & Dabholkar, 1997; Petanjek et al., 2011; although see Bourgeois, Goldman-Rakic, & Rakic, 1994 for contradictory results). Although prefrontal regions take longer to reach peak synaptic density, histological studies of superior and middle frontal gyri tissue have revealed rapid sculpting of dendritic trees in prefrontal pyramidal neurons during the first months of life. Basal dendritic trees of prefrontal pyramidal neurons in cortical layers IIIc (predominantly long-range association projections) and V (basal ganglia projections) reach 60-80% of total adult size by only three months of age. Interestingly, layer IIIc neurons display a second period of exuberant dendritic growth beginning at the end of the second year and continuing into the third year of life (Petanjek, Jadaš, Kostović, & Uylings, 2008).

Prefrontal cortex is widely recognized to show extended synaptic pruning into adolescence (e.g. Woo, Pucak, Kye, Matus, & Lewis, 1997). However, most developmental psychologists are unaware that pruning is also extensive during early infancy, particularly in layer V subcortical projection neurons (Petanjek et al., 2008);

advances in prefrontal-dependent behaviors during early infancy may therefore be linked to early refinement of fronto-striatal circuitry.

Myelination in PFC

Cortical myelin (also commonly referred to as white matter) is produced by oligodendrocytes, specialized glial cells that first emerge prenatally (as “premyelinating oligodendrocytes”) when axons are initially sprouting and elongating (Volpe, 2009). Actual myelination (wrapping of connections with a fatty membrane) occurs almost exclusively after birth (Pandit et al., 2014); as such, minimal myelinated white matter is present in the fetal brain until late in gestation, when development suddenly accelerates with a five-fold increase over the last weeks of human pregnancy (Hüppi et al., 1998).

Pre-myelination during prenatal development and actual postnatal accrual of myelin follow a posterior to anterior gradient (Dubois et al., 2014), with a growing literature indicating that myelination changes in frontal lobe extend well into late adolescence (e.g. Asato, Terwilliger, Woo, & Luna, 2010; Nagy, Westerberg, & Klingberg, 2004). Frontal lobe myelination during the early postnatal period is unique from that of other brain regions due to the longer persistence of pre-myelinating oligodendrocytes within region. Pre-myelinating oligodendrocytes, which are more vulnerable than mature oligodendrocytes to perinatal insults, remain predominant in frontal lobe regions at birth (Back et al., 2001), making early frontal lobe white matter uniquely susceptible to injury.

Neuroimaging Measures of Early PFC Development

The neurobiological processes reviewed in the previous section suggest an

important role for early-migrating prefrontal neurons in organizing early brain activity and a unique vulnerability of frontal lobe white matter to early injuries. Unfortunately, these neurobiological processes are not currently measurable in the living human brain. However, neurobiological processes contribute to structural brain changes that can be observed at a larger scale in human fetuses, infants, and toddlers using non-invasive imaging techniques.

Although quite different in level of analysis from the histological studies of neurobiological processes, pediatric neuroimaging research provides important information about trajectories of prefrontal cortex gray and white matter development that may be easier for developmental scientists to link to measurable changes in young infant's behavior. Because EEG measures do not provide conclusive information about the location of source activity (Michel et al., 2004) we restrict this review to structural magnetic resonance imaging (MRI) measures where spatial resolution is improved. We review noninvasive indices of early prefrontal structural brain development including regional volume and connectivity to emphasize that extensive prefrontal cortex structural development occurs in the first years of life. Furthermore, we highlight emerging studies on the brain's early connectome that demonstrate a critical role for prefrontal cortical hubs in the emerging connectivity structure of the brain. See Figure 1.2 for a summary of infant prefrontal cortex development.

Gray Matter Volume

Growth of prefrontal gray matter volume during the early childhood period is astoundingly rapid. However, controversy exists regarding the age window in which

growth rates are greatest and the extent to which prefrontal growth outstrips similar development in other brain regions. Although all studies converge on rapid growth occurring sometime within the first two years of life, differences in timing effects reported across studies likely reflect variation in scan parameters, scan segmentation methods, study samples (e.g. inclusion of preterm infants or infants undergoing MRI to rule out a neurodevelopmental problem; size of samples), study design (cross-sectional vs. longitudinal), and differences in covariates (e.g. adjustment for total brain size).

Multiple structural MRI studies with newborns and young infants have failed to document the expected adult pattern of prefrontal structural asymmetry (where the right hemisphere is greater than the left in adults and older children) (Gilmore et al., 2007; Li, Nie, et al., 2014; Matsuzawa et al., 2001; Tanaka, Matsui, Uematsu, Noguchi, & Miyawaki, 2013), which may reflect the relative structural immaturity of the newborn prefrontal cortex. Cross-sectional studies (Nishida et al., 2006) of infants born between 31-42 weeks gestation and imaged in the first months of life have reported that the fastest rate of cortical gray matter growth occurs in the frontal lobe of the brain (4.44 ml/week), followed by the parietal (2.93 ml/week), temporal (2.29 ml/week), occipital (2.40 ml/week) and limbic regions (.58 ml/week). Rapid growth in frontal lobe gray matter continues over the next two years of life, surpassing changes observed in other lobes of the brain (Matsuzawa et al., 2001). In contrast, longitudinal studies of full-term infants report a slightly different trajectory of frontal lobe volume gray matter increases. Here, increases are fastest in sensory and motor regions in the early postnatal period (Gilmore

et al., 2007), with prefrontal gray matter growth rates accelerating between 1-2 years of age and continuing at a rapid pace into the second year of life (Gilmore et al., 2012).

Surface Complexity

Growth of gray matter volume reflects separable contributions of change in cortical surface area and cortical thickness, both influenced by changes in surface complexity as the brain grows from a smooth surface to a complexly folded cortex. Extensive cortical folding occurs in the third trimester of pregnancy, but folding in the frontal lobe begins later (Dubois, Benders, et al., 2008) and progresses at a slower rate (Abe, Takagi, Yamamoto, Okuhata, & Kato, 2003). However, in the first two years of life, measures of cortical surface complexity such as gyration index (Li, Wang, et al., 2014) and the depth of sulcal pits (Meng, Li, Lin, Gilmore, & Shen, 2014) change most rapidly in frontal regions.

Although the major gyri and sulci are established by viable preterm birth, cortical surface area remains only one-third the size of the adult brain (Li et al., 2013). Cortical surface area expansion during infancy is highly non-uniform, with regions of prefrontal cortex expanding twice as much as primary visual areas (Hill et al., 2010). Longitudinal imaging studies of typically developing infants have more clearly delineated the timing of rapid prefrontal surface area increases. The highest expanding regions of the brain in the first year include parts of orbitofrontal and lateral anterior prefrontal cortex, with rapid expansion of superior and middle frontal regions during the second year of life (Li et al., 2013; Lyall et al., 2015). Although this growth is incredibly precocious, surface area at two years is only 70% of its eventual size in the adult brain (Lyall et al., 2015).

In contrast, cortical thickness reaches adult-like values across the brain by two years of life (Lyall et al., 2015). Areas in the infant brain where surface expansion occurs at the most rapid pace are also generally the thickest (Li, Lin, Gilmore, & Shen, 2015). At birth, regions of medial prefrontal cortex are among the thickest of all cortex in the brain (Geng et al., 2016; Li et al., 2015; Lyall et al., 2015). Thick prefrontal regions also show the fastest rate of growth in the first year of life, along with disproportionately rapid thickening in other frontal subregions (inferior frontal operculum, superior frontal gyrus) during the second year (Li et al., 2015; Lyall et al., 2015). Contrary to reports that cortical thickness peaks later in childhood (Raznahan, Greenstein, Lee, Clasen, & Giedd, 2012; Shaw et al., 2008), several subregions of the frontal lobe begin to show thinning over the second year of life (Li et al., 2015; Lyall et al., 2015; although see Croteau-Chonka et al., 2016). Changes in cortical thickness can only be used to make inferences about underlying neurobiological processes like synaptic pruning. However, these provocative results suggest an early wave of pruning may occur in frontal lobe regions during childhood, long before the classically described frontal-lobe pruning in the adolescent brain.

White Matter Organization

White matter grows more slowly than gray matter in absolute volume (Knickmeyer et al., 2008), but global changes in white matter organization measured via diffusion tensor imaging (DTI) are the most rapid in the first postnatal year (Geng et al., 2012; Sadeghi et al., 2013; see Qiu, Mori, & Miller, 2015 for review). Frontal lobe peripheral white matter shows the largest rate of increase in fractional anisotropy, a

global measure of white matter organization, across the infant brain (Gao, Lin, et al., 2009; McGraw, Liang, & Provenzale, 2002); this tissue also shows large reductions in axial diffusivity, likely due to continued axon growth, over the second year of life (Gao, Lin, et al., 2009). Smaller tracts involving projections to and from the frontal lobe such as the fronto-occipital pathways are apparent by at least three months after birth, although they may take until one year of age to be well delineated on structural MRI scans (Collin & van den Heuvel, 2013). Studies examining white matter microstructure metrics and/or graph theory derived measures of connection strength along anatomical tracts have reported that frontal lobe pathways are more immature at birth than sensory and motor tracts (Dubois, Hertz-Pannier, Dehaene-Lambertz, Cointepas, & Le Bihan, 2006; Dubois, Dehaene-Lambertz, et al., 2008; Geng et al., 2012; Pandit et al., 2014) but then show the fastest rate of maturational change over the first year of life.

The accrual of myelin occurs predominantly and/or exclusively after birth (Dubois et al., 2014). Similar to the gradient of myelination observed in post-mortem fetal brains (i.e. caudal to rostral; central to peripheral; e.g. Takahashi et al., 2012), *in-vivo* myelin-specific MRI techniques report that the frontal lobe is slower to show measurable myelination onset than other lobes of the brain (Deoni et al., 2011; Deoni, Dean, O’Muircheartaigh, Dirks, & Jerskey, 2012; Deoni, Dean, Remer, Dirks, & O’Muircheartaigh, 2015; O’Muircheartaigh et al., 2014; Oishi et al., 2011). However, these frontal regions then counter intuitively show a higher rate of myelin accrual over the first years of life in comparison to regions that began myelination earlier in development (Deoni et al., 2011).

Emergence of Functional Networks

Functional development of prefrontal cortical networks has recently been investigated using resting state functional connectivity MRI, which provides information about correlated activity between networks of brain regions at rest, and generally coincides with structurally connected regions of the brain (Vincent et al., 2007). Amazingly, frontal lobe networks are present extremely early in infant development and are similar in regional involvement and connectivity to what is observed in the adult brain.

Gao and colleagues first provided evidence that the default mode network, a set of regions in the adult brain that show more correlated activity at rest than during task completion, is present in a primitive state in 2-week-old infants (Gao, Zhu, et al., 2009). Remarkably, like network structure in older children and adults, the newborn version of the default mode network also includes substantial medial prefrontal cortex involvement. By one year of age, medial prefrontal cortex emerges as a hub region of the network, and by two years of age, the default mode network is similar in regional involvement and organization to the adult state (Fransson et al., 2013; Gao, Alcauter, Smith, Gilmore, & Lin, 2015; Gao et al., 2011, 2013; Gao, Zhu, et al., 2009). Fronto-parietal attention networks, which tend to be negatively correlated with the default mode network and involve substantial anterior prefrontal cortical regions, are also present in neonates and appear highly similar in typology to the adult network state by the end of the first year of life (Gao et al., 2013).

Graph theory analyses (see Cao, Huang, Peng, Dong, & He, 2016 for more

general review) of frontal lobe organization over the first two years of life indicate there are decreases in local efficiency and degree among frontal regions, potentially representing regional specialization and removal of redundant and/or spurious connections (Gao et al., 2011; Gao, Zhu, et al., 2009). In particular, the existence of medial prefrontal cortical regions serving as hubs this early in brain development is striking. Hub regions typically show a large degree of anatomical and functional connectivity, and are hypothesized to play a strong role in both coordinating and integrating information within and across networks of the brain (Gao, Zhu, et al., 2009). Frontal hubs in the neonate brain suggest major frontal lobe functional development has already occurred by term birth (Doria et al., 2010; Gao et al., 2011; Smyser et al., 2010) and that frontal regions may organize infant brain activity more so than posterior cortical regions (Grossmann, 2013a).

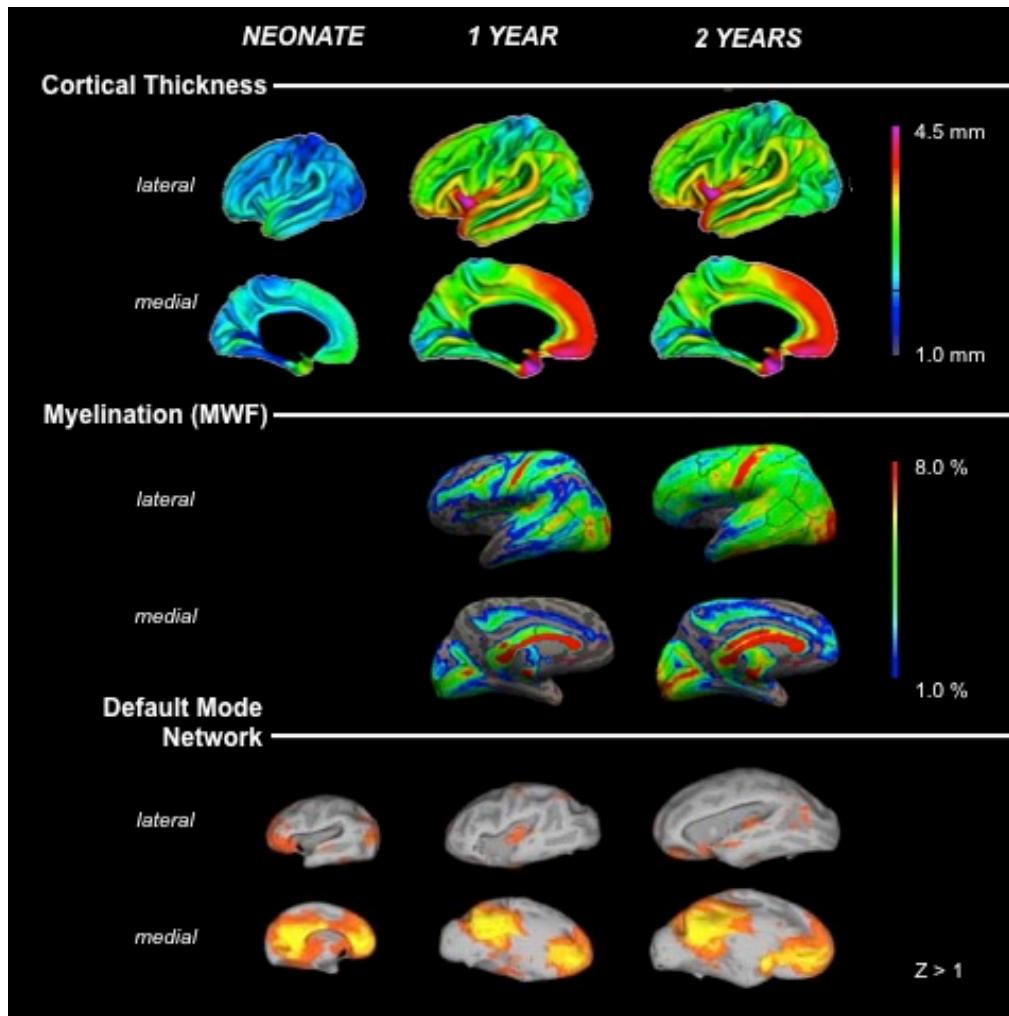


Figure 1.2. Spatial distribution of cortical thickness, inferred myelination (via myelin water fraction – MWF), and default mode network in neonates, infants, and toddlers (left hemisphere). Medial prefrontal regions are among the thickest cortex at birth and across the first years of life. Similarly, medial prefrontal involvement in the default mode network is present even in neonates. In contrast, myelin accrual in frontal lobe regions is minimal earlier in development but increases rapidly over the first year of life.

Adapted from Li, Lin, Gilmore, & Shen (2015); Deoni, Dean, Remer, Dirks, & O'Muircheartaigh (2015); Gao, Zhu, Giovanello, Smith, Shen, & Gilmore (2009)

Interim Summary: Early PFC Development

Prefrontal cortex is often referred to in the developmental psychology literature as a “late developing” region of the brain. However, rapid expansion of frontal lobe gray matter volume occurs within the first two years of life, along with dramatic changes in surface complexity. Studies mapping developmental trajectories of whole-brain surface area and cortical thickness metrics have characterized prefrontal subregions as “fast growing” areas of the brain, exemplified by thick cortex at birth and high growth rates of both surface area and cortical thickness over the first years. Both histological and neuroimaging studies of infant cortical thickness suggest frontal lobe may undergo an early wave of pruning, likely in fronto-striatal circuits, much earlier in development than previously recognized. Long-range connections involving frontal lobe are present from the second trimester of gestation; continued sculpting of frontal-cortical connectivity occurs after birth, with myelination of frontal pathways beginning later in development but then changing more quickly in comparison to other regions of the brain. Histological studies also reveal that frontal lobe white matter may be uniquely susceptible to injury. Last, the early arrival of frontal neurons via migration and the presence of medial prefrontal cortex as a “hub region” in developing brain networks suggests that prefrontal activity can influence network functionality to a greater extent than previously conceptualized. Disruptions to the development of this important, organizing region could therefore have broad, cascading effects across multiple brain networks. See Figure 1.2 for a summary of rapid infant prefrontal cortex development.

Given this evidence supporting rapid maturation of prefrontal cortex during

infancy, along with its broad role in multiple aspects of infant cognitive and socioemotional development, it is appropriate to revise the conceptualization of prefrontal cortex as a “late” developing region of the brain. Instead, prefrontal development is better described by a trajectory that shows rapid change during early infancy, along with later periods of extended refinement (Blakemore & Choudhury, 2006).

Since prefrontal cortex plays a role in some of the more unique and complex aspects of human cognition that must be learned during infancy and early childhood (Saxe, 2006), it is intuitive that this region is highly sensitive to modifications of the early environment, which is the topic of the remainder of this paper. Early and extended sensitivity of prefrontal cortex to environmental experience conveys maximum potential for the developing organism to benefit from environmentally-induced plasticity. However, if the early environment is not advantageous and/or if adaptations to the early environment are maladaptive in later contexts, this early sensitivity could serve as a risk factor for long-term neurobehavioral development.

Defining Early Experience

Converging evidence demonstrates that diverse types of early experience impact prefrontal development in young mammals, including human infants. It is beyond the scope of this paper to review all the relevant literature from multiple fields describing effects of experience on long-term prefrontal development. Instead we discuss conceptual approaches to defining experience and provide an overview of the impact of three types of adverse early environments (maltreatment, poverty, and preterm birth) on

prefrontal development, which differ in content and temporal characteristics, but result in similar neurobehavioral effects.

Characterization of Early Experience

Experience is ubiquitous and thus challenging to empirically define. The difficulty in accurately measuring and characterizing individual differences in environmental context across the lifespan has long been recognized in developmental psychology (e.g. Bronfenbrenner, 1999) and across other related fields. Embryologists examine distinctions between errors of commission vs. omission and their impact on brain development (e.g. see Cheatham, Sesma, & Georgieff, 2010 for summary). Epidemiologists use case-control designs to distinguish the impact of genetic risk vs. environmental exposure in the development of complex diseases (e.g. Clayton & McKeigue, 2001). Even cellular and molecular neuroscientists consider the impact of variation in local features of the neuronal environment within which brain cells develop (e.g. see cortex transplantation studies in Luo & O’Leary, 2005).

Characterization of the timing and nature of early experiences is necessary to more precisely link individual differences in environmental variation to concurrent and subsequent measures of brain development. Furthermore, a better understanding of the aspects of the environment that are related to the most variance in brain development could have important policy-related implications for early intervention services. Many frameworks have been developed across disciplines interested in early childhood and developmental outcomes to characterize the quality and nature of early environments. Although several of these models lack explanations for how experience is instantiated at

the neural level and most are not specific to prefrontal cortex development, they provide important background for conceptualizing the range of experiences that might shape concurrent prefrontal cortex development, how this may occur biologically, and why effects may carry forward over development.

Relation to Neurobiological Processes

Greenough and colleagues (1987) have provided a classic model of how different aspects of environmental experiences (expectant vs. dependent processes) impact specific neurobiological mechanisms of brain development. Experience-expectant processes rely on the developing organism being exposed to basic environmental information (e.g. patterned light, sequential sounds), so rudimentary that it should be universally experienced by all members of a species across variable environments. Experience-expectant processes are linked to sensitive periods: windows of time in which a developing system is highly plastic and most open to influence by the environment (e.g. Hensch, 2005). Tuning of the brain to the expectable environment during sensitive periods is manifested as retention of a subset of necessary synapses among those that were initially overproduced (Greenough, Black, & Wallace, 1987), reducing the amount of brain development that must be precisely specified by genetics.

In contrast, experience-dependent processes are not limited to early development and instead reflect exposure to environmental information that is unique to the organism over the lifespan (e.g. learning rules within a new social group, learning new fine motor skills associated with a musical instrument). Experience-dependent plasticity thus allows for learning across the lifespan, providing a powerful mechanism for individual

differences in brain development. Typically studied through environmental enrichment paradigms in animals, experience-dependent processes are associated with generation and retention of new synapses (Greenough et al., 1987) and myelination of connections (Lovden et al., 2010). However, there is no abrupt transition from reliance on experience-expectant processes to utilization of experience-dependent; instead, both processes shape neural development early in life, followed by life-long maintenance of established neural systems via experience-dependent processes.

What constitutes expectable input and the timing and existence of sensitive periods for higher-level cognitive and/or socioemotional processes in human infants remains controversial (e.g. see Fox, Levitt, & Nelson, 2010). Most developmental psychologists recognize that an expectable feature of the environment for a human infant includes a close relationship with a caregiver (Humphreys & Zeanah, 2014; Nelson, 2007); beyond fulfilling basic safety and nutritional needs, caregivers ideally regulate the physiology of the infant and provide an environment with developmentally appropriate cognitive and social stimulation. Although deprivation of expectable input is clearly detrimental, what constitutes the “optimum” level of experience is unclear; excess enrichment may also result in negative developmental effects. Furthermore, expectant and dependent processes are not completely separable, as a deficit in expectable input will also likely impact subsequent experience-dependent plasticity.

Dimensions of Experience

Although it was initially assumed that drastic variations in environmental experience would be required to alter cortical development (e.g. extreme sensory

deprivation, such as dark-rearing of infant animals), animal models suggests that relatively subtle variations in the environment can induce developmental changes in broad regions of the brain (Mychasiuk, Gibb, & Kolb, 2012). Frameworks that describe the characteristics of adverse environments hypothesize that different types of experience (e.g. exposure to inadequate vs. harmful input; Humphreys & Zeanah, 2014) will impact brain development in unique ways. McLaughlin and colleagues recently proposed a model differentiating depriving environments (those with low complexity) from those characterized by high levels of threat (to the organism's physical well-being) at the behavioral and neural level (McLaughlin, Sheridan, & Lambert, 2014; Sheridan & McLaughlin, 2014). At the neurobiological level, depriving environments are predicted to cause early pruning or over-pruning of synapses, including in prefrontal regions. Environments with high levels of threat are hypothesized to primarily alter fronto-limbic circuitry, driven by stress-induced changes in dendritic structure and arborization in limbic and ventromedial prefrontal regions. However, this approach of identifying unique characteristics of various experiences is challenged by the fact that multiple aspects of environmental risk often co-occur (Anda et al., 2006) and by a difficulty in conceptualizing how features of adverse environments are perceived and/or experienced by young infants and toddlers (e.g. see Graham et al., 2016 for discussion of normative development of fear during infancy).

Cumulative Nature of Experience

Rather than separating experiences by dimensional features, other models focus on measures of cumulative environmental adversity, combining separate environmental

risk factors into an aggregate or composite risk score (Evans, Li, & Whipple, 2013). Exposure to multiple vs. single risk factors is more detrimental for a variety of developmental outcomes and these models outperform those that consider only single exposures (Evans et al., 2013). Bronfenbrenner's bioecological systems model (Bronfenbrenner, 1999) is also a useful heuristic for conceptualizing how risk may aggregate across multiple levels of a child's environment. Here the individual child is viewed as nested within a multi-leveled environment, with the most proximal environments embodying every day exposures (e.g. familial home) and more distal environments representing broader systems that impact the sociocultural context in which development occurs (e.g. government policies that impact the availability of a caregiver). Although environmental risks most proximal to the infant would be predicted to have a greater negative effect on development, distal influences that shape functioning of the caregiver are also recognized.

Both models are largely atheoretical from a neurobiological perspective, but are broadly congruent with conceptions of toxic stress and/or allostatic load (Hertzman & Boyce, 2010; Lupien, McEwen, Gunnar, & Heim, 2009; McEwen & Morrison, 2013; Shonkoff et al., 2012), which describe the impact of increasing risk exposure on the development of the stress system, including fronto-limbic circuitry. Incorporating cumulative risk exposure across levels of the environment better reflects the co-occurring risk factors experienced in many adverse environments. However, this approach often fails to consider intensity of individual risk factors and the potential for risk factors to produce interactive, cascading effects on neurobehavioral development.

Adaptation Following Early Experience

Canalization theories (Gottlieb, 1991; Waddington, 1942) predict that even in the case of exposure to adverse environments, most developmental processes can only be temporarily derailed, instead quickly returning to and/or remaining on their previous developmental pathway. However, not all individuals respond similarly to the same early experiences, a challenge that has been addressed in recent theories describing the impact of individual differences in sensitivity to the environment. Theories rooted in evolutionary biology have posited that high sensitivity to the environment may be selected for over evolutionary history. Within this framework, individuals vary not only in sensitivity to risk, but more broadly in sensitivity to both positive and negative environmental context effects (Belsky & Pluess, 2009; Boyce & Ellis, 2005). Experience-induced changes in neurobehavioral development can be viewed as the organism's attempt to adapt to the current environment (e.g. see adaptive calibration model; Del Giudice, Ellis, & Shirtcliff, 2011). Rather than adverse environments producing detrimental outcomes, deficits may arise when the environment changes and previous adaptations become problematic. To date these models have primarily focused on genetic differences in biological reactivity and/or stress neurobiology. However, individual differences in environmental sensitivity may also be related to neurobiological mechanisms that promote homeostasis (e.g. maintaining certain synaptic connections; Johnson, Jones, & Gliga, 2015), including within prefrontal cortex.

Importance of Timing

The title of this paper implicitly conveys that early experiences show some

privilege in shaping developmental trajectories. However, the broad effects of timing (including developmental timing of exposure, duration of exposure, and frequency of exposure) of experiences on subsequent development are not well understood. Sensitive periods are widely recognized to represent the developmental window within which the impact of environmental variations will be strongest, implying that early experiences are the most transformative. Sensitive periods for higher-level cognitive functions are presumed to occur later than those for sensory or perceptual functions (Fox et al., 2010), but whether they exist for prefrontal-dependent behaviors is unclear. The impact of timing is also difficult to discern because early experience may impact prefrontal development in a way that is not easily measurable or quantifiable during early life. Deficits in prefrontal-dependent behaviors induced by early adversity may not emerge until the demands on children's cognitive processing increase during the later childhood years, a pattern that would be consistent with 'growing into deficit' (Sesma & Georgieff, 2003) or a 'sleeper effect'.

Early Adverse Experiences and PFC Development

Although defining both the timing and nature of experiences remains challenging, many studies have examined both concurrent and long-term impacts of adverse early environments on later prefrontal cortex development (see Mackey, Raizada, & Bunge, 2012 for review of additional environmental variations on prefrontal development). In the next section we provide an overview of this work within three domains: maltreatment, poverty, and preterm birth. These three types of adverse experiences were selected because they represent common risk factors for children across the world that are

disappointingly prevalent, and because they differ in temporal and dimensional characteristics which may challenge the development of prefrontal cortex in different ways.

Our intention is not to provide a comprehensive review of each domain, but rather to illustrate how seemingly different experiences can converge to produce similar impacts on prefrontal development. As in the section on normative prefrontal cortex development, we focus on the impact of early experience on structural neuroimaging metrics because of their high spatial resolution and stronger theoretical relation to neurobiological processes. Select examples of functional effects from behavioral and/or functional imaging studies are also provided to illustrate how impacts of experiences are measurable at different neurobehavioral levels. Last, few studies have concurrently measured the impact of adverse environments on neurobehavioral development in young infants or toddlers, so we also provide an overview of follow-up studies to demonstrate that impacts likely persist over development.

Maltreatment and PFC Development

Diverse forms of childhood maltreatment are associated with pervasive, long-term impacts on prefrontal cortex structure and function (see Bick & Nelson, 2016; Hart & Rubia, 2012; Humphreys & Zeanah, 2014 for recent reviews that span multiple brain systems). The impact of early maltreatment on human brain development is not surprising, given that abuse or neglect by a close caregiver represents an intense deviation from the biologically expected infant-parent caregiving relationship and likely alters both experience-expectant and experience-dependent brain development processes. Although

duration of maltreatment experiences and type of maltreatment may differentially impact brain development, most children who are exposed to maltreatment experience multiple subtypes (e.g. physical abuse, neglect) of recurring maltreatment across childhood.

Studies examining long-term impacts of maltreatment on prefrontal cortex development have generally compared individuals with a history of maltreatment at any point in childhood to non-maltreated comparison groups. In contrast, post-institutionalized (PI) or orphanage-reared children experience a time-limited period of early neglect (i.e. the institutional care environment) followed by adoption into well-resourced families.

Because the neglectful environment is limited to early life, studies with PI children demonstrate the lasting impacts of adversity limited to early childhood and the ability of the brain to adapt to the new, post-adoptive environment.

Few studies have examined the impact of maltreatment and/or institutional care on prefrontal cortex development early in life. However, because PI children are adopted at different ages, the impact of duration of exposure to early adverse environment can be assessed. We first provide a broad overview of the impact of childhood maltreatment on later prefrontal cortex development, with a primary focus on studies of PI children as this allows the timing of neglect to be constrained to the early childhood period. We then review preliminary evidence that altered prefrontal-dependent behaviors can be observed in the first years of life in children exposed to diverse forms of maltreatment; because this literature is quite small, we include findings from both maltreated and PI infants and toddlers. We close by devoting special attention to two longitudinal studies that have carefully delineated the impact of timing of early adversity in PI children.

Maltreatment across childhood. Following childhood exposure to maltreatment (see Pechtel & Pizzagalli, 2011 for review) or in the years following adoption from orphanage care (see Merz, Harlé, Noble, & McCall, 2016 for review) children show poorer EF skills. In PI children there is some evidence that longer duration of orphanage care is predictive of worse EF and regulatory abilities (Bos, Fox, Zeanah, & Nelson, 2009; Colvert et al., 2008; Loman et al., 2013; McDermott, Westerlund, Zeanah, Nelson, & Fox, 2012; Merz, McCall, Wright, & Luna, 2013; Pollak et al., 2010; Tottenham et al., 2010). Psychopathology is common across both groups of children, but higher rates of attention and hyperactivity problems in PI youth, likely reflecting poorer frontal-lobe functioning, have been argued to represent deprivation-specific patterns of functioning (e.g. see Kumsta et al., 2008). Behavioral differences in EF related to childhood maltreatment experiences are instantiated in altered prefrontal cortex functioning as indexed via fMRI. Maltreated children and adolescents show atypical functional activation during cognitive control tasks (Bruce et al., 2013; Carrion, Garrett, Menon, Weems, & Reiss, 2008; de Bellis & Hooper, 2012; Mueller et al., 2010), as well as increased frontal activation during emotion regulation (de Bellis & Hooper, 2012; McLaughlin, Peverill, Gold, Alves, & Sheridan, 2015), and error processing (Lim et al., 2015).

Neuroimaging studies of both maltreated and PI children indicate that these forms of adversity converge to impact fronto-limbic and fronto-striatal circuitry. Prefrontal cortex volumes measured at adolescence are disproportionately smaller in PI youth (Hodel, Hunt, et al., 2015) and a recent meta-analysis suggests ventro-lateral prefrontal

regions are consistently smaller in maltreated children (Lim, Radua, & Rubia, 2014; see Bick & Nelson for summary of contradictory findings). Studies of both maltreated and PI youth have also documented reductions in prefrontal surface area (Hodel, Hunt, et al., 2015), folding complexity (Kelly et al., 2013), and cortical thickness measures (Hodel, Hunt, et al., 2015; McLaughlin, Sheridan, Winter, et al., 2014). Both maltreatment and early institutional care are associated with broad changes in fronto-limbic connectivity during childhood and adolescence, including reduced white matter integrity (Eluvathingal et al., 2006; Govindan, Behen, Helder, Makki, & Chugani, 2010; Hanson, Adluru, et al., 2013; Huang, Gundapuneedi, & Rao, 2012) and decreased resting functional connectivity (Burghy et al., 2012; Herringa et al., 2013). Poor white matter organization also extends into fronto-striatal circuits in PI children (Behen et al., 2009; Kumar et al., 2014).

Impacts of childhood maltreatment on EF (Gould et al., 2012; Nikulina & Widom, 2013), prefrontal cortex gray matter volume (Ansell, Rando, Tuit, Guarnaccia, & Sinha, 2012; Kitayama, Quinn, & Bremner, 2006; Tomoda et al., 2009), frontal white matter organization (Choi, Jeong, Rohan, Polcari, & Teicher, 2009), and connectivity across frontal-lobe networks (Cisler et al., 2012; Jedd et al., 2015; Philip et al., 2013; van der Werff et al., 2013; Wang et al., 2014) have been documented in adults, suggesting prefrontal disruptions associated with adversity persist over development: a topic that has not been investigated in adults formerly adopted from orphanage care.

Maltreatment during infancy. A smaller literature has documented the impact of maltreatment during infancy on prefrontal cortex function. Measures of the impact of institutional care during a similar time range are lacking (as most infants are still in the

orphanage), but a set of recent studies has investigated prefrontal-dependent behaviors soon after children are adopted. Structural brain development early in life has not been investigated in these populations (except see Graham, Pfeifer, Fisher, Carpenter, & Fair, 2015 for a recent report of altered default mode network connectivity in infants exposed to early life stress), and is not included in this overview. Instead we consider the impact of timing of exposure to neglect on prefrontal cortex development in a subsequent section.

PFC dependent behaviors. Alterations in fronto-limbic functioning are present early in life in maltreated samples. Infants exposed to higher levels of non-physical interparental conflict show increased activity in anterior cingulate cortex when processing angry vs. neutral voices (Graham, Fisher, & Pfeifer, 2013). Differences in frontal lobe activity are also present in EEG studies with toddlers exposed to maltreatment as infants; 15 month-olds with a history of maltreatment show increased amplitude at frontal sites when attending to negative (angry) emotions in comparison to non-maltreated controls (Curtis & Cicchetti, 2013), a pattern that persists across early childhood (Curtis & Cicchetti, 2005, 2011). Deficits in EF have been documented in PI children as young as two years of age (Doom et al., 2014; Hostinar, Stellern, Schaefer, Carlson, & Gunnar, 2012). Poorer early EF skills in young PI children are related to longer duration of institutional care (Doom et al., 2014), less time spent in early family care (Hostinar et al., 2012), and poorer quality orphanage care (Hostinar et al., 2012), and are predicted by measures of frontal lobe electrical activity at 18 months (Tarullo, Garvin, & Gunnar, 2011).

Duration of early neglect. Given the lack of human studies describing early impacts of maltreatment on prefrontal cortex development, we devote special attention to studies that examine the impact of timing of exposure to early adversity. Although other studies have also documented timing effects (e.g. see Cowell et al., 2015 for evidence that maltreatment during infancy has the strongest impact on later EF), we focus on two exemplar, longitudinal projects, both conducted with cohorts of institutionally reared children: the ERA study and the BEIP.

The English and Romanian Adoptee (ERA) study has followed the development of a random sample of Romanian children, adopted from institutional care into families in the United Kingdom in the 1990s (Rutter, Sonuga-Barke, & Castle, 2010). After the fall of Ceausescu's government, children were quickly adopted out of institutions, resulting in a natural experiment in distribution of age at exit from orphanage care (0-42 months of age at adoption). The Bucharest Early Intervention Project (BEIP) is a randomized control trial of the benefits of foster care for Romanian children initially placed in institutional care as young infants (Zeanah et al., 2003). Because children were randomly assigned into foster care at different ages (6-31 months of age), the impact of duration of early adversity could be examined in a controlled design. Both studies have demonstrated that earlier timing of exit from orphanage care is associated with improved catch-up. However, the threshold at which timing matters varies across developmental domains, and results suggest that in many cases, normative prefrontal cortex development trajectories are altered for children who spend as little as six months of care in the institution.

PFC dependent behaviors. Both studies examined the relationship between length of deprivation and later Attention Deficit Hyperactivity Disorder (ADHD) symptom severity, a marker of altered frontal lobe development. In the ERA study, ADHD symptoms showed a threshold relationship with duration of early institutional care, with a steep increase in symptomatology for children adopted prior to six months of age (Kennedy et al., 2016; Kreppner, O'Connor, & Rutter, 2001; Stevens et al., 2008). The BEIP study demonstrated that EEG markers of delayed cortical maturation at study onset, including in frontal regions, (Marshall & Fox, 2004; Marshall, Reeb, Fox, Nelson, & Zeanah, 2008), underlie the later development of higher rates of ADHD symptoms (McLaughlin et al., 2010). Children placed in foster care before 24 months showed normalization of frontal EEG activity by 8 years of age (Vanderwert, Marshall, Nelson, Zeanah, & Fox, 2010). Intervention effects for ERP markers of higher-level attentional processes have also been observed in the BEIP cohort (see Bick & Nelson, 2016 for review). Interestingly, despite an impact of early placement into foster care on frontal EEG activity, ADHD symptomatology was not similarly remediated (Humphreys et al., 2015; Zeanah et al., 2009). EF deficits in the BEIP cohort were also not remediated by foster care (Bos et al., 2009) and are linked to higher ADHD symptoms (Tibu et al., 2016), perhaps because all children in the BEIP study were older than six months of age when randomization to foster care occurred.

PFC gray matter volume. The BEIP study did not report strong relationships between duration of early neglect and later measures of prefrontal cortex structure. At age 8, children who had spent any time in institutional care had smaller cortical gray

matter volumes (Sheridan, Fox, Zeanah, McLaughlin, & Nelson, 2012). Reduced cortical thickness was also observed in dorsolateral and orbitofrontal regions (McLaughlin, Sheridan, Winter, et al., 2014).

PFC connectivity. In contrast to patterns of prefrontal cortex gray matter development, the BEIP study did show positive impacts of randomization into foster care on overall white matter development (Sheridan, Fox, et al., 2012). Improvements in white matter organization at age 8 in fronto-limbic and fronto-striatal tracts were present in children assigned to foster care (Bick et al., 2015).

Poverty and PFC Development

Beyond the effects of extreme deprivation experienced by PI children, recent studies suggest that variations within a more typical range also relate to long-term measures of prefrontal development (see Hackman, Gallop, Evans, & Farah, 2015; Johnson, Riis, & Noble, 2016; Pavlakis, Noble, Pavlakis, Ali, & Frank, 2015 for reviews across multiple brain systems). Family socioeconomic status (SES) is a multifaceted construct, typically characterized by parental educational attainment, family income, and parental occupation. Specific aspects of SES shape different proximal features of the child's environment, and as such, may relate to different developmental outcomes (Duncan & Magnuson, 2012). For example, micronutrient deficiencies may be more related to insufficient familial income, while parent-child interactions may vary as a function of parental education. Variance within both of these facets of SES are likely reduced in magnitude in comparison to the extreme deprivation experienced by PI children, and as such, may not alter experience-expectant brain development processes to

the same degree. However, unlike the deprivation experienced by PI children, poverty is typically not restricted to the early childhood years. Growing up in poverty also increases children's risk for experiencing physical maltreatment and neglect (Maguire-Jack, Lanier, Johnson-Motoyama, Welch, & Dineen, 2015). As such, children living in poverty commonly experience aggregating risk, both across individual risk factors and across developmental periods.

An extensive literature supports that childhood poverty (broadly defined) impacts the development of prefrontal cortex structure, function, and dependent behaviors. The majority of these studies have investigated concurrent impacts of SES in school-aged children or aggregate measures of SES across longer developmental time periods. We highlight key findings describing the concurrent and long-term impacts of poverty on children's development, and subsequently devote more extensive coverage to the smaller literature describing the impact of "early" SES on prefrontal cortex development.

Poverty across childhood. EF skills correlate with concurrent measures of poverty across a wide variety of EF tasks, during the preschool period through the adolescent years (e.g. see Hackman & Farah, 2009; Hackman et al., 2015). Of note, in studies where additional cognitive and/or socioemotional processes have been measured, the negative impact of poverty on EF skills is disproportionately strong (e.g. Farah et al., 2006; Noble, McCandliss, & Farah, 2007). Behavioral differences in EF are reflected in fMRI measures of prefrontal functional activity. Lower SES during middle childhood is associated with reduced prefrontal engagement during complex learning tasks (Sheridan, Sarsour, Jutte, D'Esposito, & Boyce, 2012) and studies using resting EEG or ERP

measures of attention or EF have also widely documented frontal-lobe activity differences in lower-SES children and adolescents (see review in Raizada & Kishiyama, 2010).

A growing number of cross-sectional and longitudinal studies using large, population-based pediatric samples have linked measures of childhood poverty to changes in prefrontal cortex structure. In the NIH MRI Study of Normal Brain Development, lower SES during childhood predicted reduced frontal lobe gray matter volume (Hair, Hanson, Wolfe, & Pollak, 2015; although see The Brain Development Cooperative Group, 2012) and decreased cortical thickness in prefrontal sub-regions including the right anterior cingulate cortex and left superior frontal gyrus (Lawson, Duda, Avants, Wu, & Farah, 2013). Associations between SES and measures of surface area, rather than cortical thickness, were detected in the Pediatric Imaging, Neurocognition, and Genetics (PING) data set across a broadly distributed set of frontal lobe regions (Noble, Houston, et al., 2015). Smaller studies with samples of children and adolescents have provided converging results, documenting SES impacts on inferior frontal (Noble, Houston, Kan, & Sowell, 2012; Raizada, Richards, Meltzoff, & Kuhl, 2008) and superior and middle frontal gyri (Jednorög et al., 2012) volumes. Different aspects of prefrontal structural development may relate to specific constructs underlying SES (e.g. parental education vs. familial income; Lawson et al., 2013; Noble, Houston, et al., 2015). Depth of poverty is also related to prefrontal measures, where frontal lobe volume decreases (Hair et al., 2015) and reductions in surface area (Noble, Houston, et al., 2015) are non-linearly related to childhood SES. Critically, longitudinal studies have

documented that SES measures collected during childhood are predictive of prefrontal cortex development measured in adulthood, suggesting early differences can persist. Lower SES measured during childhood predicts poorer EF (Evans & Schamberg, 2009), lower orbitofrontal cortex volume (Holz et al., 2015), altered frontal connectivity in the default mode network (Sripada, Swain, Evans, Welsh, & Liberzon, 2014), and lower prefrontal activation and/or functional connectivity during emotion regulation tasks (Javanbakht et al., 2015; Kim et al., 2013; Liberzon et al., 2014) in adulthood.

Poverty during infancy. Until recently it was unclear at which age SES disparities in brain development first emerged, as very little research has been conducted in young children or using measures of SES restricted to when children were infants. Recent research suggests that the impacts of living in poverty on prefrontal cortex emerge shocking early in development.

PFC dependent behaviors. Infants living in lower-SES families perform more poorly than their higher-SES peers on a variety of behavioral tasks that reflect early EF, including the classically prefrontal-dependent A not B task (Clearfield & Niman, 2012; Lipina, Martelli, Vuelta, & Colombo, 2005) and problem solving tasks (Clearfield, Stanger, & Jenne, 2015). Deficits in higher-level memory skills are also present in the first two years of life (Markant, Ackerman, Nussenbaum, & Amso, 2016; Noble, Engelhardt, et al., 2015). Studies collecting longitudinal measures of early EF skills in infants have demonstrated that low-SES infants show a maturational lag of up to 3 months behind their higher SES peers across the first year of life (Clearfield & Niman, 2012; Clearfield et al., 2015). An EEG study of preschool aged-children also

documented that lower-SES during the toddler years predicts a maturational lag in frontal power during early childhood (Otero, 1997). Developmental trajectories of higher-level attention skills required to sustained attention (Clearfield & Jedd, 2013) and explore objects (Clearfield, Bailey, Jenne, Stanger, & Tacke, 2014; Tacke, Bailey, & Clearfield, 2015) are qualitatively different in lower-SES infants than their higher-SES peers, reflecting poorer focused attention and less advanced exploration of objects across the first year of life. Behavioral differences in attention processes may be related to differences in frontal resting EEG power that are present in lower-SES infants by 6-9 months of age (Tomalski et al., 2013).

PFC gray matter volume. Hanson and colleagues (2013) were the first to document SES-related differences in the rate of frontal lobe grey matter developmental across the first years of life (Hanson, Hair, et al., 2013). Divergence of the low-SES group from normative frontal lobe volumetric development was present within the first year of life and increased in magnitude across the toddler years (Hanson, Hair, et al., 2013). A recent study indicates that SES-differences in total cortical gray matter volume are present by 5 weeks of life (Betancourt et al., 2015), although regional lobular effects were not examined. Evidence suggests that early differences in frontal lobe gray matter volume likely persist across development; familial SES measures collected at 3 months of age are predictive of orbitofrontal cortex volumes in adulthood (Holz et al., 2015), even after controlling for current SES.

PFC connectivity. A recent study reported SES-based differences in resting state functional connectivity over the first year of life (Gao, Alcauter, Elton, et al., 2015).

Lower-SES infants showed alterations in default mode network connectivity measures at 6 months of age, including higher within-network connectivity and lower outside-network connectivity. However, these findings should be interpreted with some caution as they were marginally significant and were not detected when infants were re-scanned at 9 and 12 months.

Prematurity and PFC Development

Since SES is associated with prefrontal cortex development in young infants, it is possible SES differences begin even earlier in development, during the prenatal period. Studies with preterm (PT; birth before 37 weeks gestation) infants have clearly demonstrated that the early prenatal and postnatal environment dramatically shape prefrontal cortex development. Unlike children exposed to maltreatment or growing up in poverty, the environment of early brain development for PT infants may be one of “excessive” stimulation for an under-developed brain. Furthermore, unlike most early risk factors, the exact timing/duration of exposure is known, based on the number of weeks PT infants are born early.

Extensive alterations in frontal lobe development have been reported in children born very PT (<32 weeks gestation) and/or very low birth weight (VLBW; <1500 grams; see de Kieviet, Zoetebier, van Elburg, Vermeulen, & Oosterlaan, 2012 for a general overview of brain development in very PT children). Although medical care has improved dramatically for these young and vulnerable infants, rates of both short- and long-term major medical complications, including brain injury, remain problematic (Volpe, 2009). The prevalence of significant brain injuries is drastically reduced in

healthy PT infants born closer to term (Kinney, 2006; Sannia et al., 2013). However, a growing literature suggests that even healthy infants born PT are at risk for subtle, long-term alterations in prefrontal cortex development. To date, most long-term follow-up studies of PT birth have focused on higher-risk PT children. As such, we include literature on higher-risk PT birth within this overview, but emphasize that lower-risk PT birth is associated with similar, albeit smaller in magnitude, impacts on frontal lobe development. Lower-risk PT birth was conceptualized to include primarily moderate-to-late PT infants (32-36 weeks gestation) without major medical complications and/or children born more preterm without any major neurological deficits. We first provide an overview of the long-term correlates of PT birth, followed by a more extended discussion of emerging impacts that are detectable during the infant and toddler years.

Prematurity and later development. Specific deficits in EF in very PT and/or VLBW children, not explained by general cognitive impairments (see review in Mulder, Pitchford, Hagger, & Marlow, 2009), have been consistently documented across the preschool, childhood, and adolescent years (Aarnoudse-Moens, Duivenvoorden, Weisglas-Kuperus, Van Goudoever, & Oosterlaan, 2012; Aarnoudse-Moens & Smidts, 2009; Anderson, Doyle, & Victorian Infant Collaborative Study Group, 2004; Bayless & Stevenson, 2007; Bohm, Smedler, & Forssberg, 2004; Harvey, O'Callaghan, & Mohay, 1999; Loe, Lee, Luna, & Feldman, 2012; Luu, Ment, Allan, Schneider, & Vohr, 2011; Marlow, Hennessy, Bracewell, & Wolke, 2007; Narberhaus, Segarra, Cald, & Gim, 2008; Ritter, Nelle, Perrig, Steinlin, & Everts, 2013; Saavalainen et al., 2007). Children and adolescents born very PT also show reduced prefrontal engagement during EF tasks

(Griffiths et al., 2013; Mürner-Lavanchy, Ritter, et al., 2014; although see de Kieviet et al., 2014) and atypical patterns of functional activation (Nosarti et al., 2006), with group differences extending into fronto-striatal regions (Curtis, Zhuang, Townsend, Hu, & Nelson, 2006) and fronto-parietal attention networks (Carmody et al., 2006).

Higher-risk PT birth is also associated with decreased prefrontal gray matter volume (Ball et al., 2012; Nagy et al., 2009; Nosarti et al., 2008; Peterson et al., 2000; Zhang et al., 2015) and surface area (Grunewaldt et al., 2014; Lax et al., 2013; Sølsnes et al., 2015) throughout childhood and adolescence. Both prefrontal thinning (Lax et al., 2013; Nagy, Lagercrantz, & Hutton, 2011) and thickening have been reported in very PT children and adolescents vs. full-term controls (Bjuland, Løhaugen, Martinussen, & Skranes, 2013; Grunewaldt et al., 2014; Martinussen et al., 2005; Mürner-Lavanchy, Steinlin, et al., 2014; Sølsnes et al., 2015), with some suggestion that cortical maturation may be delayed in higher-risk PT children (Mürner-Lavanchy, Steinlin, et al., 2014; although see Rimol et al., 2016). Decreased frontal white matter volume (Giménez et al., 2006; Kesler et al., 2008; Nosarti et al., 2008) and poorer WM integrity in frontal-lobe tracts (Constable et al., 2008; Duerden, Card, Lax, Donner, & Taylor, 2013; Mullen et al., 2011; Skranes et al., 2007; Sølsnes et al., 2016) are also present in children and adolescents born very PT. Studies examining integrity of whole brain networks report aberrant connectivity patterns across the default mode and dorsal attention networks in higher-risk PT individuals (see Kwon et al., 2016 for recent review). Alterations in both behavioral and fMRI measures of frontal lobe volume persist into adulthood (Daamen et al., 2015; Furre et al., 2016; Kalpakidou et al., 2012; Lawrence et al., 2009; Nosarti et al.,

2009), as do changes in frontal lobe volume (Nosarti et al., 2014), cortical thickness (Nam et al., 2015), surface area (Furre et al., 2016), and connectivity (Eikenes, Lohaugen, Brubakk, Skranes, & Haberg, 2011), suggesting effects persist across development.

Lower-risk PT children also have poorer EF skills in comparison to full-term children during the preschool years (Baron et al., 2009; Baron, Kerns, Muller, Ahronovich, & Litman, 2012; Baron, Weiss, Litman, Ahronovich, & Baker, 2014; Brumbaugh, Hodel, & Thomas, 2014; Caravale, Tozzi, Albino, & Vicari, 2005; Hodel, Brumbaugh, Morris, & Thomas, 2015; Vicari, Caravale, Carlesimo, Casadei, & Allemand, 2004; although see Baron, Erickson, Ahronovich, Litman, & Brandt, 2010). Critically, although PT birth does occur at higher rates in low-SES families, negative impacts on frontal lobe development are detectable even in middle to upper class samples of lower-risk PT children (Brumbaugh et al., 2014; Hodel, Brumbaugh, et al., 2015), suggesting unique impacts of prematurity. Impacts of lower-risk PT birth on EF are generally smaller in magnitude than those observed in higher-risk PT cohorts, less consistent across EF tasks, and have not been detected after early school age (Baron et al., 2014; Brumbaugh et al., 2016; Gurka, LoCasale-Crouch, & Blackman, 2010; Tideman, 2000).

Few studies have examined long-term structural correlates of lower-risk PT birth, and those published are restricted to follow-up during the late school age-early adolescent period. A recent study suggests lower-risk PT children have smaller cortical surface area than full-term controls and may show delayed cortical maturation (Brumbaugh et al.,

2016), as neither cortical thickness nor surface area measures showed expected relationships with PT children's age. However, a second study did not report differences in frontal lobe volume or overall cortical surface area and thickness in lower-risk PT children (Rogers et al., 2014). Prefrontal functional connectivity was also altered in default mode and attentional networks in two small studies examining the same sample of lower-risk, PT children (Degnan et al., 2015a, 2015b).

Prematurity and infant development. Most differences in prefrontal cortex development described during the childhood years can be observed in PT infants within the first two years of life. When examining infant outcomes, correction for degree of prematurity is important in order to match "developmental" time for PT children to their full-term peers. As such, PT infants are typically compared to full-term infants based on their "corrected" age (age adjusted for degree of prematurity), and corrected-ages are routinely used at least through age 2, including in the studies described below.

PFC dependent behaviors. The development of early attention skills that underlie later EF abilities have been well-characterized in PT infants and toddlers (see review in van de Weijer-Bergsma, Wijnroks, & Jongmans, 2008). In a series of elegant, longitudinal studies beginning in infancy, Rose, Feldman, and Jankowski demonstrated that higher-level attentional processes are altered across the first years of life in higher-risk PT infants, contributing to later differences in adolescent EF skills (see Rose, Feldman, & Jankowski, 2016 for summary). Interestingly, lower-risk PT infants may show a slight "benefit" in attentional processing earlier in development; lower-risk PT infants are faster at disengaging and shifting attention than their full-term peers, although

this “benefit” in attention typically disappears by 4-6 months of age (Hitzert et al., 2015, 2014; Hunnius, Geuze, Zweens, & Bos, 2008). Other studies have also found that lower-risk PT infants perform better on early attention measures than their higher-risk PT peers (Landry & Chabieski, 1988; Reuner, Weinschenk, Pauen, & Pietz, 2015). However, by 18 months, lower-risk PT children show poorer orienting and alerting than full-term toddlers (Jong, Verhoeven, & Baar, 2015), suggesting deficits may emerge over time or may induced by atypical early attention patterns.

Early EF differences have been detected in very PT infants (Sun, Mohay, & Callaghan, 2009) and toddlers (Clark, Woodward, Horwood, & Moor, 2008; Pozzetti et al., 2013) across the first two years of life in comparison to full-term infants (see review in Gonzalez-Valenzuela et al., 2015). A small study using the A not B task found that lower-risk PT infants outperformed full-term infants when tested at their corrected-age and performed equivalently on other early measures of EF (Matthews, Ellis, & Nelson, 1996); however, this advantage for lower-risk PT infants disappeared when comparing groups based on chronological age (i.e., age from birthdate). By toddlerhood, poorer performance on measures of inhibitory control and working memory are present in both higher-risk (Lejeune, Tolsa, Graz, Hüppi, & Barisnikov, 2015; Phillips, Ruhl, et al., 2011; Woodward, Edgin, Thompson, & Inder, 2005) and lower-risk PT children (de Haan et al., 2000; Voigt, Pietz, Pauen, Kliegel, & Reuner, 2012; although see Evrard et al., 2010). Neuroimaging measures suggest higher-risk PT infants show atypical brain activity in comparison to their full-term peers (see Mento & Bisacchi, 2012 for review of recent literature) and this effect may also be present in lower-risk PT infants in

orbitofrontal cortex regions (Wu et al., 2016). However, most studies have focused on whole-brain rather than frontal-specific differences and have not imaged frontal-dependent tasks.

PFC gray matter volume. Studies with higher-risk PT infants overwhelmingly indicate that PT birth disrupts normative trajectories of prenatal brain development (Kapellou et al., 2006), including that of prefrontal cortex gray matter. At term-equivalent age (see Anderson, Cheong, & Thompson, 2015 for review), higher-risk PT infants show regionally specific volumetric reductions in orbitofrontal cortex volume (30% decrease in higher-risk PT vs. full-term infants), and additional decreases in dorsal prefrontal regions in infants with documented brain injuries (Thompson et al., 2007). Individual differences in term frontal lobe volume are predictive of long-term neurodevelopmental outcomes (see Anderson et al., 2015 for review), including toddler measures of EF (Woodward et al., 2005). Volumetric alterations in higher-risk PT toddlers are driven by overall thicker cortex that is smaller in surface area (Phillips, Montague, et al., 2011), a pattern consistent with later childhood and adolescent brain measures in this population.

At term-equivalent age, lower-risk PT infants also show widespread changes in gray matter development, including smaller overall brain size (Munakata et al., 2013; Walsh, Doyle, Anderson, Lee, & Cheong, 2014; although see Mewes et al., 2006) and immature gyration (Walsh et al., 2014). Similar to higher-risk PT infants, volumetric differences in lower-risk PT infants at term-equivalent age are related to later neurodevelopmental outcomes (Cheong et al., 2016; Walsh et al., 2014). However,

alterations in gray matter volume in lower-risk PT infants appear to be global, rather than specific to frontal lobe.

PFC connectivity. At term-equivalent age, higher-risk PT infants show overall reductions in white matter volume and poorer white matter integrity in comparison to their full-term peers (see Pannek, Scheck, Colditz, Boyd, & Rose, 2014 for review), including poorer organization of frontal lobe white matter (Anjari et al., 2007; Rose et al., 2008). Individual differences in white matter integrity at term-equivalent age are predictive of long-term neurodevelopmental outcomes (see Pannek et al., 2014 for review), including EF during the toddler (Edgin et al., 2008) and preschool years (Woodward, Clark, Pritchard, Anderson, & Inder, 2011). Several studies have investigated functional connectivity in the higher-risk PT infant brain (see review in Kwon et al., 2016). Resting-state networks are present in PT infants by term-equivalent age (Fransson et al., 2013), but network organization is less complex in higher-risk infants born PT (Pandit et al., 2014; Smyser et al., 2010, 2016), including within frontal-lobe networks (Pandit et al., 2014; Smyser et al., 2016).

At term-equivalent age lower-risk PT infants also have decreased white matter volume (Mewes et al., 2006) and poorer white matter organization across the majority of the brain's major white matter pathways (Kelly et al., 2016), including in fronto-limbic and fronto-striatal tracts. White matter microstructure in the lower-risk PT infant's brain is characterized by changes in several diffusion metrics, suggesting broad alterations in myelination, axonal packing, and/or axon diameter following even lower-risk PT birth.

Interim Summary: Early Experience Shapes PFC Development

Across diverse variations in early life experience (maltreatment, poverty, PT birth) a common theme emerges: early differences in the environment impact prefrontal cortex development. Alterations in prefrontal cortex development are present within the first year of life, show continuity over developmental time, and are detectable across multiple levels of neurobehavioral development including measures of behavior, gray matter volume, white matter microstructure, and network organization. Interestingly, most long-term impacts of early life experience on prefrontal cortex development appear to be quite similar, despite vast differences in the characteristics of early risk exposure. Poorer EF skills, beginning during late infancy, are a consistently reported in children exposed to adverse early environments. Similarly, reductions in prefrontal gray matter volume were common across all the experiences reviewed, along with changes in cortical thickness and surface area, as well as poorer white matter microstructural organization within fronto-limbic and/or fronto-striatal circuits.

Some diverging impacts across the three types of experience reviewed also warrant attention. Both PI children and children growing up in poverty generally had thinner frontal cortex, while higher-risk PT children had thicker frontal cortex, suggesting different disruptions in underlying neurobiological processes. Although differences in fronto-striatal functions appeared to be consistent across all three experiences reviewed, different patterns of fronto-limbic findings emerged. Children and adults exposed to childhood maltreatment generally showed increased activation of frontal circuits during emotion regulation tasks, while adults with a history of childhood poverty showed opposing effects. Differential connectivity and functioning of fronto-limbic circuits

across experiences may relate to differing dimensions of early adverse environments (McLaughlin, Sheridan, & Lambert, 2014; Sheridan & McLaughlin, 2014) and/or changes in brain development that convey an advantage in certain adverse environments (Del Giudice et al., 2011). However, even in these cases where effects were not comparable in direction among the three experiences reviewed, an overall consistent pattern remained: across development, individuals exposed to early life adversity show broad alterations in frontal lobe structure, function, and dependent-behaviors in comparison to their lower-risk peers.

Potential Mechanisms for PFC Impacts

Given that relatively diverse variations in early life experience all impact long-term prefrontal cortex development, it is unlikely that there is one specific mechanism by which early experience shapes prefrontal circuits. Studies of human infants and children clearly provide little control in investigating mechanisms. Across the three example experiences previously reviewed (maltreatment, poverty, PT), early environmental risks typically overlap; for example, children who are maltreated are also more likely to live in poverty, and poverty itself is a risk factor for PT birth. Animal models of early experience are promising in their ability to delineate separable mechanisms. However, even in these cases of greater experimental control, one change in the early rearing environment (e.g. maternal deprivation) may produce additional confounding experiences (e.g. changes in nutrient impact and thermoregulation for deprived infant animals). We discuss multiple potential mechanisms via which early experience may produce long-term impacts on prefrontal neurobehavioral development, with the explicit recognition

that these likely act in combination to impact later development.

1. Rapid Development Conveys Vulnerability

It is widely hypothesized that the fastest structurally growing regions of the brain are the most metabolically active, and may thus be the most susceptible to the negative effects of early environmental and/or biological insults (Hüppi et al., 1998; Volpe, 2009). Evidence was presented in the first section of this review that prefrontal cortex exhibits rapid development during early infancy, including changes in structure, connectivity, and function, often at a greater relative rate than other regions of the brain. Basic neurobiological processes including synaptogenesis, synaptic pruning, and myelination within prefrontal cortex also extend well into the early childhood period. Since prefrontal cortex grows at a rapid or perhaps even an accelerated rate in comparison to other brain regions during early life, it may be particularly sensitive to adverse early environments.

Small, early changes in rapidly developing prefrontal white matter are known to result in larger structural and functional deficits that emerge over time. Preterm infants with relatively minor white matter lesions at birth have abnormal cortical folding patterns in the central sulcus and frontal lobe sulci by term-equivalent age, but not in other regions of the brain, in comparison to PT infants without such lesions (Dubois, Benders, et al., 2008). White matter injury in neonates also causes direct effects on pre-myelinating oligodendrocytes, which remain predominant in frontal lobe regions at birth (Back et al., 2001), as well as general axonal damage and gliosis (see Smyser et al., 2013). Early, relatively minor disruptions to vulnerable prefrontal cortex white matter may result in delayed or atypical myelination effects (Nishida et al., 2006), providing a neurobiological

explanation for the emergence of “sleeper effects” associated with early adverse environments.

Prefrontal cortex may also be vulnerable to variations in early experience due to its broad interconnectivity with other rapidly developing, subcortical brain regions. The putamen shows the highest relative growth rate over the first year of infancy in comparison to all other regions of the brain (Choe et al., 2013), and has extensive connections with prefrontal cortex through fronto-striatal tracts. Vulnerability of subcortical gray matter to early insults has been widely demonstrated in PT infants (Baldoli et al., 2014; Ball et al., 2013; Toulmin et al., 2015). Experience-induced changes in the development of subcortical regions could result in aberrant input to prefrontal cortex, as structural and functional connectivity between subcortical and prefrontal regions increases with developmental time.

Because much of the basic structure and connectivity of prefrontal cortex is determined prenatally, variations in experience during this time period could impact the gross architecture of prefrontal cortex structure and connectivity. Studies examining birth weight variation within the normative range, a proxy for “optimal” prenatal experience, have shown that higher-normal birth weights are associated with increased surface area in the superior and inferior frontal gyri from childhood through adolescence (Raznahan et al., 2012), suggesting that prenatal experiences can have long-term impacts on frontal-lobe development. Although joint effects of variations in prenatal and postnatal environments have not been extensively explored, cumulative exposure to negative environments would likely have the largest impact on prefrontal development.

Studies with PI children provide preliminary insight into the extreme vulnerability of the developing brain when exposed to both pre- and postnatal insults. The BEIP study documented that children who were both low birth weight and experienced longer institutional care showed the most extreme cognitive vulnerability as measured by lower developmental quotient/IQ score (Johnson et al., 2010). Although IQ is not strictly prefrontal-dependent (Roca et al., 2010), in typically developing children IQ and prefrontal-dependent EF skills overlap. Global deficits in IQ in these higher-risk PI children highlight the cumulative and interactive effects of disruptions to both the prenatal and postnatal environment on rapidly developing frontal circuits.

2. Sensitivity to Stress

An extensive animal literature supports the argument that stress is a form of environmental variation that can differentially alter prefrontal cortex structure and function. All of the variations in early experience that have previously been discussed (maltreatment, poverty, PT birth) share the potential to be biologically and/or psychologically challenging to the developing organism. Altered cortisol production is present in lower-SES infants within the first year of life (Blair, Raver, Granger, Mills-Koonce, & Hibell, 2011; Clearfield, Carter-Rodriguez, Merali, & Shober, 2014) and is predictive of later individual differences in early childhood measures of EF (Blair, Granger, et al., 2011; see Berry et al., 2016 for review). Infants who have experienced maltreatment (Cicchetti, Rogosch, Toth, & Sturge-Apple, 2011) and children currently residing in orphanages (Carlson & Earls, 1997) have altered cortisol rhythms, as do infants exposed to prenatal risk factors (Osterholm, Hostinar, & Gunnar, 2012) and/or

born very PT (Grunau et al., 2007). It is probable that, at least for some early variations in environmental experience, the physiological and/or subjective experience of stress provides a final common pathway to altered prefrontal development. For example, models of toxic stress and/or allostatic have been widely used in characterizing the converging impact of multiple stressors present in the lowest-SES environments on children's development (Evans et al., 2013), and are consistent with previously discussed studies documenting non-linear relationships between depth of poverty and prefrontal cortex development.

Animal models of early life stress allow for a more thorough investigation of how the timing and nature of specific stressors impact prefrontal cortex development. Since parent-offspring interactions are comprehensive and necessary for the survival of offspring in many mammalian species, these studies typically use paradigms involving temporary separations of young animals from parental care. Maternal deprivation in rodents is associated with an increased rate of apoptotic cell death in frontal cortex of neonatal animals, suggesting specific vulnerability of this brain region (Zhang et al., 2002). Parental deprivation in highly social Octodon degus results in a cascade of prefrontal alterations including increased synaptic density in medial prefrontal cortex (Ovtcharoff & Braun, 2001), lowered spine density and reduced dendritic length in orbitofrontal cortex (Helmeke et al., 2009), and a shift in the balance between serotonergic and dopaminergic innervations in both medial (Braun, Lange, Metzger, & Poeggel, 2000) and orbital (Poeggel, Nowicki, & Braun, 2003) frontal regions. This pattern of results suggests that early deprivation of normative parental care interferes with

both typical prefrontal synapse formation (Bock et al., 2005) and pruning (Ovtcharoff & Braun, 2001), with effects persisting into adulthood. Similar long-term impacts of early life stress on prefrontal circuits have been detected following stress limited to the prenatal period (Murmu et al., 2006), in paradigms in which young rodents are handled by humans rather than deprived of maternal care (Helmeke, Ovtcharoff, Poeggel, & Braun, 2001), and in measures of altered prefrontal gray matter volumes in squirrel (Lyons, Afarian, Schatzberg, Sawyer-Glover, & Moseley, 2002) and rhesus monkeys (Spinelli et al., 2009) following maternal deprivation.

The impact of early life stress on prefrontal cortex development varies based on the age at which effects are assessed and the timing and nature of the stressor. For example, when rodents were exposed to mild stress from embryonic days 12-16, offspring showed increases in spine density in both medial prefrontal and orbitofrontal cortex as juveniles; however if offspring were instead examined at adulthood, there was no effect of early life stress on orbitofrontal cortex spine density and the medial prefrontal cortex effect was now reversed in direction (Muhammad, Carroll, & Kolb, 2012; Mychasiuk et al., 2012). These results suggest a potential neurobiological correlate of “sleeper effects” sometimes observed in studies of human children, as long-term impacts of early life experience may take time to fully emerge. Timing of stressor exposure also predicts neurodevelopmental outcomes, with some suggestion that prenatal stressors are more disruptive to long-term development than stress during the early postnatal period (Muhammad et al., 2012). Even prenatal stressors that are distal to the actual pregnant animal (e.g. stressing a neighboring cage mate) have been associated with

changes in microstructural properties of prefrontal cortical neurons in offspring (Mychasiuk, Gibb, & Kolb, 2011), an interesting parallel to models of human experience that consider the impact of risk at proximal vs. distal levels of the environment on children's development. Since prenatal stress occurs before dendritic growth and synaptic formation have plateaued, it has a stronger impact on the formation of neural networks (Kolb et al., 2012), and may set the range of physiological systems for the later course of development (McEwen, 2012). For human children exposed to early life adversity, prenatal and postnatal stress likely co-occur, a topic that will be discussed at the end of this review.

Animal studies also indicate that prefrontal cortex is sensitive not only to parental deprivation, but also to other forms of atypical social experience that activate stress biology. Mice who experience periods of complete social isolation at any age show similar patterns of alterations in prefrontal microstructure that persist following social reintegration. However, younger animals show more pronounced changes in prefrontal-dependent behaviors and oligodendrocyte microstructure than those observed in adults (Liu et al., 2012; Makinodan, Rosen, Ito, & Corfas, 2012). Deprivation of social experiences during specific, early developmental time windows results in dramatic long-term changes in prefrontal cortex myelination and function (Makinodan et al., 2012), an argument for a potential sensitive period for early social interaction in relation to prefrontal cortex white matter development. In comparison to young rodents, human infants experience a much longer period of extensive social interaction with their caregivers and a higher reliance on learning from others in social contexts (Csibra &

Gergely, 2006), suggesting impacts of atypical social environments may be even greater for human infants and toddlers.

Ultimately, the importance of stress as a major mechanism by which early experience impacts prefrontal development cannot be ignored. However, there is a substantial literature indicating that prenatal and early postnatal stress in both animals and human infants does not uniquely impact prefrontal development. Stress has well-known effects across multiple regions of the brain, with an extensive literature documenting its unique and differential impacts on hippocampal and amygdala development (see review in McEwen, 2012). All of the subcortical regions that have been shown to be “stress-sensitive” project directly or indirectly to prefrontal cortex. It is unclear if the vulnerability of prefrontal cortex to early life stress is due to: 1) intrinsic properties of prefrontal cortex itself, 2) receipt of aberrant input from other stress-sensitive brain regions, or 3) some combined, interactive effect. In the context of understanding early life stress and prefrontal development, we argue it is best to view prefrontal cortex as part of several integrated systems that are highly reactive to stressful early experiences.

3. Importance in Early Learning

If prefrontal cortex constitutes a critical hub region for early learning and brain development, small disruptions to normative processing could have cascading impacts across multiple cognitive and brain systems. The traditional view of infant brain development as strictly hierarchical, with organization and specialization moving from lower-level sensory circuits to higher-level cortical regions, does not appropriately capture the early functional characteristics of infant frontal lobe (Dehaene-Lambertz &

Spelke, 2015). Instead, evidence has already been presented earlier in this review that infant prefrontal cortex is broadly active across a variety of infant cognitive and social information processing tasks, suggesting this brain region may play an important role in early learning from the environment and in shaping patterns of cortical development.

Studies of learning in adults routinely report increased prefrontal activity during skill acquisition and learning of new motor behaviors, with prefrontal activity decreasing once skills have become well-learned (Fletcher et al., 2001; Sigman et al., 2005). Similarly, fMRI studies with young children report that diffuse patterns of activation, including in frontal regions, decrease with development to be replaced by more task-specific activation (Casey et al., 1997; Durston et al., 2006). Much of this apparently age-related change might be due to underlying learning processes. In infants, broad prefrontal cortical activity observed across diverse tasks could reflect active learning from predictable, yet complexly organized, environmental stimuli. For example, a recent study demonstrated that 8-month old infants are able to spontaneously learn hierarchical rule structures, and that this learning is related to eye-blink rate, an indirect measure of early fronto-striatal dopaminergic functioning (Werchan, Collins, Frank, & Amso, 2015). Many cognitive and socioemotional processes likely place high attentional and memory demands on the young infants' brain. There is also increasing recognition that even young infants exhibit sophisticated information processing capabilities that serve as precursors to later EF (Hendry, Jones, & Charman, 2016; Rose, Feldman, & Jankowski, 2012), which may be broadly engaged across a variety of learning contexts. As attentional and memory demands of learning become less effortful with development,

prefrontal-involvement likely decreases.

Considering learning more broadly at the circuit level, Grossman (2013) has argued that a major task of prefrontal cortex in infancy is to learn to select the appropriate pattern of posterior regional activity for a given cognitive or motor task. Accordingly, this “efficient selection” cannot happen until better prefrontal long-range structural and functional connectivity develop with time and experience (Grossmann, 2013a). A role for prefrontal cortex in coordinating network activity is consistent with conceptualizations of medial prefrontal cortex as an early “hub-region” for brain development, playing a strong role in coordinating information within and across brain networks (Gao, Zhu, et al., 2009). Although this account has not been tested empirically, it would predict high levels of prefrontal activity across tasks during early infancy, followed by decreases in prefrontal activation across tasks as children age. Decreasing prefrontal activity would be replaced by activation in more posterior regions, along with concomitant changes in integrity of long-range prefrontal structural and functional connections, a pattern that could be tested in a longitudinal fNIRS/DTI data set.

The ability of humans to efficiently learn from others is a key adaptation of the human species (Csibra & Gergely, 2006), and developing an understanding of other people is a fundamental task for the human infant in learning about the environment (Grossmann & Johnson, 2007). In the adult brain, a network of brain regions commonly referred to as the “social brain” exists which specializes in learning from and processing information related to social agents (Adolphs, 2009). Portions of infant medial prefrontal cortex also demonstrate functional specialization for detection of social signals early in

development (Grossmann, 2013a, 2013b, 2015) and early attentional mechanisms exist which enhance infant attention to social stimuli (Johnson, 2005). Differences in frontal lobe processing of social information for infants who experience atypical social environments (i.e. maltreatment) are present with the first years of life (Curtis & Cicchetti, 2013). Furthermore, because infants develop in socially complex environments, developmental pathways for what appear to be basic cognitive skills (e.g. sustained attention) may also be dependent on normative social experiences (Yu & Smith, 2015) and functioning of early social information processing networks that include medial prefrontal cortex.

It is also possible that early learning experiences during infancy “prime” or shape later learning capabilities within prefrontal circuits. Multiple studies have reported that training in young animals improves learning measured on equivalent tasks at adulthood, even though young animals may not show evidence of learning during training (see review in Bock, Poeggel, Gruss, Wingenfeld, & Braun, 2014). For example, on an avoidance learning paradigm young rats who were trained between postnatal days 17-21 did not show behavioral evidence of learning, but did show changes in spine formation rates in ventromedial and lateral orbitofrontal cortex (Bock et al., 2014). Changes in spine formation appeared to reflect a form of “tagging” functionally relevant synapses, protecting them from synaptic elimination during later development. As adults, these rodents are able to activate circuits that were “pre-shaped” by early training experience, accelerating learning in comparison to animals who were not trained during early life (Bock et al., 2014). Environmental entraining of frontal circuits has also been

demonstrated in the adult human neuroimaging literature using measures of functional connectivity (Kelly & Castellanos, 2015). Viewed from this perspective, infant learning experiences broadly optimize the prefrontal cortex for adult learning, due to microstructural changes in prefrontal circuitry as a result of early experience.

In combination, these results broadly demonstrate the underappreciated importance of prefrontal cortex for infant learning across multiple contexts, including in behavioral measures of learning and in organizing and constraining brain development at both the synaptic and network level. Many of the hypotheses put forward here require further testing. For example, whether the absence of normative learning experiences (i.e. neglect) or presence of highly aberrant learning experiences (i.e. maltreatment) impact the ability of prefrontal hub regions to organize and/or constrain trajectories of brain development at the synaptic or circuit level has not been empirically tested. However, from this broader perspective, relatively small changes in prefrontal cortex development could have both immediate impacts on vast aspects of infant neurobehavioral development and initiate cascading changes in future cognitive abilities that build on earlier skills.

4. “Poor” Prefrontal Functioning as a Risk Factor

Johnson (2012) has recently argued that the reason prefrontal-dependent abilities such as EF may appear to be affected in children with a variety of neurodevelopmental disorders is not because prefrontal cortex is especially vulnerable to developmental perturbations, but is instead because individuals with “good” prefrontal skills are better able to compensate for atypicalities in other brain systems (Johnson, 2012). This

argument does not specifically discuss the role of differences in early environmental experiences, but the logic follows similarly. Prefrontal functions may appear vulnerable to early life experience because individuals with “poor” prefrontal function due to genetic risk are unable to compensate for aberrant development in other brain systems induced by a combination of genetic risk and environmental variation. In sum, being at the lower end of normative variation in prefrontal skills may be considered a risk factor that interacts with exposure to adverse early experiences, ultimately disrupting development in multiple neural systems that cannot be compensated for by “good” EF.

Currently there is no experimental evidence that adverse environments alter EF via experience-induced changes in underlying neural systems, along with failure of compensatory activity by prefrontal cortex. This hypothesis could be tested by examining whether differences in neurobehavioral outcomes following exposure to early adversity are related to individual differences in EF in biological relatives who were not exposed to adverse early environments. For example, if unexposed, typically-developing siblings of children diagnosed with PTSD were tested on EF tasks, this logic would predict that siblings would also show lower average levels of EF in comparison to other lower-risk control children. This result would imply that some initial genetic risk in the form of “poorer” prefrontal function, in combination with exposure to an adverse early environment, resulted in failure of prefrontal cortex to compensate for disruptions in other neural systems (e.g. limbic circuitry) in children who developed PTSD following adverse early experiences. A recent DTI paper reported greater white matter microstructural integrity across several frontal lobe tracts in young adults who were not

diagnosed with depression despite high levels of both genetic (affected first degree relatives) and environmental risk (high levels of early childhood risk vs. a lower-risk control group; Frodl et al., 2012), suggesting that latent differences in frontal lobe connectivity may serve as a protective factor in the presence of diverse risk factors.

Although individual variation in latent prefrontal functional capacity may provide some predictive power, it is important to recognize that this effect is likely subtle. Individual variation in prefrontal function may be more relevant in predicting outcomes when experiences fall within the realm of the biologically expected, species-typical environment. When environments fall outside the realm of experience-expectant processes (e.g. complete deprivation of language exposure for humans) and severely disrupt basic prefrontal structure and connectivity, it is unlikely that individual differences in latent prefrontal cortical functioning can sufficiently compensate. More broadly, we argue that this perspective, perhaps in combination with other frameworks that also conceptualize individual differences in sensitivity to early environments (Belsky & Pluess, 2009; Boyce & Ellis, 2005), are useful in considering the role of individual differences in prefrontal cortex development following exposure to variations in the environment.

General Discussion

Infant prefrontal cortex shows rapid structural, connectivity-based, and functional development during the late prenatal period and into the first years of life. Sensitivity of this rapidly developing brain region to environmental influences allows for efficient tuning of prefrontal circuits to the early environment. Unfortunately, evidence from both

human and animal studies highlights the vulnerability that goes along with this normally adaptive process. Exposure to biological and environmental risk factors (e.g. maltreatment, poverty, PT birth) during this time period of rapid frontal-lobe development induces deficits within the first year of life that may persist over time. The similar neural phenotype of diverse forms of early risk (e.g. reduced prefrontal gray matter, atypical prefrontal cortical thickness, lower frontal electrical activity, etc) suggests diverse early risk factors may be instantiated in prefrontal cortex in similar ways. However, differences in prefrontal outcomes across early risk exposure (e.g. frontal lobe cortical thinning following neglect but thickening in PT children) emphasize that the timing and nature of early adverse experiences may differentially impact developmental trajectories of this brain region.

Characterizing longitudinal trajectories of normative prefrontal cortex development and development following adversity is difficult for a myriad of reasons. However, this work is critical to understand both why prefrontal circuits may be vulnerable to early experiences, and how or if trajectories of brain development may recover from exposure to adverse early environments. The urgent societal need to provide normative environments that support prefrontal cortex development in young infants is quite clear. Despite massive recovery in children adopted from institutional care, six months of institutional rearing in infancy can produce permanent changes in prefrontal cortex development. Near the end of the first year of life, lower-SES infants show a maturational lag of approximately three months on measures of early EF skills in comparison to their higher-SES peers. Differences of only 4-8 weeks of gestation in

lower-risk PT infants are associated with alterations in brain volume and white matter connectivity at term-equivalent age, and lasting differences in prefrontal-dependent behavior when children reach preschool. That these experiences are detectable in young infants so early in life emphasizes that continued research in this field is imperative. We close by synthesizing current challenges within the field, and highlighting two themes deserving more extended inquiry, along with a brief discussion of the translational importance of this work.

Challenges and Recommendations

Measuring infant outcomes. Innovations in infant multimodal imaging have been critical in determining the neural correlates of early experience during the infant and toddler years. Advances in the development of sensitive behavioral measures of early prefrontal cortex skills have also been dramatic, but measurement of these higher-level constructs in young infants remains challenging (see Hendry, Jones, & Charman, 2016 for recent discussion). An important future direction will be to determine the degree to which various infant and toddler measures of early EF abilities show developmental stability (e.g. Rose, Feldman, & Jankowski, 2012) and to more carefully test their reliance on prefrontal circuitry using functional neuroimaging techniques. Most studies examining prefrontal functioning in young infants have used fNIRS, which has limited spatial resolution in comparison to fMRI and is restricted to measurement of superficial cortical activity. Cognitive neuroscience approaches that more carefully segregate measures of infant sensory, cognitive, and social information processing into constituent components and/or parametrically vary task processing demands will be useful in

determining if infant prefrontal cortex subserves unique functions, or if broader cross-task activations are due to the increased attention and memory demands for young infants inherent in processing complex stimuli.

The development and utilization of sensitive measures of both behavioral and brain differences in prefrontal circuits are likely especially important to detect altered functioning in children who have experienced more subtle forms of early adversity. For example, in lower-risk PT children, recent studies suggest that behavioral EF impairments do not persist into the school years (e.g. Baron, Weiss, Litman, Ahronovich, & Baker, 2014). However, this is not consistent with large, population-based studies demonstrating higher rates of attention problems and poorer school performance in lower-risk PT individuals across development (e.g. Chan, Leong, Malouf, & Quigley, 2016; Chan & Quigley, 2014; Talge et al., 2010), suggesting that development of more sensitive behavioral measures of prefrontal functioning may be necessary. Measures across various levels of neurobehavioral development may be particularly helpful to determine if, even in the context of equivalent behavior, prefrontal circuitry has been resculpted by early life experience, and to determine how early adversity impacts different levels of organization within prefrontal systems in tandem (e.g. reductions in regional prefrontal volume but increased fronto-limbic connectivity, etc).

Characterizing early and later environments. We have already discussed at length inherent difficulties in defining and measuring experiences. Substantial progress has been made in developing frameworks that characterize differences in the timing and nature of early experiences. Critically, some of these perspectives have also highlighted

the importance of viewing changes induced by the early environment in prefrontal circuitry not as “deficits” in brain development, but as attempts to support adaptation within the context of adversity (Callaghan & Tottenham, 2016; McEwen, 2012). For example, a history of early institutional care is associated with atypical patterns of functional connectivity within fronto-limbic systems. Rather than “deficits” in connectivity, fronto-limbic circuits instead mature early, perhaps reflecting an adaptive trade-off for life in the orphanage environment that may have negative consequences later in the post-adoptive environment (Callaghan & Tottenham, 2016; Gee et al., 2013). We suggest that considering the nature of environments that follow exposure to early adversity may lead to important advances in our understanding of how delayed or “sleeper” effects of early adversity emerge over developmental time.

The corollary of understanding the sensitivity of prefrontal cortex to negative environmental experiences is considering the role of both normative and positive experiences in its development. Longitudinal studies have demonstrated that normative variations in maternal sensitivity during infancy are predictive of individual differences in children’s EF skills later during toddlerhood and into the preschool years (Bernier, Carlson, Deschenes, & Matte-Gagne, 2012; Bernier, Carlson, & Whipple, 2010; Blair, Granger, et al., 2011; Cuevas et al., 2014). However, there is little information about how normative or positive environmental variations influence prefrontal cortex structure and/or connectivity over development. Rodent studies of enriched neonatal tactile stimulation produce long-term, positive changes in prefrontal cortex structure and prefrontal-dependent behaviors at adulthood (Kolb et al., 2012). One recent study

demonstrated that early individual differences in human parenting behaviors, within the normative range, were prospectively related to EEG measures of infant frontal lobe maturation (Bernier, Calkins, & Bell, 2016). Similarly, interventions for PT infants that minimize mother-infant separation in the Neonatal Intensive Care Unit (e.g. skin-to-skin holding, sustained touching and vocal soothing in isolettes) are associated with more typical patterns of frontal lobe EEG activity and maturation in vulnerable infants (Myers et al., 2015; Welch et al., 2014). Investigating how normative and positive environments influence developmental trajectories of prefrontal cortex has important implications for both describing the biological mechanisms via which experiences are instantiated in the brain, and for considering how normative or positive experiences may partially ameliorate the impacts of exposure to negative environments.

Considering timing and plasticity. An implicit assumption across many studies examining neural correlates of early adversity is that early experiences show some privilege over later experiences in shaping developmental trajectories. In addition to denoting impacts of timing, longitudinal study designs are needed to determine the trajectory of prefrontal cortex development following adversity. In studies which examine outcomes years following early adversity it is impossible to distinguish if subsequent exposure to positive environments has reduced the negative impact of early adversity over time, if impacts have remained relatively constant since early childhood, or if impacts are emerging or increasing as children age and the environment becomes more cognitively demanding. There is some evidence that early experiences do matter more in shaping trajectories of prefrontal cortex development. Measures of childhood

poverty are predictive of adulthood prefrontal cortex structure (Holz et al., 2015), connectivity (Sripada et al., 2014) and function (Javanbakht et al., 2015; Muscatell et al., 2012) even after controlling for concurrent, adulthood measures of social status and/or income. Rare studies that have used random assignment out of early adverse environments (e.g. BEIP study) also allow for causal inferences to be made about the impact of subsequent exposure to positive environments, although ethical considerations make this type of work inappropriate in almost all contexts (Millum & Emanuel, 2007).

A very limited number of studies have specifically compared the impact of early vs. later experiences on trajectories of prefrontal cortex development, few studies have longitudinal measures, and even fewer examine the impact of “early” experiences in the first years of life vs. childhood more broadly. Many children exposed to early adverse environments also unfortunately go on to experience risk factors across subsequent environments. As such, the strength of causal inferences regarding impacts of early experience on long-term prefrontal development is quite tenable. Integration of results from correlational studies in humans with animal models of early adversity, in which temporal and dimensional characteristics of experience can be tightly controlled, is an extremely valuable approach, although cross-species comparisons of animal and human experiences are not without difficulties (Brett, Humphreys, Fleming, Kraemer, & Drury, 2015).

Incorporating basic neuroscience approaches is also necessary to conceptualize how the brain may demonstrate enhanced sensitivity to experiences early in life. Whether sensitive periods exist for higher-level prefrontal-dependent behaviors in human

infants and/or toddlers is unclear (Fox et al., 2010), although emerging evidence supports the existence of early sensitive periods for the development of emotion regulatory systems that include fronto-limbic networks (Callaghan & Tottenham, 2015). Adaptive calibration models (Del Giudice et al., 2011) also posit that there are multiple developmental periods in which biological systems are highly sensitive to environmental input, potentially including prefrontal systems that undergo continued refinement during adolescence (Fuhrmann, Knoll, & Blakemore, 2015). As such, important future directions to better characterize the impact of timing of early adversity on prefrontal development include: 1) utilizing longitudinal study designs, beginning early in development, to determine the trajectory of neurobehavioral changes, 2) integrating results with animal studies in which timing and dimensional characteristics of adverse environments can be tightly controlled, and 3) determining when prefrontal systems are more or less sensitive to the environment across development.

Themes for Future Inquiry

Systems perspectives. The human brain develops as an integrated system, across neural circuits, across biological systems, across levels of environment, within the growing individual. An important theme for future research is to better integrate findings at the “systems” level. For example, describing how rapidly changing subcortical and prefrontal cortical systems interact across development in the infant and possibly even fetal brain (Thomason et al., 2015) will likely improve our understanding of how neural systems organize and reciprocally shape one another’s early functional activity. In tandem, delineating the impacts of early experience on separable frontal circuits (e.g.

fronto-limbic vs. fronto-striatal) is an important step in documenting specificity and/or convergence of effects across frontal systems and fits well within existing frameworks that characterize the nature of early adverse environments (Humphreys & Zeanah, 2014; Sheridan & McLaughlin, 2014). An additional “system” of development that has been too often ignored in the literature on early adversity is the prenatal period. Impacts of variations in the prenatal environment in shaping long-term physiology of the organism are well-known in epidemiology (Godfrey & Barker, 2001), and accordingly, shape children’s later brain development (e.g. Raznahan, Greenstein, Lee, Clasen, & Giedd, 2012; Sarkar et al., 2014; Sowell et al., 2008). As prenatal risk and postnatal risk are often confounded in human children, the prenatal period must be incorporated as another system of influence on children’s development that may shape trajectories of how young infants and toddlers respond to early adversity (Fisher et al., 2016). Last, the brain does not develop in isolation from the body. Understanding interactions between multiple biological systems sensitive to adversity, including physical growth and maturation rate, immunological functioning, and epigenetic modifications will more clearly illuminate how broader prefrontal cortex development is sensitive to environmental variations.

Individual differences. Resilience processes explain the variability of outcomes in individuals following exposure to past or concurrent adversity (Masten, 2001). Most studies investigating either normative infant prefrontal cortex development or development of this region following adversity have focused on age-related or group-level changes, rather than characterization of individual differences (although see Humphreys & Zeanah, 2014). As previously discussed, evolutionary biology theories

posit that individuals vary in their degree of sensitivity to both positive and negative features of the environment (Belsky & Pluess, 2009; Boyce & Ellis, 2005). Although individual differences may exist, prefrontal cortex development is sensitive to the environment in all individuals and this sensitivity continues across the entire lifespan at the neurobiological level (Greenough et al., 1987; Lovden et al., 2010). Understanding normative individual differences in prefrontal development, as well as individual differences in prefrontal circuitry following exposure to adverse environments, is an important theme for future research; however, in tandem, we must also recognize that prefrontal cortex is always plastic to some degree, for every individual, at every point in development.

Translational implications. The public health and policy implications of this growing body of literature are quite clear. Disparities in prefrontal cortex development induced by diverse early risk factors (e.g. maltreatment, poverty, PT birth) are observable shockingly early in development, and infants at the highest levels of biological and environmental risk are disproportionately impacted. Waiting to intervene until children are preschool-aged misses an early window of opportunity, when prefrontal circuits organize and are especially sensitive to the environment. Although much remains to be learned about the mechanisms underlying sensitivity of prefrontal cortex to the early environment, intervention programs designed to target environmental disparities may produce a better return on investment earlier in development: in the toddler, infant, or even prenatal periods (see Doyle, Harmon, Heckman, & Tremblay, 2009 for a discussion on timing).

There is also little evidence to suggest that differences in prefrontal cortex development induced by early experience are completely immutable. Designing or targeting interventions to promote typical prefrontal cortex development in infants who are at risk is an emerging science (e.g. see Wass, Porayska-Pomsta, & Johnson, 2011; Wass, Scerif, & Johnson, 2012). Because early prefrontal-dependent skills develop in the context of the parent-child relationship (Swingler, Perry, & Calkins, 2015), interventions to improve infant prefrontal cortex development may need to be targeted at the dyadic level. Experiences or interventions that occur beyond early childhood can also have profound impacts on prefrontal cortex development (Diamond & Lee, 2011). However, the possibility of intervention should not diminish the severity of potential long-term disruptions in prefrontal cortex development (DiPietro, 2000). Even following years of exposure to positive environments, the literature reviewed in this paper suggests that some differences in prefrontal cortex development are not fully ameliorated. To fully reduce the impact of adverse early experiences on subsequent prefrontal cortex development, changes to broader social policies that reduce disparities are likely necessary.

Conclusion

Once characterized as “late-developing”, human prefrontal cortex is a “rapidly maturing” region of the brain, which functions earlier and shapes cortical development more broadly than previously appreciated. Substantial evidence indicates that diverse forms of early risk impact the development of prefrontal cortex structure, function, and dependent-behaviors within the first years of life. Multiple mechanisms exist via which

the timing and nature of early experiences may shape early prefrontal cortex development, although this work has not sufficiently investigated correlates of normative and positive variations in the environment. Pervasive, early emerging impacts of adverse environments on prefrontal cortex development in young infants highlight the importance of understanding: 1) interactions among rapidly developing biological systems, 2) differences in sensitivity of prefrontal cortex to the environment both across individuals and over developmental time, 3) and when and how to target interventions to reduce the negative impacts of early adverse experiences.

CHAPTER 2: Study 1a

Early Executive Function Differences in Infants Born Moderate-to-Late Preterm¹

Outline

Individuals who are born very preterm (<32 weeks gestation) show differential development of prefrontal cortex structure, function, and dependent behaviors, including executive function (EF) skills, beginning during late infancy and extending into adulthood. Preschool-aged children born moderate-to-late preterm (PT; 32-36 weeks gestation) show smaller discrepancies in EF development, but it is unclear whether these differences first emerge during the early childhood years, when EF is rapidly developing, or if they arise from alterations in complex cognitive skills measurable in late infancy. In the current study, we examined whether differences in complex attention, memory, and inhibition skills (precursor skills to EF) are altered in healthy infants born moderate-to-late PT at 9-months corrected age. Infants born PT demonstrated poorer memory at test following habituation than their full-term peers. Furthermore, lower gestational age at birth was associated with poorer performance on five of the six early EF tasks. Results indicate that even in the context of low medical and environmental risk, performance on the Bayley within the normal range, and no group-level differences in processing speed, infants born moderate-to-late PT show subtle alterations in cognitive skills presumed to

¹ Kate L. Senich, Claire Jokinen, Oren Sasson, Alyssa R. Morris, and Kathleen M. Thomas are listed as co-authors on this publication

be dependent on prefrontal cortex by 9-months of age, likely setting the stage for long-term differences in EF development.

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Early Executive Function Differences in Infants Born Moderate-to-Late Preterm

Preterm (PT; <37 weeks gestation) birth represents a major public health concern both in the United States and across the globe. While the long-term correlates of very PT birth (<32 weeks) have been extensively documented, interest has recently increased in monitoring outcomes of children born only moderate-to-late preterm (32-36 weeks gestation). Infants born moderate-to-late PT represent approximately 8% of all births in the United States (and 80% of all PT births; Hamilton, Martin, Osterman, Curtin, & Matthews, 2015). Long-term impacts of birth within this gestational age range remain relatively unknown, largely because most moderate-to-late PT infants demonstrate good neonatal outcomes and are not routinely followed in neurodevelopmental centers.

Although the risk of serious medical problems for moderate-to-late PT infants is low, short-term morbidity is still higher in comparison to full-term (FT) infants (for recent reviews, see Ananth, Friedman, & Gyamfi-Bannerman, 2013; Kugelman & Colin, 2013). Emerging evidence suggests there are also long-term impacts of moderate-to-late prematurity, even for healthy infants. For example, toddlers born moderate-to-late PT perform more poorly than their FT peers on gross developmental measures such as the Bayley or similar metrics derived from parental reports (Hillemeier, Farkas, Morgan, Martin, & MacZuga, 2009; Johnson, Evans, et al., 2015; Romeo et al., 2010; Schonhaut, Armijo, & Perez, 2015; Voigt, Pietz, Pauen, Kliegel, & Reuner, 2012; Woythaler, McCormick, & Smith, 2011). Older children and adolescents born moderate-to-late PT are also at higher risk than their FT peers for a diverse set of problematic outcomes, including developmental disability, lower IQ score, poor school performance, and

externalizing disorders (Chan, Leong, Malouf, & Quigley, 2016; Natarajan, 2016; Vohr, 2013; although see Gurka, LoCasale-Crouch et al., 2010).

There is relatively little information about the neurodevelopmental impacts of birth within this gestational age range on specific cognitive or socioemotional processes, as most prior research has focused on mortality, global developmental assessments (e.g. Bayley), or coarser measures of behavior (e.g. teacher reports of externalizing problems). In contrast, the impact of prematurity on higher-order cognitive abilities, including executive function (EF) skills such as attention flexibility, working memory, and inhibitory control has been well-characterized in individuals born very PT (<32 weeks gestation). EF impairments in individuals born very PT are measurable by late infancy (Sun, Mohay, & Callaghan, 2009) and persist into the childhood, adolescent, and adulthood years (Aarnoudse-Moens & Smidts, 2009; Anderson, Doyle, & Victorian Infant Collaborative Study Group, 2004; Luu, Ment, Allan, Schneider, & Vohr, 2011; Marlow, Hennessy, Bracewell, & Wolke, 2007; Narberhaus, Segarra, Cald, & Gim, 2008). A complimentary neuroimaging literature indicates that behavioral differences in EF in individuals born very PT are likely related to disruptions in prefrontal cortex structure and function (Ball et al., 2012; Bjuland, Løhaugen, Martinussen, & Skranes, 2013; Duerden, Card, Lax, Donner, & Taylor, 2013; Giménez et al., 2006; Kesler et al., 2008; Lax et al., 2013; Mullen et al., 2011; Mürner-Lavanchy et al., 2014; Nagy et al., 2009; Nosarti et al., 2008; Peterson et al., 2000; Zhang et al., 2015).

Growing evidence suggests that brain development in moderate-to-late PT infants differs in key ways from that of FT infants, including the development of the prefrontal

cortex. Critical developmental changes that occur in the fetal brain over the last weeks of gestation are often under appreciated (Makropoulos et al., 2016). Prefrontal cortical circuits show rapid development from the third trimester of gestation through the early neonatal period and may serve an organizing role in human brain development (Fransson et al., 2013; Gao et al., 2009; van den Heuvel et al., 2015). For the moderate-to-late PT infant, these neurodevelopmental changes occur in the postnatal world: an environment characterized by greater visual, auditory, and tactile stimulation compared to the biologically expected in-utero environment. It is not possible to disentangle the contributions of potential pre-existing differences in brain development from those induced by unexpected exposure to the stimulating postnatal environment. However, at term-equivalent age, moderate-to-late PT infants show widespread changes in both gray and white matter development, including smaller overall brain size (Munakata et al., 2013; Walsh, Doyle, Anderson, Lee, & Cheong, 2014), altered gyration (Walsh et al., 2014), and poorer white matter organization across the majority of the brain's major white matter pathways (Kelly et al., 2016). Alterations to developing hub regions (Wu et al., 2016) or the brain's broader connectivity structure in the brain of moderate-to-late PT infants could initiate a cascade of alterations in the development of higher-level circuits (Mento & Nosarti, 2015), including prefrontal circuits that subserve EF. Although longitudinal neuroimaging studies of prefrontal development in moderate-to-late PT infants have not been conducted, cross-sectional work indicates that older children born moderate-to-late PT also show altered structural and functional prefrontal cortex development (Degnan et al., 2015a, 2015b; although see Rogers et al., 2014).

Like children born very PT, preschool-aged children born within the moderate-to-late PT range also show poorer EF development than their FT peers (Baron et al., 2009; Baron, Kerns, Muller, Ahronovich, & Litman, 2012; Brumbaugh, Hodel, & Thomas, 2014; Hodel, Brumbaugh, Morris, & Thomas, 2015). However, it is unclear if alterations in prefrontal-dependent behaviors first emerge during the early preschool period, when EF is rapidly developing and the demands of the environment are increasing, a pattern that would be consistent with ‘growing into deficit’ (Sesma & Georgieff, 2003), or if differential EF development begins earlier in life. Some studies suggest that healthy PT infants are faster at disengaging and shifting attention than FT infants (Hitzert et al., 2015; Hitzert, Van Braeckel, Bos, Hunnius, & Geuze, 2014; Hunnius, Geuze, Zweens, & Bos, 2008), but this “benefit” in attentional processing disappears by 4-6 months of age. Similarly, healthy PT infants outperform FT infants on early measures of working memory and inhibitory control when tested at their corrected-age (Matthews, Ellis, & Nelson, 1996), but this advantage disappears when comparing infants based on chronological age (i.e. age from birthdate). By 18 months, toddlers born moderate-to-late PT show poorer orienting and alerting than those born FT (Jong, Verhoeven, & Baar, 2015), suggesting early “benefits” in attentional processing may instead reflect an altered trajectory of development.

EF has traditionally been conceptualized as a later developing skill, but precursor skills to EF can be measured in typically developing young infants and toddlers (see Hendry, Jones, & Charman, 2016 for recent discussion). Rudimentary EF abilities are clearly evident by the end of the first year of life, as infants become increasingly able to

both pass and tolerate delays during the classic A not B task, representing advancing inhibition and working memory skills (Diamond, 1990a, 1990b). Improvements in performance on early measures of EF like the A not B task have been clearly linked to prefrontal cortex maturation. Non-human primate models indicate that behavior on this task is disrupted by dorsolateral prefrontal cortex lesions (Diamond, 1990b). In human infants measures of frontal lobe activation (Baird et al., 2002) and changes in frontal EEG activity (Bell & Fox, 1992, 1997; Cuevas, Bell, Marcovitch, & Calkins, 2012; Cuevas, Swingler, Bell, Marcovitch, & Calkins, 2012) are correlated with age-related improvements in task performance. Related research has also documented the predictive validity of other infant measures of complex attention, memory, and inhibition skills with later EF skills measured during childhood. For example, novelty preference measures derived from infant habituation tasks have been linked to frontal lobe activity in young infants (Nakano, Watanabe, Homae, & Taga, 2009), and individual differences in both brain and behavioral measures of habituation and novelty preference are predictive of EF during the preschool years (Cuevas & Bell, 2014; Perry, Swingler, Calkins, & Ann, 2016). To date, this longitudinal work has focused primarily on normative, low-risk populations. Describing the early developmental antecedents of atypical EF in at-risk infants, including children born moderate-to-late PT, is critical to understanding how disruptions emerge.

In the current study, we examined whether infants born moderate-to-late PT showed differential development of complex attention, memory, and inhibition skills presumed to be partially dependent on prefrontal cortex (referred to as “early EF” skills

for brevity) within the first year of life. Given studies with very PT children that suggest that differences in complex cognitive skills are measurable by late infancy (Sun et al., 2009) and cascade over the course of development into later EF impairments (Rose, Feldman, & Jankowski, 2012), we predicted that infants born moderate-to-late PT would also show differential development of early EF skills by the end of the first year of life. Previous studies have documented that EF development in older children is sensitive to medical complications (Baron et al., 2009) and sociodemographic risk factors (Raver, Blair, & Willoughby, 2012) which commonly co-occur with PT birth. As such, we recruited a low-medical and low-environmental risk (i.e. middle-to-upper socioeconomic status families) sample of moderate-to-late PT infants in order to minimize impacts of these potentially confounding factors.

Method

Participants

Nine-month-old infants were recruited based on gestational age from a database of families who endorsed interest in participating in child development research. Families in this database were recruited via birth records from local hospitals. The sample consisted of 71 infants born moderate-to-late preterm (PT; 30-36 weeks gestation) and 67 infants born full-term (FT; 37-42 weeks gestation). Infants were tested within \pm 1 week of turning 9-months-old (9-months corrected-age for PT infants). Infants were predominantly Caucasian (90.6%), lived in college-educated (91.3%), two-parent families (99.3%), with median household incomes between \$101,000-\$125,000. Exclusion criteria included neurological insult or disease, intrauterine growth restriction,

congenital heart disease, serious medical illness (e.g. organ transplant), and for FT children only, admission to a special care or intensive care nursery for > 24 hours as a newborn. Hollingshead scores (Hollingshead, 1975), reflecting overall familial socioeconomic status, did not differ for the two groups. See Table 2.1 for demographic characteristics of the sample.

Birth hospitalization records and newborn well-child check records were obtained for 97% of the sample to confirm gestational age and to document perinatal history; midwife records were obtained for the remaining 3% of infants who were planned home births. See Table 2.2 for perinatal characteristics of the sample.

General Procedure

Infants completed a battery of behavioral and looking-time tasks designed to target early frontal lobe functions, selected from the adult and child neuropsychology literature. All infants also completed the Bayley-III Screening Test as a global developmental assessment of cognitive, motor, and language skills (Bayley, 2006). The entire testing session lasted approximately 90 minutes. Parents of infants completed a questionnaire measure of their child's early attention skills (Infant Behavior Questionnaire, IBQ; Garstein & Rothbart, 2003). Written informed consent was obtained from parents. Families received a small present (infant board book or infant T-shirt) as compensation. Study procedures were approved by the University of Minnesota's Institutional Review Board.

Additional methodological details of the infant "early EF" measures are included in the Appendix. Each infant completed the tasks in a fixed order (reversal learning, A

not B, problem solving, habituation, attention flexibility, processing speed/attention shifting, Bayley). The tasks were presented in a fixed order because we anticipated infants' energy and interest would decline across the session and could best be maintained by intermixing behavioral and eye-tracking tasks.

For eye-tracking tasks, infants were seated on their parent's lap, approximately 48 inches from the screen, in a darkened room. An opaque curtain separated the parent and infant from the experimenter. Computerized stimuli were presented via Macromedia Director MX 2004 on a 42 inch LCD monitor. Infant eye movements were recorded using a hidden digital video camera, located directly below the screen, with infrared night vision. Video feed of the infant was presented live to the experimenter, who was blind to what stimuli were presented to that infant, for preliminary online data coding and to enable repositioning of the camera. The experimenter used key presses to indicate whether the infant was looking at the center, left side, right side, or away from the screen. The live video feed was burned to DVD for final offline coding of eye movement data.

For behavioral tasks, infants were seated on their parent's lap so that they were able to reach stimuli presented on a 31.5 x 31.5 inch square white table. Infant behavior was recorded using a hidden digital video camera located on an adjacent table (either facing the infant directly or in a profile view, depending on the task) and also from overhead using a ceiling mounted webcam. Both video feeds were burned to DVD for offline coding of behavior.

Table 2.1

Demographic Characteristics

	<u>Preterm (n = 71)</u>	<u>Full-Term (n = 67)</u>	<i>p</i>
	<i>n</i> (%)	<i>n</i> (%)	
Chronological Age in Months - <i>M</i> (<i>SD</i>)	10.30 (.43)	9.14 (.14)	.00*
Corrected Age in Months - <i>M</i> (<i>SD</i>)	9.13 (.15)		
Child's Sex - # male	38 (53.5)	33 (49.3)	.61
Child's Ethnicity - # Caucasian	67 (94.4)	58 (86.6)	.15
Maternal Education			.42
High school degree or GED	4 (5.6)	1 (1.5)	
Associate degree	3 (4.2)	4 (6.0)	
Bachelor's degree	28 (39.4)	25 (37.3)	
Graduate or professional degree	36 (50.7)	37 (55.2)	
Maternal Work			.08
Full-time work for pay	34 (47.9)	41 (61.2)	
Part-time work for pay	25 (35.2)	11 (16.4)	
Student	3 (4.2)	2 (3.0)	
Stay at home parent	9 (12.7)	13 (19.4)	
Annual Household Income			.68
≤ \$50,000	3 (4.3)	4 (6.3)	
\$51,000 - \$100,000	17 (23.2)	9 (14.1)	
\$101,000 - \$150,000	27 (39.1)	26 (40.6)	
≥ \$151,000	23 (33.3)	25 (39.1)	
Marital Status - # married	70 (98.6)	65 (97.0)	.61
Hollingshead Score – <i>M</i> (<i>SD</i>)	52.62 (7.74)	53.37 (9.57)	.61

Notes. Five families (3 FT, 2 PT) declined to provide annual household income. **p*<.05

Table 2.2

Perinatal Characteristics

	<u>Preterm (n = 71)</u>	<u>Full-Term (n = 67)</u>	<i>p</i>
	<i>M (SD)</i>	<i>M (SD)</i>	
Birth History			
Gestational age (weeks)	35.01 (1.72)	39.94 (1.05)	<.01*
Birth weight (grams)	2467.92 (542.61)	3546.38 (467.36)	<.01*
Apgar at 1 minute	7.43 (1.45)	8.15 (1.22)	<.01*
Apgar at 5 minutes	8.47 (1.05)	8.94 (.35)	<.01*
Length of hospital stay (days)	11.10 (10.96)	1.75 (.80)	<.01*
Maternal age at delivery (years)	31.90 (3.27)	31.15 (3.54)	.20
	<i>n (%)</i>	<i>n (%)</i>	<i>p</i>
Pregnancy Related Characteristics			
Twin gestation ^a	25 (35.2)	0 (0)	<.01*
Preeclampsia or hypertension	16 (22.5)	1 (1.5)	<.01*
Gestational diabetes	8 (11.3)	4 (6.0)	.27
Maternal obesity	4 (5.6)	0 (0)	.12
Placenta previa	3 (4.2)	1 (1.5)	.62
Preterm labor	12 (17.0)	0 (0)	<.01*
Prolonged ROM (>18 hours)	11 (15.5)	3 (4.5)	.05
Cesarean delivery	38 (53.5)	13 (19.4)	<.01*
Neonatal Complications			
Hypoglycemia	39 (54.9)	11 (16.4)	<.01*
<i>Glucose treatment</i>	8 (11.3)	0 (0)	<.01*
Phototherapy	33 (46.5)	2 (3.0)	<.01*
Respiratory distress	28 (39.4)	1 (1.5)	<.01*
<i>Positive pressure ventilation</i>	25 (35.2)	1 (1.5)	<.01*
<i>Corticosteroid treatment</i>	17 (24.0)	0 (0)	<.01*
Apnea episodes	20 (28.2)	1 (1.5)	<.01*
Hypovolemia	0 (0)	0 (0)	
PDA	2 (2.8)	1 (1.5)	.99
IVH/PVL	0 (0)	0 (0)	

Notes. ^aPT group includes data from both twins in 9 twin pairs. **p* < .05.

Infant Eye-Tracking Tasks

Reversal learning. A deterministic reversal learning task was used (Kovács & Mehler, 2009; Wass, Porayska-Pomsta, & Johnson, 2011) in which infants were expected to learn that a visual reward would appear reliably on one side of the screen. Imaging studies with adults have indicated that reversal learning is ventral-frontostriatal dependent (Cools, Clark, Owen, & Robbins, 2002). Prior studies with young infants have also linked individual differences in performance to higher level cognitive skills (Kovács & Mehler, 2009) and demonstrated the sensitivity of this task to attention training (Wass et al., 2011). This eye-tracking task consisted of two phases: a learning phase (9 trials) followed by a reversal phase (9 trials), in which the location of the visual reward switched. Anticipatory eye movements were defined as initial eye movements to the correct side of the screen beginning within 250 ms of the visual reward onset. Perseverative eye movements were coded during the reversal phase only using similar criteria. Outcome measures included percentage of anticipations and percentage of perseverative looks (reversal phase only). Three infants (2 FT, 1 PT) did not provide complete data due to parent refusal (1), infant fussiness (1), and a technical error in data recording (1).

Habituation. A standard habituation task using an infant-driven, sliding window design with NimStim face stimuli (<http://www.macbrain.org/faces/index.htm>) was used (based on Markant, Cicchetti, Hetzel, & Thomas, 2014). Novelty detection/dishabituation in young infants is associated with prefrontal activation (Nakano et al., 2009) and individual differences in habituation metrics are longitudinally related to

other measures of frontal-dependent behaviors (Cuevas & Bell, 2014). In this eye-tracking task, one female Caucasian face was presented centrally for up to 15 seconds per trial. The habituation criterion was met when the infant's average look duration over three consecutive trials was less than 50% of his/her average look duration from the first three trials of the experiment. A maximum of 21 trials to reach habituation was allowed. Following habituation, infants completed six additional trials in randomized order: three in which the now-familiar habituation face was presented and three trials in which the novel face was presented. Outcome measures included latency to habituate (trials to habituation, average look duration per trial) and novelty preference at test (comparison of cumulative looking-times for the novel and familiar test faces). Fourteen infants (11 FT, 3 PT) did not provide complete data due to parent refusal (1), insufficient time to administer the task (1), infant fussiness (5), and technical errors in data recording (7).

Processing speed/attention shifting. A basic visual attention task was used as a measure of infant processing speed and attention shifting. Infants oriented attention to a peripheral target following disengagement from a central stimulus. Processing speed measures are predictive longitudinally of later EF (Rose, Feldman, Jankowski, & Van Rossem, 2011) and age-related changes in infant attention shifting are related to maturation of frontal regions including the frontal eye fields (e.g. see discussion in Wass & Smith, 2014). Outcome measures included average reaction time to the peripheral target and the average number of attention shifts per trial. Fifteen infants (7 FT, 8 PT) did not provide complete data due to parent refusal (1), insufficient time to administer the task (1), insufficient valid trials (11), and technical errors in data recording (2).

Infant Behavioral Tasks

A not B. Working memory and inhibitory control were assessed using a reaching version of the classic A not B task in which the delay between hiding and object retrieval was incremented to determine the ceiling of each infant's abilities (Diamond, 1985). As previously discussed, this task has been demonstrated to be frontal-lobe dependent through lesion studies in non-human primates (Diamond, 1990a, 1990b) and measures of frontal lobe activation in typically developing infants (Baird et al., 2002). We utilized a graded A not B task in which the delay length between hiding and searching increased by 3 seconds for each successful trial set. Training trials and pre-test items were administered prior to the task. In the A not B task, the minimum delay length tested was 0 seconds; 9 seconds was set as the ceiling delay length tested. The outcome measure of interest corresponded to the highest level of the task the infant successfully completed and whether or not the infant was able to pass the 0-second, A not B trial. Four infants (0 FT, 4 PT) did not provide complete data due to infant fussiness (2), experimenter error (1), and insufficient time to administer the task (1).

Problem solving. Infants were asked to complete a sequence of steps to uncover and retrieve an attractive toy (Willatts, Forsyth, DiModugno, Varma, & Colvin, 1998). In older children, EF is often conceptualized as a series of problem-solving processes resulting in goal-oriented behavior, requiring representation, planning, and evaluation skills (Zhou, Chen, & Main, 2012). We tested infants on three problem-solving sequences, including one-step, two-step, and three-step (e.g. remove a barrier, pull a cloth, and lift a cover to retrieve a toy) problems. Infants attempted three trials at each

level and only advanced to the next level if they were able to solve the previous stage within 30 seconds. Data were coded using a scheme adapted from Willatts et al. (1998) for evidence of intentional behavior (e.g. maintaining fixation on the goal object, lack of exploratory play with the props) and latency to solve each problem. Outcome measures of interest included total intentionality scores and the minimum latency required to solve one-step, two-step, and three-step problems. Ten infants (4 FT, 6 PT) did not provide complete data due to infant fussiness (4), experimenter error (3), and insufficient time to administer the task (3).

Attention flexibility. Flexibility of attention was assessed during a standard free play with toys task (Ruff, 1986). Efficient attention shifting behavior is related to individual differences in prefrontal dopamine levels (Markant et al., 2014) and studies with young infants have also found relationships between measures of frontal lobe electrical activity and the duration of infant sustained attention (Perry et al., 2016). Infants were presented with a colorful rattle with small moveable parts and given two minutes to explore it. If the toy was out of reach for the infant (drop, thrown, pushed away), the experimenter returned it to the presentation tray. Data were coded offline and segmented into bouts of different attention types, including two types of focused attention (based on Clearfield & Jedd, 2013): focused attention towards toys and focused attention towards people (the parent or experimenter). The average duration of each type of attention bout was calculated for each infant. Eleven infants (8 FT, 3 PT) did not provide complete data due to infant fussiness (3), technical error in data recording (7), and insufficient time to administer the task (1).

Statistical Analyses

Effects of prematurity were initially analyzed with gestational age as a categorical variable (PT vs. FT). Independent samples t-tests were used to compare group means of continuous variables, Chi-square tests were used to compare means of categorical variables, and logistic regression was used to compare performance on binary outcome measures. For variables showing evidence of skew (e.g. some reaction time measures), non-parametric analyses (Mann-Whitney U tests) were instead conducted. All group difference analyses were also repeated including corrected age at test, sex, and the interaction of sex and group as predictors. The reported results (i.e. significance of main effect of group status) were not altered, so analyses are presented without these extra predictors for brevity.

Effects of prematurity were also analyzed with gestational age as a continuous variable in linear regression models (for tasks with continuous outcome measures) or logistic regression (for tasks with binary outcome measures). Regression analyses were conducted including both the entire sample's gestational range (30–42 weeks gestation) and within the PT group only, as linear effects of gestational age would not necessarily be predicted to extend into the FT range. For variables that showed evidence of skew, non-parametric analyses (Spearman's rank correlation coefficient) were instead conducted.

All parametric results are reported with group means and standard deviations. Non-parametric results report group medians. For regression models the unstandardized B value and parameter-level statistics are reported. Effect sizes are reported using Cohen's d when applicable.

Results

Bayley

All FT and PT infants performed within the normal range on the Bayley-III screening test. Cognitive, language (receptive and expressive), and motor (fine and gross) subscale scores did not differ between FT and PT infants in this low-risk, highly resourced sample (e.g. cognitive subscale, $t(135) = .34, p < .73, d = -.06, M_{FT} = 12.85 \pm 1.36, M_{PT} = 12.93 \pm 1.29$). Bayley scores were not related to continuous measures of gestational age within the entire sample or within the PT group alone.

Parent Report of Early Regulatory Skills

Parents of FT and PT children did not differ in their report of infants' early regulatory skills, based on the Infant Behavior Questionnaire's regulation composite scale, $t(123) = 1.49, p < .14, d = .26, M_{FT} = 4.40 \pm .39, M_{PT} = 4.30 \pm .38$. Parent-reported regulatory skills were not related to continuous measures of gestational age within the entire sample or within the PT group alone.

Infant Eye-Tracking Tasks

Reversal learning. FT and PT infants showed equivalent levels of anticipatory eye movements across the reversal learning task, $t(133) = -.24, p < .81, d = -.06, M_{FT} = .37 \pm .16, M_{PT} = .38 \pm .15$, and were equally likely to make perseverative eye movements in the reversal phase of the task, $t(123) = .31, p < .75, d = .05, M_{FT} = .43 \pm .31, M_{PT} = .41 \pm .31$. Task performance was not related to continuous measures of gestational age within the entire sample or within the PT group alone.

Habituation. FT and PT infants did not differ in trials to reach habituation,

$t(118) = .38, p < .70, d = .07, M_{FT} = 12.31 \pm 4.89, M_{PT} = 11.95 \pm 5.38$, or in average look duration during the habituation phase, $U = 2056.00, p < .81, Mdn_{FT} = 9054.13$ ms, $Mdn_{PT} = 9014.39$ ms. These measures were not correlated with gestational age in the entire sample of infants. However, within the PT group, higher gestational age at birth predicted shorter average look durations across habituation trials, $\rho(68) = -.24, p < .05$.

Among infants who met the habituation criterion, one-sample t-tests indicated that both the FT, $t(48) = 4.76, p < .00$, and PT, $t(58) = 3.72, p < .00$, groups showed evidence of a novelty preference at test. Novelty preference scores were significantly greater in FT infants versus PT infants, $t(106) = 1.95, p < .05, d = .37, M_{FT} = 1796.71 \pm 2642.68$ ms, $M_{PT} = 936.44 \pm 1931.51$ ms. There was a trend-level linear relationship between lower gestational age at birth and smaller novelty preference scores across the entire gestational age at birth range, $r(108) = .18, p < .06$, see Figure 2.1, although this relationship was not present within the PT group alone, $r(59) = .02, p < .86$.

Processing speed/attention shifting. Processing speed (average latency to shift attention to a peripheral target) derived from the computerized reaction-time task did not differ by group, $t(121) = .03, p < .97, d = -.01, M_{FT} = 418.76 \pm 46.96$ ms, $M_{PT} = 419.04 \pm 48.12$ ms. Processing speed was also not related to continuous measures of gestational age within the entire sample or within the PT group alone.

Additional analyses investigated a secondary measure of interest from this task: attention shifting. Average number of attention shifts did not differ by group, $U = 1859.00, p < .88, Mdn_{FT} = 1.11, Mdn_{PT} = 1.13$. However, within the PT group, there was a trend-level relationship between lower gestational age at birth and less frequent

attention shifting, $\rho(63) = .23, p < .08$.

Infant Behavioral Tasks

A not B. FT and PT infants did not differ in median scaled performance scores on the A not B task, $U = 2446.50, p < .65, Mdn_{FT} = 3, Mdn_{PT} = 3$. However, lower gestational age at birth predicted poorer task performance across the entire sample of infants, $\rho(133) = .17, p < .05$. This relationship was also separately present within the PT infant group, $\rho(66) = .29, p < .02$.

We also investigated potential group differences in infants' abilities to pass the classic A not B trial (0 second delay). Similar to the scaled performance scores, there was no group difference in likelihood of passing the classic A not B trial, $B = .30, se(B) = .36, p < .41, Exp(B) = 1.35, M_{FT} = .40 \pm .49, M_{PT} = .33 \pm .48$. However, across the entire sample, lower gestational age at birth predicted a higher likelihood of failing the A not B trial, $B = .16, se(B) = .07, p < .02, Exp(B) = 1.17$, see Figure 2.2. This relationship was also present separately within the PT group, $B = .42, se(B) = .21, p < .04, Exp(B) = 1.52$.

Problem solving. FT and PT infants did not differ in overall problem solving scores, $t(126) = .16, p < .87, d = .03, M_{FT} = 67.67 \pm 30.87, M_{PT} = 66.80 \pm 29.41$, or in the minimum amount of time to correctly solve one-step, two-step, or three-step problems (one-step: $U = 1888.50, p < .54, Mdn_{FT} = 2950.00 \text{ ms}, Mdn_{PT} = 3133.33 \text{ ms}$; two-step: $U = 1169.50, p < .84, Mdn_{FT} = 12700.00 \text{ ms}, Mdn_{PT} = 12766.67 \text{ ms}$; three-step: $U = 514.00, p < .70, Mdn_{FT} = 15733.33 \text{ ms}, Mdn_{PT} = 18500.00 \text{ ms}$).

Across the entire sample there was a trend level relationship between lower gestational age at birth and slower latencies on two-step problems, $\rho(98) = -.19, p < .06$.

This relationship was also present within the PT infant group, $\rho_{\text{PT}}(51) = -.31$, $p < .03$.

Attention flexibility. Average duration of attention toward the toy, $t(125) = .54$, $p < .59$, $d = .10$, $M_{\text{FT}} = 6789.36 \pm 3334.74$ ms, $M_{\text{PT}} = 6479.56 \pm 3157.79$ ms, and average duration of social attention episodes did not differ by group, $t(125) = .25$, $p < .80$, $d = .05$, $M_{\text{FT}} = 2774.22 \pm 1163.81$ ms, $M_{\text{PT}} = 2702.13 \pm 1927.34$ ms. These measures were not linearly related to gestational age in the entire sample of infants. However, within the PT group, lower gestational age at birth predicted longer average bouts of attention toward the toy, $r(68) = -.37$, $p < .02$, and toward people (experimenter and/or caregiver), $r(68) = -.25$, $p < .04$.

Exploratory follow-up analyses in the PT group indicated that this pattern of attention (longer average attention bouts to both the toy and person) was reflected by less overall attention shifting, $r(68) = .32$, $p < .01$, including less frequent attention shifting away from the toy and toward a person, $r(68) = .21$, $p < .08$, with decreasing gestational age.

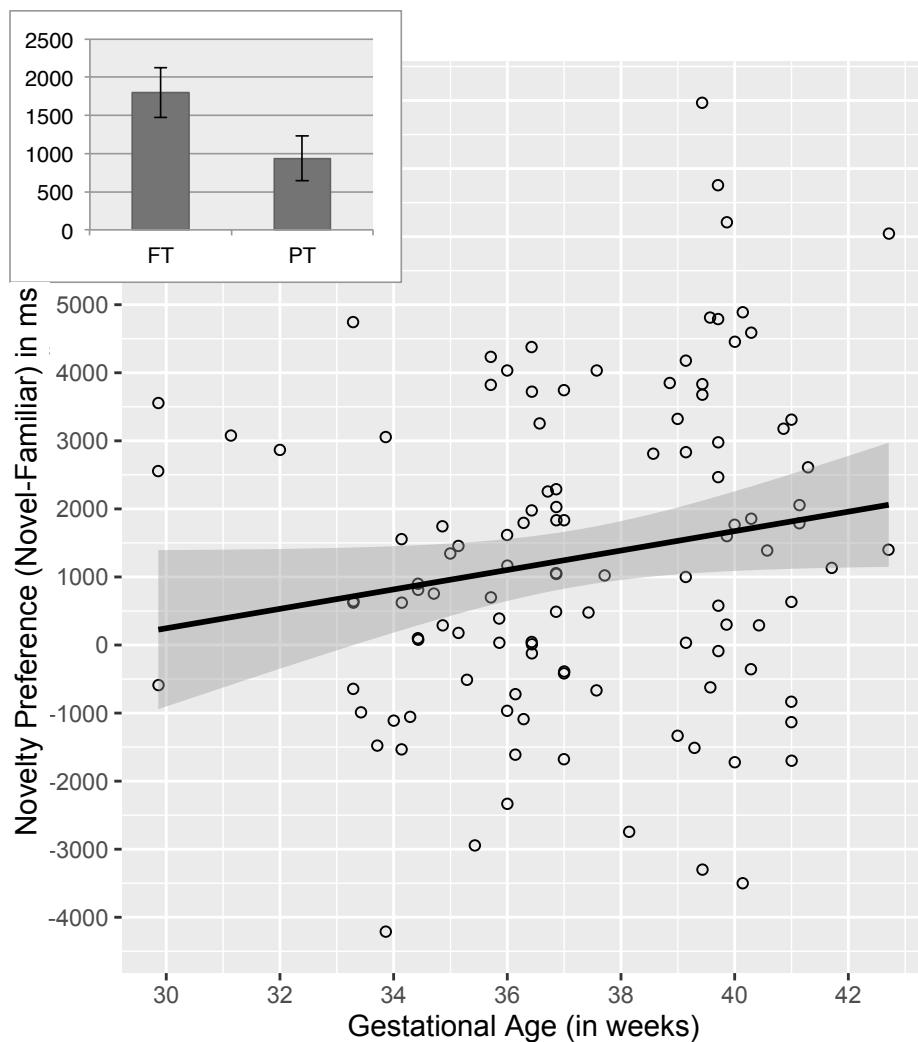


Figure 2.1. Novelty preference scores by group (inset) and gestational age. Infants born moderate-to-late PT had smaller novelty preference scores in comparison to their FT peers ($p < .05$), and individual differences in the magnitude of novelty preference were related to gestational age across the entire sample of infants ($p < .06$).

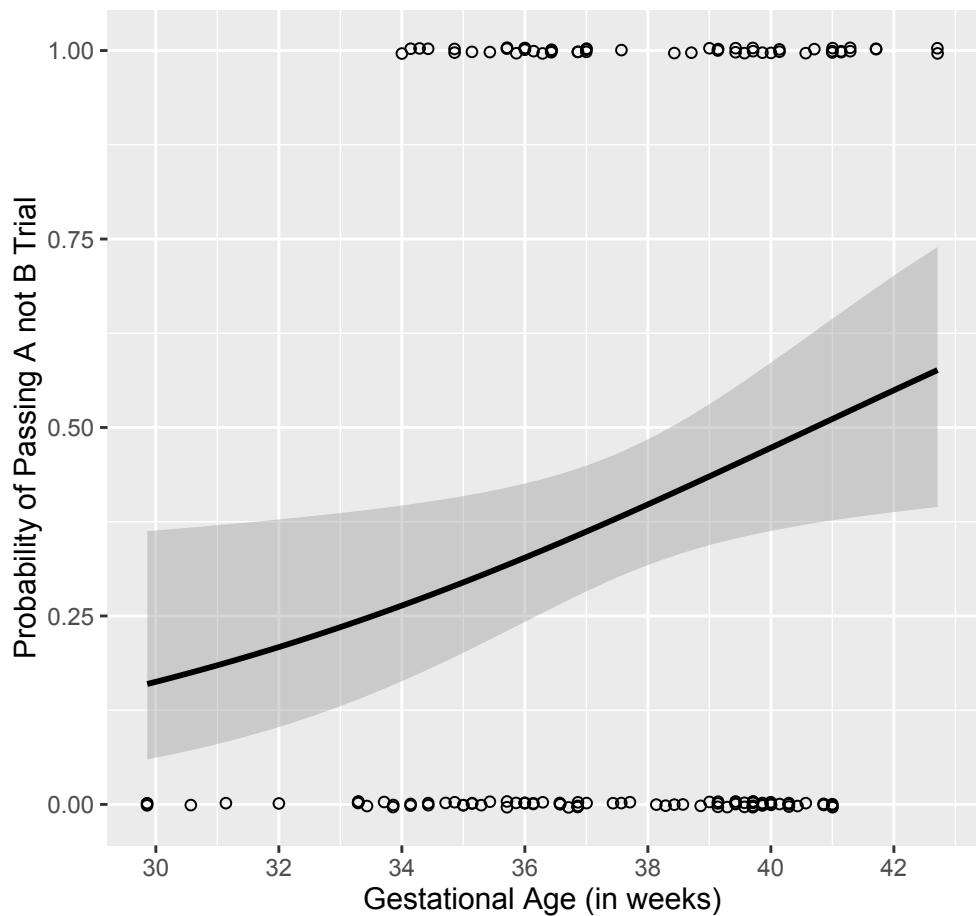


Figure 2.2. A not B performance and gestational age. Infants born moderate-to-late PT and infants born FT were equally likely to pass the classic A not B task (0 second delay; $p < .41$); however, lower gestational age at birth across the entire sample of infants predicted an increased likelihood of failing the task ($p < .02$).

Discussion

This is one of the first studies to report group differences in higher-level cognitive skills in young infants born moderate-to-late PT. Across a diverse battery of behavioral and eye-tracking tasks, we found that healthy infants born moderate-to-late PT showed subtle differences in the development of precursor skills to EF at 9-months of age. Specifically, moderate-to-late PT infants showed smaller novelty preference scores following habituation, an early measure of working memory. Lower gestational age at birth was also associated with poorer performance on five of the six early EF tasks. Importantly, these relationships were observed even in the context of low environmental risk (middle-to-high socioeconomic status) and even when moderate-to-late PT infants were tested at corrected, rather than chronological, ages. This pattern of results is consistent with prior reports of subtle alterations to EF skills in preschool-aged children born moderate-to-late PT (Baron et al., 2009, 2012; Brumbaugh et al., 2014; Hodel et al., 2015) and with a growing literature documenting alterations in structural and functional prefrontal cortex development in this population (Degnan et al., 2015a, 2015b; Kelly et al., 2016; Munakata et al., 2013; Walsh et al., 2014). In addition, we found that individual differences in task performance were related to gestational age at birth across the entire gestational age range of our sample (30-42 weeks) on three early measures of EF. This extension of effects into the term range is consistent with an emerging literature describing neurodevelopmental risks of early-term (37-38 weeks gestation) birth (Espel, Glynn, Sandman, & Davis, 2014; Noble, Fifer, Rauh, Nomura, & Andrews, 2012; Rose et al., 2013), and likely underscores the importance of rapid changes in brain

development that extend across the third trimester of gestation.

Although multiple cognitive processes are required for infants to successfully perform on the habituation task, a working memory component is clearly involved. Classic information processing models of the habituation task (Sokolov, 1963) assume that infants must compare the stimulus presented on each trial to one held in mind to determine whether the two are identical. Furthermore, the ability to discriminate between the novel and familiar stimulus following a delay requires a representation of the original stimulus to be held in mind. Typically developing infants who score higher on other laboratory measures presumed to rely on working memory also show stronger habituation and dishabituation responses (Ropeter & Pauen, 2013), providing converging evidence that this task taps early working memory skills. Given that previous studies with older children born moderate-to-late PT have also reported group differences on working memory tasks (Baron et al., 2012; Brumbaugh et al., 2016; Hodel et al., 2015), our results may reflect continuity across development in subtle working memory impairments in children born moderate-to-late PT. However, since several of the tasks included in our battery ostensibly contained some level of working memory demand (e.g. delay trials on the A not B task, holding a goal in mind during the problem solving task, etc); why between-group differences were only detected on the habituation task is unclear.

Similar to prior studies with preschoolers, group differences in early EF skills in moderate-to-late PT versus FT infants were not present across all EF tasks and were generally small in magnitude. The lack of group differences across the broader set of tasks may be related both to the specific cognitive skills measured and to the difficulty of

the tasks. For example, older moderate-to-late PT children perform equivalently on measures of inhibitory control in comparison to FT children (Baron et al., 2012; Brumbaugh et al., 2016; Hodel et al., 2015), suggesting that infant measures of inhibitory control precursors (e.g. perseverative looking on reversal learning, the A not B task, etc) perhaps should not be expected to differ by group. It is also possible that ceiling and floor effects made it difficult to detect between group differences on other tasks in our battery. Studies with older PT children have demonstrated that individuals born very PT and moderately PT are more likely to demonstrate impaired performance as the cognitive load of tasks becomes higher (Jaekel, Baumann, & Wolke, 2013). In the current study, the reversal learning task was the only task that did not demonstrate a group difference or any relationship with gestational age; however, given the average percent of correct anticipatory looks across the task (~40% of trials in both groups), it seems more likely that this task was quite difficult for 9-month-old infants. Alternatively, the inherent difficulty of reliably measuring infant cognitive skills may also contribute to the lack of group differences. Two recent studies (Johansson, Marciszko, Brocki, & Bohlin, 2015; Miller & Marcovitch, 2015) employing a battery of EF tasks in young toddlers have both reported absent or small correlations across EF measures, perhaps because children do not respond in consistent ways across laboratory measures of higher-order cognitive skills at young ages. Last, the lack of group differences across tasks may simply reflect the nature of EF differences in this population; group differences in older moderate-to-late PT children are relatively subtle and likely do not fall in the range of a clinical impairment (Brumbaugh et al., 2014; Hodel et al., 2015).

In addition to group differences in early working memory performance, gestational age at birth was linearly related to early EF task performance across five of the six tasks. Infants born at earlier gestational ages had smaller novelty preference scores on the habituation task, poorer performance on the graded A not B task, slower problem solving task latency for problems of moderate difficulty, less frequent attention shifting during a visual orienting task, and longer average attention bouts during free play. Rather than reflecting inattentive behavior or a lack of appropriate sustained attention, the direction of the attention shifting and attention bout duration effects are consistent with development of volitional attentional control during later infancy (Lansink, Mintz, & Richards, 2000), likely reflecting more efficient encoding and sampling of the environment for novel information. Infants who demonstrate shorter and/or less variable fixation durations at the end of the first year have higher scores on concurrent measures of cognitive control (Wass & Smith, 2014) and shorter look duration in young infants has also been linked longitudinally to higher vocabulary and EF skills in the toddler and preschool years (Cuevas & Bell, 2014; Kannass & Oakes, 2008). Shorter bouts of attention and more frequent shifts of attention between the toy and experimenter/caregiver on the attention flexibility task also likely reflect the emergence of joint attention skills, rather than poorer sustained attention. Unfortunately, the attention flexibility task used in the current study was not designed to measure joint attention. Two recent studies (Guy et al., 2015; Johnson, Matthews, et al., 2015) of social attention processes in infants and/or toddlers born moderate-to-late PT have reported that risk for Autism and delayed social competence is higher in this population. Future studies

should more carefully investigate the development of joint attention processes in infants born moderate-to-late PT, particularly given their relation to early EF development in typically developing toddlers (Miller & Marcovitch, 2015). Ultimately, associations between gestational age and early EF task performance that extend into the FT range highlight that there is no finite cut-off point at which the neurodevelopmental impacts of PT birth are eliminated. Previous studies with preschool-aged children born moderate-to-late PT have also reported that gestational age associations with task performance extend into the FT range (Brumbaugh et al., 2014; Hodel et al., 2015). Future studies are needed to determine whether subtle biological and environmental differences associated with early-term birth alter long-term trajectories of EF development, or if these associations are only present during the early childhood period when prefrontal-dependent behaviors are first emerging and rapidly changing.

Three features of the sample of PT infants tested in this study warrant additional discussion. First, our sample is not representative of the moderate-to-late PT population at large. Instead, infants were pre-selected based on specific medical criteria to be of low medical risk (e.g. no documented growth restriction, no known brain injury, etc). Based on sample demographic characteristics (e.g. maternal education, family income) the infants tested were also of low postnatal environmental risk. Importantly, the PT and FT groups were well-matched on demographic characteristics. Effects of moderate-to-late PT birth in samples with higher medical and/or environmental risk would be predicted to be larger in magnitude, a pattern that has been demonstrated in older children born moderate-to-late PT (Baron et al., 2009). Second, we elected to test our sample of

moderate-to-late PT infants at their corrected age. There is little consensus across studies, particularly for those including late PT infants and toddlers, regarding whether it is necessary to adjust ages for children born within this gestational age range (Vohr, 2013). Recent studies have suggested that moderate-to-late PT infants perform less favorably if compared against chronological-age rather than corrected-age metrics (Parekh et al., 2016). Group differences and/or associations with gestational age described in the current study would likely be even stronger if moderate-to-late PT infants were tested at their chronological age. Last, all moderate-to-late PT infants scored within the typically developing range on the Bayley-III screening test and performed equivalently as a group to FT infants in measures of processing speed. Therefore the effects of moderate-to-late PT birth we report extend beyond variation in general cognitive and information processing skills at 9-months of age.

In summary, this is one of the first reports of altered development of higher-order cognitive skills, including early EF precursor abilities, in healthy infants born moderate-to-late PT. We provide preliminary evidence that variation in gestational age within the moderate-to-late PT range is associated with the development of complex attention, memory, and inhibitory skills across a diverse battery of infant behavioral and looking-time tasks. Based on studies with very PT children demonstrating continuity of group differences in information processing over development (Rose, Feldman, Jankowski, & Van Rossem, 2012; Rose, Feldman, & Jankowski, 2009; Rose et al., 2011) and normative work demonstrating the predictive validity of early infant attentional processes for later EF development during childhood (Cuevas & Bell, 2014; Kraybill, 2013; Perry et al.,

2016), we posit that the effects detected in the current study reflect early markers of alterations in prefrontal-dependent behavior. Future longitudinal studies are necessary to determine whether differences in infant precursors of EF are related to later developmental problems in moderate-to-late PT children, including poorer academic performance and increased rates of behavioral and emotional disorders (Chyi, Lee, Hintz, Gould, & Sutcliffe, 2008; Morse, Zheng, Tang, & Roth, 2009). Longitudinal studies also have the potential to illuminate the mechanisms underlying atypical cognitive and/or socioemotional development in moderate-to-late PT children. Although we hypothesize that prematurity-induced alterations in structural and functional prefrontal cortex development are responsible for the observed differences in our behavioral measures of EF, a multitude of other environmental factors (e.g. parenting behaviors, Bernier, Calkins, & Bell, 2016; Bernier, Carlson, Deschenes, & Matte-Gagne, 2012), are known to impact the development of EF skills. Understanding both the mechanisms related to, and developmental antecedents of, altered EF in moderate-to-late PT children is critical, given that EF skills are also impacted in children with diverse forms of early risk (e.g. poverty, maltreatment, institutional care; Bick & Nelson, 2016; Hackman, Gallop, Evans, & Farah, 2015; Merz, Harlé, Noble, & McCall, 2016). A more sophisticated understanding of how and when differences in EF precursor skills first emerge will inform our efforts to design and provide interventions when the brain is most malleable and when transfer of training across cognitive domains may be most effective (Wass et al., 2011; Wass, Scerif, & Johnson, 2012).

CHAPTER 3: Study 1b

Development of Early Executive Function Skills in Infancy: Biological and Environmental Contributions²

Outline

Variation in infant information processing skills, including measures of attention, processing speed, and memory is predictive of long-term executive function (EF) development. Studies with high-risk populations of children such as children born very preterm, living in poverty, or exposed to neglect or maltreatment have demonstrated that both prefrontal cortex development and prefrontal-dependent behaviors including EF are negatively impacted by early biological and environmental risk. We examined the structure of complex cognitive skills in 9-month old infants (referred to as “early EF” skills for brevity) and their sensitivity to more subtle variations in biological and environmental risk factors. Using a battery of eye-tracking and behavioral tasks, we determined that variance in early EF skills can be accounted for by core information processing skills (e.g. processing speed) and higher-order cognitive constructs (e.g. inhibition). Early EF development was also sensitive to variations in both biological and environmental risk. Healthy infants born moderate-to-late preterm (32-36 weeks gestation), a form of biological risk, showed poorer development of attention shifting

² Kate L. Senich, Claire Jokinen, Hillary Hercules, Matthew Ozerkov, and Kathleen M. Thomas are listed as co-authors on this publication

skills. Environmental variations including lower income-to-needs ratios and less sensitive parenting were also related to poorer early EF development in both moderate-to-late preterm and typically developing full-term children. Impacts of early risk were most consistently found for infant attention shifting abilities, suggesting alterations in early attentional processes may represent a pathway for impaired EF development. Our results highlight the sensitivity of the developing prefrontal cortex to more subtle, normative variations in the early environment, and emphasize the importance of considering late infancy as a key period during which differences in developmental trajectories for later EF abilities likely emerge.

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*Development of Early Executive Function Skills in Infancy: Biological and
Environmental Contributions*

Exciting new neuroimaging research has indicated that prefrontal cortex, typically conceptualized as a late-maturing region of the brain, undergoes rapid development beginning during the end of pregnancy and extending across the early childhood period. Dramatic structural and functional changes in the first year of life include expanding gray matter volume (Gilmore et al., 2012; Nishida et al., 2006) and cortical complexity (Kim et al., 2016; Li et al., 2014; Lyall et al., 2015), accelerating myelin accrual (Dean et al., 2014; O’Muircheartaigh et al., 2014), increases in glucose metabolism (Chugani & Phelps, 1986), and the organization of functional brain networks (Gao et al., 2009; Gao, Alcauter, Smith, Gilmore, & Lin, 2015) guided by frontally-located hubs (Johnson, Jones, & Gliga, 2015). Rapid development of prefrontal cortex during the early childhood years allows for the environment to flexibly shape the development of prefrontal-dependent behaviors, including executive function (EF) skills. Near the end of the first year of life infants show evidence of increasingly sophisticated early EF skills (see Hendry, Jones, & Charman, 2016 for excellent recent review), including improvements in working memory and inhibitory control (Diamond, 1985, 1990a, 1990b), goal-directed planning and problem-solving skills (Willatts, Forsyth, DiModugno, Varma, & Colvin, 1998), and increasing attentional control (Ruff & Rothbart, 1996). Changes in behavioral performance on early prefrontal-dependent tasks are associated with age-related and/or developmental differences in frontal lobe functional activation (Baird et al., 2002) and EEG activity (Bell & Fox, 1992, 1997).

Given the sensitivity of the developing prefrontal cortex to the environment (Kolb et al., 2012), late infancy is a key period in which to study the impact of both biological and environmental variations on the development of early prefrontal-dependent behaviors.

Structure of EF in Young Children

In older children and adults, EF is classically composed of separable working memory, attention shifting, and inhibitory components (Miyake et al., 2000), although recent conceptual approaches emphasize latent updating and shifting factors (Miyake & Friedman, 2012). During the preschool years, a period of rapid EF development, abilities may be better described by a unitary factor model (Wiebe et al., 2011; Willoughby, Wirth, Blair, & Family Life Project Investigators, 2012). This developmental trajectory suggests that EF skills differentiate over time and may develop in a hierarchical fashion. However, other studies do report separable EF factors in 2- and 3-year-old children (Bernier, Carlson, Deschenes, & Matte-Gagne, 2012; Mulder, Hoofs, Verhagen, van der Veen, & Leseman, 2014). Interestingly, several recent studies have indicated that there are only small concurrent associations between EF measures in young toddlers (Johansson, Marciszko, Brocki, & Bohlin, 2015; Johansson, Marciszko, Gredebäck, Nyström, & Bohlin, 2015; Miller & Marcovitch, 2015), with cross-task correlations reliably emerging around 24 months of age. Multiple explanations have been offered for this lack of cohesion, including difficulties in accurately measuring EF in young children and the potential that toddlers have yet to develop consistent internal strategies for responding to varying environmental demands (Miller & Marcovitch, 2015).

Given the lack of cohesion in toddler measures of early EF skills, it seems likely that similar constructs would show little relation during infancy. However, foundational studies have demonstrated that core information processing skills, including attention, processing speed, and memory are separable in infants and that the underlying factor structure of infant cognitive skills shows developmental continuity from 7 to 12 months (Rose, Feldman, & Jankowski, 2004, 2005). Additionally, when measures of prefrontal-dependent behaviors such as object permanence (Baird et al., 2002) are included, these tasks load on factors related to mental representation (Rose, Feldman, et al., 2005). Relationships among other early EF skills in young infants (e.g. means-end problem solving, cognitive flexibility, etc) have not been well-characterized.

Individual differences in infant cognitive measures are also sensitive, early predictors of children's long-term neurodevelopmental trajectories. Infant information processing skills predict later general intellectual development (Rose, Feldman, Jankowski, & Rossem, 2008; Rose, Feldman, Jankowski, & Van Rossem, 2012; Rose, Jankowski, Feldman, & Van Rossem, 2005), show developmental continuity within specific information processing domains (Rose, Feldman, Jankowski, et al., 2012), and contribute to individual differences in EF during early adolescence (Rose, Feldman, & Jankowski, 2012). For example, the predictive power of early differences in attention has been well studied; longitudinal associations exist between diverse infant attention measures including fixation duration, length of sustained attention, and peak look duration, and later measures of EF during childhood and adolescence (Cuevas & Bell, 2014; Johansson, Marciszko, Gredebäck, et al., 2015; Papageorgiou et al., 2014; Sigman,

Cohen, & Beckwith, 1997; Sigman, Cohen, Beckwith, Asarnow, & Parmelee, 1991). Importantly, the predictive value of infant cognitive measures for later EF development has been demonstrated in both typically developing and at-risk populations (Hitzert, Van Braeckel, Bos, Hunnius, & Geuze, 2014; Rose, Feldman, Jankowski, et al., 2012). Longitudinal prediction of EF from these early infant cognitive measures is striking, and may reflect early differences in core information processing abilities cascading forward into the development of more complex cognitive skills (Rose et al., 2008). Thus, these higher-level cognitive processes in infants represent early emerging precursor skills to later EF (Hendry et al., 2016).

Biological & Environmental Influences of Early EF

Despite the predictive power of early infant cognitive measures, less is known regarding mechanisms that support the development of these precursor skills (referred to as “early EF” skills for brevity). Most cognitive neuroscience models posit that dynamic, bi-directional interactions between the developing child’s biology and environmental influences jointly shape the emergence of EF over childhood. However, to date, most studies investigating biological and environmental correlates of EF development have focused only on older children (i.e. predominantly preschoolers) and/or high-risk samples (e.g. children growing up in poverty, children born very preterm).

Familial influences: Socioeconomic status, parental mental health, and parenting. There has been an explosion of interest in describing associations between distal indicators of family functioning including socioeconomic status (SES) and parental mental health, and developmental trajectories of EF. Most of this work has focused on

preschool-age children, given rapid development of EF within this time period. SES-related disparities in EF are present in preschool-aged children across diverse measures of EF (e.g. Blair et al., 2011; Noble, Norman, & Farah, 2005; Raver, Blair, & Willoughby, 2012; Rhoades, Greenberg, Lanza, & Blair, 2011; Wiebe et al., 2011) and have been shown to persist over time (e.g. Hackman, Gallop, Evans, & Farah, 2015). In contrast, studies examining the influence of parental mental health on children's EF development have been less consistent. Although children of mothers with a history of depression show poorer EF during the preschool years (Hughes, Roman, Hart, & Ensor, 2013), studies with older children have not detected differences in EF skills (Klimes-Dougan, Ronsaville, Wiggs, & Martinez, 2006; Micco et al., 2009). It is possible that the impact of parental mental health on children's EF development varies over development or that the effects of SES-disparity, which commonly co-occur with poorer parental mental health, may be stronger in magnitude (Rhoades et al., 2011).

Distal indicators of family functioning such as parental mental health and SES are presumed to impact the development of EF in older children through common influences on parenting processes. Variations within the normative range of parenting that may support optimal EF development during childhood include differences in scaffolding, sensitivity, stimulation, and control (see Fay-Stammbach, Hawes, & Meredith, 2014 for review). To date, studies in young children have primarily investigated the impact of variation in parental scaffolding (Hammond, Müller, Carpendale, Bibok, & Liebermann-Finstone, 2012; Hughes & Ensor, 2009) and sensitivity (Blair, Raver, & Berry, 2014; Towe-Goodman et al., 2014), demonstrating that higher levels of these positive parenting

behaviors, across both mothers and fathers, during the toddler years are predictive of better EF skills during the preschool period (Lucassen et al., 2015).

Less is known about the influences of both distal and proximal environmental factors and their impact on the development of early EF skills in children prior to age 2. Neuroimaging studies indicate that familial environmental differences shape the trajectory of prefrontal cortex development within the first year of life (Hanson et al., 2013). There is some evidence to suggest that the impact of the early environment can be detected in measures of higher-order cognitive skills in young infants. Recent cross-sectional and longitudinal work has suggested that SES-disparities in early memory abilities are detectable within first two years (Markant, Ackerman, Nussenbaum, & Amso, 2016; Noble et al., 2015). Associations between lower familial SES and poorer planning (Clearfield et al., 2015), attention shifting (Clearfield & Niman, 2012), and sustained attention (Clearfield & Jedd, 2012) skills have also been documented in small samples of infants followed longitudinally over the first year of life.

Recent studies have also investigated parenting behaviors in infancy and their longitudinal relation to EF. Similar to studies with older children, maternal sensitivity during infancy is predictive of EF during toddlerhood and into the preschool years (Bernier et al., 2012; Bernier, Carlson, & Whipple, 2010; Blair et al., 2011; Cuevas et al., 2014). Early individual differences in parenting behaviors within the normative range are also prospectively related to measures of infant frontal lobe maturation (Bernier, Calkins, & Bell, 2016). Over the first years of life there is a gradual transition from caregiver regulation of the infant's arousal and affect to a child-led, internally-driven process

(Swingler, Perry, & Calkins, 2015). It is possible that parenting behaviors that concurrently support optimal early EF development in infants may differ from associations that have been longitudinally observed in toddlers. To our knowledge, concurrent associations between normative variations in parenting and early infant EF skills have not been investigated.

Biological influences: Preterm birth. Biological influences on the development of EF have been studied extensively in individuals born very PT (<32 weeks gestation) or very low birth weight. Alterations in prefrontal-dependent behaviors have been demonstrated throughout childhood, adolescence, and into adulthood in these medically high-risk, PT samples (Aarnoudse-Moens & Smidts, 2009; Anderson, Doyle, & Victorian Infant Collaborative Study Group, 2004; Luu, Ment, Allan, Schneider, & Vohr, 2011; Marlow, Hennessy, Bracewell, & Wolke, 2007; Narberhaus, Segarra, Cald, & Gim, 2008; Sun, Mohay, & Callaghan, 2009). The biological mechanisms underlying altered EF skills in this population are presumed to be prematurity-induced differences in structural and functional development of fronto-striatal brain circuits (Ball et al., 2012; Bjuland, Løhaugen, Martinussen, & Skranes, 2013; Duerden, Card, Lax, Donner, & Taylor, 2013; Giménez et al., 2006; Kesler et al., 2008; Lax et al., 2013; Mullen et al., 2011; Mürner-Lavanchy et al., 2014; Nagy et al., 2009; Nosarti et al., 2008; Peterson et al., 2000; Zhang et al., 2015). Long-term EF deficits in children born very PT are related to differences in infant attention, memory, and processing speed (Rose, Feldman, Jankowski, et al., 2012), and are detectable using traditional infant measures of EF (e.g. A not B task) before 12 months of age (Sun et al., 2009).

Although they account for 8% of total births and 80% of all PT births in the United States (Hamilton, Martin, Osterman, Curtin, & Matthews, 2015) children who are born only moderate-to-late PT (32-36 weeks gestation) are an understudied, lower-risk PT population. Like children born very PT, preschool-aged children born moderate-to-late PT also demonstrate discrepant EF development (Baron et al., 2009; Baron, Kerns, Muller, Ahronovich, & Litman, 2012; Hodel, Brumbaugh, Morris, & Thomas, 2015). Discrepant development of EF has been identified even in healthy moderate-to-late PT children with low levels of neonatal risk, indicating these differences are not solely related to post-birth medical complications (Brumbaugh, Hodel, & Thomas, 2014; Hodel et al., 2015). Neuroimaging studies indicate that prefrontal cortex structure and connectivity is also altered following moderate-to-late PT birth (Degnan et al., 2015a, 2015b), again suggesting a biological mechanism for poorer EF. When and how differences in early EF skills emerge within this lower-risk PT population has not been documented. A recent study suggests that discrepant development is apparent by 9-months of age (see Study 1a), but which aspects of early EF are most affected in moderate-to-late PT infants remains to be characterized.

Combined biological and environmental risk. Although moderate-to-late PT birth is itself a risk factor for altered neurobehavioral development, there is substantial variation in outcomes across children born PT, suggesting environmental risk and protective factors strongly shape developmental trajectories (Gueron-Sela, Atzaba-Poria, Meiri, & Marks, 2015, 2016; Poehlmann et al., 2011, 2012). One confounding factor in describing the long-term impact of PT birth on neurobehavioral development is that

prematurity often co-occurs with other environmental risk factors, including lower maternal education and lower-SES (Margerison-Zilko et al., 2015), creating compounding effects of biological and environmental risk. The additive risk of socioeconomic adversity for very PT children has been reported across many studies. For example, greater socioeconomic adversity is associated with poorer cognitive outcomes during the toddler years for very PT children (see Linsell, Malouf, Morris, Kurinczuk, & Marlow, 2015 for review) and predicts poorer cognitive developmental trajectories through later childhood (Mangin, Horwood, & Woodward, 2016).

Parental mental health issues, including depression and anxiety, are also disproportionately common within families of PT children (Poehlmann, Schwichtenberg, Bolt, & Dilworth-Bart, 2009; Rogers, Lenze, & Luby, 2013). Higher rates of mental health issues in mothers of PT infants are likely driven by multiple factors, including higher sociodemographic risk (Davis, Edwards, Mohay, & Wollin, 2003), perception of the infant as more vulnerable (Stern & Karraker, 1990), and poorer self-efficacy due to difficulties in caring for an infant that may be behaviorally disorganized (Hughes, Shults, McGrath, & Medoff-Cooper, 2002; Voegtline & Stifter, 2010). Maternal depression in parents of PT infants is predictive of poorer infant cognitive development during the toddler and early childhood years (Shah, Robbins, Coelho, & Poehlmann, 2013), even after controlling for sociodemographic risk (Mcmanus & Poehlmann, 2012). However, poor parental mental health is not limited to families of high-risk, very PT infants. Parents of moderate-to-late PT infants are also more likely than parents of full-term (FT) children to report depression and/or anxiety symptoms (Cheng, Kotelchuck, Gerstein,

Taveras, & Poehlmann-Tynan, 2015; Rogers et al., 2014, 2013; Voegtline & Stifter, 2010).

It is plausible that sociodemographic and parental mental health impacts on PT children's cognitive development are driven by variations in parenting behaviors. However, a recent meta-analysis did not detect differences between PT and FT families in measures of parental sensitivity (Bilgin & Wolke, 2015). Studies using self-report parenting measures have also not found differences in parenting practices within PT families (Westrupp, Mensah, Giallo, Cooklin, & Nicholson, 2012). Although families may not differ on average in parenting practices, there is evidence to suggest that children born PT may be even more sensitive to variations in the familial environment than their FT peers, a pattern consistent with differential susceptibility models (Gueron-Sela et al., 2015, 2016; Poehlmann et al., 2011, 2012). Multiple studies have demonstrated that sensitive parenting during the toddler and early childhood years is predictive of better intellectual development in very PT or low birth weight children (Shah et al., 2013; Treyvaud et al., 2016) as well as improvements in childhood EF skills (Camerota, Willoughby, Cox, & Greenberg, 2015), although these associations may not be present within lower-risk PT cohorts (Shah et al., 2013).

Collective research investigating the relationship between environmental variables and neurocognitive development in PT children suggests that for many children born PT, multiple sources of risk (e.g. lower SES, poorer maternal health, increased sensitivity to parenting behaviors) likely interact to shape future cognitive development. However, this work has been almost exclusively conducted in higher-risk PT samples,

has relied on more global, summary outcome measures of development (e.g. IQ score), and has not examined whether environmental influences on EF skills can be detected early in development.

Current Study

The overarching goal of the current study was to describe how individual differences in more subtle biological and environmental risk factors are related to the development of complex cognitive skills during the first year of life. Although studies with toddlers have suggested poor cohesion among early measures of EF, only one study (Rose, Feldman, et al., 2005) has described the structure of higher-level cognitive skills in infants. Our first goal was to characterize the structure of higher-level cognitive skills in typically developing FT infants as measured from a battery of looking-time and behavioral tasks designed to tap early prefrontal-dependent behaviors (“early EF” skills). Based on previous studies of cross-task relationships, we predicted that correlations across measures would be relatively small and that shared variance would be explained mostly by variation in information processing factors. We also predicted that infants born moderate-to-late PT, a group characterized by early biological risk, would perform more poorly than their FT peers on composite measures of early EF skills. As previously mentioned, sociodemographic risk factors of interest (e.g. SES) are typically confounded with PT birth. We intentionally selected our participants to represent both a low-medical (healthy, moderate-to-late PT infants) and low-environmental (high SES, high parental education) sample in order to minimize this association. Last, we conducted exploratory analyses to examine the relationships between environmental variation (i.e. family SES,

parental mental health, perception of children's medical vulnerability, parenting styles and beliefs) and infant cognitive development in both PT and FT infants. Given studies suggesting differential susceptibility of PT infants to environmental variation, we hypothesized that correlations between environmental measures and early EF performance would be more prevalent within the moderate-to-late PT group.

Method

Participants

Nine-month-old infants were recruited based on gestational age at birth from a University-managed database of families who endorsed interest in participating in child development research. Families in this database were recruited via birth records from local hospitals. The sample consisted of 71 infants born moderate-to-late preterm (PT; 30-36 weeks gestation) and 67 infants born full-term (FT; 37-42 weeks gestation). Infants were tested within \pm 1 week of turning 9 months old (9-months corrected-age for PT infants). Exclusion criteria included neurological insult or disease, intrauterine growth restriction, serious medical illness (e.g. organ transplant, heart disease), and for FT children only, admission to a special care or intensive care nursery for > 24 hours as a newborn. Gestational age at birth and newborn health information were verified via birth hospitalization records. Neonatal health characteristics for this sample have been described in a previous report (see Study 1a).

This sample was predominately composed of middle-to-upper class, college-educated families. Households were headed by two-parent families (99.3%), with at least one college-educated parent (91.3%), and median incomes between \$101,000-\$125,000.

All families lived above the federal poverty level. Demographic characteristics of the FT and PT sub-samples were equivalent, see Table 3.1.

General Procedure

Infants completed a battery of behavioral and computerized looking-time tasks designed to measure the development of complex attention, learning, and memory skills that serve as precursors to later EF (Hendry et al., 2016). Tasks were selected from the adult and child neuropsychology literatures to target early frontal lobe functions (see Study 1a for details). The entire testing session lasted approximately 90 minutes. Parents of infants completed questionnaire measures of their child's early attention skills (Infant Behavior Questionnaire, IBQ-R; Garstein & Rothbart, 2003). Parents also completed a questionnaire battery measuring differences in family environments. Written informed consent was obtained from parents. Families received a small present (infant board book or infant T-shirt) as compensation. Study procedures were approved by the University of Minnesota's Institutional Review Board.

Table 3.1

Demographic Characteristics

	<u>Preterm (n = 71)</u>	<u>Full-Term (n = 67)</u>	
	<i>n</i> (%)	<i>n</i> (%)	<i>p</i>
Child's Sex - # male	38 (53.5)	33 (49.3)	.61
Child's Ethnicity - # Caucasian	67 (94.4)	58 (86.6)	.15
Marital Status - # married	70 (98.6)	65 (97.0)	.61
Maternal Education			.42
High school degree or GED	4 (5.6)	1 (1.5)	
Associate degree	3 (4.2)	4 (6.0)	
Bachelor's degree	28 (39.4)	25 (37.3)	
Graduate or professional degree	36 (50.7)	37 (55.2)	
Paternal Education			.34
Less than high school degree	1 (1.4)	1 (1.5)	
High school degree or GED	15 (21.1)	8 (12.1)	
Associate degree	3 (4.2)	7 (10.6)	
Bachelor's degree	35 (49.3)	29 (43.9)	
Graduate or professional degree	17 (24.0)	21 (31.8)	
Maternal Work			.08
Full-time work for pay	34 (47.9)	41 (61.2)	
Part-time work for pay	25 (35.2)	11 (16.4)	
Student	3 (4.2)	2 (3.0)	
Stay at home parent	9 (12.7)	13 (19.4)	
Paternal Work			.28
Full-time work for pay	61 (85.9)	63 (94.0)	
Part-time work for pay	6 (8.5)	2 (3.0)	
Student	1 (1.4)	0 (0)	
Stay at home parent	3 (4.2)	1 (1.5)	
Annual Household Income			.68
≤ \$50,000	3 (4.3)	4 (6.3)	
\$51,000 - \$100,000	17 (23.2)	9 (14.1)	
\$101,000 - \$150,000	27 (39.1)	26 (40.6)	
≥ \$151,000	23 (33.3)	25 (39.1)	
Income-to-Needs Ratio – Mean	5.33	5.12	.62

Notes. Five families (3 FT, 2 PT) declined to provide annual household income. One family included a single-parent household (1 FT). **p* < .05

Infant Cognitive Measures

This task battery has been described in greater detail by our group in a previous report (Study 1a). Each infant completed the tasks in a fixed order (reversal learning, A not B, problem solving, habituation, attention flexibility, processing speed). For eye-tracking tasks, infants were seated on their parent's lap in a darkened room, separated from the experimenter by an opaque curtain. Stimuli were presented on a 42 inch LCD monitor and eye movements were recorded using a hidden digital video camera with infrared night vision. Video feed of the infant was presented live to the experimenter for preliminary online data coding and to enable repositioning of the camera. For behavioral tasks, infants were seated on their parent's lap, in front of a table, across from the experimenter. Infant behavior was recorded using a hidden digital video camera located on an adjacent table (either facing the infant directly or in a profile view, depending on the task) and also from overhead using a ceiling mounted webcam. Live video feed of all tasks was burned to DVD for final offline coding.

Reversal learning. A deterministic, reversal learning task was used (Kovács & Mehler, 2009; Wass, Porayska-Pomsta, & Johnson, 2011) in which infants were expected to learn that a visual reward would reliably appear on one side of the screen. This eye-tracking task consisted of two phases: a learning phase (9 trials) followed by a reversal phase (9 trials), in which the location of the visual reward switched. Anticipatory eye movements were defined as initial eye movements to the correct side of the screen beginning within 250 ms of the visual reward onset. Perseverative eye movements were coded during the reversal phase only using similar criteria. Outcome measures included

average eye movement latency and variability, percentage of anticipations, and percentage of perseverative looks (reversal phase only). Three infants (2 FT, 1 PT) did not provide complete data due to parent refusal (1), infant fussiness (1), and a technical error in data recording (1).

Habituation. An infant-driven, sliding window habituation task with two Caucasian, female face stimuli (<http://www.macbrain.org/faces/index.htm>) was used (Markant, Cicchetti, Hetzel, & Thomas, 2014). In this eye-tracking task, one face was presented centrally for up to 15 seconds per trial. The habituation criterion was met when the infant's average look duration over three consecutive trials was less than 50% of his/her average look duration from the first three trials of the experiment. A maximum of 21 trials to reach habituation was allowed. Following habituation, infants completed six additional trials in randomized order: three in which the now-familiar habituation face was presented and three trials in which the novel face was presented. Outcome measures included the value of each infant's habituation criterion, average looking time per trial during the habituation phase, and novelty preference (looking time difference between novel and familiar stimuli) at test. Fourteen infants (11 FT, 3 PT) did not provide complete data due to parent refusal (1), insufficient time to administer the task (1), infant fussiness (5), and technical errors in data recording (7).

Processing speed. A basic visual attention, eye-tracking task was used to measure speed of orienting to a peripheral target following disengagement from a central stimulus. Trials were discarded in which the infant looked away prior to the onset of the peripheral stimulus, if the infant broke fixation prior to the target onset, or if the infant

failed to orient to the target. Infants were required to have a minimum of 10 valid trials. Outcome measures included average reaction time and reaction time variability to the peripheral target and the maximum number of attention shifts per trial. Fifteen infants (7 FT, 8 PT) did not provide complete data due to parent refusal (1), insufficient time to administer the task (1), insufficient valid trials (11), and technical errors in data recording (2).

A not B. Infants completed a graded version of the classic A not B task in which the delay between hiding and object retrieval was incremented to determine the ceiling of each infants' abilities (Diamond, 1985). Delay length increased by 3 seconds for each successful trial set, and 9 seconds was set as the ceiling delay length tested. The outcome measure of interest corresponded to the highest level of the task the infant successfully completed (based on (Bell & Fox, 1997). Four infants (0 FT, 4 PT) did not provide complete data due to infant fussiness (2), experimenter error (1), and insufficient time to administer the task (1).

Problem solving. Infants were asked to complete a sequence of steps to uncover and retrieve a hidden toy (Willatts et al., 1998). Sequences that were tested included one-step, two-step, and three-step (e.g. remove a barrier, pull a cloth, and lift a cover to retrieve a toy) problems. Infants attempted three trials at each level and only advanced to the next level if they were able to solve the previous stage within 30 seconds. Data were coded using a scheme adapted from Willatts et al. (1998) for evidence of intentional behavior (e.g. maintaining fixation on the goal object) and latency to solve each problem. Outcome measures of interest included total intentionality scores and the minimum

latency required to solve a one-step problem. Because not all infants advanced to the later stages, we chose to only use latencies from the one-step problem to minimize missing data. Ten infants (4 FT, 6 PT) did not provide complete data due to infant fussiness (4), experimenter error (3), and insufficient time to administer the task (3).

Attention flexibility. Flexibility of attention was assessed during a standard free play with toys task (Ruff, 1986). Infants were presented with a colorful rattle with smaller moveable parts and given two minutes to explore it. Data were coded offline and segmented into bouts of different attention types (based on Clearfield & Jedd, 2013): focused attention towards toys, focused attention towards people, quiet disengagement, and inattention. The average length of attention bout across the two minute period was calculated for each infant. Eleven infants (8 FT, 3 PT) did not provide complete data due to infant fussiness (3), technical error in data recording (7), and insufficient time to administer the task (1).

Parent-report of infant attention. Parents completed the Revised Infant Behavior Questionnaire (IBQ-R; Garstein & Rothbart, 2003) as a measure of infant temperament. Based on a priori interest, we selected the duration of orienting and perceptual sensitivity sub-scales as potential measures of relevant individual differences in early attention skills. Duration of orienting was selected due to its strong loading on the orienting/regulation factor (Garstein & Rothbart, 2003). Perceptual sensitivity was selected as it likely measures attention shifting driven by distracting stimuli in young infants and loads on effortful control in older children (Garstein & Rothbart, 2003). Nine

infants (4 FT, 5 PT) were missing IBQ data because parents failed to return the completed questionnaire.

Family Environment Measures

Parents all received questionnaires designed to measure differences in family environments during their laboratory visit and were instructed to return them via mail. The demographics questionnaire was completed at the laboratory visit. Nine infants (4 FT, 5 PT) were missing family environment measures because their parents failed to return any completed questionnaires. Questionnaires were mostly completed by mothers (93%).

Mental health and stress. Parental mental health and familial stress levels were measured using the Center for Epidemiological Studies Depression Scale (CES-D; Radloff, 1977) and Cohen's Perceived Stress Scale (PSS; Cohen, 2016). Higher total scores reflect poorer mental health and greater stress. Data from two additional families (2 FT) were missing because the parent returned one of the questionnaires only partially completed.

Perceptions of child's vulnerability. A 16-question measure of the child's perceived medical vulnerability, rated along a 4-point Likert scale, was used (e.g. "I often check on my child at night to make sure s/he is okay"; Perrin, West, & Culley, 1989). Higher total scores indicate greater perceived vulnerability. Data from two additional families (1 FT; 1 PT) were missing because the parent returned the questionnaire only partially completed.

Parenting styles and beliefs. Beliefs about parenting and differences in parenting style across the dimensions of discipline (belief that infant can manipulate adults), routine (following sleeping and eating schedules), anxiety (anxiety related to the infant's development), nurturance (keeping infant in close proximity), and involvement (selecting activities to promote infant development) were measured using the 25-item, 5-point Likert scale Infancy Parenting Styles Questionnaire (Arnott & Brown, 2013). Responses were aggregated such that higher scores indicate greater endorsement of parenting beliefs specific to each scale. We focused analyses on the discipline, routine, and involvement scales. The discipline and routine scales map onto a 'control' type construct (Arnott & Brown, 2013), likely reflecting less sensitive parenting. Involvement was selected as items in this scale primarily assess endorsement of developmentally-appropriate interactions with the infant (e.g. "I make sure I read, play, or sing with my baby very regularly"), likely reflecting more sensitive parenting and/or a construct in older children similar to stimulation (Fay-Stammbach et al., 2014). Data from one additional family (1 FT) were missing because the parent returned the questionnaire only partially completed.

Demographic information. Parents reported demographic information including family structure, occupations, education levels, and pre-tax household income over the past year using a self-report questionnaire at the laboratory visit. Income-to-poverty ratios were calculated using the 2014 Census Bureau cut-offs. Five families (3 FT, 2 PT) declined to provide annual household income.

Statistical analysis

Infant cognitive measures.

Outliers and imputation. Infant cognitive measures with skew or kurtosis >3 were log-transformed. Outlying values that were >3.5 standard deviations above the group mean were replaced with the trimmed value (1 data point).

The expectation-maximization (EM) algorithm in SPSS was used to impute missing behavioral and/or looking-time data from infants, separately within the PT and FT groups, to maximize the data set available for factor analysis and subsequent generation of composite variables. Prior to imputation, approximately 6% of outcome measures were missing from the FT and PT groups. In many cases, missing data were caused by events unlikely to be systematically related to the cognitive measure outcome (e.g. experimenter error, technical errors in video recording). Non-significant Little's MCAR tests supported that data could be treated as missing completely at random in both the PT and FT subgroups, $\chi_{FT}^2(163) = 191.220, p < .07$, $\chi_{PT}^2(136) = 154.13, p < .14$. EM is justifiable given that the proportion of missing data was small (5%; Schafer, 1999). Furthermore, when the proportion of missing data is low, violation of the missing at random assumption has minimal effects on outcomes, even if the cause of missingness is moderately related to the missing data (Collins, Schafer, & Kam, 2001). Following imputation, multivariate outlier analyses were calculated using Mahalanobis distance; no multivariate outliers were detected.

Exploratory factor analysis. The matrix of correlations generated via EM were used as input for exploratory factor analysis (Graham, 2009) via a custom-macro (Weaver & Maxwell, 2014). Previous studies have demonstrated that infants born

preterm show early differences in cognitive development (e.g. Sun et al., 2009). We therefore chose to conduct the factor analysis in only FT participants to best estimate the cross-task relationships within a normative population.

Composite variable generation. Prior to creating composite variables, all of the infant cognitive measures were standardized across all participants due to differences in standard deviations of the original variables. Composite variables based on the factor analysis were then generated by averaging the standardized scores for measures that produced a factor loading $>.3$. Composite variables were created rather than weighted factor scores as composites are typically more generalizable across samples (Grices & Harris, 1998). Composites for attention shifting and speed were reverse scored such that higher values reflected better scores (more flexible attention, faster looking).

Group difference and correlational analyses. We first examined group differences between PT and FT children in cognitive composite and family environment measures using gestational age as a categorical variable (PT vs. FT). Independent samples t-tests were used to compare group means and results are reported including means and standard deviations. Associations between prematurity and cognitive composite scores and family environment measures were also examined with gestational age as a continuous variable using Pearson's correlations. These analyses were conducted including both the entire sample's gestational age range (30-42 weeks) and within the PT group alone, given that linear effects of gestational age would not necessarily be predicted to extend into the FT range.

Last, exploratory analyses investigated associations between familial environment measures and cognitive composite scores using Pearson's correlations. These analyses were conducted in both the entire sample of children and within the PT group alone. Given associations between gestational age and some of the familial environment measures, correlations that were significant across the entire sample of participants were subjected to secondary analyses in which the linear effects of gestational age were statistically controlled.

Results

Structure of Complex Cognitive Skills at 9-Months

Cognitive measure correlations. The correlation matrix (using pair-wise deletion to account for missing data) in FT participants indicated that correlations across cognitive outcome measures were generally absent or only modest in size, see Table 3.2. Measures of reaction time and/or reaction time variability derived from the eye-tracking tasks produced the highest correlations both within and across tasks. The correlation matrix produced via list-wise deletion was highly similar.

Table 3.2

Correlations of Measures Used in Factor Analysis in FT Participants

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1. Reversal learning RT	1	.59**	-.45**	-.47**	.14	-.14	.077	-.40**	-.28*	-.14	-.05	.32*	0.23	.06	.26*	.23
2. Reversal learning RT variability		1	-.36**	-.25*	.24	-.03	.123	-.34**	-.26*	-.20	.28*	.30*	.40**	-.16	.11	.00
3. Reversal learning % perseverative looks			1	-.16	-.20	-.07	.085	.18	.15	.04	.00	-.08	-.09	-.10	-.07	-.17
4. Reversal learning % anticipatory looks				1	.25*	.08	-.077	.20	.17	.16	-.14	-.13	-.10	-.11	-.09	-.09
5. A not B graded score					1	.21	.114	-.08	-.11	.03	.10	.03	.08	-.06	.23	.01
6. Problem solving intentionality score						1	-.186	-.14	-.14	-.12	.09	.03	.08	.28*	-.08	.08
7. Problem solving minimum solve time ⁺							1	-.06	.00	-.09	.24	.22	.01	-.19	.15	.06
8. Habituation average looking time								1	.80**	.30*	-.03	-.34**	-.21	-.01	.02	-.29*
9. Habituation criterion									1	.24	-.04	-.24	-.27*	-.10	-.01	-.30*
10. Habituation novelty preference										1	-.27	.04	.11	.12	.00	.04
11. Attention flexibility bout duration ⁺											1	-.02	-.17	-.20	.11	-.26
12. Processing speed RT												1	.57**	-.13	-.07	-.07
13. Processing speed RT variability ⁺													1	.10	-.15	-.06
14. Processing speed maximum shifts														1	-.05	.25
15. IBQ duration of orienting															1	.45*
16. IBQ perceptual sensitivity																1

Notes. ⁺log-transformed. **p* < .05. ***p* < .01.

Exploratory factor analysis. The matrix of correlations generated from the imputed data was subjected to principal axis factor analysis. Seven factors were justified by the criterion of eigenvalues greater than 1.0. However, elbows within the scree plot indicated that a one-factor or a five-factor solution were more justifiable. Given previous research that also reported a five-factor solution for a diverse set of infant cognitive tasks (Rose, Feldman, et al., 2005) and our interest in separable cognitive processes, the five-factor solution was retained. When rotated (varimax), the factors each individually accounted for 6.00-18.80% of the variance, for a collective total of 46.64% of the variance. An oblique rotation, allowing correlated factors, produced a similar factor structure and loadings, so varimax rotation was retained for simplicity of interpretation. The rotated, five-factor solution derived from the FT group is given in Table 3.3.

The first factor, encoding, was represented by look duration measures and novelty preference scores from the habituation task. The second factor, speed, was represented by reaction time and reaction time variability on the two eye-tracking tasks that required either anticipatory or reactionary looks to peripheral stimuli (reversal learning, processing speed). The third factor, inhibition, was represented by a more diffuse group of measures including A not B scores and perseverative looking during reversal learning. Parent-reported attention measures and anticipatory eye movement speed and variability also loaded on this factor. The fourth factor, shifting, was represented by attentional bout length during free play, attention shifting rate during the processing speed task, and parent-reported perceptual sensitivity. Anticipatory eye movement variability and novelty preference scores also loaded on this factor. The fifth factor, learning/memory,

was defined by anticipatory looking during the reversal learning task; A not B scores and reaction time for anticipatory looks had a secondary loading on this factor.

The one-factor solution accounted for only 16.914% of the variance and was composed only of measures generated from the looking-time tasks, perhaps due to the increased precision of these measures. The one-factor solution included mostly loadings from the original encoding and speed factors, see Table 3.4. Due to our interest in separable cognitive processes and the small amount of overall variance accounted for by this model, we do not discuss it further.

Table 3.3

Principal Axis Factor Analysis in FT Participants: 5-Factor Solution

	Task & Measure	Encoding	Varimax rotated factor structure				
			Speed	Inhibition	Attention Shifting	Learning/	Memory
	I	II	III	IV	V		
Reversal learning	<i>RT</i>		.401	.690			-.391
	<i>RT variability</i>		.473	.437	.452		
	<i>% perseverative looks</i>			-.462			
	<i>% anticipatory looks</i>						.879
A not B Problem solving	<i>Graded score</i>				.325		.364
	<i>Intentionality score</i>						
	<i>Minimum solve time*</i>						
Habituation	<i>Average looking time</i>		.832				
	<i>Criterion</i>		.818				
	<i>Novelty preference</i>		.359			-.361	
Attention flexibility	<i>Average bout duration*</i>						.609
Processing speed	<i>RT</i>		.647				
	<i>RT variability*</i>		.766				
	<i>Maximum shifts</i>						-.433
IBQ parent-report	<i>Duration of orienting</i>			.529			
	<i>Perceptual sensitivity</i>				.515		-.393

Notes. *log-transformed. Loadings <.3 are not shown.

Table 3.4

Principal Axis Factor Analysis in FT Participants: 1-Factor Solution

Task & Measure		I
Reversal learning	<i>RT</i>	.716
	<i>RT variability</i>	.668
	<i>% perseverative looks</i>	-.347
	<i>% anticipatory looks</i>	-.322
A not B	<i>Graded score</i>	
Problem solving	<i>Intentionality score</i>	
	<i>Minimum solve time*</i>	
	<i>Average looking time</i>	-.728
Habituation	<i>Criterion</i>	-.642
	<i>Novelty preference</i>	-.322
	<i>Average bout duration*</i>	
Attention flexibility		
Processing speed	<i>RT</i>	.441
	<i>RT variability*</i>	.385
	<i>Maximum shifts</i>	
IBQ parent-report	<i>Duration of orienting</i>	
	<i>Perceptual sensitivity</i>	

Notes. *log-transformed. Loadings <.3 are not shown.

Prematurity – Relation to Infant Cognitive and Family Environment Measures

Infant cognitive measures. Group differences on individual outcome measures from this task battery have been reported in a prior report (Study 1a); in the previous study we found evidence that degree of prematurity was related to performance on five of the six tasks. Additionally, as a group, infants born moderate-to-late PT showed poorer evidence of a novelty preference on the habituation task than their full-term peers.

Similar to our previous results, the PT and FT groups did not differ in the newly generated composite measures of encoding, speed, inhibition, shifting, and learning/memory (p 's > .20). Across the entire sample of participants, gestational age at birth was also not related to any composite measure (p 's > .21). However, within the PT group alone, higher gestational age at birth was related to better performance on the attention shifting composite, $r(71) = .32, p < .01$, see Figure 3.1.

Mental health and stress. Only two parents (both from the FT group) reported CES-D scores within the clinical range. Neither CES-D nor PSS scores differed by group (CES-D: $t(125) = -.17, p < .87, d = -.02, M_{FT} = 5.18 \pm 5.19, M_{PT} = 5.32 \pm 4.16$; PSS: $t(125) = .06, p < .95, d = .01, M_{FT} = 11.82 \pm 6.01, M_{PT} = 11.76 \pm 5.85$). Across the entire sample, gestational age was also not related to CES-D scores, $r(127) = -.04, p < .65$, nor PSS scores, $r(127) = -.12, p < .20$. However, with the PT group alone, lower gestational age at birth predicted higher current levels of family stress, $r(66) = -.28, p < .02$.

Perception of child's vulnerability. Parents of PT and FT infants did not differ as a group in perceptions of their child's vulnerability, $t(125) = -1.13, p < .26, d = -.20, M_{FT} = 21.15 \pm 3.09, M_{PT} = 21.88 \pm 4.14$. However, across the entire sample of infants,

higher gestational age at birth predicted lower perceived vulnerability scores, $r(127) = -.22, p < .01$. This effect also was present within the PT group alone, $r(65) = -.25, p < .04$.

Parenting beliefs and styles. Parents of PT infants endorsed higher levels of discipline than parents of FT infants, $t(126) = -2.07, p < .04, d = -.36, M_{FT} = 2.33 \pm .77, M_{PT} = 2.60 \pm .71$. Scores on the involvement and routine subscales were equivalent across groups (p 's $> .27$). Across the entire sample of infants, higher gestational age was associated with lower parental report of discipline, $r(128) = -.25, p < .01$. The relationship between gestational age and discipline was also of trend-level significance within the PT group alone, $r(65) = -.23, p < .07$. There were no other significant associations between parenting beliefs and gestational age within the entire sample or within the PT group alone (p 's $> .12$).

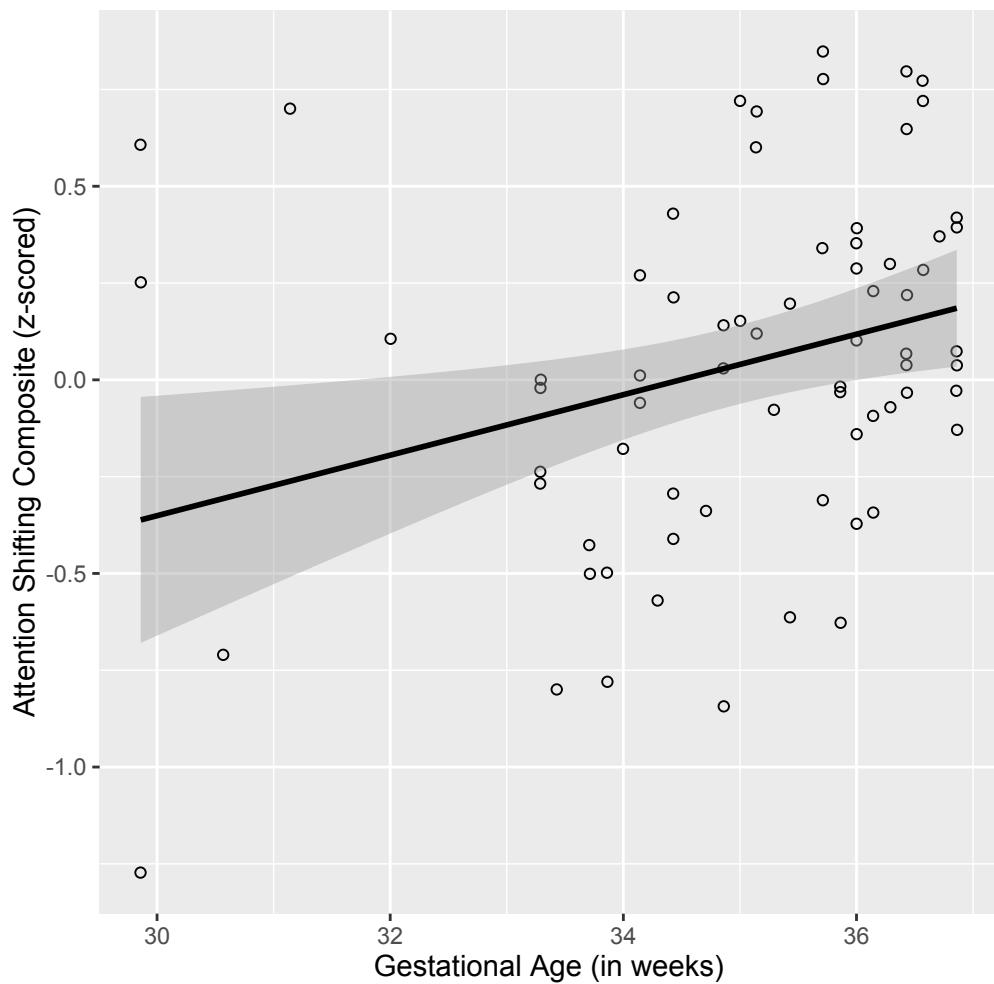


Figure 3.1. Degree of prematurity and relation to attention shifting composite scores.

Although PT and FT infants did not differ in average attention shifting scores, higher gestational age within the PT group was predictive of better performance.

Environmental Influences on Infant Cognitive Development

Family income. Across the entire sample, income-to-poverty ratios were related to both encoding, $r(133) = .18, p < .04$, and attention shifting, $r(133) = .20, p < .02$ composites, see Figure 3.2. These effects remained significant after controlling for gestational age. The relationship between family income and the encoding and attention shifting composites was also significant within the PT group alone (encoding: $r(69) = .23, p < .05$; shifting: $r(69) = .30, p < .01$).

Mental health and stress. Across the entire sample, CES-D and PSS scores were not associated with any of the cognitive composite measures (p 's $> .21$). Similarly, there were also no significant relationships between mental health measures and cognitive composite scores within the PT group alone (p 's $> .12$).

Perception of child's vulnerability. Across the entire sample, parent ratings of infant vulnerability were not associated with any of the cognitive composite measures (p 's $> .55$). However, within the PT group there was a trend-level association between greater perceived vulnerability and poorer encoding scores, $r(65) = -.24, p < .06$.

Parenting beliefs and styles. Higher levels of discipline were related at the trend level to poorer attention shifting, $r(128) = -.15, p < .09$, and better inhibition, $r(128) = .15, p < .10$, across the entire sample of participants. The relationship between discipline and the shifting composite remained at trend-level after controlling for gestational age, while the inhibition composite reached statistical significance, $r(125) = .18, p < .05$). However, discipline was not a significant predictor of attention shifting or inhibition scores within PT infants (shifting: $r(66) = -.18, p < .14$; inhibition: $r(66) = .16, p < .20$).

Higher levels of parental involvement predicted better attention shifting, $r(128) = .24$, $p < .01$, and better inhibition, $r(128) = .26$, $p < .01$, across the entire sample of participants. These effects also remained significant after controlling for gestational age. The relationship between involvement and inhibition was also present within the PT group, $r(66) = .31$, $p < .01$. However, the relationship between involvement and attention shifting was not significant within the PT group alone, $r(66) = .06$, $p < .63$. Additionally, with PT infants, higher levels of involvement were related to better scores on the learning composite, $r(66) = .28$, $p < .02$.

The routine subscale was not related to any of the cognitive composites within the full sample of participants or within the PT group alone (p 's $> .15$).

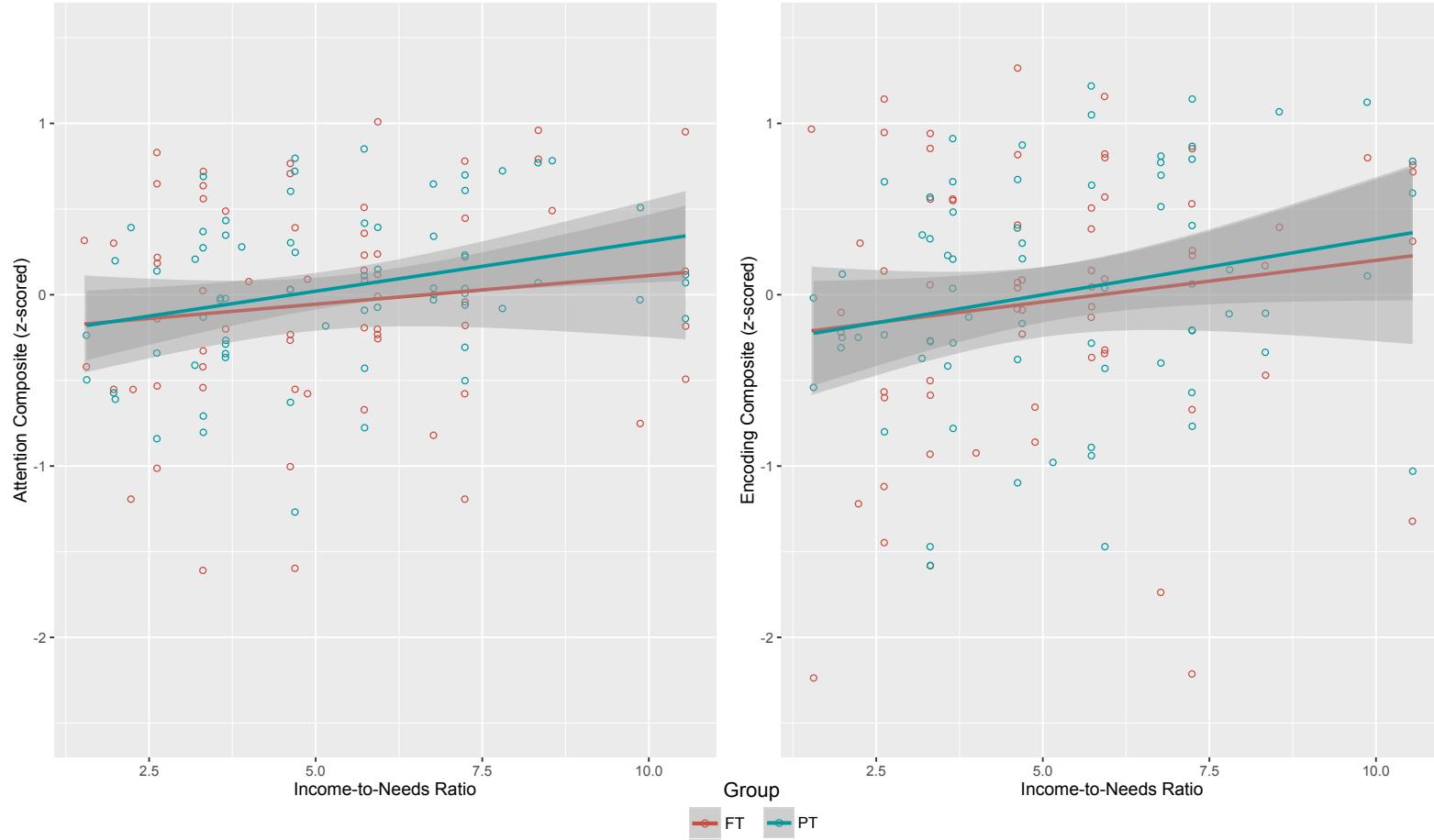


Figure 3.2. SES predicts infant attention shifting and encoding. Lower income-to-needs ratio was a predictor of poorer attention shifting and poorer encoding composite scores across the entire sample of infants, as well as within the FT and PT groups.

Discussion

The current study describes the structure of higher-order cognitive abilities in late infancy and their relation to biological and environmental risk factors. Previous studies of infant information processing skills (Rose et al., 2004; Rose, Feldman, et al., 2005) conducted in the first year of life have reported that infant task performance can be decomposed into attention, processing speed, and memory components. Using a battery of behavioral and looking-time tasks that were likely reliant on early prefrontal cortex development, we found evidence that early EF skills in 9-month-old infants can be similarly deconstructed into separable components. Previous studies of the structure of infant cognition have generally not included prefrontal-dependent tasks. However, the factors extracted in the present study are similar both in structure and number to those reported by Rose et al. (2005) in 12-month-old infants. Variance was best described by a factor structure that included information processing skills (e.g. measures of encoding and speed) and higher-order cognitive constructs (e.g. inhibition). All of the factors included loadings from more than one task except the encoding factor, which was represented only by measures derived from the habituation task. However, individual measures from the habituation task loaded on multiple cognitive factors. Future studies should include other measures that tap encoding skills (e.g. change detection tasks, deferred imitation, visual-paired comparison tasks) to better delineate what underlies this construct. Alternatively, it is also possible that habituation to social stimuli is a very salient measure of individual differences in 9-month old infants that is not highly related to other cognitive abilities.

Our results provide a potential explanation for why previous studies with toddlers have generally reported few cross-task correlations in measures of EF (Johansson, Marciszko, Brocki, et al., 2015; Johansson, Marciszko, Gredebäck, et al., 2015; Miller & Marcovitch, 2015). At a young age, when EF precursor skills are rapidly developing, individual differences in more basic information processing skills may show more stability within individuals or account for more variance across tasks. In the current study, cross-task correlations were generally greatest in magnitude for reaction time measures, such as eye movement latency. Additionally, the one-factor model of the infant cognitive task battery was completely represented by measures of look duration, eye movement reaction time, and eye movement reaction time variability. Studies examining the coherence of EF measures in younger children may benefit from inclusion of more basic measures of processing speed and/or from using outcome measures of children's performance that provide more sensitive measures of individual differences than dichotomous variables (i.e. pass/fail).

Although low-risk, moderate-to-late PT infants did not differ from their FT peers on the encoding, speed, attention, inhibition, or learning/memory composite measures, higher gestational age at birth predicted better attention shifting performance among moderate-to-late PT infants. The attention shifting composite was primarily composed of measures reflecting rate of attention shifting and ease of disengagement. Longitudinal studies of individual differences in similar measures of infant attention have demonstrated their predictive validity for later EF development (Cuevas & Bell, 2014; Johansson, Marciszko, Gredebäck, et al., 2015; Papageorgiou et al., 2014; Sigman et al.,

1997, 1991). In very PT infants, alterations in basic information processing skills underlie later impairments in EF (Rose, Feldman, & Jankowski, 2012). Preschool aged children born moderate-to-late PT show discrepant EF development (Baron et al., 2009; Brumbaugh et al., 2014; Hodel et al., 2015) and are at higher risk for the development of attention problems during childhood (Shah et al., 2013). Early differences in attention shifting detected within this lower-risk, moderate-to-late PT population may be the developmental antecedent of later attention and EF difficulties. Future studies should characterize the development of separable attentional processes over time (Jong, Verhoeven, Hooge, & Baar, 2016; Rueda, Checa, & Cóbitala, 2012) in moderate-to-late PT children, as they may represent a key component of altered EF development.

In higher-risk PT populations (e.g. very PT and/or very low birth weight children), sociodemographic risk factors are often confounded with PT birth. In the current study, we intentionally selected all participants to be of relatively low environmental risk (e.g. high SES, high parental education, equivalent SES measures across groups) in order to minimize this association. Unlike previous studies involving PT cohorts of both higher medical and environmental risk, we did not detect group differences in parental mental health and/or familial stress in the current sample. FT and PT parents also did not differ in their perception of their child's medical vulnerability, emphasizing the minimal neonatal complications present within our healthy PT sample. However, consistent with studies of higher-risk PT children, parents of PT infants born at earlier gestational ages endorsed higher levels of familial stress and higher levels of perceived infant medical vulnerability approximately nine months after the birth of their

child. Families of very PT infants also show higher levels of mental health issues and stress over the first years of their child's life, indicating these are not transient issues only related to the infant's hospitalization in the NICU (Treyvaud et al., 2010, 2016; Treyvaud, Lee, Doyle, & Anderson, 2014).

This study provides preliminary evidence that parents of low-risk, moderate-to-late PT children may differ from FT families in parenting styles during infancy. As a group, parents of PT infants endorsed higher levels of discipline, and across the entire sample of infants, lower gestational age at birth was related to higher levels of parent-reported discipline. The discipline scale of the Infancy Parenting Styles Questionnaire includes items reflecting parental beliefs about whether infants are capable of manipulating the parent's behavior and the degree to which parents should shape an infant's behavior (Arnott & Brown, 2013). Higher responding on this scale likely reflects an "over-controlling" pattern of parenting and thus poorer parental sensitivity. Although a recent meta-analysis did not identify differences in parental sensitivity within parents of PT children (Bilgin & Wolke, 2015), few studies have investigated parenting behaviors of moderate-to-late PT families, especially those of low sociodemographic risk, during infancy. Differences in infant temperament and physiology related to PT birth may drive a need for parents of PT children to endorse higher levels of discipline/control. Studies with very PT infants have documented that they show poorer behavioral regulation and are rated as higher in negative emotionality than their FT peers (Hughes et al., 2002). Alternatively, higher levels of familial anxiety and/or anxiety about the child's well-being

observed in families of moderate-to-late PT infants who were born at earlier gestational ages may underlie differences between the groups in parenting styles and beliefs.

An additional goal of the current study was to describe how individual differences in familial environmental risk factors were related to the development of early EF skills. Across the entire sample of participants, we found evidence that variations within familial environments, even in the low-risk, normative range, are associated with early differences in infant cognitive development. Income-to-needs ratio, in this sample of highly educated families, was related to both infant encoding and attention shifting composites. Because all families were of middle-to-upper SES, associations detected between income-to-needs ratio and infant cognitive development likely reflect not only familial income, but also co-variation in parental education, home environment characteristics, and familial stress levels. SES differences in infant attention (Clearfield & Jedd, 2013) and memory (Clearfield & Niman, 2012; Markant et al., 2016; Noble et al., 2015) are consistent with a growing literature documenting the emergence of SES-disparities within the first years of life. In the current study, all families were above the federal poverty level threshold. SES-disparities in early EF skills are likely larger in families that are at higher levels of risk.

Although perceived vulnerability and familial stress levels were related to gestational age within the PT group, these variables were generally not predictive of early EF development. Similarly, parental mental health, almost exclusively within the normative range in both the PT and FT groups, was also not related to individual differences in infant cognitive development. Previous studies with higher risk PT infants

have documented negative associations between perceived vulnerability and global metrics of infant development, although interestingly, associations with cognitive scores on the Bayley were not detected (Allen et al., 2004). It is possible that effects of medical vulnerability, familial stress, and parental mental health are not observed unless levels of risk are higher. Alternatively, other biological (e.g. prematurity in and of itself) and/or environmental (e.g. SES, insensitive parenting) risk factors may more robustly impact the development of higher-order cognitive skills in infants.

Numerous studies have documented both concurrent and longitudinal associations between sensitive parenting and children's EF development (e.g. Bernier et al., 2012). Our analyses extend these results into late infancy. Higher parental involvement, reflecting a combination of sensitive parenting (e.g. choosing activities that are developmentally appropriate for the infant) and cognitive stimulation, was associated with better infant attention shifting and inhibition composite scores. These relationships persisted after controlling for gestational age, suggesting sensitive parenting practices during infancy are beneficial for both FT and PT infants. Marginal associations between discipline, reflecting over-control and/or less sensitive parenting, and the infant attention shifting and inhibition composites were also detected. Overall, our results are consistent with studies that have documented the positive influence of supportive, higher-quality parenting for children's EF outcomes. It is unclear why benefits were observed for only the infant attention shifting and inhibition composites, as we would expect these parenting behaviors to be globally beneficial for EF. One recent study has also documented associations between maternal sensitivity and inhibition, but not cognitive

flexibility, in preschool-aged children (Lucassen et al., 2015). Our results should be interpreted with caution because our analyses were largely exploratory and relied on self-reported parenting data. Additional studies are warranted characterizing which parenting behaviors support the development of EF precursor skills in both normative and at-risk populations of infants, ideally using observational measures of parenting.

One of the primary limitations of this study is that effect sizes for both biological and environmental influences in relation to early infant EF were small and are only correlational. Given the exploratory nature of our analyses, we also did not correct for multiple comparisons; correlations should therefore be subject to replication in future studies and interpreted here with caution. The small effect sizes for these relationships may be expected in our low-risk sample as they likely reflect variance within the normative range of infant cognitive development. It is also possible that environmental factors will show stronger correlations as children age and EF skills become more contextually relevant (Blair & Raver, 2012). An additional limitation is that the sample size used to derive the factor structure for the infant cognitive measures is smaller than ideal. Simulation studies (MacCallum, Widaman, Zhang, & Hong, 1999) suggest that for sample sizes of only 60 cases, good modeling of population-level factors can occur when certain cases are met (i.e. wide communality values and 10:3 ratio of variables to factors), which were consistent with the data set used in the current study. Our confidence in the derived factors is also bolstered by the similarity of our results to models produced in previous studies with infants using different task batteries (Rose et al., 2004; Rose, Feldman, et al., 2005).

Understanding the early antecedents of EF development is critical given that EF impairments are observed in children with diverse biological and environmental risk factors. The current study adds to this literature by providing evidence that both biological and environmental variations in lower-risk infants are predictive of EF precursor skills. Impacts of early risk were most consistently associated with infant attention shifting skills. Early attentional development may show heightened susceptibility to biological and environmental influences because even small differences in attentional processing fundamentally alter the way in which infants sample information from the world (see recent review Amso & Scerif, 2015). Multiple mechanisms likely underlie the influence of biological and environmental influences on early infant EF skills, including effects of chronic stress on the developing prefrontal cortex (Raver et al., 2012), variation in parenting practices which promote early regulation skills in children (Bernier et al., 2010), biological differences in infant attention processing present at birth (Papageorgiou, Farroni, Johnson, Smith, & Ronald, 2015), and shared parent-child genetic influences (Leve et al., 2013). Studies reporting successful training of higher-order cognitive skills in infants (Wass et al., 2011; Wass, Scerif, & Johnson, 2012) and training of parenting behaviors that support EF (Landry, Smith, & Swank, 2006) provide potential avenues for intervention for infants at risk for atypical EF development.

CHAPTER 4: Study 2

Long-Term Alterations in Prefrontal Structural and Functional Brain Development in Adolescents Born Moderately Preterm³

Outline

Individuals who are born very preterm (<32 weeks gestation) are at increased risk for altered development of prefrontal-dependent behaviors including executive functions (EF). Behavioral impairments in EF are likely related to both structural and functional brain changes in frontostriatal circuits that have been reported across childhood, adolescence, and young adulthood in very preterm cohorts. While emerging research suggests that individuals born only moderate-to-late preterm (PT; 32-36 weeks gestation) also show differential EF development, prior studies have not investigated how these differences are instantiated in prefrontal structure or functional activity, particularly at adolescence when prefrontal circuits are rapidly developing. The present study examined whether low-risk, healthy adolescents born moderate-to-late PT exhibit altered prefrontal structural and functional development. Adolescents born PT did not demonstrate behavioral impairments on a fMRI Flanker Go/No-Go task designed to challenge multiple aspects of EF. However, PT birth was associated with reduced left prefrontal cortex gray matter volume and altered functional brain activity. Adolescents born PT

³ Ruskin H. Hunt, Heather W. Sesma, Sara E. Van Den Heuvel, Shelby T. Rentmeester, and Kathleen M. Thomas are listed as co-authors on this publication

showed increased activity in classical motor regions during sustained attention, while full-term children showed higher levels of brain activity across frontal regulatory circuits during all components of the EF task. The relationship between gestational age at birth and both prefrontal volume and levels of functional activity extended across the entire gestational age range of this sample (31-42 weeks). Results indicate that even in the context of equivalent behavior, moderate-to-late PT birth results in broad, long-term alterations in prefrontal cortex development. Given increases world-wide in the number of moderate-to-late PT births, results indicate it is necessary to better understand the neurodevelopmental sequelae of moderate-to-late PT birth and highlight the plasticity of the developing prefrontal cortex to early variations in perinatal experience.

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*Long-Term Alterations in Prefrontal Structural and Functional Brain Development in
Adolescents Born Moderately Preterm*

There is a growing literature reporting differences in prefrontal-dependent behaviors including executive functions (EF) such as working memory, inhibitory control, and attention shifting in individuals born preterm (PT; born before 37 weeks gestation; e.g. Aarnoudse-Moens & Smidts, 2009; Anderson, Doyle, & Group, 2004; Marlow, Hennessy, Bracewell, & Wolke, 2007). Atypical EF in individuals born PT is detectable during infancy (Sun, Mohay, & Callaghan, 2009), is apparent during the preschool period when EF rapidly develops (Brumbaugh, Hodel, & Thomas, 2014; Hodel, Brumbaugh, Morris, & Thomas, 2015), and persists into later adolescence (Luu, Ment, Allan, Schneider, & Vohr, 2011; Narberhaus, Segarra, Cald, & Gim, 2008). Deficits in EF appear to be relatively broad and non-specific, occurring across a wide variety of measures and remaining after controlling for individual variance in IQ. Impairments in EF within this population are likely related to critical developmental changes that occur in the fetal prefrontal cortex during the late second and third trimesters of pregnancy, including rapid cortical gray matter growth (e.g. Hüppi et al., 1998; Nishida et al., 2006), gyration (e.g. Dubois et al., 2008), and the establishment of important anatomical and functional white matter tracts (e.g. Collin & van den Heuvel, 2013; Hermoye et al., 2006; Huang et al., 2006; Takahashi, Folkerth, Galaburda, & Grant, 2012).

Several structural MRI studies have reported alterations in regional prefrontal cortex volume in children and/or young adolescents born PT and/or very low birth weight

(VLBW; <1,500 grams), including reduced gray matter volume (e.g. Ball et al., 2012; Nagy et al., 2009; Nosarti et al., 2008; Peterson et al., 2000; Thompson et al., 2007), lower white matter density and/or volume (e.g. Giménez et al., 2006; Kesler et al., 2008; Mullen et al., 2011; Nosarti et al., 2008), and atypical cortical thinning and/or morphology (e.g. Bjuland, Løhaugen, Martinussen, & Skranes, 2013; Lax et al., 2013; Mürner-Lavanchy et al., 2014; Zhang et al., 2015). Although deviations from normative patterns of brain development appear to decrease in magnitude as individuals born PT enter mid-to-late adolescence, group differences remain at young adulthood (e.g. Nam et al., 2015; Nosarti et al., 2014), suggesting that both delayed and/or atypical trajectories of frontal lobe development may be present following PT birth.

Alterations in structural development of prefrontal cortex reported in PT and/or VLBW populations likely result in functional brain changes in prefrontal cortex and distributed frontostriatal systems (Nosarti, 2010). However, relatively few studies have specifically investigated classically prefrontal-dependent behaviors like EF using functional imaging in PT populations. To date, studies have indicated that individuals born PT show weaker engagement of frontal regions during working memory tasks in comparison to their full-term peers during childhood (Griffiths et al., 2013; Mürner-Lavanchy et al., 2014). These differences in frontal activation in the context of EF demands do not resolve by adolescence when prefrontal circuits undergo a period of rapid structural development (Sowell, Thompson, Holmes, Jernigan, & Toga, 1999; Sowell, Thompson, Tessner, & Toga, 2001). Instead, adolescents and adults born PT utilize different neural circuitry during inhibitory control (Lawrence et al., 2009; Nosarti

et al., 2006) and cognitive flexibility tasks (Nosarti et al., 2009) in comparison to their full-term peers, including group differences in extent and/or magnitude of functional activity within inferior frontal, middle frontal, and anterior cingulate regions.

Interestingly, these group differences in prefrontal activation have been documented both in the presence and absence of behavioral differences in performance. Functional activation differences in individuals born PT also appear to extend into broader frontostriatal networks (Curtis, Zhuang, Townsend, Hu, & Nelson, 2006), may be related to broad differences in engagement of frontoparietal attention networks (Carmody et al., 2006; Daamen et al., 2015), and are amplified in individuals with higher levels of neonatal risk (Réveillon & Urben, 2013).

In combination, neuroimaging studies of both prefrontal structure and function in individuals born PT suggest long-term, broad alterations to the development of prefrontal circuits. However, almost all longitudinal follow-up of PT children using neuroimaging measures has focused exclusively on those born very PT (<32 weeks gestation) and/or VLBW. According to the most recent statistics (Center for Disease Control and Prevention's Births: Final Data for 2013), infants born very PT represented less than 2% of total US births in 2013 (Martin et al., 2015). In contrast, individuals born in the moderate-to-late PT range (32-36 weeks gestation) comprised almost 10% of total US births during the same time period (Martin et al., 2015). Because they are often relatively healthy at birth, infants born within this gestational age range are not routinely followed in neurodevelopmental clinics and thus remain a significantly understudied population. However, emerging research suggests that moderate-to-late PT birth, even in the absence

of major medical complications, may have a more dramatic impact on early brain growth and maturation than previously assumed (Schonhaut, Armijo, & Perez, 2015; Walsh, Doyle, Anderson, Lee, & Cheong, 2014). For example, even when tested at term equivalent age, infants born moderate-to-late PT have smaller total brain volume, more immature gyration, and poorer global white matter organization than their term peers (Kelly et al., 2016; Munakata et al., 2013; Walsh et al., 2014). These early neurodevelopmental changes extend into the childhood years (Rogers et al., 2014) and may represent the biological underpinnings of subtle behavioral differences in EF that are measurable in toddler (Voigt, Pietz, Pauen, Kliegel, & Reuner, 2012) and preschool-aged children (Brumbaugh et al., 2014; Hodel et al., 2015) born moderate-to-late PT.

To date, no study has examined whether prefrontal functional activity differences are present in lower risk PT individuals, including those born moderate-to-late PT. Furthermore, it is unclear whether early neurobehavioral differences persist in lower-risk PT children into the adolescent years. Describing the long-term impact of moderate-to-late PT birth on functional brain development is critical, as this work broadly informs our understanding of how more subtle variations in early environmental experience impact subsequent neurobehavioral development. The current study aimed to investigate whether disruptions in functional activation in prefrontal systems would be observed in low-risk individuals born moderately PT during early adolescence. Unlike previous studies that have focused almost exclusively on higher risk individuals born in the very PT (<32 weeks gestation) range, our sample of PT adolescents was carefully selected for low neonatal risk, such that PT children did not have a significant history of medical

complications other than PT birth. Second, the use of a narrow age-range (12-13 years) provided the opportunity to examine the long-term effects of PT birth on prefrontal cortex development during a time window when both prefrontal dependent behaviors (e.g. Prencipe et al., 2011) and structural anatomy (Sowell et al., 1999, 2001) are undergoing rapid development. Based on previous behavioral and neuroimaging studies with higher risk, very PT populations, we hypothesized that adolescents born moderate-to-late PT would show poorer behavioral performance and reduced engagement of associated frontal systems during an EF task.

Method

Participants

Young adolescents were recruited from an existing longitudinal sample (Stolarova et al., 2003) and from a database of families who endorsed interest in participating in child development research. The sample consisted of 19 children (11 males) born moderately PT (31-34 weeks gestation) without significant medical complications and 20 children (11 males) born full-term (FT; 38-42 weeks gestation). All children were between 12-13 years at test and were predominately Caucasian (87%), lived in college-educated (87%), two-parent families (97%), with median incomes between \$101,000-\$150,000. Hollingshead scores (Hollingshead, 1975) reflecting overall familial socioeconomic status, were equivalent for the two groups.

PT children were born within the specified gestational age range, were appropriate for gestational age (AGA) in size and weight at birth, and had 5-minute Apgar scores > 7. Exclusion criteria included severe medical risk factors such as

intraventricular hemorrhage, mechanical ventilation for > 24 hours, and maternal drug or alcohol use. FT children were additionally required to have no history of major pre- or perinatal medical complications. Importantly, these inclusion and exclusion criteria ensured that our PT adolescent sample was extremely low-risk, such that individuals did not have a significant history of medical complications other than prematurity itself.

All children were required to have normal or corrected-to-normal hearing and vision, no documented intellectual impairments, and no current or past diagnoses of neurological or major psychiatric disorders. Children were also prescreened for contraindications for MRI (including braces, permanent retainer, history of moderate or severe claustrophobia, or implanted metal).

See Tables 4.1 and 4.2 for demographic and perinatal characteristics of the sample.

Table 4.1

Demographic Characteristics

	<u>PT (n = 19)</u>	<u>Full-Term (n = 20)</u>	<i>p</i>
	<i>n (%)</i>	<i>n (%)</i>	
Child's Sex - # male	11 (57.9)	11 (55.0)	.86
Child's Ethnicity - # Caucasian	16 (84.2)	18 (90.0)	.59
Maternal Education			.32
High school degree or GED	3 (15.8)	4 (20.0)	
Associate degree	3 (15.8)	0 (0)	
Bachelor's degree	9 (47.4)	12 (60.0)	
Graduate or professional degree	4 (21.1)	4 (20.0)	
Maternal Work			.04*
Full-time work for pay	12 (63.2)	6 (30.0)	
Part-time work for pay	2 (10.5)	9 (45.0)	
Stay at home parent	5 (26.3)	5 (25.0)	
Annual Household Income			.57
≤ \$50,000	0 (0)	1 (5.0)	
\$51,000 - \$100,000	7 (36.8)	11 (55.0)	
\$101,000 - \$150,000	6 (31.6)	4 (20.0)	
\$151,000 - \$200,000	2 (10.5)	2 (10.0)	
≥ \$201,000	4 (21.1)	2 (10.0)	
Marital Status - # married	18 (94.7)	20 (100.0)	.49
Hollingshead Score - Mean	48.47	52.40	.17

Notes. **p* < .05.

Table 4.2

Perinatal Characteristics

	<u>PT (n = 19)</u>	<u>Full-Term (n = 20)</u>	<i>p</i>
	<i>M (SD)</i>	<i>M (SD)</i>	
Birth History			
Gestational age (weeks)	32.70 (.93)	40.23 (1.03)	< .01*
Birth weight (lbs)	4.58 (.87)	7.80 (1.02)	< .01*
Length of NICU stay (days) ^a	20.28 (9.59)		
Maternal age at delivery (years)	32.83 (3.04)	32.66 (4.77)	.90
	<i>n (%)</i>	<i>n (%)</i>	<i>p</i>
Pregnancy Related Characteristics			
Twin gestation	12 (63.2)	0 (0)	< .01*
Cesarean delivery	9 (47.4)	2 (10.0)	.01*
Preeclampsia or hypertension	7 (36.8)	0 (0)	< .01*
Maternal diabetes	2 (10.5)	1 (5.0)	.61
Neonatal Complications^b			
Hyperbilirubinemia	6 (31.6)	1 (5.0)	.04*
Respiratory distress	4 (21.1)	1 (5.0)	.18
Apnea of prematurity	3 (15.8)	0 (0)	.11
Sepsis	0 (0)	0 (0)	
Brain injury (IVH/PVL)	0 (0)	0 (0)	

Notes. **p* < .05.

^aOne FT child was admitted to the NICU for congenital diaphragmatic hernia repair.

^bTwo PT children (twin pair) were diagnosed with G6PD enzyme deficiency following the neonatal period.

Procedure

As part of a larger study investigating neurobehavioral development following moderate-to-late PT birth using multiple imaging modalities, children completed two testing sessions at the University of Minnesota. The second session included structural and functional neuroimaging measures described in detail below. Written informed consent and assent were obtained from parents and children, respectively. Both parents and children received a gift card for their travel time and participation. Study procedures were approved by the University of Minnesota's Institutional Review Board.

Since prefrontal-dependent functions and general intelligence overlap in typically developing children and are known to be impacted by PT birth, participants also completed the vocabulary and matrix reasoning subtests of the Wechsler Abbreviated Scale of Intelligence (WASI; Weschler, 1999) as a measure of IQ, the Wechsler Intelligence Scale for Children (WISC-IV; Weschler, 2004) coding and symbol search subtests as a measure of processing speed, and the WICS-IV digit span and letter number sequencing subtests as a measure of working memory immediately following their scan session. Independent samples t-tests were used to compare performance of PT and FT children on estimated IQ, processing speed, and working memory composite scores. Means and standard deviations are reported.

A processing speed score could not be calculated for one child (1 PT male) due to an experimenter error.

fMRI task paradigm. The combined Flanker Go/No-Go paradigm was derived from the classic Eriksen flanker paradigm, with the addition of an inhibitory control

component (modeled on a version used by Crone and colleagues (Crone, Jennings, & Van Der Molen, 2003) and was designed as a rapid, event-related fMRI paradigm. This task was selected to challenge multiple aspects of EF, including inhibitory control, set-shifting, and attention. Each trial began with a brief fixation cross (20 ms), followed by the simultaneous appearance of five, horizontally spaced arrows. Children were required to pay attention to the middle arrow (the target stimulus) on the screen, and to indicate via a button press the direction the arrow was pointing (left thumb or right thumb press). Stimuli remained on the screen until the child responded, or for a maximum of 2000 ms. On Congruent-Go trials (33% of trials), the flanking stimuli were oriented in the same direction as the target, whereas on Incongruent-Go trials (33% of trials), flanking stimuli provided conflicting information about the target orientation. Additionally, if the No-Go stimulus appeared in the flanking symbols (diamond stimulus; 33% of trials), children were required to inhibit responding. The intertrial interval was jittered to allow separation of the hemodynamic response to individual stimulus types. Children completed four task runs, each approximately 5.75 minutes long and 84 trials in length.

MRI data acquisition. Magnetic resonance imaging was performed on a Siemens 3T Tim Trio MRI scanner. Children watched a movie of their choice during the collection of structural MRI images. A sagittal scout series was first used to verify participant position. A T1-weighted, three-dimensional (3-D) magnetization prepared rapid gradient echo (MPRAGE) sequence was used to acquire 240 contiguous slices of 1 mm thickness in the sagittal plane (TR = 2530 ms, TE = 3.65 ms, FOV = 256 mm, matrix = 256 x 256, flip angle = 7°). The Flanker Go/No-Go paradigm was presented on a

projector and viewed by the participant using an inclined mirror attached to the top of the head coil. Accuracy and reaction time data were collected using an MR-compatible button box. Whole brain T2* weighted EPI BOLD images were collected using 34 interleaved slices for four runs of the task (TR = 2000 ms, TE = 28 ms, FOV = 200 mm, matrix = 64 x 64, flip angle = 80°, slice thickness = 3.0 mm with a 33% gap, 172 acquisitions/run). Each run was padded by 2 TRs (4 seconds) at the beginning to allow for T1 equilibrium to be reached, as well as by 2 TRs at the end to capture signal from the final trial. A field map with identical positioning was collected immediately prior to the first EPI sequence so that distortion caused by magnetic field inhomogeneity could be corrected offline (TR = 400 ms, TE1 = 2.71 ms, TE2 = 5.17 ms, FOV = 200 mm, matrix = 64 x 64, flip angle = 50°, 34 interleaved slices, slice thickness = 3.0 mm).

Data Analyses

Structural MRI analyses. Cortical reconstruction and volumetric segmentation was performed with the Freesurfer image analysis suite version 5.1.0, which is documented and freely available for download online (<http://surfer.nmr.mgh.harvard.edu/>; Dale, Fischl, & Sereno, 1999). Technical details are described in previous publications (Dale et al., 1999; Dale & Sereno, 1992; Fischl & Dale, 2000; Fischl, Liu, & Dale, 2001; Fischl, Sereno, Tootell, & Dale, 1999; Fischl, 2004; Fischl et al., 2002, 2004; Han et al., 2006; Jovicich et al., 2006; Reuter & Fischl, 2011; Reuter, Rosas, & Fischl, 2010; Ségonne et al., 2004). Importantly, Freesurfer's segmentation procedures have been shown to be comparable to hand tracing (Morey et al., 2009) and are appropriate for use in pediatric populations (Ghosh et al., 2010). Data

quality control mechanisms were used to attempt to match the PT and FT groups on MRI scan quality. Specifically, all image outputs were visually inspected prior to and following segmentation and were rejected for excess participant motion and/or gross segmentation errors. Because previous developmental studies have reported changes in brain structure associated with age and sex in pediatric populations during early adolescence (Sowell et al., 1999, 2001), all volumetric analyses include age at test, sex, and total intracranial volume (ICV) as covariates. Group differences (PT vs. FT) were investigated using one-way analysis of covariance (ANCOVA) models and were restricted to prefrontal lobar and sub-region volumes based on a priori interests. In regions where group differences were observed, continuous linear effects of gestational age (31-42 weeks) were also investigated.

Seven children were excluded from volumetric analyses due to excess motion in structural scans (3 PT males, 2 FT males, 1 FT female) or a MRI scan abnormality requiring clinical follow-up (1 FT male).

fMRI analyses. Functional imaging data were preprocessed and analyzed using standard FSL tools (FMRIB Software Library, <http://fsl.fmrib.ox.ac.uk/fsl>; v 4.1.9; Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012). Initial preprocessing steps included skull stripping using BET (Brain Extraction Tool), motion correction using MCFLIRT (Motion Correction FMRIB's Linear Image Registration Tool), slice scan time correction, field map unwarping, spatial smoothing using a 7 mm FWHM Gaussian filter, and high pass temporal filtering (50 sec). Each participant's EPI images were registered to their MPRAGE structural image (6 degrees of freedom), and structural

images were registered to the Montreal Neurological Institute's anatomical standard (MNI 152 T1 2mm template; 12 degrees of freedom). Confound predictors were used to censor TRs with excessive participant head motion. Excessive motion was defined as: 1) a TR with greater than 3.125 mm of absolute motion from the initial reference volume or 2) a TR with greater than 1.5625 mm of motion relative to the immediately preceding volume, with additional censoring of the immediately preceding and following TRs. Participants were excluded from fMRI analyses if they had fewer than 56 valid trials of each trial type (Congruent-Go, Incongruent-Go, No-Go) that met motion inclusion criteria.

For first level analyses (single participant analyses), a general linear model (GLM) was fit for each run of the preprocessed data with 6 regressors for each of the task conditions (Congruent-Go, Incongruent-Go, No-Go; separately for both left and right facing arrows) relative to fixation. Confound predictors included motion (3 linear, 3 rotational) and motion censoring predictors. First-level contrasts were derived by combining left and right regressors for each task condition in comparison to fixation and to the other task conditions. Second-level analyses combined contrasts of interest across runs for each participant. Third-level group difference analyses included group (PT vs. FT) as a between participant variable for each of the contrasts. Separate third-level analyses investigated potential linear effects of gestational age by treating gestational age as a mean-centered predictor. For all third-level analyses, the significance threshold was set at $Z = 2.575$ ($p < .005$) with a minimum cluster threshold of 10 contiguous raw voxels.

Six children were excluded from fMRI analyses due to excess motion (1 PT female, 2 PT males, 1 FT male), poor quality EPI data related to a scanner artifact (1 FT female), or a MRI scan abnormality requiring clinical follow-up (1 FT male).

Results

IQ, Processing Speed, and Working Memory

IQ did not differ by group, but was above the population mean for both FT and PT children in this low-risk, middle to high socioeconomic status sample, $t(37) = -.30, p < 0.76$; $M_{FT} = 112 \pm 11, M_{PT} = 111 \pm 10$. Similarly, processing speed quotient, $t(36) = .52, p < 0.61$; $M_{FT} = 106 \pm 14, M_{PT} = 109 \pm 15$, and working memory quotient, $t(37) = -1.03, p < 0.31$; $M_{FT} = 106 \pm 11, M_{PT} = 102 \pm 15$, did not differ by group.

Structural MRI

PT children had smaller left prefrontal cortex volumes than their full-term peers, left: $F(1, 27) = 43.94, p < .06, \eta_{\text{partial}}^2 = .13$; right: $F(1, 27) = .92, p < .35, \eta_{\text{partial}}^2 = .03$, see Figure 4.1. Across the entire sample of children, higher gestational age at birth was associated with larger left prefrontal cortex volumes, $F(1, 27) = 4.92, p < .04, \eta_{\text{partial}}^2 = .15$.

Follow-up analyses indicated the reduction in left lobar volumes in the PT group was driven primarily by volumetric decreases in the middle frontal (rostral middle frontal gyrus, $F(1, 27) = 8.69, p < .01, \eta_{\text{partial}}^2 = .24$) and inferior frontal (pars triangularis, $F(1, 27) = 3.98, p < .06, \eta_{\text{partial}}^2 = .13$) gyri. Similar to lobar effects, within these regions of interest, higher gestational age at birth was associated with larger volumes (rostral middle frontal gyrus, $F(1, 27) = 9.29, p < .01, \eta_{\text{partial}}^2 = .26$; pars triangularis, $F(1, 27) = 3.53, p < .07, \eta_{\text{partial}}^2 = .12$).

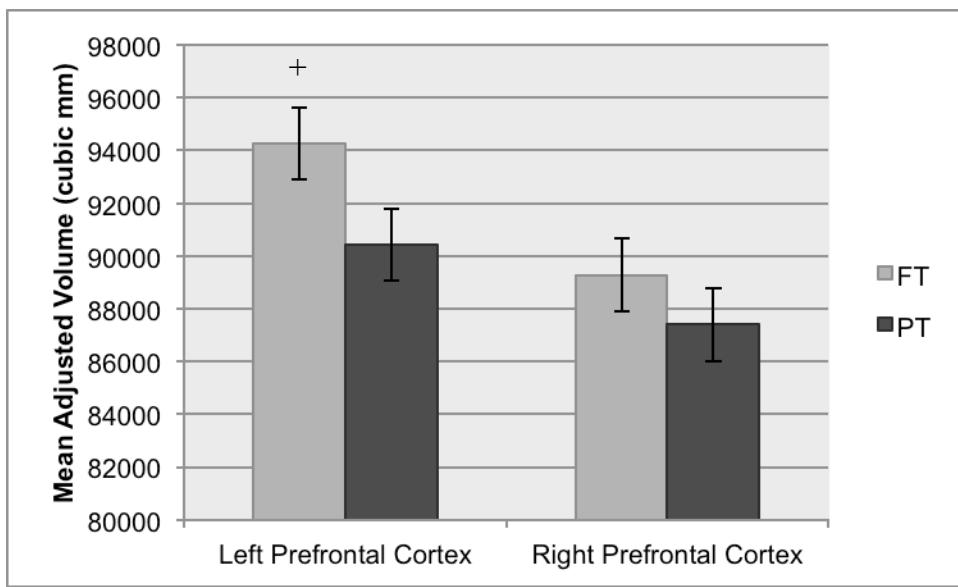


Figure 4.1. Group differences in prefrontal cortex gray matter volume. PT children had smaller left prefrontal cortex volumes than their FT peers. $+p < .06$.

Flanker Go/No-Go

Behavioral results. Reaction time and accuracy on the fMRI task were analyzed separately for Flanker and inhibitory control effects. Due to a technical error in data recording during fMRI scanning, in-session behavioral data were available for only 8 PT (4 female) and 7 FT (2 female) participants.

Accuracy and reaction time (on correct trials) for the Flanker component of the task were analyzed using separate 2 x 2 repeated measures ANOVAs with condition (Congruent-Go, Incongruent-Go) as a within subjects factor and group (PT vs. FT) as a between subjects factor. For accuracy, there was a significant effect of condition, $F(1, 13) = 9.49, p <.01$, but no effect of group, $F(1, 13) = 1.81, p <.20$, and no interaction between group and condition, $F(1, 13) = .36, p <.56$. Similarly, for reaction time, there was a significant effect of condition, $F(1, 13) = 171.61, p <.00$, but no effect of group, $F(1, 13) = ..86, p <.37$, and no interaction between group and condition, $F(1, 13) = .57, p <.46$. Behavioral evidence for the classic Flanker effect was therefore found in both accuracy and reaction time measures, such that all children performed better on the easier, Congruent-Go trials ($M_{Acc} = .99; M_{RT} = 547.01$ ms) than the Incongruent-Go trials ($M_{Acc} = .96; M_{RT} = 596.56$ ms).

Accuracy for the inhibitory control component of the task was analyzed using a 2 x 2 repeated measures ANOVA with condition (Congruent-Go, No-Go) as a within subjects factor and group (PT vs. FT) as a between subjects factor. There was a trend-level effect of condition, $F(1, 13) = 3.07, p <.10$, but no effect of group, $F(1, 13) = 2.28, p <.16$, and no interaction between group and condition, $F(1, 13) = .01, p <.91$. This

provided some evidence for an effect of inhibitory control demands, given that children in both groups performed slightly worse on the harder, No-Go trials ($M_{Acc} = .96$) than Congruent-Go trials ($M_{Acc} = .99$). However, performance was at ceiling levels overall.

All participants (N = 33) had behavioral data outside of the scanner from an identical version of this task (completed at a prior behavioral session) that were consistent with the reported pattern of results (i.e. high accuracy across all task conditions, a Flanker effect in both accuracy and reaction time). In this larger data set, the effect of inhibitory control demands on accuracy reached statistical significance, $F(1, 31) = 22.41, p < .01$, and a significant interaction between group and condition was observed for inhibitory control accuracy, $F(1, 31) = 9.11, p < .01$, such that PT children performed slightly more poorly on the No-Go trials ($M_{Acc} = .90$) in comparison to their FT peers ($M_{Acc} = .94$).

Overall task effects. Because no prior fMRI studies exist using this task with an adolescent sample, patterns of activation across all subjects were first examined separately for contrasts that reflected attentional (Incongruent-Go > Congruent-Go) and inhibitory control (No-Go > Congruent-Go; Congruent-Go > No-Go) specific effects.

As a group, children activated canonical regions associated with attention and executive control, including prefrontal (superior frontal gyrus, inferior frontal gyrus, cingulate) and parietal (inferior parietal/supramarginal gyrus, superior parietal lobule) regions for the attentional control contrast, see Figure 4.2 and Table 4.3. For the inhibitory control contrast (No-Go > Congruent-Go), no statistically significant patterns of activation were observed. However, the inverse contrast (Congruent-Go > No-Go)

examining the effects of motor responding in a sustained attention context was associated with activity expected motor response regions including bilateral premotor and motor cortex, basal ganglia, and cerebellum, see Figure 4.3 and Table 4.4. In combination, this pattern of activation likely reflects children's high level of behavioral accuracy and corresponding low levels of inhibitory control demands.

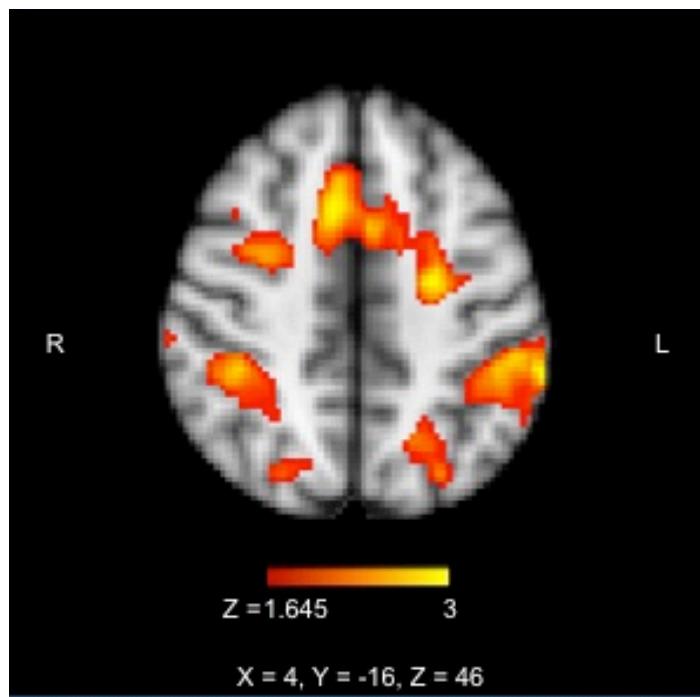


Figure 4.2. Activation for attentional control contrast for all participants. As a group, adolescents activated canonical regions associated with attention and executive control (cingulate and superior parietal lobule depicted) for the attentional control contrast (Flanker effect; Incongruent-Go > Congruent-Go).

Table 4.3

Attentional Control Effects for All Participants

Region	Side	Voxels	Z-max	MNI Coordinates			Mean % change in signal
				x	y	z	
<i>Incongruent-Go > Congruent-Go</i>							
Superior frontal gyrus (BA6)	L	367	3.649	-28	-2	66	.0871
Inferior parietal/supramarginal gyrus (BA40)	L	315	3.592	-42	-40	40	.0990
Superior frontal gyrus (BA6)	R	271	3.661	32	8	62	.1343
Cingulate (BA32/BA6)	R	259	3.274	10	20	42	.0718
Insula/frontal operculum	L	120	3.434	-40	10	12	.0612
Precentral gyrus (BA4)	L	110	3.443	-38	-6	30	.0634
Superior parietal lobule (BA7)	R	97	3.620	26	-70	54	.1315
Inferior parietal/supramarginal gyrus (BA40)	R	92	3.246	38	-38	40	.0724
Insula	R	86	3.068	34	20	6	.0737
Inferior frontal gyrus (BA44)	R	42	3.226	50	14	26	.0879

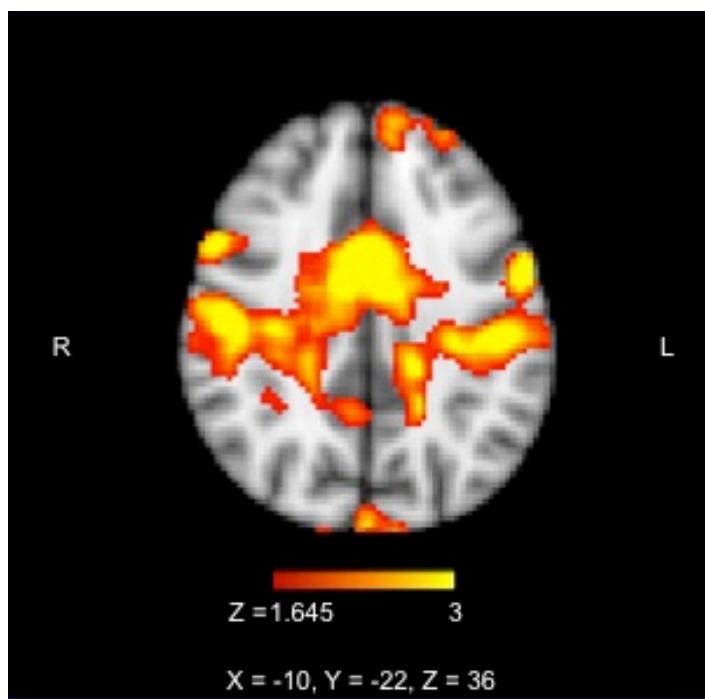


Figure 4.3. Activation for sustained attention contrast for all participants. As a group, adolescents activated expected motor response regions when required to make a motor response within a sustained attention context (Congruent-Go > No-Go).

Table 4.4

Inhibitory Control Effects for All Participants

Region	Side	Voxels	Z-max	MNI Coordinates	Mean % change in signal
<i>No-Go > Congruent-Go</i>					
<i>ns</i>					
<i>Congruent-Go > No-Go</i>					
Extended motor activation		36570	7.22	-32 -22 62	0.1256
Dorsal ACC	L/R		2	12 28	
Caudate	L		-16	-6 20	
Caudate	R		16	-8 22	
Putamen	L		-22	2 2	
Putamen	R		24	2 -6	
Insula	L		-42	2 -4	
Insula	R		38	4 8	
Precentral gyrus (BA6)	L		-58	2 34	
Premotor/motor cortex (BA4)	L		-38	-20 60	
Premotor/motor cortex (BA4)	R		38	-20 60	
Hippocampus	R		18	-18 -16	
Thalamus	L		-14	-16 12	
Thalamus	R		16	-18 6	
Occipital Cortex	L		-18	-82 4	
Occipital Cortex	R		22	-82 4	
Cerebellum	L		-18	-60 -24	
Cerebellum	R		20	-60 -24	
Vermis			0	-66 -20	
Frontal pole	L/R	257	3.32	-2 64 0	0.1612
Occipital cortex	R	144	3.44	52 -60 8	0.0853
Inferior frontal gyrus (BA45)	L	139	3.66	-46 44 18	0.1576
Precentral gyrus (BA6)	R	137	3.61	56 10 36	0.1190
Corpus callosum		124	3.48	2 16 10	0.0873
Middle temporal	R	55	3.61	56 -14 -26	0.1055

gyrus								
Superior frontal gyrus <u>(BA6)</u>	R	48	3.15	22	34	44		0.0850
Cerebellum	R	47	3.32	48	-62	-24		0.1799

Group differences in task effects. Patterns of activation for the previously described task effects (attentional and inhibitory control) were examined for potential group differences ($FT > PT$ and $PT > FT$).

There were no group differences in the attentional control contrast (Incongruent-Go $>$ Congruent-Go). However, for the Congruent-Go $>$ No-Go contrast (reflecting motor activity in the context of sustained attention), PT children exhibited greater activity across motor regions, including premotor and motor cortex and the cerebellum, see Figure 4.4 and Table 4.5. Follow-up analyses indicated that lower gestational age at birth was associated with increased activation within this network of motor regions.

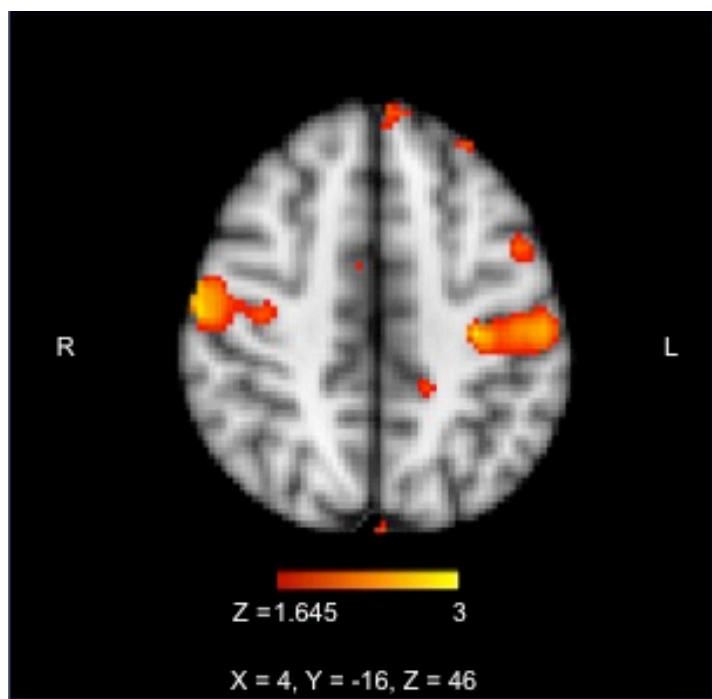


Figure 4.4. Greater activation for PT adolescents in motor regions. PT children exhibited greater activation than their FT peers in motor regions for the contrast Congruent-Go > No-Go.

Table 4.5

Group Differences in Inhibitory Control Effects

Region	Side	Voxels	Z-max	MNI Coordinates			Mean % change in signal			
<i>Congruent-Go > No-Go</i>										
<i>FT > PT</i>										
<i>ns</i>										
<i>Congruent-Go > No-Go</i>										
<i>PT > FT</i>										
Precentral/postcentral gyrus (BA6/4/3)	L	524	4.21	-24	-22	74	0.2289			
Vermis		507	3.99	-6	-64	-18	0.0937			
Postcentral gyrus (BA3)	R	143	4.81	54	-10	54	0.2167			
Precentral gyrus/premotor (BA4/6)	L	105	3.90	40	-8	62	0.1890			
Cerebellum	R	101	3.19	24	-52	-26	0.0816			
Precentral gyrus/premotor (BA4/6)	R	55	3.34	18	-26	76	0.1892			
Occipital pole	R	52	3.14	20	-96	-14	0.1801			
Superior frontal gyrus/premotor (BA6)	L/R	42	3.57	-4	10	70	0.2420			

Group differences in global activity. The previously described analyses examined regions that differed by group as a function of task condition (i.e. attentional control effect, inhibitory control effect). We also examined whether global differences (Task > Fixation) between PT and FT children (FT > PT and PT > FT) existed in activation that were not specific to task contrasts.

There was a main effect of group such that FT adolescents had greater activation across canonical frontal-parietal regulatory networks in comparison to PT adolescents, including bilateral superior, middle, and inferior frontal gyri, medial prefrontal cortex and the superior parietal lobule, see Figure 4.5 and Table 4.6. Follow-up analyses indicated that higher gestational age at birth was associated with increased activity in this network of frontal and parietal regions across the entire gestational age range of our sample.

Supplemental analyses indicated that global group differences were present for all three task conditions (Congruent-Go vs. Fixation, Incongruent-Go vs. Fixation, No-Go vs. Fixation) and included a similar set of highly overlapping frontal and parietal regions, see Inline Supplemental Tables 4.1-4.3.

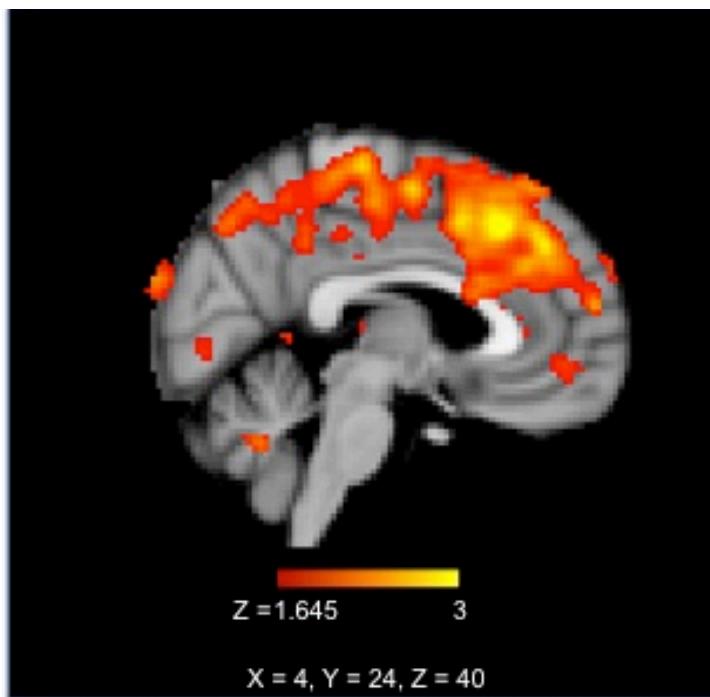


Figure 4.5. Greater activation for FT adolescents across frontal-parietal regulatory regions. FT adolescents demonstrated greater global activity across canonical frontal-parietal regulatory regions for the contrast Task > Fixation (medial prefrontal cortex activation depicted). This main effect of group was consistent across all task conditions (Congruent-Go, Incongruent-Go, No-Go) in relation to fixation baseline.

Table 4.6

Group Differences in Global Activity (Task > Fixation)

Region	Side	Voxels	Z-max	MNI Coordinates			Mean % change in signal			
<i>Task > Fixation</i>										
<i>FT > PT</i>										
Medial prefrontal/premotor (BA6)	L/R	646	3.75	-14	20	38	0.4010			
Extended frontal regions	L	351	3.89	-34	6	54	0.5977			
Middle frontal (BA8)	L			-50	12	34				
Middle frontal/premotor (BA6)	L			-34	6	54				
Extended frontal regions		303	4.29				0.2356			
Medial prefrontal (BA9)	L			-14	52	6				
Inferior frontal gyrus (BA47)	L			-32	30	-6				
Premotor cortex (BA6)	R	218	3.34	10	-8	56	0.2460			
Superior temporal gyrus (BA38)	R	212	3.90	34	4	-28	0.4477			
Inferior frontal gyrus (BA44)	L	171	3.73	-50	12	12	0.3011			
Superior parietal lobule (BA7)	R	140	3.36	34	-64	56	0.8775			
Middle frontal gyrus (BA46)	L	59	3.24	-44	32	26	0.3932			
Precentral gyrus (BA6/Ba4)	R	55	3.37	8	-22	64	0.3053			
Middle frontal gyrus (BA6/8)	R	55	2.90	38	14	52	0.4360			
Precuneus/superior parietal lobule (BA7)	L	55	3.22	-6	-70	50	0.4407			
Postcentral gyrus (BA3)	L	54	3.53	-24	-34	50	0.2068			

Middle frontal gyrus (BA8)	R	49	2.96	38	26	42	0.3984
Middle frontal gyrus (BA10)	L	47	3.08	-38	42	-10	0.4106
Superior frontal gyrus (BA6)	L	44	3.65	-12	6	72	0.7516
Superior frontal gyrus (BA6)	R	43	3.49	20	8	64	0.5676
Inferior frontal gyrus (BA9)	R	43	3.18	28	20	20	0.1839
<i>Task > Fixation</i>							
<i>PT > FT</i>							
<i>ns</i>							

Inline Supplemental Table 4.1

Group Differences in Global Activity (Congruent-Go > Fixation)

Region	Side	Voxels	Z-max	MNI Coordinates			Mean % change in signal			
<i>Congruent-Go > Fixation</i>										
<i>FT > PT</i>										
Medial prefrontal (BA6/8)	L/R	675	3.58	-14	20	38	0.3502			
Middle frontal gyrus (BA9/BA44)	L	622	4.11	-34	6	54	0.4953			
Extended frontal regions		490	3.43	10	-8	56	0.3364			
Middle frontal gyrus (BA6/8)	R			30	10	52				
Medial prefrontal (BA6)	R			10	-8	54				
Precentral gyrus (BA6/4)	R			22	-16	54				
Inferior frontal gyrus (BA44)	L	211	3.89	-48	10	12	0.2872			
Superior parietal lobule (BA7)	R	195	3.54	34	-66	56	0.7600			
Medial prefrontal (BA9/10)	L	193	4.13	-20	50	2	0.2259			
Superior temporal gyrus (BA38)	R	183	3.90	32	4	-26	0.4432			
Precuneus/superior parietal lobule (BA7)	L	119	3.86	-6	-70	50	0.4501			
Orbitofrontal cortex (BA11)	L	81	3.20	-22	34	-6	0.1801			
Orbitofrontal cortex (BA47/11)	L	51	3.28	-38	42	-10	0.3903			
Precentral gyrus (BA4/6)	R	46	3.35	8	-22	64	0.2869			
<i>Congruent-Go > Fixation</i>										
<i>PT > FT</i>										
<i>ns</i>										

Inline Supplemental Table 4.2

Group Differences in Global Activity (Incongruent-Go > Fixation)

Region	Side	Voxels	Z-max	MNI Coordinates			Mean % change in signal			
<i>Incongruent-Go > Fixation</i>										
<i>FT > PT</i>										
Extended frontal regions		441	3.53	14	-14	54	0.2366			
Precentral gyrus/medial prefrontal (BA4/6)	R			8	-22	60				
Postcentral gyrus (BA3)	R			10	-36	60				
Extended frontal regions		245	4.25	-18	50	4	0.2232			
Medial prefrontal (BA10)	L			-16	52	4				
Orbitofrontal cortex (BA11)	L			-22	32	-8				
Inferior frontal gyrus (BA45)	R	204	3.47	28	20	20	0.1755			
Superior temporal gyrus (BA38)	R	203	3.99	32	4	-28	0.4521			
Medial prefrontal cortex (BA6)	L/R	180	3.03	6	24	44	0.5626			
Superior frontal gyrus (BA8)	L	135	3.74	-2	46	38	0.3637			
Superior parietal lobule (BA7)	R	106	3.20	34	-64	56	0.8741			
Inferior frontal gyrus (BA44)	L	97	3.23	-50	14	12	0.2672			
Middle frontal gyrus (BA44)	L	85	3.25	-56	12	32	0.6356			
Medial prefrontal cortex (BA9)	L	82	3.64	-14	20	38	0.1538			
Middle frontal gyrus (BA6)	L	68	3.52	-34	6	54	0.4732			
Postcentral gyrus (BA3)	L	65	3.49	-24	-34	50	0.2032			

Incongruent-Go > Fixation

PT > FT
ns

Inline Supplemental Table 4.3

Group Differences in Global Activity (No-Go > Fixation)

Region	Side	Voxels	Z-max	MNI Coordinates			Mean % change in signal			
<i>No-Go > Fixation</i>										
<i>FT > PT</i>										
Medial prefrontal cortex (BA6/8)	L/R	910	3.91	-10	26	38	0.4613			
Inferior frontal gyrus (BA9/44)	L	488	4.03	-56	12	32	0.6104			
Superior temporal gyrus (BA38)	R	197	3.74	34	4	-28	0.4045			
Inferior frontal gyrus (BA44)	L	184	3.84	-50	12	12	0.3023			
Inferior frontal gyrus (BA46)	L	147	3.75	-42	28	-4	0.2391			
Medial prefrontal cortex (BA9)	L	118	4.19	-18	50	4	0.2360			
Superior frontal gyrus (BA6)	R	105	3.82	20	8	64	0.4600			
Superior frontal gyrus (BA6)	L	97	3.85	-12	6	72	0.7123			
Superior parietal lobule (BA7)	R	87	3.21	34	-64	58	0.8878			
Orbitofrontal cortex (BA47/11)	L	80	3.40	-34	46	-8	0.3922			
Middle frontal gyrus (BA8/9)	R	78	3.07	38	26	42	0.3857			
Inferior frontal gyrus (BA45)	L	76	3.32	-50	44	14	0.6465			
Middle frontal gyrus (BA46)	L	67	3.35	-42	32	26	0.3581			
Insula/postcentral gyrus	L	52	3.20	-50	-10	16	0.2398			
Postcentral gyrus (BA3)	L	46	3.16	-24	-34	50	0.2210			
Superior frontal gyrus (BA6)	L	44	3.51	-22	16	66	0.6425			
Precentral gyrus (BA4)	R	43	3.24	8	-24	64	0.3197			

Supramarginal gyrus (BA40)	L	42	3.11	-62	-52	26	0.5565
Precentral gyrus (BA4/6)	R	40	2.99	24	-18	50	0.2561
Insula	L	37	3.15	-32	2	4	0.2070
<i>No-Go > Fixation</i>							
<i>PT > FT</i>							
<i>ns</i>							

Discussion

The current study is the first multimodal neuroimaging investigation of altered brain structure and function in low-risk adolescents born in the moderate-to-late PT range. Results indicated that moderate-to-late PT birth is associated with both structural and functional brain changes across frontal regulatory systems previously reported to be sensitive to the effects of more severe prematurity. Like children born very PT, our lower-risk moderate-to-late PT cohort demonstrated regional reductions in prefrontal cortex volume and altered activity in frontal regulatory systems. These alterations in both brain structure and function were present even in the context of equivalent behavioral performance and IQ. While the magnitude of group differences was reduced in comparison to what is observed in higher risk PT samples, these effects suggest that a difference of only 4-8 weeks in children's early life experiences continues to impact neurobehavioral development at adolescence.

Children born moderate-to-late PT showed reductions in left prefrontal cortex gray matter volume in comparison to full-term children, even after accounting for individual variation in intracranial volume. Furthermore, individual differences in prefrontal volume were related to gestational age at birth across the entire sample of participants (including into the FT gestational age range). These results complement the existing structural neuroimaging literature following individuals born very PT and/or VLBW which also report global and regional reductions in prefrontal cortex gray matter volume (e.g. Ball et al., 2012; Nagy et al., 2009; Nosarti et al., 2008; Peterson et al., 2000; Thompson et al., 2007). Current results also indicated that changes in prefrontal

cortex volumes were driven primarily by volumetric reductions in regions of the middle and inferior frontal gyri. Reduced middle and inferior frontal gyri volume have previously been reported in higher-risk PT samples, including adolescent males born very PT (Kesler et al., 2008), and alterations in cortical thickness within these regions have also been reported in very PT adolescent and young adult samples (Bjuland et al., 2013; Mürner-Lavanchy et al., 2014). In combination, our volumetric results suggest that there is not a clear threshold at which PT birth no longer impacts prefrontal structural development, given that associations with gestational age and prefrontal volume at adolescence extended across the entire gestational age range spectrum tested (31-42 weeks).

Subtle differences in functional brain activation between children born moderate-to-late PT and FT controls were also detected on an EF task that tapped attentional control and response inhibition networks (combined Flanker Go/No-Go Task). Specifically, PT children showed increased activity across motor regions (including premotor cortex, motor cortex, and the cerebellum) during task conditions that required a motor response in the context of sustained attention. Changes in motor system activity in the context of sustained attention have also been reported in very PT samples; for example, Lawrence and colleagues (2014) reported increased cerebellar activation for very PT adults compared to FT controls on a cued motor task. However, the magnitude of differences in task-specific functional brain activity between PT and FT adolescents in the current study was relatively minimal. This lack of effect of moderate-to-late PT birth on task-specific functional activity is especially striking given that differences across

frontal regulatory and motor circuitry have been reported for similar cognitive tasks with higher risk PT participants (e.g. response inhibition task in Nosarti et al., 2006; although see De Kieviet et al., 2014).

The lack of dramatic group differences in functional brain activation specific to EF may be related to adolescents' behavioral performance. Accuracy and reaction time measures of behavior on the Flanker/Go No-Go task were equivalent and at ceiling levels for both PT and FT participants. Previous behavioral studies of EF in younger moderate-to-late PT populations have also found inconsistent results across various EF tasks; for example, two studies have reported poorer verbal working memory, but not spatial working memory, in low-risk preschool-aged children born in the moderate-to-late PT range (Brumbaugh et al., 2014; Hodel et al., 2015). These results suggest that unlike very PT birth, moderate-to-late PT birth exerts subtle, rather than global, impacts on EF development. Alternatively, it is also possible that equivalent EF task-related functional activity reflects reorganization and/or compensatory activity across supporting brain systems in adolescents born moderate-to-late PT that are required to achieve equivalent levels of behavioral performance. We speculate that a more challenging EF task that produces group differences in behavior may also result in larger group differences in functional activation even in this low-risk population. However, because few studies have examined neurobehavioral sequelae of moderate-to-late PT birth using laboratory measures of EF, the selection of a behavioral task that effectively taps the most vulnerable cognitive abilities is difficult. Detection of behavioral differences in EF in a low-risk population likely requires a task that adequately challenges the specific impacted

aspect of EF (i.e. lack of ceiling effects) and is sensitive to individual and group differences in behavior. Thus, equivalent behavioral performance is one potential reason for the lack of functional brain differences in the current study. However, it should be noted that prior studies have reported group differences between very PT individuals and FT controls in functional brain activation during EF tasks despite equivalent behavioral performance (e.g. Nosarti et al., 2006).

Interestingly, rather than observing group differences in contrasts related to specific EF demands, our results suggested that the largest difference between moderate-to-late PT and FT children lies in global activity. Specifically, results indicated that PT adolescents had reduced activation in comparison to their FT peers across frontal-parietal regulatory networks during cognitive processing (Task > Fixation contrast). This main effect of group was not specific to individual task conditions and was instead observed for all contrasts relative to a fixation baseline. Similar to our volumetric results, individual differences in functional activation were related to gestational age at birth, such that higher gestational age at birth was associated with increased activity in attention and regulatory networks across the entire gestational age spectrum tested. Ultimately, these results suggest there are potentially broad alterations to early neurodevelopmental processes initiated by moderate-to-late PT birth that have not normalized by adolescence.

The presence of such a large and consistent group difference in global cognitive activity was surprising given the low-risk nature of our sample. Our PT adolescents were intentionally selected to be of low-medical risk, such that they experienced few neonatal medical complications other than PT birth itself. Because of these inclusion criteria,

children were not recruited from a specific hospital or epidemiological cohort. While this may be viewed as a limitation, the low medical-risk nature of this sample combined with children's middle to high socioeconomic status is also a strength. Like low medical risk (e.g. Vohr et al., 2000), higher socioeconomic status is a known protective factor for neurobehavioral development in PT children (e.g. Patrianakos-Hoobler et al., 2010). The long-term effects of moderate-to-late PT birth detected in our sample are likely greater at the population level given the potential for higher levels of medical and environmental risk.

Although we observed large differences in global cognitive activity in the context of an EF task, it is unclear whether these effects are specific to the fMRI task used or if they are related to more general differences between PT and FT children in cognitive processing. fMRI studies of EF traditionally report group differences within task conditions or contrasts rather than in task activity relative to a fixation baseline (a "main effect" of group), making comparison of this result with previous work challenging. However, a related literature examining the neural correlates of language processing in very PT and/or VLBW individuals suggests that the alterations we observed in frontal-parietal attention systems may be non-specific to EF. These studies have indicated that language impairments in very PT or VLBW children may be due to broad changes in neural organization of language systems, including global differences in prefrontal activation in PT children and adolescents (Ment & Constable, 2007; Ment, Peterson, Meltzer, et al., 2006; Ment, Peterson, Vohr, et al., 2006; Peterson et al., 2002). For example, during semantic and phonological processing tasks, PT children activated a

similar set of brain regions as FT children, including portions of the left inferior frontal gyrus, but showed less signal change between tasks than control children (Ment, Peterson, Vohr, et al., 2006).

Group differences in brain activity in frontal regulatory systems across various cognitive tasks could also be related to differences in resting state networks. The current study did not collect resting state data and thus cannot specifically address this question. However, several recent studies have reported widespread changes in resting state networks in individuals with a history of PT birth (e.g. Bäuml et al., 2014; White et al., 2014) that are even observable during infancy (Smyser et al., 2014). Although these studies have again mostly focused on higher-risk PT populations (very PT and/or VLBW), emerging evidence suggests alterations to the brain's resting and attentional networks are present even in children born in the moderate-to-late PT range (Degnan et al., 2015). Future studies should more carefully characterize the involvement of prefrontal hubs in resting and attention networks in individuals born moderate-to-late PT, in order to better characterize the relationship between altered brain structure, connectivity, and function within this population.

The exact biological mechanism by which moderate-to-late PT birth exerts an impact on prefrontal-dependent behavior, structure, and function remains unclear. Instead, multiple pathways likely exist through which PT birth may impact long-term frontal cortex development. One potential explanation is that the frontal lobe, in and of itself, exhibits enhanced vulnerability to early environmental perturbations. This may occur both as a function of the rapid changes in gray matter volume (Hüppi et al., 1998;

Nishida et al., 2006) and white matter volume and connectivity (Collin & van den Heuvel, 2013; Hermoye et al., 2006; Huang et al., 2006; Takahashi et al., 2012) that occur during the neonatal period, or as a result of its ultimately prolonged maturational time course (e.g. see discussion in Réveillon & Urben, 2013). Alternatively, given that PT birth is known to result in changes in basal ganglia microstructural and volumetric development (e.g. Bjuland, Rimol, Løhaugen, & Skranes, 2014; Grunewaldt et al., 2014; Lax et al., 2013; Nosarti et al., 2008, 2014), it is possible that PT birth may exert its eventual effects on frontal lobe development through early alterations to striatal circuits that cascade forward into frontostriatal abnormalities with increasing age.

Given the known vulnerability of glial precursor cells to PT birth (Volpe, 2009), it is also possible that alterations in prefrontal cortex grey matter volume and function may also reflect secondary or combined effects of early white matter injuries. For example, frank white matter injuries in higher risk PTs (periventricular leukomalacia; PVL) are associated with reduced frontal and parietal functional brain activation during paired-associate learning (Kalpakidou et al., 2012). Therefore, it is also likely that more subtle alterations to white matter which have been shown to occur in the moderate-to-late PT infants' brain (Kelly et al., 2016) could also be responsible for altered prefrontal cortex development at adolescence. Future studies will be needed to more carefully delineate the development of white matter and subcortical gray matter structures in low-risk PT individuals and their potential role in later frontal lobe development.

Finally, for individuals born moderate-to-late PT, the last 4-8 weeks of brain development unfolds in the ex-utero world, which differs dramatically from the

biologically expected in-utero environment in visual, auditory, and tactile stimulation. An extensive animal literature exists documenting the effects of seemingly subtle (e.g. increased tactile stimulation) variations in the early postnatal environment and their impact on long-term prefrontal cortex structure and function (see review in Kolb et al., 2012). Neurodevelopment in the ex-utero environment for PT children may therefore result in the formation of different functional brain circuitry due to changes in both experience-expectant and experience-dependent developmental processes (Greenough, Black, & Wallace, 1987).

In conclusion, we provide evidence that moderate-to-late PT birth is associated with differences in frontal cortex structure and function that persist into the adolescent age range. Future studies of low-risk PT individuals followed into adulthood will be critical to determine whether the differences detected reflect a delay in typical development or a functionally different pattern. Recent epidemiological data suggest that adults born late PT demonstrate socioeconomic disadvantages across the lifespan, even after controlling for parental socioeconomic status (Heinonen et al., 2013). Given high rates of birth in the moderate-to-late PT range in industrialized countries and increasing rates of survival in lower-income countries, it is thus critical from a public health perspective to better understand the mechanisms through which moderate-to-late PT birth conveys long-term impacts on neurobehavioral functioning. Furthermore, given evidence that moderate-to-late PT birth alters the structural and functional development of prefrontal cortex, a better understanding of the sequelae of lower-risk prematurity informs our global understanding of how the brain is both influenced by and recovers

from diverse forms of early risk.

CHAPTER 5: Study 3

*Non-linear Impacts of Early Adversity on White Matter Organization at Adolescence*⁴

Outline

The current diffusion tensor imaging study examined the long-term correlates of early life stress in a large sample of adolescent children ($N = 73$) who were internationally adopted from institutional care during early childhood, relative to an age- and sex-matched comparison group raised within biological families in the United States. A history of institutionalization was associated with long-term decreases in total cortical white matter volume, as well as broad reductions in white matter microstructural integrity across the brain, including in fronto-limbic and fronto-striatal circuits. Results suggested that differences in white matter integrity may be related to altered myelination following early life stress. Unexpectedly, children who were adopted prior to 12 months of age showed larger disruptions in white matter development than their later-adopted peers, despite evidence of better behavioral functioning (higher IQ). These non-linear effects of timing suggest that the functional implications of white matter organization are different within this population. Furthermore, long-term white matter plasticity may be dynamically altered by the timing of exposure to early life stress. Future studies characterizing the interaction between multiple biological processes impacted by early life stress (e.g.

⁴ Ruskin H. Hunt, Kelly J. McKenzie, Megan R. Gunnar, and Kathleen M. Thomas are listed as co-authors on this publication

growth, pubertal timing, immunological functioning) and their relation to neurobehavioral development are warranted.

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Non-linear Impacts of Early Adversity on White Matter Organization at Adolescence

The sensitivity of the developing brain to the early environment has been elegantly demonstrated through animal models (Greenough, Black, & Wallace, 1987; Knudsen, 2004) and studies of human development. Early and extended sensitivity of the brain conveys the maximum potential for the individual to benefit from positive experiences and for biological processes to become efficiently tuned to the current environment. However, sensitivity can instead become a risk factor for altered trajectories of neurobehavioral development if the environment is non-optimal. The human prefrontal cortex is among a network of brain regions that are highly sensitive to the early rearing environment. Diverse experiences that alter the developmental trajectory of prefrontal cortex structure, function, and/or dependent behaviors include childhood poverty (see Hackman, Gallop, Evans, & Farah, 2015 for review), exposure to maltreatment (see Bick & Nelson, 2016 for review), and even normative variations within the infant-parent caregiver relationship (Whittle et al., 2014).

Unfortunately, many children who experience adversity during early childhood continue to be exposed to adverse environments later in development. In contrast, post-institutionalized (PI) or orphanage-reared children experience a temporally discrete period of early deprivation (i.e. the institutional care environment) followed by the enriched environment of the adoptive family (i.e. most typically middle-to-high socioeconomic status and high parental education). Institutional care is still a primary method of non-parental care for children in many European and Asian countries, in comparison to alternatives such as foster care or guardian care (UNICEF, 2012; see

Berens & Nelson, 2015 for a recent discussion). Multiple studies have documented that children who live for some or all of their lives in institutional care show discrepant cognitive development, including poorer executive function skills, (see Merz, Harlé, Noble, & McCall, 2016 for review), and higher rates of attention (Stevens et al., 2008) and emotional problems (Wiik et al., 2011), presumably due to long-term alterations in fronto-limbic and front-striatal circuitry. Fortunately, many of the negative effects of institutionalization are at least partially ameliorated in the years following adoption or transfer to foster-care (e.g. Van IJzendoorn, Bakermans-Kranenburg, & Juffer, 2007).

The timing of early institutional care is widely presumed to be important for children's long-term outcomes. For example, earlier entry into institutional care and/or longer duration of care is associated with poorer growth recovery, poorer cognitive development, and higher rates of problem behaviors (Beckett et al., 2006; Johnson et al., 2010; O'Connor, Rutter, Beckett, Keaveney, & Kreppner, 2000; van IJzendoorn & Juffer, 2006). However, considerable variability exists across studies regarding the threshold at which timing matters (e.g. adoption prior to 6 months vs. adoption prior to 24 months). There is also significant heterogeneity in how children respond to and recover from severe deprivation. For example, in their sample of 6-year-old children previously adopted from Romanian orphanages, Rutter et al. reported that most children adopted prior to 6-months of age achieved normal functioning across multiple outcome domains; however, a full 25% of those adopted after 24 months of age were also functioning normally (Rutter, Kreppner, O'Connor, & ERA Study Team, 2001).

Measures of individual differences in structural and functional brain development,

including alterations in the brain's white matter organization, may scale more reliably with the timing of early adverse experiences than behavioral measures. Animal models of visual system development have clearly demonstrated that sensitive periods exist early in life, during which the long-term functioning of circuits is shaped by the environment (Hensch, 2005). Although defining sensitive periods for cognitive and socioemotional processes is inherently more difficult, deprivation of social stimuli during an early sensitive period in rodents is linked to disruptions in oligodendrocyte complexity and signaling, resulting in long-term changes in prefrontal cortex myelination and function (Makinodan, Rosen, Ito, & Corfas, 2012). Unlike the rapid prenatal development of gray matter, accrual of myelinated white matter does not begin until the second trimester of human gestation (Davison & Dobbing, 1966) and changes most rapidly during the first years of life, suggesting an early sensitive period (Dean et al., 2014). Normative studies have documented the effects of subtle variations in children's environments (e.g. musical training, mathematics training) on long-term measures of white matter organization (Jolles et al., 2016; Steele, Bailey, Zatorre, & Penhune, 2013). Furthermore, individual differences in white matter integrity have been related to children's cognitive development (Nagy, Westerberg, & Klingberg, 2004), including during the early childhood years (Dean et al., 2014; Deoni et al., 2016). Myelination across frontal regions extends well into adolescence and adulthood (Asato, Terwilliger, Woo, & Luna, 2010; Miller et al., 2012), indicating that individual differences in white matter development, especially in frontal circuits, may be a sensitive measure of how the brain responds to and recovers from early adversity across development.

Diffusion tensor imaging (DTI) allows for estimation of the developing brain's white matter architecture *in vivo*. Fractional anisotropy (FA) represents the most commonly used, yet indirect, measure of white matter structural integrity (Beaulieu, 2002). FA reflects combined effects of myelination, fiber number, extent of axonal crossing, axon diameter, loss of axons, gliosis, and/or nascent axon sprouting (Alexander, Lee, Lazar, & Field, 2007; Beaulieu, 2002).

Decomposing FA into axial diffusivity (AD) and radial diffusivity (RD) is of interest given that these metrics may reflect more specific aspects of white matter organization. AD indexes diffusion of water parallel to large fiber bundles and is associated with axonal degeneration, while RD measures diffusion of water perpendicular to large fibers and may be more indicative of alterations in myelination (Alexander et al., 2008; Kumar, Nguyen, Macey, Woo, & Harper, 2012).

Disruptions in white matter volume and microstructural integrity have already been reported across multiple studies in children and adolescents with a history of institutional care. In addition to reductions in total white matter volume (Sheridan, Fox, Zeanah, McLaughlin, & Nelson, 2012), PI children show atypical white matter organization across multiple brain systems, including, but not limited to, fronto-limbic circuitry (Eluvathingal et al., 2006; Govindan, Behen, Helder, Makki, & Chugani, 2010; Hanson et al., 2013) and fronto-striatal circuitry (Behen et al., 2009; Kumar et al., 2014). However, the effects of timing and duration of early deprivation on white matter organization remain unclear. For example, although work from the Bucharest Early Intervention Project (BEIP) has convincingly demonstrated that random assignment of

institutionalized children into foster care during early childhood is associated with normalization of white matter development (Bick, Zhu, et al., 2015; Sheridan et al., 2012), individual differences in timing of entry into foster care were not predictive of white matter integrity (Bick, Zhu, et al., 2015). Similarly, although poorer white matter integrity in tracts such as the uncinate fasciculus, a major projection linking frontal and limbic areas, have been reported to linearly scale with duration of institutional care (Govindan et al., 2010; Kumar et al., 2014), similar dose-response relationships have not been detected in other samples of PI children (Hanson et al., 2013; Mehta et al., 2009). Differences across studies may relate to variations in sample size and statistical power, country of origin differences, the age at which children were imaged, DTI parameters (e.g. number of diffusion directions collected, image resolution), and analysis techniques (e.g. quality control for motion, inclusion of demographic covariates like age and sex in models, use of pediatric brain templates, etc).

The nature of broad white matter microstructure changes in PI youth also remains unclear. To date, most studies of PI children have reported only FA or mean diffusivity (MD) metrics; the complementary characterization of RD and AD is needed to infer whether changes are likely driven by differences in myelination or are related to differences in white matter volume and axonal organization. Rodent models of early life stress have documented that poorer white matter organization is driven by alterations in myelination (Makinodan et al., 2012), and primate studies using DTI have confirmed that following early life stress, increases in RD are observed in the absence of AD differences, a pattern consistent with poorer myelination (Howell et al., 2013). Recent work from the

BEIP (Bick, Zhu, et al., 2015) has suggested that FA changes associated with institutionalization are related to a variety of alterations in white matter integrity, but by design this work is representative only of children adopted from particular orphanage environments (Romanian adoptees).

In the current study, we aimed to characterize long-term associations between early institutional rearing and multiple aspects of white matter integrity or organization in a large sample ($N = 73$) of PI children tested at early adolescence. Our diverse sample of PI children was selected to be more representative of formerly institutionalized children who are adopted into the United States and was carefully screened for in-scanner motion, in order to reduce the possibility of spurious DTI findings (Yendiki, Koldewyn, Kakunoori, Kanwisher, & Fischl, 2014). We hypothesized that PI children would show decreases in FA, primarily driven by higher RD, especially in fronto-striatal and fronto-limbic circuits: a pattern consistent with animal models of early life stress (Howell et al., 2013). Second, our sample size enabled us to examine whether the magnitude of disruption in white matter development was related to duration of early institutional care. Previous studies of frontal lobe gray matter development in PI children and adolescents have failed to detect an association between duration of institutional care and prefrontal cortex development (Hodel et al., 2015; McLaughlin et al., 2014). However, PI children randomly assigned into foster care prior to age 3 show partial normalization of cortical white matter volume (Sheridan et al., 2012) and white matter organization in frontal tracts (Bick, Zhu, et al., 2015). Therefore, we hypothesized that earlier-adopted children

would show more typical patterns of white matter microstructural development than their later-adopted peers.

Methods

Participants

Seventy-three post-institutionalized children (PI group: 57 females, 16 males, $M_{age} = 13.27$ years, $SD = .59$, range = 12.12 - 14.22 years) and a comparison group of 32 children raised with their biological families in Minnesota (control group: 22 females, 10 males, $M_{age} = 12.91$ years, $SD = .47$, range = 12.04 - 13.92 years) completed a 12-direction DTI scan. A partially overlapping sample of PI children completed a higher-quality, 56-direction DTI scan, see Appendix.

PI children were recruited through a registry of families with internationally adopted children maintained by the International Adoption Project (IAP) at the University of Minnesota. PI children were required to have been adopted before 72 months of age and to have spent at least 50% of their pre-adoptive care in an institutional setting, with a total of 4 - 60 months spent in an institution prior to adoption. PI children were pre-screened to exclude known neurological disorders (e.g. epilepsy), known chromosomal or genetic conditions (e.g. Down's Syndrome), past or current serious medical illness (e.g. cancer), developmental disorders (e.g. Autism Spectrum Disorders), known or suspected Fetal Alcohol Spectrum disorder, previous IQ score below 80, or contraindications for MRI (including braces, permanent retainer, history of moderate or severe claustrophobia, or implanted metal).

Psychological and/or psychiatric disorder was not an exclusionary criterion for PI

children. Sixteen (22%) of the PI children included in the final sample met criteria on the Kiddie-Sads-Present and Lifetime Version (K-SADS-PL; Kaufman et al., 1997) for an axis I disorder based on caregiver interviews with a trained clinician. Attention Deficit Hyperactivity Disorder ($N = 10$), Anxiety disorders ($N = 4$), and Mood disorders ($N = 3$) were the most common forms of psychopathology. PI children in the final sample were adopted primarily from China (38.4%), Russia (28.8%), and India (12.3%), and had been living with their adoptive families for an average of 11.80 years ($SD = 1.38$, range = 6.78 - 13.50 years). Impacts of timing of early adversity were assessed using duration of institutional care as a measure of the dosage of children's early deprivation experiences. As such, the larger sample of PI children was also subdivided into earlier-adopted (PI-EA group: $N = 36$, 32 females) and later-adopted (PI-LA group: $N = 37$, 25 females) subgroups based on a median split of age at adoption (12 months of age). Earlier- and later-adopted PI children differed in IQ score (see Table 5.2) but not in rate of axis I disorders ($p < .285$).

Families of comparison (non-adopted) children were recruited from a community volunteer participant pool maintained by the Institute of Child Development. Comparison children met the same screening criteria as the PI sample, but were also pre-screened for history of birth complications (including known prenatal drug exposure, premature birth, or birth complications resulting in neonatal intensive care unit admission for > 24 hours), and for personal history of diagnosed psychiatric and/or psychological disorders, including learning disabilities. One control child met criteria on the K-SADS-PL for Oppositional Defiant Disorder but did not have a pre-existing diagnosis. The non-

adopted and PI groups did not differ in demographic characteristics including family income and parental education (see Tables 5.1, 5.2, and Appendix for details about the sample and children's adoption histories).

Excluded participants. Additional PI and comparison children were tested who did not provide useable data. Data from 78 PI children and 28 comparison children were excluded from the final sample for the following reasons: significant health issues not detected in pre-screening (1 PI), failure to meet study requirements for duration of institutional care not detected on pre-screening (3 PI), structural MRI scan anomaly (3 control, 7 PI), neuroimaging data collection errors (11 PI, 1 control), excess motion in MPRAGE scan (2 PI), and excess motion in DTI data (54 PI, 24 control). PI and non-adopted control children were equally likely to be excluded ($p < .513$). Children who were younger ($p < .006$), male ($p < .007$), or diagnosed with an axis I disorder ($p < .070$) were more likely to be excluded. Thirty percent of the PI children who were excluded met criteria for an axis I disorder on the K-SADS-PL. After controlling for group membership (PI vs. control), IQ scores did not differ between excluded and included children ($p < .823$). Within the PI group, age at adoption also did not differ between excluded and included children ($p < .318$).

Procedure

Participants were part of a larger study examining learning, attention, executive function, and brain development in internationally adopted youth using behavioral, neuroimaging, and genetic measures. Primary caregiver(s) provided verbal and written consent, children provided verbal and written assent, and both caregivers and children

were compensated for their time and effort. Study procedures were approved by the Institutional Review Board at the University of Minnesota. DTI scanning took place on the second day of a two-day session. Children watched a movie of their choice during the DTI scan.

Structural MRI and DTI acquisition. Magnetic resonance imaging was performed on a Siemens 3T Trio MRI scanner. A sagittal scout series was first used to verify participant position. A T1-weighted, three-dimensional (3-D) magnetization prepared rapid gradient echo (MPRAGE) series was used to acquire 240 contiguous slices of 1 mm thickness in the sagittal plane (TR = 2530 ms, TE = 3.65 ms, FOV = 256 mm, flip angle = 7°). All participants completed a 12-direction DTI sequence (TR = 8500 ms, TE = 90 ms, FOV = 256 mm, 2 mm slice thickness) covering 64 slices with a b-value of 1000. Additionally, a subset of participants also completed a higher quality, 56-direction DTI sequence (TR = 8600 ms, TE = 90 ms, FOV = 256 mm, 2 mm slice thickness), also covering 64 slices with a b-value of 1000, see Appendix. Field maps were collected immediately prior to each DTI sequence in order to correct for distortion caused by magnetic field inhomogeneity.

Pubertal status. Pubertal status was measured using the Petersen Pubertal Developmental Scale, a self-report questionnaire measure (PDS; Petersen, Crockett, Richards, & Boxer, 1988). PDS scores differed as a function of institutional care, see Tables 1 and 2. PDS scores were not available for 4 PI children and 4 controls.

IQ. IQ data were collected using the Weschler Abbreviated Scales of Intelligence (WASI; Weschler, 1999). IQ differed as a function of institutional care, but was in the

normal or above-average range for all groups, see Tables 5.1 and 5.2. IQ scores were not available for 6 PI children and 1 control.

Table 5.1

Demographic Characteristics

	PI Adolescents N = 73	Non-Adopted Controls N = 32
<i>Sample Characteristics</i>		
Age in years, <i>M</i> (<i>SD</i>); range	13.27 (.59) 12.12-14.22	12.91 (.47)* 12.04-13.92
Male, <i>n</i> (%)	16 (21.9)	10 (31.3)
Two Parent Household, <i>n</i> (%)	50 (68.4)	30 (93.8)*
IQ score, <i>M</i> (<i>SD</i>); range	104.69 (13.52) 77-139	116.45 (7.04)* 99-130
Pubertal score, <i>M</i> (<i>SD</i>); range	2.62 (.83) 1-4	2.28 (.69)* 1-3.2
<i>Primary Caregiver Education</i>		
High school degree or GED, <i>n</i> (%)	2 (2.7)	0 (0)
Some college, <i>n</i> (%)	5 (6.8)	3 (9.4)
Associate degree, <i>n</i> (%)	7 (9.6)	1 (3.1)
Bachelor's degree, <i>n</i> (%)	32 (43.8)	16 (50.0)
Master's degree, <i>n</i> (%)	23 (31.5)	10 (31.3)
Doctoral or professional degree, <i>n</i> (%)	4 (5.4)	2 (6.3)
<i>Annual Household Income^a</i>		
Income, <i>M</i> (<i>SD</i>); range	\$107,242 (\$88,439); \$32,000-\$500,000	\$116,115 (\$47,251); \$20,000-\$200,000

$\leq \$50,000$, n (%)	6 (9.2)	3 (10.3)
\$51,000 - \$100,000, n (%)	42 (64.6)	10 (34.5)
\$101,000 - \$150,000, n (%)	11 (16.9)	10 (34.5)
$\geq \$151,000$, n (%)	7 (10.8)	6 (20.7)

Notes. ^aNot all families provided full demographic data; percentages thus reflect the percent of total responses. * $p < .050$.

Table 5.2

Adoption History of Post-Institutionalized Youth

	PI – Earlier Adopted <i>N</i> = 36	PI – Later Adopted <i>N</i> = 37
<i>Sample Characteristics</i>		
Age in years, <i>M</i> (<i>SD</i>)	13.33 (.59)	13.22 (.59)
Male, <i>n</i> (%)	4 (11.1)	12 (32.4)*
IQ score, <i>M</i> (<i>SD</i>); range	108.62 (12.74) 78-139	100.64 (13.28)* 77-128
Pubertal score, <i>M</i> (<i>SD</i>); range	2.99 (.69) 1.20-4.00	2.22 (.85)* 1.00-3.80
<i>Adoption History</i>		
Age at adoption in months, <i>M</i> (<i>SD</i>); range	8.64 (2.10) 4-12	26.43 (15.77) 13-72
Institutional care in months, <i>M</i> (<i>SD</i>); range	8.07 (2.08) 3.5-12	23.22 (12.57) 12-60
Percent of care in institution, <i>M</i> (<i>SD</i>); range	93.88 (11.02) 56-100	91.18 (14.18) 53-100
Time since adoption in years, <i>M</i> (<i>SD</i>); range	12.61 (.67) 11.13-13.50	11.01 (1.44) 6.78-12.95
<i>Country of Origin</i>		
Bulgaria, <i>n</i> (%)	0 (0)	1 (2.7)
China, <i>n</i> (%)	19 (52.8)	9 (24.3)
Guatemala, <i>n</i> (%)	1 (2.8)	1 (2.7)
India, <i>n</i> (%)	6 (16.7)	3 (8.1)

Philippines, <i>n</i> (%)	0 (0)	1 (2.7)
Romania, <i>n</i> (%)	0 (0)	4 (10.8)
Russia, <i>n</i> (%)	8 (22.2)	13 (35.1)
Ukraine, <i>n</i> (%)	0 (0)	3 (8.1)
Vietnam, <i>n</i> (%)	2 (5.6)	2 (5.4)

Notes. * $p < .050$ for tested sample characteristics. Adoption-related variables were not tested between the two groups as they differed by design.

MRI and DTI Processing

Structural MRI data. Cortical reconstruction and volumetric segmentation were performed with the Freesurfer image analysis suite version 5.3.0 which is documented and freely available for download online (<http://surfer.nmr.mgh.harvard.edu/>). The technical details of these procedures are described in prior publications (Dale, Fischl, & Sereno, 1999; Fischl & Dale, 2000; Fischl, 2004; Fischl et al., 2002, 2004; Fischl, Liu, & Dale, 2001; Fischl, Sereno, Tootell, & Dale, 1999; Han et al., 2006; Jovicich et al., 2006; Reuter & Fischl, 2011; Reuter, Rosas, & Fischl, 2010; Ségonne et al., 2004). Freesurfer morphometric procedures generate comparable volumes to hand tracing (Morey et al., 2009), and are valid for use in pediatric populations (Ghosh et al., 2010). We have previously reported on group differences in cortical and subcortical gray matter volumes within a set of participants that partially overlaps with those in the current report (Hodel et al., 2015). Analyses for the current paper focus on a different Freesurfer outcome metric: total cortical white matter volume.

DTI data. DTI preprocessing was conducted using standard FSL pipelines (FMRIB Software Library, <http://fsl.fmrib.ox.ac.uk/fsl>). Initial preprocessing steps include skull stripping of the brain using BET (Brain Extraction Tool) along with manual edits for each participant, eddy current correction, unwarping of the geometric distortion using the collected field map, and fitting the tensor model (DTIFIT) to obtain voxel-wise estimates of scalar metrics including fractional anisotropy (FA), radial diffusivity (RD), axial diffusivity (AD), and mean diffusivity (MD).

Unlike functional MRI, which has established methods for quantifying participant motion and best-practices for assuring adequate data quality, there is less consensus regarding appropriate practices to control for motion in DTI data, despite evidence that group differences in head motion produce spurious results (Yendiki et al., 2014). To determine whether to exclude participants for excess motion, we used the output matrices resulting from FSL’s eddy current correction procedure. These matrices contain rotation and translation information for each DTI series volume in relation to volume 0 at the individual participant level. Similar to fMRI, we converted these metrics into a summary root-mean-squared-deviance in mm per volume to examine absolute (from volume 0) and relative (from volume t-1) head motion for each participant, separately for the B0 and gradient images. We originally intended to include participants who had <2 mm of absolute motion (in both B0 and gradient image series) and <1 mm of relative motion (in both B0 and gradient image series). However, because our sample is restricted to young adolescents, these relatively stringent criteria resulted in the exclusion of an excess number of subjects. As such, we relaxed the relative maximum motion criteria for gradient images to <1.5 mm to maximize the number of participants included in analyses who had reasonably low-motion data.

We used two complementary methods to analyze white matter microstructural differences following early life adversity: tract-based spatial statistics (TBSS) and tracts of interest (TOI) analyses. Using the two approaches together is beneficial as they may help to characterize different alterations in white matter microstructure. TBSS is a whole-brain analysis that quantifies white matter metrics of interest at the voxel level

along a computed white matter skeleton. Restriction of analyses to the internal white matter skeleton reduces partial volume effects, allows for correction for multiple comparisons across voxels, and is very sensitive to local white matter changes. In TOI analyses, average white matter metrics are computed for atlas-defined regions of interest. These metrics represent a summary measure of white matter integrity within a larger area and may be more sensitive to diffuse white matter alterations.

TBSS analyses. Voxel-wise statistical analyses of the FA, RD, AD, and MD data were carried out using the TBSS (Tract-Based Spatial Statistics) module of FSL with two important modifications. First, in FSL’s default TBSS pipeline, FA images are eroded to remove the ring of high intensity voxels (“halo”) that typically surround the brain due to eddy current induced distortions. In our data set, this default erosion process (tbss_1_prepoc) resulted in the removal of white matter in interior regions of the brain, particularly in parts of the temporal poles and the midbrain, due to the presence of isolated voxels with no data. We instead filled isolated empty interior voxels in the FA images with a small nominal value (0.001) to prevent erosion around them. We then performed erosion using a 3 x 3 x 3 mm kernel (similar to Schwarz et al., 2014), which effectively removed “halo” voxels while retaining interior white matter.

Second, given our pediatric population and studies demonstrating that PI children show different brain morphology than typically developing children, we developed a study-specific template using a group-wise registration method as described in previous studies (Keihaninejad et al., 2012; Schwarz et al., 2014). The template was initiated by randomly selecting a single participant’s eroded FA image for use as a registration target.

Each participant's eroded FA image was then registered to this target using a rigid linear transformation. On completion, the newly registered data sets were averaged to produce an updated registration target. This process was iteratively repeated four more times using full-affine linear registration, followed by an additional ten iterations of non-linear registration using FSL's FNIRT. The final average template was then non-linearly registered to the JHU-ICBM-FA-1mm FA atlas and thresholded at .05 to remove non-zero values outside the skull.

As in standard analyses using the TBSS pipeline, each participant's eroded FA image was then aligned to the study-specific template and into common space (MNI-152) using FNIRT. A mean FA image was created and then thinned to form a mean FA skeleton representing the centers of all tracts common to the group of participants. Each participant's aligned FA data set was then projected onto this group-derived skeleton (thresholded at .2) and the resulting data were fed into voxel-wise cross-subject statistics. For RD, AD, and MD analyses, the FA images were used for nonlinear registration, skeleton creation, and generation of the projection vectors from each participant onto the mean skeleton. FA skeletonized data were then subjected to voxel-wise statistics to visually represent group differences. Spatial correction for multiple comparisons was conducted using the TFCE (Threshold-Free Cluster Enhancement) option in randomise with 5000 permutations. Significant clusters meeting a corrected p-value of $p < .050$ were extracted and labeled.

Tracts of interest (TOI) analyses. Tract-based region of interest analyses for the scalar white matter metrics were generated using the Johns Hopkins University white

matter tractography atlas (JHU-ICBM-tracts-maxprob-thr25-1mm). Mean FA, RD, AD, and MD were separately calculated across all non-zero voxels within each of the tracts defined by the white matter atlas. These values were extracted at the individual participant level for statistical analyses. Although we expected that effects of institutionalization would most likely be detected in fronto-striatal and fronto-limbic circuits, we included other available tracts for comparison. The selected atlas includes the forceps major and minor, along with 10 major white matter tracts separated by hemisphere: anterior thalamic radiations, corticospinal tract (CST), cingulum (superior portion along cingulate gyrus), cingulum (inferior portion along ventral hippocampus), inferior fronto-occipital fasciculus (IFOF), inferior longitudinal fasciculus (ILF), superior longitudinal fasciculus (SLF), superior longitudinal fasisculus (temporal portion only), and uncinate fasciculus (UF).

Statistical Analyses

All analyses include age at test and sex as covariates of non-interest, due to known relations with gray and white matter organization (Asato et al., 2010; Giedd et al., 1996; Sowell, Thompson, Tessner, & Toga, 2001). As in our previous paper (Hodel et al., 2015), we also report total white matter volume differences with and without correction for intracranial volume (ICV).

Group difference analyses. We first fit one-way ANCOVAs within tracts of interest comparing PI vs. control children. This two-group comparison was undertaken to parallel previous DTI studies in this population. Group effects at $p < .050$ were considered significant. We elected not to control for multiple comparisons across white

matter metrics and tracts as many statistical tests were intended to be complementary (e.g. comparison of effects within the 12-direction and 56-direction data sets) and because our aim was to characterize group differences in white matter organization, rather than argue for the specificity of differences within any particular tract.

Age at adoption group analyses. To investigate effects of timing of early adversity, we refit ANOVAs within the tracts comparing PI-EA vs. PI-LA vs. control children. Categorical rather than continuous measures of duration of institutional care were used to allow comparison to non-adopted children who had no history of institutional care. Although no corrections for multiple comparisons were made across tracts or white matter metrics, planned comparisons between groups were set to a corrected p-value of $p < .020$, representing the three potential pairwise group comparisons (comparison vs. PI-EA vs. PI-LA).

Age at adoption correlational analyses. To assess potential linear effects of duration of institutional care, the PI group was truncated to include only children who were ≤ 24 months of age at time of adoption. This retained approximately 80% of the PI sample via elimination of the 13 children who may have represented extreme cases of deprivation. Truncation also substantially reduced the skew (.646, $se = .309$) and kurtosis (-.416, $se = .608$) of the age at adoption variable into an acceptable range. To reduce the number of statistical tests, we restricted exploratory correlational analyses to tracts that differed between PI and control children in FA.

Supplemental analyses. The results of TOI analyses controlling for individual differences in total white matter volume are presented in the Appendix, along with ethnic

sub-group analyses. Group comparisons (PI vs. control) using the higher-quality, but smaller sample size, 56-direction data set were largely consistent with the 12-direction data set (especially for FA) and are presented in the Appendix.

Results

White Matter Volume

PI children had smaller total left, $F(2, 100) = 7.678, p < .001, \eta_{\text{partial}}^2 = .133$, and right white matter volume, $F(2, 100) = 6.936, p < .002, \eta_{\text{partial}}^2 = .122$, than non-adopted comparison children. Both the PI-EA and PI-LA groups (p 's $< .001$) showed significant reductions in comparison to controls, but no difference was observed between the PI groups (p 's $> .811$). Group differences remained significant after controlling for individual differences in total intracranial volume, although the pair-wise differences between PI-EA and control children were reduced to trend-level, see Figure 1.

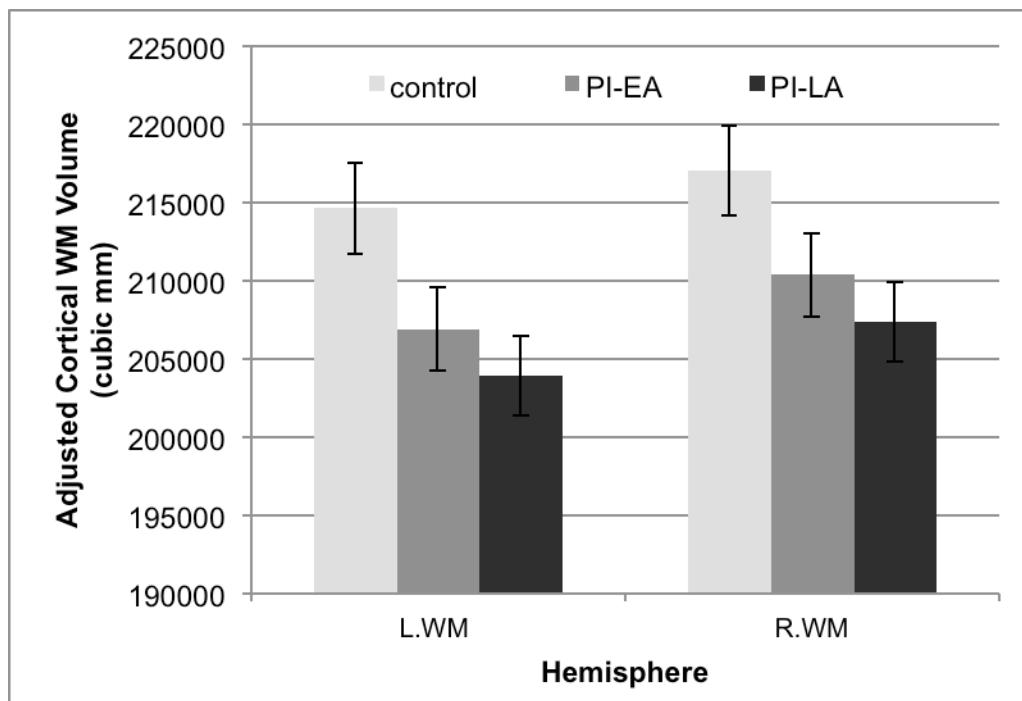


Figure 5.1. Group differences in cortical white matter volume, adjusted for age, sex, and total intracranial volume. PI children had smaller adjusted cortical white matter volume than non-adopted controls. Differences between controls and PI-EA children were only of trend-level significance.

Group Differences in TBSS

PI children showed reductions in FA, coupled with increases in RD, across several major white matter pathways, including the bilateral anterior thalamic radiations, CST, IFOF, ILF, SLF, cingulum (cingulate portion) and UF, as well as the forceps minor, and right cingulum (hippocampal portion), see Figure 5.2. Increases in RD for PI children were also detected in the forceps major that were not accompanied by FA changes. There were no regions in which PI children showed greater FA than controls (or reduced RD).

Group differences in AD (PI > control) were more restricted in spatial extent, predominantly affecting regions of the corpus callosum (forceps major and minor), right IFOF, and bilateral anterior thalamic radiations, see Figure 5.3. Increases in MD for PI children were detected in a set of regions overlapping heavily with locations of FA and RD changes, including bilateral anterior thalamic radiations, CST, IFOF, ILF, SLF, and cingulum (cingulate portion), as well as the right UF and forceps major, see Figure 3. There were no regions in which PI children showed reduced MD versus controls (or lower AD). See Appendix for comparisons of earlier- and later-adopted PI children to controls.

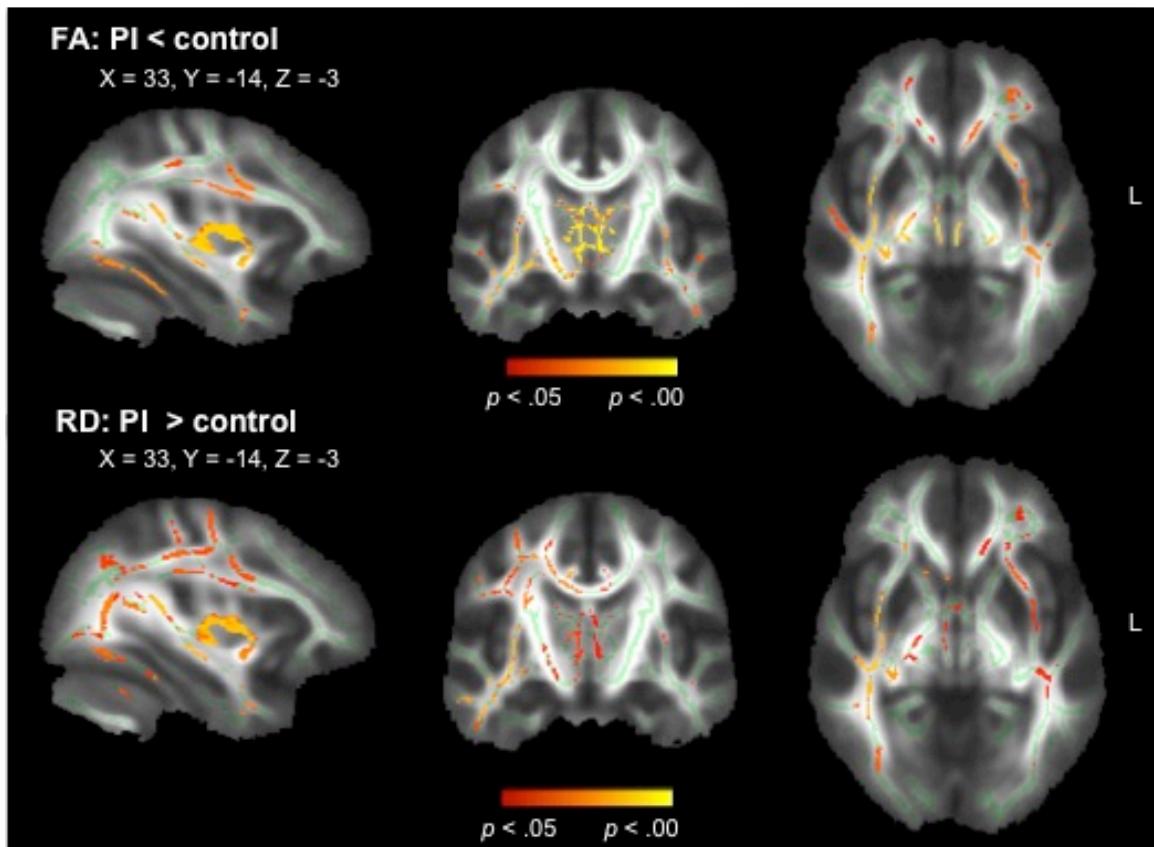


Figure 5.2. TBSS group differences in FA and RD. Voxel-wise white matter microstructure differences by group along the derived white matter skeleton (in green). Spatially corrected via multiple comparisons using TFCE at $p < .050$ and overlaid on the group mean FA image. In comparison to non-adopted controls, PI children showed broad reductions in FA accompanied by increases in RD.

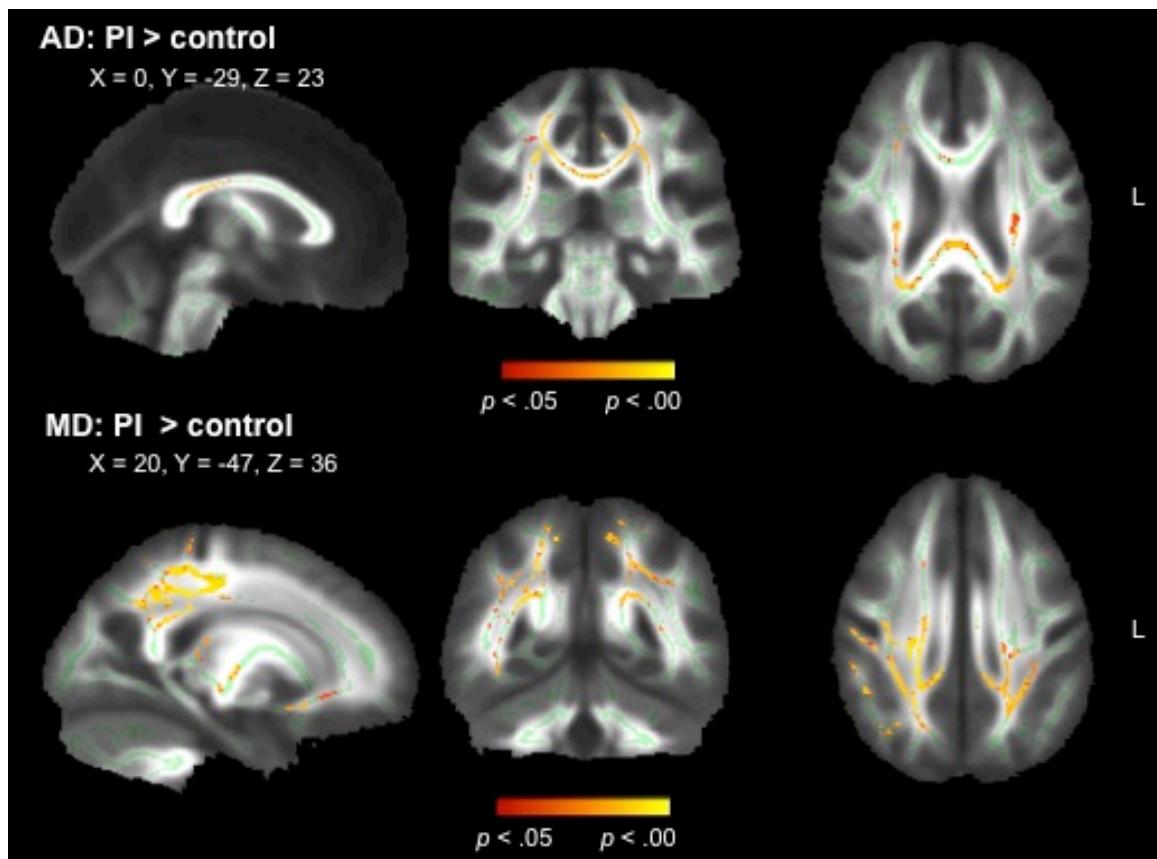


Figure 5.3. TBSS group differences in AD and MD. Voxel-wise white matter microstructure differences by group along the derived white matter skeleton (in green). Spatially corrected via multiple comparisons using TFCE at $p < .050$ and overlaid on the group mean FA image. In comparison to non-adopted controls, PI children showed increased AD primarily in the forceps and anterior thalamic radiations. MD changes were more extensive, especially in posterior pathways.

Group Differences in Scalar Metrics of White Matter Organization

See Inline Supplemental Table 5.1 for details of these analyses.

Fractional anisotropy (FA). PI children had reduced FA in comparison to control children across several major white matter pathways, including the bilateral anterior thalamic radiations, bilateral cingulum (cingulate portion), right cingulum (hippocampal portion), bilateral IFOF, right ILF, and bilateral UF.

Radial diffusivity (RD). A history of institutionalization was also associated with a broad pattern of increased RD across many of the major white matter pathways that differed in FA. Group differences were present in the bilateral anterior thalamic radiations, bilateral cingulum (bilateral cingulate portion, right hippocampal portion), bilateral IFOF, right ILF, right SLF, and right UF.

Axial diffusivity (AD). There were few group differences in AD. PI children had increased AD in the right CST but lower AD in the bilateral cingulum (hippocampal portion).

Mean diffusivity (MD). A history of institutionalization was associated with increased MD across several tracts of interest in the right hemisphere, including the right CST, IFOF, ILF, SLF, and UF.

Inline Supplemental Table 5.1

Comparison of Age and Sex Adjusted White Matter Scalar Metrics In Controls and PI Children (12-Direction and 56-Direction DTI Data)

	12-Direction Data				56-Direction Data			
	F	p	η_{partial}^2	PI B (se)	F	p	η_{partial}^2	PI B (se)
L. Anterior Thalamic Radiations								
FA	4.524	.042*	.040	-.008 (.004)	2.356	.131	.047	-.008 (.005)
RD	4.042	.047*	.038	.104 x 10 ⁻⁴ (.519 x 10 ⁻⁵)	.933	.339	.019	.740 x 10 ⁻⁵ (.766 x 10 ⁻⁵)
AD	1.023	.314	.010	.471 x 10 ⁻⁵ (.466 x 10 ⁻⁵)	.040	.843	.001	-.149 x 10 ⁻⁵ (.747 x 10 ⁻⁵)
MD	3.675	.058	.035	.857 x 10 ⁻⁵ (.447 x 10 ⁻⁵)	.364	.549	.008	.421 x 10 ⁻⁵ (.698 x 10 ⁻⁵)
R. Anterior Thalamic Radiations								
FA	10.565	.002*	.095	-.011 (.003)	2.463	.123	.049	-.007 (.005)
RD	5.001	.028*	.047	.122 x 10 ⁻⁴ (.545 x 10 ⁻⁵)	.000	1.000	.000	-.387 x 10 ⁻⁶ (.726 x 10 ⁻⁵)
AD	.738	.392	.007	.465 x 10 ⁻⁵ (.541 x 10 ⁻⁵)	2.626	.112	.052	-.106 x 10 ⁻⁴ (.654 x 10 ⁻⁵)
MD	3.674	.058	.035	.965 x 10 ⁻⁵ (.503 x 10 ⁻⁵)	.354	.555	.007	-.390 x 10 ⁻⁵ (.656 x 10 ⁻⁵)
L. CST								
FA	.001	.979	.000	.000 (.005)	.295	.590	.006	.003 (.006)
RD	.345	.558	.003	.361 x 10 ⁻⁶ (.614 x 10 ⁻⁵)	.000	1.000	.000	.633 x 10 ⁻⁶ (.879 x 10 ⁻⁵)
AD	.871	.353	.009	.663 x 10 ⁻⁵ (.708 x 10 ⁻⁵)	1.298	.260	.026	.110 x 10 ⁻⁴ (.964 x 10 ⁻⁵)
MD	.738	.392	.007	.461 x 10 ⁻⁵ (.537 x 10 ⁻⁵)	.276	.602	.006	.397 x 10 ⁻⁵ (.757 x 10 ⁻⁵)
R. CST								
FA	.030	.863	.000	-.001 (.004)	1.502	.225	.030	.008 (.006)
RD	2.257	.136	.022	.817 x 10 ⁻⁵ (.544 x 10 ⁻⁵)	.284	.596	.006	-.421 x 10 ⁻⁵ (.791 x 10 ⁻⁵)
AD	5.974	.016*	.056	.145 x 10 ⁻⁴ (.588 x 10 ⁻⁵)	3.118	.084	.061	.135 x 10 ⁻⁴ (.765 x 10 ⁻⁵)

	MD	5.805	.018*	.054	$.103 \times 10^{-4} (.428 \times 10^{-5})$.075	.786	.002	$.172 \times 10^{-5} (.630 \times 10^{-5})$
L. Cingulum - Cingulate									
	FA	4.690	.033*	.044	-.013 (.006)	2.278	.138	.045	-.014 (.009)
	RD	4.291	.041*	.041	$.154 \times 10^{-4} (.742 \times 10^{-5})$.087	.769	.002	$.271 \times 10^{-5} (.917 \times 10^{-5})$
	AD	.018	.893	.000	$.121 \times 10^{-5} (.901 \times 10^{-5})$	3.911	.054	.075	$-.263 \times 10^{-4} (.133 \times 10^{-4})$
	MD	2.615	.109	.025	$.107 \times 10^{-4} (.661 \times 10^{-5})$.818	.370	.017	$-.688 \times 10^{-5} (.760 \times 10^{-5})$
R. Cingulum - Cingulate									
	FA	5.199	.025*	.049	-.018 (.008)	.684	.412	.014	-.010 (.012)
	RD	4.884	.029*	.046	$.155 \times 10^{-4} (.702 \times 10^{-5})$.415	.522	.009	$-.612 \times 10^{-5} (.949 \times 10^{-5})$
	AD	.552	.459	.005	$-.850 \times 10^{-5} (.144 \times 10^{-5})$	3.900	.054	.075	$-.301 \times 10^{-4} (.152 \times 10^{-4})$
	MD	1.359	.246	.013	$.752 \times 10^{-5} (.645 \times 10^{-5})$	3.537	.066	.069	$-.141 \times 10^{-4} (.750 \times 10^{-5})$
L. Cingulum - Hippocampus									
	FA	1.023	.314	.010	-.006 (.006)	2.510	.120	.050	-.014 (.009)
	RD	.225	.636	.002	$-.342 \times 10^{-5} (.719 \times 10^{-5})$.124	.727	.003	$.310 \times 10^{-5} (.882 \times 10^{-5})$
	AD	5.171	.025*	.049	$-.220 \times 10^{-4} (.969 \times 10^{-5})$	2.164	.148	.043	$-.211 \times 10^{-4} (.144 \times 10^{-4})$
	MD	2.091	.151	.020	$-.961 \times 10^{-5} (.665 \times 10^{-5})$.337	.564	.007	$-.520 \times 10^{-5} (.865 \times 10^{-5})$
R. Cingulum Hippocampus									
	FA	9.940	.002*	.090	-.021 (.007)	6.078	.017*	.112	-.023 (.009)
	RD	5.437	.022*	.051	$.166 \times 10^{-4} (.712 \times 10^{-5})$	1.071	.306	.022	$.103 \times 10^{-4} (.993 \times 10^{-5})$
	AD	4.603	.034*	.044	$-.168 \times 10^{-4} (.783 \times 10^{-4})$	8.551	.005*	.151	$-.309 \times 10^{-4} (.106 \times 10^{-4})$
	MD	.964	.329	.009	$.557 \times 10^{-5} (.564 \times 10^{-5})$.207	.651	.004	$-.340 \times 10^{-5} (.747 \times 10^{-5})$
L. IFOF									
	FA	12.020	.001*	.106	-.014 (.004)	8.193	.006*	.146	-.015 (.005)
	RD	7.012	.009*	.062	$.144 \times 10^{-4} (.543 \times 10^{-5})$	3.963	.052	.076	$.123 \times 10^{-4} (.628 \times 10^{-5})$
	AD	.539	.464	.005	$-.440 \times 10^{-5} (.599 \times 10^{-5})$	2.673	.109	.053	$-.123 \times 10^{-4} (.754 \times 10^{-5})$
	MD	2.758	.100	.027	$.805 \times 10^{-5} (.485 \times 10^{-5})$.635	.429	.013	$.432 \times 10^{-5} (.542 \times 10^{-5})$
R. IFOF									
	FA	4.595	.034*	.044	-.009 (.0054)	8.158	.006*	.145	-.014 (.005)

RD	5.958	.016*	.056	.123 x 10 ⁻⁴ (.502 x 10 ⁻⁵)	3.719	.060	.072	.120 x 10 ⁻⁴ (.620 x 10 ⁻⁵)
AD	.151	.699	.001	.228 x 10 ⁻⁵ (.589 x 10 ⁻⁵)	1.472	.231	.030	-.978 x 10 ⁻⁵ (.806 x 10 ⁻⁵)
MD	4.203	.043*	.040	.898 x 10 ⁻⁵ (.438 x 10 ⁻⁵)	.718	.401	.015	.476 x 10 ⁻⁵ (.562 x 10 ⁻⁵)
L. ILF								
FA	1.616	.207	.016	-.005 (.004)	.346	.559	.007	-.003 (.005)
RD	.407	.525	.004	.389 x 10 ⁻⁵ (.610 x 10 ⁻⁵)	.215	.645	.004	.333 x 10 ⁻⁵ (.719 x 10 ⁻⁵)
AD	.204	.653	.002	-.328 x 10 ⁻⁵ (.726 x 10 ⁻⁵)	.043	.838	.001	-.186 x 10 ⁻⁵ (.902 x 10 ⁻⁵)
MD	.080	.778	.001	.168 x 10 ⁻⁵ (.593 x 10 ⁻⁵)	.048	.827	.001	.153 x 10 ⁻⁵ (.698 x 10 ⁻⁵)
R. ILF								
FA	6.191	.014*	.058	-.010 (.004)	5.601	.022*	.104	-.013 (.005)
RD	9.870	.002*	.089	.176 x 10 ⁻⁴ (.562 x 10 ⁻⁵)	2.635	.111	.052	.107 x 10 ⁻⁴ (.662 x 10 ⁻⁵)
AD	1.316	.254	.013	.851 x 10 ⁻⁵ (.742 x 10 ⁻⁵)	1.096	.300	.022	-.102 x 10 ⁻⁴ (.970 x 10 ⁻⁵)
MD	7.529	.007*	.069	.146 x 10 ⁻⁴ (.532 x 10 ⁻⁵)	.321	.574	.007	.360 x 10 ⁻⁵ (.635 x 10 ⁻⁵)
L. SLF								
FA	.207	.620	.002	-.002 (.004)	.287	.595	.006	-.003 (.005)
RD	.000	1.000	.000	-.465 x 10 ⁻⁷ (.653 x 10 ⁻⁵)	1.053	.310	.021	-.831 x 10 ⁻⁵ (.810 x 10 ⁻⁵)
AD	.531	.468	.005	-.442 x 10 ⁻⁵ (.606 x 10 ⁻⁵)	3.548	.066	.069	-.141 x 10 ⁻⁴ (.750 x 10 ⁻⁵)
MD	.045	.832	.000	-.123 x 10 ⁻⁵ (.603 x 10 ⁻⁵)	1.884	.176	.038	-.103 x 10 ⁻⁴ (.749 x 10 ⁻⁵)
R. SLF								
FA	3.664	.058	.035	-.007 (.004)	1.562	.217	.032	-.006 (.005)
RD	6.532	.012*	.061	.130 x 10 ⁻⁴ (.510 x 10 ⁻⁵)	.000	1.000	.000	.487 x 10 ⁻⁶ (.615 x 10 ⁻⁵)
AD	2.867	.093	.028	.981 x 10 ⁻⁵ (.579 x 10 ⁻⁵)	1.822	.183	.037	-.880 x 10 ⁻⁵ (.652 x 10 ⁻⁵)
MD	6.575	.012*	.061	.120 x 10 ⁻⁴ (.469 x 10 ⁻⁵)	.241	.626	.005	-.262 x 10 ⁻⁵ (.533 x 10 ⁻⁵)
L. SLF temporal								
FA	.023	.881	.000	.001 (.009)	2.217	.143	.044	.015 (.010)
RD	.134	.716	.001	-.319 x 10 ⁻⁵ (.871 x 10 ⁻⁵)	2.552	.117	.050	-.135 x 10 ⁻⁴ (.846 x 10 ⁻⁵)
AD	.199	.656	.002	.428 x 10 ⁻⁵ (.959 x 10 ⁻⁵)	1.527	.223	.031	.178 x 10 ⁻⁴ (.144 x 10 ⁻⁴)
MD	.017	.895	.000	-.808 x 10 ⁻⁶ (.613 x 10 ⁻⁵)	.190	.664	.004	-.302 x 10 ⁻⁵ (.691 x 10 ⁻⁵)

R. SLF temporal								
FA	.081	.776	.001	.002 (.008)	.435	.513	.009	.006 (.010)
RD	.015	.902	.000	.895 x 10 ⁻⁶ (.725 x 10 ⁻⁵)	.175	.677	.004	-.389 x 10 ⁻⁵ (.928 x 10 ⁻⁵)
AD	.188	.666	.002	.484 x 10 ⁻⁵ (.112 x 10 ⁻⁴)	1.492	.229	.030	.137 x 10 ⁻⁴ (.112 x 10 ⁻⁴)
MD	.179	.673	.002	.231 x 10 ⁻⁵ (.545 x 10 ⁻⁵)	.097	.757	.002	.200 x 10 ⁻⁵ (.642 x 10 ⁻⁵)
L. UF								
FA	4.237	.042*	.040	-.008 (.004)	3.155	.082	.062	-.009 (.005)
RD	2.774	.099	.027	.992 x 10 ⁻⁵ (.596 x 10 ⁻⁵)	1.948	.169	.039	.922 x 10 ⁻⁵ (.661 x 10 ⁻⁵)
AD	.044	.835	.000	.157 x 10 ⁻⁶ (.752 x 10 ⁻⁵)	.000	1.000	.000	-.611 x 10 ⁻⁶ (.887 x 10 ⁻⁵)
MD	1.519	.221	.015	.714 x 10 ⁻⁵ (.579 x 10 ⁻⁵)	.938	.338	.019	.586 x 10 ⁻⁵ (.605 x 10 ⁻⁵)
R. UF								
FA	9.430	.003*	.085	-.014 (.005)	9.637	.003*	.167	-.017 (.005)
RD	8.072	.005*	.074	.152 x 10 ⁻⁴ (.569 x 10 ⁻⁵)	6.831	.012*	.125	.172 x 10 ⁻⁴ (.657 x 10 ⁻⁵)
AD	.053	.819	.001	.144 x 10 ⁻⁵ (.627 x 10 ⁻⁵)	.171	.681	.004	-.306 x 10 ⁻⁵ (.740 x 10 ⁻⁵)
MD	5.598	.020*	.053	.113 x 10 ⁻⁴ (.478 x 10 ⁻⁵)	3.680	.061	.071	.104 x 10 ⁻⁴ (.543 x 10 ⁻⁵)
Forceps Major								
FA	.788	.377	.008	-.004 (.005)	.102	.750	.002	-.002 (.007)
RD	1.356	.247	.013	-.967 x 10 ⁻⁵ (.830 x 10 ⁻⁵)	5.623	.002*	.105	-.272 x 10 ⁻⁴ (.115 x 10 ⁻⁴)
AD	2.870	.093	.028	-.254 x 10 ⁻⁴ (.150 x 10 ⁻⁴)	11.666	.001*	.196	-.591 x 10 ⁻⁴ (.173 x 10 ⁻⁴)
MD	2.573	.112	.025	-.150 x 10 ⁻⁴ (.934 x 10 ⁻⁵)	10.380	.002*	.178	-.380 x 10 ⁻⁴ (.118 x 10 ⁻⁴)
Forceps Minor								
FA	1.200	.276	.012	-.003 (.003)	3.008	.089	.059	-.007 (.004)
RD	.309	.579	.003	.288 x 10 ⁻⁵ (.517 x 10 ⁻⁵)	.769	.385	.016	.552 x 10 ⁻⁵ (.630 x 10 ⁻⁵)
AD	.247	.621	.002	-.274 x 10 ⁻⁵ (.552 x 10 ⁻⁵)	.973	.329	.020	-.679 x 10 ⁻⁵ (.688 x 10 ⁻⁵)
MD	.404	.843	.000	.967 x 10 ⁻⁶ (.485 x 10 ⁻⁵)	.050	.825	.001	.126 x 10 ⁻⁵ (.568 x 10 ⁻⁵)

Notes. F-values represent the test statistic value for the effect of group status on the DTI parameter of interest, with corresponding *p*-value and effect size. *B* and associated standard errors give the parameter estimates for the contrast of PI vs. controls.

Corticospinal tract (CST), inferior fronto-occipital fasciculus (IFOF), inferior longitudinal fasciculus (ILF), superior longitudinal fasciculus (SLF), uncinate fasciculus (UF).

*Main effect of group status significant at $p < .050$.

Age at Adoption Group Analyses

In adoption group analyses, we compared white matter metrics between PI-EA, PI-LA, and control children. Categorical rather than continuous measures of duration of institutional care were used to allow comparison to non-adopted children who had no history of institutional care. See Inline Supplemental Table 5.2 for details of these analyses.

Fractional anisotropy (FA). Adoption group was a significant predictor of FA across major white matter pathways, including significant group differences in the bilateral anterior thalamic radiations, bilateral cingulum (both cingulate and hippocampal portions), bilateral IFOF, right ILF, right UF, and the forceps minor. In general, although both earlier and later-adopted children had reduced FA values in comparison to non-adopted controls, group differences were driven by greater FA reductions in the PI-EA group.

Radial diffusivity (RD). Adoption group was a significant predictor of RD across many of the white matter pathways that differed in FA. Significant effects were present in the right anterior thalamic radiations, bilateral cingulum (cingulate portion, right hippocampal portion), bilateral IFOF, bilateral ILF, bilateral SLF (left temporal portion, right entire SLF), and the right UF. In general, although both earlier and later-adopted children had increased RD in comparison to non-adopted controls, group differences were driven by higher RD in PI-EA children.

Axial diffusivity (AD). In contrast to widespread changes in FA, there were no significant effects of adoption group on AD.

Mean diffusivity (MD). Adoption group was a significant predictor of MD across several tracts of interest, primarily in the right hemisphere, including the right anterior thalamic radiations, CST, ILF, SLF, and UF. There was also an effect of group status in the bilateral cingulum (cingulate portion), bilateral IFOF, and bilateral effects in the temporal portion of the SLF. In general, although both earlier and later-adopted children had increased MD in comparison to non-adopted controls, group differences were driven by greater MD in the PI-EA children. In one tract, the forceps major, there was an effect of group such that PI children had lower MD than non-adopted controls, although individual pair-wise comparisons were not statistically significant following correction for multiple comparisons.

Inline Supplemental Table 5.2

*Comparison of Age and Sex Adjusted White Matter Scalar Metrics in Controls, PI-EA,
and PI-LA Children (12-Direction DTI Data)*

	<i>F</i>	<i>p</i>	η^2	PI-EA <i>B</i> (<i>se</i>)	PI-LA <i>B</i> (<i>se</i>)	EA vs. LA <i>p</i>
L. ATR						
FA	3.718	.028*	.069	-.012* (.005)	-.005 (.004)	.082
RD	2.878	.061	.054	.143 x 10 ⁻⁴ * (.597 x 10 ⁻⁵)	.796 x 10 ⁻⁵ (.580 x 10 ⁻⁵)	.197
AD	.515	.599	.010	.506 x 10 ⁻⁵ (.540 x 10 ⁻⁵)	.441 x 10 ⁻⁵ (.524 x 10 ⁻⁵)	.897
MD	2.349	.101	.045	.112 x 10 ⁻⁴ (.516 x 10 ⁻⁵)	.629 x 10 ⁻⁵ (.500 x 10 ⁻⁵)	.314
R. ATR						
FA	7.392	.001*	.129	-.015* (.004)	-.008 (.004)	.051
RD	4.328	.016*	.080	.180 x 10 ⁻⁴ * (.621 x 10 ⁻⁵)	.709 x 10 ⁻⁵ (.602 x 10 ⁻⁵)	.063
AD	.802	.451	.016	.756 x 10 ⁻⁵ (.625 x 10 ⁻⁵)	.211 x 10 ⁻⁵ (.607 x 10 ⁻⁵)	.354
MD	3.342	.039*	.063	.146 x 10 ⁻⁴ * (.576 x 10 ⁻⁵)	.534 x 10 ⁻⁵ (.558 x 10 ⁻⁵)	.090
L. CST						
FA	1.525	.223	.030	-.005 (.005)	.004 (.005)	.084
RD	1.099	.337	.022	.841 x 10 ⁻⁵ (.706 x 10 ⁻⁵)	-.582 x 10 ⁻⁶ (.685 x 10 ⁻⁵)	.177
AD	.657	.520	.013	.387 x 10 ⁻⁵ (.822 x 10 ⁻⁵)	.902 x 10 ⁻⁵ (.797 x 10 ⁻⁵)	.505
MD	.643	.528	.013	.692 x 10 ⁻⁵ (.621 x 10 ⁻⁵)	.260 x 10 ⁻⁵ (.602 x 10 ⁻⁵)	.459
R. CST						
FA	.544	.582	.011	-.003 (.005)	.002 (.005)	.306
RD	2.028	.137	.039	.124 x 10 ⁻⁴ (.626 x 10 ⁻⁵)	.452 x 10 ⁻⁵ (.607 x 10 ⁻⁵)	.185
AD	2.979	.055	.056	.151 x 10 ⁻⁴ (.682 x 10 ⁻⁵)	.138 x 10 ⁻⁴ (.661 x 10 ⁻⁵)	.839
MD	3.688	.028*	.069	.136 x 10 ⁻⁴ * (.492 x 10 ⁻⁵)	.764 x 10 ⁻⁵ (.477 x 10 ⁻⁵)	.218
L. CingC						
FA	3.802	.026*	.071	-.019* (.007)	-.008 (.007)	.096
RD	5.304	.006*	.096	.257 x 10 ⁻⁴ * (.836 x 10 ⁻⁵)	.637 x 10 ⁻⁵ (.811 x 10 ⁻⁵)	.015*
AD	1.608	.205	.031	.104 x 10 ⁻⁴ (.103 x 10 ⁻⁴)	-.682 x 10 ⁻⁵ (.998 x 10 ⁻⁵)	.077
MD	5.028	.009*	.091	.207 x 10 ⁻⁴ * (.740 x 10 ⁻⁵)	.198 x 10 ⁻⁵ (.718 x 10 ⁻⁵)	.008*
R. CingC						
FA	3.751	.027*	.070	-.024* (.009)	-.012 (.009)	.138
RD	7.577	.001*	.132	.277 x 10 ⁻⁴ * (.777 x 10 ⁻⁵)	.488 x 10 ⁻⁵ (.754 x 10 ⁻⁵)	.002*
AD	1.540	.219	.030	.189 x 10 ⁻⁵ (.131 x 10 ⁻⁴)	-.176 x 10 ⁻⁴ (.127 x 10 ⁻⁵)	.116
MD	5.986	.004*	.107	.190 x 10 ⁻⁴ * (.712 x 10 ⁻⁵)	-.254 x 10 ⁻⁵ (.691 x 10 ⁻⁵)	.002*
L. CingH						
FA	3.210	.045*	.060	-.015 (.007)	.001 (.007)	.023

RD	1.907	.154	.037	.434 x 10 ⁻⁵ (.820 x 10 ⁻⁵)	-.102 x 10 ⁻⁴ (.796 x 10 ⁻⁵)	.061
AD	2.798	.066	.053	-.258 x 10 ⁻⁴ (.112 x 10 ⁻⁴)	-.187 x 10 ⁻⁴ (.109 x 10 ⁻⁴)	.502
MD	1.577	.212	.031	-.567 x 10 ⁻⁵ (.767 x 10 ⁻⁵)	-.131 x 10 ⁻⁴ (.744 x 10 ⁻⁵)	.305
R. CingH						
FA	9.641	.000*	.162	-.032* (.007)	-.012 (.007)	.004*
RD	7.295	.001*	.127	.283 x 10 ^{-4*} (.792 x 10 ⁻⁵)	.639 x 10 ⁻⁵ (.769 x 10 ⁻⁵)	.004*
AD	2.661	.075	.051	-.207 x 10 ⁻⁴ (.905 x 10 ⁻⁵)	-.134 x 10 ⁻⁴ (.878 x 10 ⁻⁵)	.395
MD	2.502	.087	.048	.120 x 10 ⁻⁴ (.645 x 10 ⁻⁵)	-.695 x 10 ⁻⁷ (.626 x 10 ⁻⁵)	.048
L. IFOF						
FA	8.417	.000*	.144	-.019* (.005)	-.010 (.004)	.038
RD	7.384	.001*	.129	.226 x 10 ^{-4*} (.608 x 10 ⁻⁵)	.720 x 10 ⁻⁵ (.589 x 10 ⁻⁵)	.008*
AD	1.744	.180	.034	.146 x 10 ⁻⁵ (.684 x 10 ⁻⁵)	-.952 x 10 ⁻⁵ (.664 x 10 ⁻⁵)	.090
MD	5.314	.006*	.096	.156 x 10 ^{-4*} (.542 x 10 ⁻⁵)	.150 x 10 ⁻⁵ (.526 x 10 ⁻⁵)	.007*
R. IFOF						
FA	5.498	.005*	.099	-.014* (.005)	-.004 (.004)	.015
RD	8.107	.001*	.140	.209 x 10 ^{-4*} (.556 x 10 ⁻⁵)	.468 x 10 ⁻⁵ (.539 x 10 ⁻⁵)	.002*
AD	.787	.458	.015	.632 x 10 ⁻⁵ (.678 x 10 ⁻⁵)	-.125 x 10 ⁻⁵ (.658 x 10 ⁻⁵)	.236
MD	6.545	.002*	.116	.161 x 10 ^{-4*} (.488 x 10 ⁻⁵)	.276 x 10 ⁻⁵ (.473 x 10 ⁻⁵)	.004*
L. ILF						
FA	2.591	.080	.049	-.009 (.004)	-.001 (.004)	.063
RD	3.392	.038*	.064	.125 x 10 ⁻⁴ (.686 x 10 ⁻⁵)	-.366 x 10 ⁻⁵ (.666 x 10 ⁻⁵)	.013*
AD	.798	.453	.016	.165 x 10 ⁻⁵ (.837 x 10 ⁻⁵)	-.758 x 10 ⁻⁵ (.811 x 10 ⁻⁵)	.241
MD	2.448	.092	.047	.904 x 10 ⁻⁵ (.476 x 10 ⁻⁵)	-.476 x 10 ⁻⁵ (.652 x 10 ⁻⁵)	.031
R. ILF						
FA	9.043	.000*	.153	-.018* (.005)	-.004 (.004)	.001*
RD	13.42	.000*	.212	.296 x 10 ^{-4*} (.606 x 10 ⁻⁵)	.721 x 10 ⁻⁵ (.588 x 10 ⁻⁵)	.000*
AD	7					
MD	1.263	.287	.025	.132 x 10 ⁻⁴ (.855 x 10 ⁻⁵)	.441 x 10 ⁻⁵ (.830 x 10 ⁻⁵)	.275
MD	9.420	.000*	.159	.241 x 10 ^{-4*} (.587 x 10 ⁻⁵)	.626 x 10 ⁻⁵ (.569 x 10 ⁻⁵)	.002*
L. SLF						
FA	1.903	.154	.037	-.005 (.004)	.002 (.004)	.061
RD	3.037	.052	.057	.901 x 10 ⁻⁵ (.736 x 10 ⁻⁵)	-.796 x 10 ⁻⁵ (.714 x 10 ⁻⁵)	.015*
AD	2.360	.100	.045	.261 x 10 ⁻⁵ (.690 x 10 ⁻⁵)	-.106 x 10 ⁻⁴ (.668 x 10 ⁻⁵)	.044
MD	3.018	.053	.057	.702 x 10 ⁻⁵ (.680 x 10 ⁻⁵)	-.855 x 10 ⁻⁵ (.660 x 10 ⁻⁵)	.016*
R. SLF						
FA	2.752	.069	.052	-.010 (.004)	-.005 (.004)	.181
RD	4.449	.014*	.082	.175 x 10 ^{-4*} (.585 x 10 ⁻⁵)	.918 x 10 ⁻⁵ (.568 x 10 ⁻⁵)	.134
AD	2.158	.121	.041	.138 x 10 ⁻⁴ (.667 x 10 ⁻⁵)	.632 x 10 ⁻⁵ (.647 x 10 ⁻⁵)	.233
MD	4.625	.012*	.085	.163 x 10 ^{-4*} (.537 x 10 ⁻⁵)	.826 x 10 ⁻⁵ (.521 x 10 ⁻⁵)	.112
L. SLF temporal						
FA	2.200	.116	.042	-.009 (.010)	.011 (.010)	.039

RD	3.292	.031*	.062	.924 x 10 ⁻⁵ (.980 x 10 ⁻⁵)	-.141 x 10 ⁻⁴ (.950 x 10 ⁻⁵)	.013*
AD	.412	.664	.008	.866 x 10 ⁻⁵ (.111 x 10 ⁻⁴)	.544 x 10 ⁻⁶ (.108 x 10 ⁻⁴)	.431
MD	4.127	.019*	.076	.899 x 10 ⁻⁵ (.684 x 10 ⁻⁵)	-.937 x 10 ⁻⁵ (.663 x 10 ⁻⁵)	.005*
R. SLF temporal						
FA	1.501	.228	.029	-.005 (.009)	.009 (.009)	.091
RD	2.668	.074	.051	.103 x 10 ⁻⁴ (.819 x 10 ⁻⁵)	-.735 x 10 ⁻⁵ (.795 x 10 ⁻⁵)	.023
AD	.378	.687	.007	.971 x 10 ⁻⁵ (.129 x 10 ⁻⁴)	.590 x 10 ⁻⁶ (.125 x 10 ⁻⁴)	.452
MD	3.374	.038*	.063	.101 x 10 ⁻⁴ (.612 x 10 ⁻⁵)	-.454 x 10 ⁻⁵ (.594 x 10 ⁻⁵)	.012*
L. UF						
FA	3.063	.051	.058	-.011* (.004)	-.005 (.004)	.177
RD	2.891	.060	.055	.158 x 10 ⁻⁴ (.681 x 10 ⁻⁵)	.481 x 10 ⁻⁵ (.661 x 10 ⁻⁵)	.089
AD	.544	.582	.011	.699 x 10 ⁻⁵ (.868 x 10 ⁻⁵)	-.230 x 10 ⁻⁵ (.842 x 10 ⁻⁵)	.309
MD	2.057	.133	.040	.125 x 10 ⁻⁴ (.664 x 10 ⁻⁵)	.250 x 10 ⁻⁵ (.643 x 10 ⁻⁵)	.112
R. UF						
FA	5.970	.004*	.107	-.018* (.005)	-.011 (.005)	.126
RD	6.136	.003*	.109	.226 x 10 ⁻⁴ (.647 x 10 ⁻⁵)	.105 x 10 ⁻⁴ (.628 x 10 ⁻⁵)	.049
AD	.303	.740	.006	.413 x 10 ⁻⁵ (.723 x 10 ⁻⁵)	-.915 x 10 ⁻⁶ (.704 x 10 ⁻⁵)	.459
MD	4.635	.012*	.085	.164 x 10 ⁻⁴ * (.545 x 10 ⁻⁵)	.684 x 10 ⁻⁵ (.529 x 10 ⁻⁵)	.063
Forceps Major						
FA	1.135	.325	.022	-.008 (.006)	-.001 (.006)	.227
RD	2.405	.095	.046	-.920 x 10 ⁻⁶ (.947 x 10 ⁻⁵)	-.173 x 10 ⁻⁴ (.919 x 10 ⁻⁵)	.067
AD	2.591	.080	.049	-.125 x 10 ⁻⁴ (.172 x 10 ⁻⁴)	-.367 x 10 ⁻⁴ (.170 x 10 ⁻⁴)	.135
MD	3.123	.048*	.059	-.489 x 10 ⁻⁵ (.106 x 10 ⁻⁴)	-.238 x 10 ⁻⁴ (.103 x 10 ⁻⁴)	.060
Forceps Minor						
FA	3.387	.038*	.063	-.007 (.003)	.000 (.003)	.021
RD	2.420	.094	.046	.911 x 10 ⁻⁵ (.587 x 10 ⁻⁵)	-.257 x 10 ⁻⁵ (.569 x 10 ⁻⁵)	.036
AD	.895	.412	.018	.120 x 10 ⁻⁵ (.636 x 10 ⁻⁵)	-.619 x 10 ⁻⁵ (.617 x 10 ⁻⁵)	.217
MD	1.955	.147	.038	.639 x 10 ⁻⁵ (.552 x 10 ⁻⁵)	-.378 x 10 ⁻⁵ (.536 x 10 ⁻⁵)	.052

Notes. F-values represent the test statistic value for the effect of adoption group on the DTI parameter of interest, with corresponding *p*-value and effect size. *B* and associated standard errors give the parameter estimates for the contrast of PI-EA or PI-LA in comparison to controls, and EA vs. LA *p* represents the contrast between the adjusted means for the earlier and later adopted groups.

Anterior thalamic radiations (ATR), corticospinal tract (CST), cingulum-cingulate bundle (Cing-C), cingulum-hippocampal bundle (Cing-H), inferior fronto-occipital fasciculus (IFOF), inferior longitudinal fasciculus (ILF), superior longitudinal fasciculus (SLF), uncinate fasciculus (UF).

*Main effect of group status significant at $p < .050$ or pair-wise comparison between groups significant at $p < .020$.

Age at Adoption Correlational Analyses

In general, there were few linear associations between age at adoption within the PI group and white matter scalar metrics of interest. Statistically significant associations were found within the bilateral cingulate (cingulate portion) and the right ILF. Within the bilateral cingulate (cingulate portion), increasing age at adoption was associated with reduced AD and MD. Within the right ILF, increasing age at adoption was also associated with reduced RD, see Inline Supplemental Table 5.3.

Inline Supplemental Table 5.3

Associations Between Age and Sex Adjusted White Matter Scalar Metrics and Age At Adoption (prior to 24 months of age), in Tracts that Differed by Group (12-Direction DTI Data)

	Left Hemisphere				Right Hemisphere			
	<i>r</i>	<i>p</i>	<i>r_{adj}</i>	<i>p_{adj}</i>	<i>r</i>	<i>p</i>	<i>r_{adj}</i>	<i>p_{adj}</i>
ATR								
FA	.141	.292	.138	.304	.136	.307	.133	.323
RD	-.090	.501	-.092	.496	-.162	.223	-.160	.234
AD	-.002	.986	-.006	.963	-.153	.252	-.152	.260
MD	-.079	.590	-.075	.580	-.173	.194	-.171	.203
Cing-C								
FA	-.025	.853	-.034	.803	.031	.816	.038	.781
RD	-.106	.428	-.103	.444	-.280	.033*	-.285	.032*
AD	-.297	.021*	-.328	.013*	-.297	.024*	-.296	.026*
MD	-.208	.118	-.211	.116	-.361	.005*	-.363	.006*
R. Cing-H								
FA					.244	.065	.241	.071
RD					-.187	.160	-.183	.173
AD					.143	.284	.138	.307
MD					-.098	.465	-.097	.475
IFOF								
FA	.154	.249	.154	.252	.078	.562	.082	.547
RD	-.214	.107	-.208	.120	-.149	.266	-.151	.263
AD	-.150	.261	-.169	.208	-.195	.143	-.197	.142
MD	-.214	.106	-.226	.091	-.194	.144	-.197	.142
R. ILF								
FA					.251	.058	.252	.059
RD					-.287	.029*	-.288	.030*
AD					-.113	.399	-.117	.384
MD					-.254	.054	-.257	.054
UF								
FA	-.111	.405	-.128	.344	-.057	.668	-.070	.606
RD	.017	.899	.020	.883	-.017	.899	-.010	.941
AD	-.129	.334	-.143	.288	-.074	.583	-.079	.559
MD	-.044	.743	-.047	.731	-.041	.758	-.038	.780

Notes. r and p represent the age- and sex-adjusted Pearson partial correlation value and corresponding p-value. r_{adj} and p_{adj} are additionally adjusted for individual differences in total white matter volume.

Anterior thalamic radiations (ATR), corticospinal tract (CST), cingulum-cingulate bundle (Cing-C), cingulum-hippocampal bundle (Cing-H), inferior fronto-occipital fasciculus (IFOF), inferior longitudinal fasciculus (ILF), superior longitudinal fasciculus (SLF), uncinate fasciculus (UF).

*Correlation significant at $p < .050$.

Discussion

Our results highlight the complex, long-term impacts of early life experience on both the global and microstructural development of white matter. Adolescents who experienced a discrete period of deprivation limited to the infant and early childhood years had lower total cortical white matter volume and reduced white matter microstructural integrity across most of the brain's major white matter pathways, including front-limbic and fronto-striatal circuits. Results are consistent both with previous neuroimaging studies of PI children and the neural correlates of other types of early adversity (e.g. childhood maltreatment), as well as rodent and primate models of early life stress. Poorer white matter microstructural integrity following early deprivation was driven by more extensive changes in radial, rather than axial, diffusivity, a pattern consistent with altered myelination. Last, we also report novel, non-linear associations between the duration of early adversity and subsequent white matter development. Unexpectedly, while PI children as a group had poorer white matter integrity than non-adopted controls, group differences were driven by greater reductions in fractional anisotropy within the earlier-adopted (prior to 12 months) children.

White matter microstructural alterations at adolescence following early life stress were quite global, rather than predominantly localized to certain tracts. Previous imaging studies of PI children have also reported global white matter changes including reductions in total white matter volume (Hanson et al., 2013; Sheridan et al., 2012) and smaller corpus callosum volumes (Mehta et al., 2009). Similarly, both human and non-human primates also show long-term volumetric changes in white matter following

maltreatment in early life (e.g. De Bellis et al., 1999; Sánchez, Hearn, Do, Rilling, & Herndon, 1998; Teicher et al., 2004). Based on animal models of early life stress, previous studies with PI children have focused on characterizing white matter microstructural alterations in fronto-limbic (Eluvathingal et al., 2006; Kumar et al., 2014) and fronto-striatal (Behen et al., 2009) pathways. Although we report extensive differences within these frontal white matter tracts, our results are also consistent with previous research reporting poorer white matter integrity extending across temporal, parietal, occipital, and subcortical regions following institutional care (Bick, Zhu, et al., 2015; Govindan et al., 2010; Hanson et al., 2013).

Heightened vulnerability of prefrontal gray matter development has already been emphasized in previous studies with this population (Hodel et al., 2015; McLaughlin et al., 2014), a pattern consistent with both non-human primate (Howell et al., 2014) and rodent (Stamatakis, Manatos, Kalpachidou, & Stylianopoulou, 2015) models of early life stress. In the current study, some of the most robust correlates of early deprivation were within the inferior fronto-occipital fasciculus (IFOF), cingulum (hippocampal portion) and uncinate fasciculus (UF), all projections involving the frontal lobe. The IFOF is one of the major efferent and afferent projections to the frontal lobes (Kier et al., 2004). Individual differences in white matter integrity in this region are associated with variation in processing speed, complex learning, and executive function skills during childhood (Peters et al., 2014), all documented difficulties for many PI children (Merz et al., 2016). The hippocampal portion of the cingulum bundle and the UF are major fronto-limbic projections, broadly supporting emotion processing abilities including emotional

regulation (Keedwell et al., 2016) and emotion-dependent learning and memory (Von Der Heide, Skipper, Klobusicky, & Olson, 2013): functions that are disrupted by early life stress (Bick & Nelson, 2016). FA reductions in the IFOF, cingulum, and UF have also been reported in smaller samples of PI children predominantly adopted from Eastern Europe (Behen et al., 2009; Bick, Zhu, et al., 2015; Eluvathingal et al., 2006; Govindan et al., 2010; Hanson et al., 2013; Kumar et al., 2014), and in older adolescents and adults previously exposed to domestic violence (Choi, Jeong, Polcari, Rohan, & Teicher, 2012), parental verbal abuse (Choi, Jeong, Rohan, Polcari, & Teicher, 2009), and maltreatment during early childhood (Huang, Gundapuneedi, & Rao, 2012).

Mechanisms of White Matter Disorganization

A novel contribution of the current study was the characterization of multiple indices of white matter microstructural organization in PI youth. Although changes in FA, MD, and RD were detected across the majority of tested tracts, AD differences were generally restricted to corticospinal and thalamic radiations. DTI does not allow for direct measurement of myelination. However, increases in RD without substantial alterations in AD within PI children is a pattern consistent with reduced myelination (see reviews in Alexander et al., 2008; Kumar et al., 2012). There are multiple mechanisms via which early deprivation could shape long-term white matter microstructural organization. Perinatal risk factors, including preterm birth, are likely over-represented in populations of PI children and are known to disrupt long-term global white matter volume (Kesler et al., 2008) and microstructural integrity (Nagy et al., 2003), including in fronto-striatal pathways (Duerden, Card, Lax, Donner, & Taylor, 2013). The orphanage

environment typically lacks at least some aspects of developmentally-appropriate sensory, cognitive, and/or socioemotional stimulation. Given the reliance of early neurobiological processes like synaptic pruning on appropriate environmental input (Greenough et al., 1987), broad neurodevelopmental trajectories are likely altered as a result of institutional care. Although the literature investigating the cellular mechanisms of experience-dependent and experience-expectant plasticity has focused primarily on synaptic changes, activity-dependent changes in myelination, indexed in measures like FA, are also sensitive to changes in neuronal firing (Fields, 2005).

Children currently residing in institutions show biological evidence of chronic stress, including disruptions in cortisol rhythms (Carlson & Earls, 1997). Glucocorticoid-mediated decreases in glial cell number and density within fronto-limbic brain regions have been linked to volumetric changes following chronic stress in adult animals (Jauregui-Huerta et al., 2010). However, evidence suggests that the impact of stress on glial cells is quite dynamic, varying by developmental timing, cell type (i.e. astrocytes vs. oligodendrocytes), and brain region (Jauregui-Huerta et al., 2010). Normative brain development is also intimately related to nutrition, including levels of long-chain polyunsaturated fatty acids (Janssen & Kiliaan, 2014) and availability of micronutrients such as iron (Georgieff, 2011). Micronutrient deficiency (Fuglestad et al., 2008; Fuglestad, Kroupina, Johnson, & Georgieff, 2016) and growth failure indicative of macronutrient deficiencies (Hearst et al., 2014) have been well-documented in children following international adoption and also likely contribute to differential white matter development. Last, it is critical to recognize that white matter organization differences

associated with early adversity may be secondary, cascading effects, induced by early disruptions in subcortical and/or cortical gray matter development.

Importance of Timing

Previous studies of PI children have not found robust effects of the *duration* of early life stress on long-term measures of gray matter development; instead, differences have primarily been detected between PI children and non-adopted controls. In the current study, associations between duration of institutional care and later white matter development were detected across a diverse set of major white matter pathways. Counter to our hypotheses, earlier-adopted children (<12 months at adoption) showed poorer white matter microstructural organization (e.g. lower FA, higher RD, higher MD) across multiple tracts of interest in comparison to non-adopted controls. Correlational analyses also indicated that within the PI group, higher age at adoption (within the range of 4-24 months) was predictive of greater white matter integrity within the bilateral cingulum bundle (cingulate portion) and the right inferior longitudinal fasciculus. Although the later-adopted PI children did not show increased FA relative to non-adopted controls, increased FA following early life stress has been reported within fronto-limbic tracts in non-human primates (Howell et al., 2014) and in other samples of PI children within sensory pathways (Bick, Zhu, et al., 2015).

In the current study, despite ostensibly poorer white matter organization, earlier-adopted PI children had higher IQ scores than their later adopted peers. Higher FA is typically associated with better intellectual functioning across childhood and adolescence in normative populations (Nagy et al., 2004; Peters et al., 2014). However, higher FA is

not universally associated with improved performance across all functional domains or across the lifespan. For example, increased FA in frontal tracts involved in emotional control has been linked to higher emotional reactivity in adults with anxiety disorders (Han et al., 2008). The developmental timing of changes in white matter microstructure also matters; higher FA in fronto-striatal circuits during development has been suggested to reflect overly-rigid behavior, including reduced cognitive flexibility (e.g. see Thomason & Thompson, 2011 for discussion). In this case, higher FA within the later-adopted PI children relative to their earlier-adopted peers may not reflect better functionality of white matter. Instead, given that later-adopted children are at higher risk for both emotion regulation and executive function difficulties (Colvert et al., 2008; Merz, McCall, Wright, & Luna, 2013; Pollak et al., 2010; Tottenham et al., 2010), higher white matter microstructural organization within later-adoptees may be indicative of an altered, atypical trajectory of white matter development.

What constitutes “optimal” white matter for PI children, both within the orphanage environment and following adaptation to the environment of the adoptive family may not be intuitive. For example, a history of institutional care is associated with altered patterns of functional connectivity within fronto-limbic systems. However, rather than “disruptions” or “deficits” in connectivity, these circuits appear to reach adult-like functioning earlier in development than would be expected, likely reflecting an adaptive trade-off in the orphanage context that may have negative consequences later in the post-adoptive environment (Callaghan & Tottenham, 2016; Gee et al., 2013). Animal models have also demonstrated that milder forms of early life stress shape prefrontal white matter

volume (Lyons, Afarian, Schatzberg, Sawyer-Glover, & Moseley, 2002) and microstructure (Katz et al., 2009) in ways that are potentially adaptive for the organism's ability to cope with later changes in the environment. Direct translation of effects of timing and aspects of environmental deprivation in animal models to human instances of early life stress is difficult. In the present study, children in the PI-EA group were by definition adopted prior to 12 months; these children therefore experienced a dramatic shift from the orphanage environment into their post-adoptive homes during the brain's most rapid period of white matter development (Dean et al., 2014). The timing of these dramatic environmental transitions may spur adaptations in the trajectory of white matter development that ultimately result in the dissociation between reduced white matter organization yet improved functional outcomes.

The non-linear effects of duration of adversity on white matter microstructure observed here strongly suggest that more than just the timing of early adverse experiences matter. Instead, early adversity may dynamically alter both the current state of brain development as well as the capability of the brain to respond adaptively to future environments. Animal models of bird song learning and of cat visual cortex development have demonstrated that long-term deprivation of environmental stimulation can increase the duration of sensitive periods. Yet this comes at a high cost: circuits may consolidate with aberrant connectivity patterns (Knudsen, 2004), permanently altering the capacity of the brain to adapt to future changes in the environment. Beyond differences in timing, it is also important to recognize that multiple biological processes, in addition to brain development, are disrupted in instances of severe early life stress. A large percentage of

PI children show evidence of severe growth restriction at adoption (Rutter, 1998), along with atypical growth trajectories and altered pubertal timing (Johnson, 2002). Immune system dysregulation is also associated with early life stress (Bilbo & Schwarz, 2009) and has not yet been characterized in PI youth. The potential for dynamic interactions between immunological functioning, growth stunting, rapid catch-up growth, and altered pubertal timing may more clearly illuminate the effects of timing of early deprivation on long-term measures of gray and white matter development.

Duration of institutional care experienced by PI children is only one, coarse measure of the nature of children's early life experiences, and is strongly affected by adoption policies in individual countries. Our diverse sample of PI children was intentionally selected to be representative of children entering the United States via international adoption, improving the generalizability of our results. Follow-up analyses described in the Appendix also demonstrated that ethnicity effects alone could not account for greater white matter alterations in the PI-EA group. Although country policies may primarily dictate the age at which children are adopted, PI children are not randomly assigned to receive orphanage care. Thus, this population is likely over-representative of other prenatal and/or perinatal risk factors, such as preterm birth (Duerden et al., 2013; Kesler et al., 2008; Nagy et al., 2003), prenatal drug or alcohol exposure (Archibald et al., 2001; Sowell et al., 2008; Warner et al., 2006), and prenatal stress (Lebel et al., 2015; Sarkar et al., 2014), that are known to affect white matter organization. However, our results are consistent with DTI studies of non-human primates exposed to early life stress (Coplan et al., 2010; Howell et al., 2013; Jackowski

et al., 2011) in which these confounding factors can be controlled.

Limitations

Several methodological concerns related to neuroimaging in developmental and/or at-risk populations and DTI-specific issues warrant further discussion. There are no standard metrics or best practices for censoring data and/or culling subjects with excess motion from analyses in the DTI literature. Although much attention has been devoted to motion in functional MRI and resting state data, motion presents the same issue for DTI studies involving children and/or clinical populations, who are typically more likely to exhibit in-scanner motion. Unfortunately, very few DTI studies, especially those with developmental populations, report information on motion differences across groups. Small increases in motion can result in changes in FA, leading to spurious group differences, especially in tracts near non-brain voxels (e.g. corpus callosum, cingulum bundle; Yendiki et al., 2014). We undertook extra precautions to eliminate data from children with in-scanner motion, ultimately resulting in the exclusion of a large percentage of our original data set (e.g. an additional 54 PI children were tested but excluded for in-scanner motion in the 12-direction data set). Alternative approaches to controlling for motion include using a composite measure of motion as a predictor of non-interest or discarding subsets of a participant's data, although the second of these approaches is not feasible unless redundant estimates of each diffusion direction are present (Yendiki et al., 2014). Our aggressive approach to exclusion likely resulted in a sample composed of higher functioning children (i.e. able to hold still for the duration of scanning), making group differences more difficult to detect (a more conservative test).

There are also limitations to TBSS analyses that could complicate interpretation of the current results. TBSS lacks specificity in regions where multiple white matter structures converge (i.e. crossing and kissing fibers; Bach et al., 2014). Improved registration methods, including the use of a study-specific template given our developmental population, partially circumvents this problem by improving cross-subject alignment (Schwarz et al., 2014). The use of a probabilistic white matter tract atlas generated from adult participants in our pediatric sample is also potentially problematic, given known anatomical differences in the developing brain. However, because results obtained from the TBSS and TOI analyses were largely convergent, this minimizes potential issues with our approach. Similarly, the interpretation of white matter metrics and their relation to myelination remains somewhat controversial (Wheeler-Kingshott & Cercignani, 2009) and has been less studied during development. As such, we are only able to speculate that differences in myelination exist between groups, although this result is congruent with animal models of early life stress using DTI metrics (Howell et al., 2013) and histological techniques (Makinodan et al., 2012).

Future Directions

Longitudinal imaging studies are the next important step in determining the trajectory of altered neurodevelopment within PI children. At this point it remains unclear at what age differences in gray and white matter development first emerge and how long they persist, as no studies with PI children have conducted neuroimaging during early childhood or after late adolescence. The non-linear effects of duration of deprivation on white matter development clearly demonstrate that additional studies

characterizing the relationship between structural and functional brain development indices and real-world behavior are needed to understand the implications of trajectories of altered neurodevelopment (e.g. see Bick, Fox, Zeanah, & Nelson, 2015). Adolescence, in particular, may represent a second period of heightened biological sensitivity to the environment (Fuhrmann, Knoll, & Blakemore, 2015). Characterization of white matter development across the adolescent years in at-risk children is warranted to delineate how early experience does or does not constrain neurodevelopment during later sensitive periods. Last, complementary studies of experiential variations within normative environments and their impacts on human brain development (e.g. normative variation in parenting, Whittle et al., 2014) are critical to understanding how we can support neurodevelopment in children who are recovering from early adversity.

GENERAL DISCUSSION

The goal of this dissertation was to characterize the dynamic impact of early experience on trajectories of prefrontal cortex development. We examined concurrent and long-term correlates of early risk in two different populations of children: children born moderate-to-late preterm (PT; 32-36 weeks gestation) and children adopted from orphanage care prior to five years of age (post-institutionalized or PI children). We first integrate findings that emerged from the research included in this dissertation, and conclude by highlighting two key themes for further inquiry and the translational importance of this work.

Impacts of Early Experience Can Be Detected in Infancy

Many studies have documented the impacts of early adversity on long-term measures of neurobehavioral development in children and adolescents. We add to a growing body of literature demonstrating that these are not latent effects that emerge slowly over time (see Chapter 1). Instead, the impact of early variations in the environment on prefrontal cortex development is measurable within the first year of life. We demonstrated that subtle differences in both biological and environmental risk were associated with the development of early executive function (EF) skills in 9-month-old infants. In healthy, moderate-to-late preterm infants, lower gestational age at birth was associated with poorer performance on five of six early EF tasks (Study 1a), perhaps driven by underlying differences in early attention shifting skills (Study 1b). Normative variations in the familial environment including income-to-needs ratio and self-reported measures of parental sensitivity were also related to infants' early EF development (Study

1b) in our large sample of full-term and moderate-to-late PT infants. Associations between environmental and biological risk factors were most consistent for measures of infant attention shifting, suggesting alterations in this core cognitive skill may represent a developmental pathway for altered EF.

Individual differences in early EF development measured in Study 1a and 1b were quite small and likely reflect variability within the normative range. Our sample of infants was intentionally selected to be of both low medical risk (including moderate-to-late PT infants) and low environmental risk (all families were above the federal poverty threshold). Subtle impacts of variation with the normative range of familial environments and the normative range of gestation (i.e. some gestational age-EF performance relationships spanned across the full-term group) highlight the plasticity of prefrontal circuits during the first years of life (see Chapter 1). Previous studies have reported non-linear associations between severity of childhood poverty and prefrontal cortex structural development (Hair, Hanson, Wolfe, & Pollak, 2015; Noble et al., 2015), where children from the poorest families show disproportionately worse outcomes. Similarly, disruptions in EF development in older children born moderate-to-late PT are greater in children with higher levels of medical risk (Baron et al., 2009). For infants exposed to higher degrees of early adversity than our relatively low-risk sample, trajectories of altered prefrontal cortex development may be stronger in magnitude and present earlier in life.

Impacts of Early Experience Persist

Prospective neuroimaging studies have demonstrated that poverty during

childhood predicts smaller prefrontal cortex volume (Holz et al., 2015), reduced connectivity within frontal-lobe functional networks (Sripada, Swain, Evans, Welsh, & Liberzon, 2014), and altered activation patterns during regulatory tasks (Javanbakht et al., 2015; Muscatell et al., 2012) in adulthood, even after controlling for concurrent measures of social status and/or income. Our results similarly demonstrate that the impact of adversity limited to the early childhood period persists at least into the adolescent years. Adolescents born moderate-to-late PT had reduced prefrontal cortex volume and altered prefrontal functional activity during an EF task in comparison to full-term controls (Study 2). A history of early childhood institutional care was also associated with reductions in whole brain white matter volume and poorer white matter organization in PI youth (Study 3).

Our studies were not designed to distinguish the contributions of early versus later experiences on prefrontal cortex development. Developmental neuroimaging studies have convincingly demonstrated that prefrontal cortex undergoes continued refinement into late adolescence (Asato, Terwilliger, Woo, & Luna, 2010; Nagy, Westerberg, & Klingberg, 2004; Sowell, Thompson, Holmes, Jernigan, & Toga, 1999; Sowell, Thompson, Tessner, & Toga, 2001). The adolescent years may also reflect an additional time window of enhanced brain plasticity (Fuhrmann, Knoll, & Blakemore, 2015). In the current studies, the “later” environments for both samples of adolescents would likely be characterized as normative or even enriched. Biological families of adolescents born PT and the adoptive families of PI children were generally from middle-to-upper class backgrounds and were highly educated. Thus, despite exposure to later positive

environments, the impacts of moderate-to-late PT birth and early orphanage rearing on prefrontal cortex development are not fully ameliorated by adolescence.

Timing of Early Experience & Trajectories of PFC Development

An implicit assumption guiding this dissertation was that early experiences show some privilege over later experiences in shaping developmental trajectories. Sensitive periods, windows of time in which the developing organism is most sensitive to environmental differences, do tend to occur early in development for basic sensory processes (Hensch, 2005). Whether sensitive periods exist for higher-level prefrontal-dependent behaviors in human infants and/or toddlers is unclear (Fox, Levitt, & Nelson, 2010). However, we did not explicitly test the impact of exposure to adverse environments at different points in development; also, because our studies were cross-sectional, it is unclear how trajectories of prefrontal cortex development are altered following early adversity. It is possible that subsequent exposure to positive environments has reduced the negative impact of early adversity over time, that impacts have remained relatively constant since early childhood, or that impacts are increasing as children age and the environment becomes more cognitively demanding. Future studies that characterize longitudinal trajectories of prefrontal cortex development following adversity are needed to disentangle these possibilities. However, a few key comparisons across studies provide hints about the trajectory of frontal lobe development following early adversity.

First, we suspect that differences in early EF skills in moderate-to-late PT infants (Study 1a and 1b) are not a transient delay. Although behavioral differences in EF were

not detected in adolescents born moderate-to-late PT (Study 2), both frontal lobe structure and function were altered, suggesting continuity in atypical prefrontal cortex development following moderate-to-late PT birth. Equivalent behavior in the context of altered prefrontal structure and functional activation suggests that for children born moderate-to-late PT, prefrontal cortex development may follow a qualitatively different trajectory. These studies also revealed that subtle differences in the timing of gestational length, including into the full-term range, are correlated with differential development of prefrontal circuits. Similar to large, cohort-based studies that have documented neurobehavioral differences in children born in the “early-term” or “near-term” range (37-38 weeks gestation; Boyle & Boyle, 2013; Espel, Glynn, Sandman, & Davis, 2014; Quigley et al., 2012; Schonhaut, Armijo, & Perez, 2015; Vohr, 2013), our results indicate there is not a definitive cut-off point at 37 weeks where the neurodevelopmental impacts of PT birth end. Subtle differences in timing of early perinatal risk factors (e.g. 36 weeks of in-utero brain development versus 37 weeks) may have long-lasting impacts on prefrontal development due to the rapid growth in prefrontal circuits during the last weeks of term pregnancy and the organizing role that prefrontal regions serve in establishing connectivity patterns in the developing brain (see Chapter 1).

Second, in our sample of adolescents adopted from early institutional care, earlier-adopted PI children had greater disruptions in white matter microstructural organization than their later-adopted peers. Previous studies have documented that later-adopted PI children are at higher risk for EF problems (see review in Merz, Harlé, Noble, & McCall, 2016). Although we did not report on behavioral measures of EF in our

population of PI youth, IQ scores were similarly lower in later-adoptees. The dissociation between ostensibly poorer white matter microstructural integrity and better intellectual functioning in earlier-adopted PI youth again suggests that trajectories of brain development after early adversity may follow a fundamentally different pattern. One caveat is that very few of the earlier-adopted PI children in the current study were adopted prior to 6 months of age. The English and Romanian Adoptees study has suggested that for many developmental domains, adoption prior to 6 months of age may reflect a critical threshold, past which the negative impacts of the orphanage environment cannot be fully ameliorated (e.g. Beckett et al., 2006). Thus, in our current study, adoption between 4-12 months of age may not be “early” enough given the rapid pace of brain development over the first year of life.

Last, non-linear impacts of timing in severe forms of early adversity like institutional care but generally linear effects in our lower-risk, moderate-to-late PT infant studies suggest that differences in the nature of these early life experiences are relevant. One possibility is that early experience-expectant brain development is perturbed in opposing directions in children born PT and children exposed to early institutional care. In infants born PT, exposure to an environment with increased visual, auditory, and tactile stimulation when the immature prefrontal cortex is establishing basic patterns of connectivity may permanently alter functional organization. For PI children, developmentally appropriate stimulation is instead largely absent in the early orphanage environment, leaving prefrontal circuits to stabilize without guidance from a normative environment, which may alter long-term plasticity. The presence of a responsive,

contingent caregiver is a core feature of the expectable environment for all human infants (Humphreys & Zeanah, 2014). Because development occurs within the context of close relationships for young infants, the lack of a normative caregiver relationship also changes the infant's everyday interactions with the environment. As such, the absence of this organizing relationship for institutionalized infants alters both experience-expectant and experience-dependent processes, and in tandem may result in large, non-linear changes in early brain development.

Important future directions to better characterize the impact of timing of early adversity on prefrontal development include: 1) utilizing longitudinal study designs, beginning early in development, to determine the trajectory of neurobehavioral changes, 2) recognizing that early experience does not induce “deficits” in brain development but may alter prefrontal cortex circuits to support adaptation within the current environment (Callaghan & Tottenham, 2016; McEwen, 2012), 3) measuring the quality of environments following early adversity and the impact of variation within normative and/or positive environments on brain development (Whittle et al., 2014), and 4) integrating results with animal studies in which timing and dimensional characteristics of adverse environments can be more tightly controlled.

Utility of Multiple Measures of PFC Development

A strength of the current dissertation was the ability to combine different conceptual approaches (examining early and long-term impacts of experience) with multiple measures of brain development (behavioral, structural neuroimaging, functional neuroimaging, diffusion tensor imaging) across diverse experiences (PT birth, early

deprivation) to characterize the impact of the early environment on prefrontal cortex development. Developing sensitive measures of early prefrontal-dependent behaviors was a particular challenge in this dissertation (Study 1a and 1b) and remains a difficult task for the field of developmental science (see Hendry, Jones, & Charman, 2016 for recent discussion). Important future directions related to this work will be to determine whether the derived early measures of infant EF show developmental stability and to test their reliance on prefrontal circuitry using techniques such as functional near infrared spectroscopy (fNIRS).

Developing and utilizing sensitive measures of both behavioral and brain differences is especially necessary to detect altered functioning in lower-risk populations. For example, in Study 2, adolescents born moderate-to-late PT did not differ from their full-term peers on behavioral measures of EF or in overall IQ scores. However, neuroimaging measures of brain structure and functional activation were more sensitive to group differences in prefrontal cortex development. Detection of differences in EF in low-risk populations, who may show differences from control subjects that lie within the normative range of functioning, requires behavioral tasks that adequately challenge the intended construct (i.e. no ceiling or floor effects).

Including multiple measures of neurobehavioral development also allows for a more comprehensive description of brain and behavioral changes induced by early adversity, as impacts may differ across levels of measurement. For example, in Study 2, despite smaller prefrontal cortex volumes, adolescents born PT performed equivalently to their FT peers on an EF task and showed similar patterns of functional activation in

conditions that required attentional control. Interestingly, sometimes these measures of brain development are related differently in typically developing versus at-risk populations. In Study 3, different associations between measures of whole brain white matter volume and white matter microstructural organization were observed for PI children than for non-adopted comparison children. Understanding when in development and why typical structure-function-behavior relations are disrupted is an important next step in delineating how early adversity shapes prefrontal systems at the circuit level.

Challenges and Future Directions

The converging effects of two different types of early adversity, that differ greatly in timing and context, on prefrontal cortex development suggest that frontal-lobe circuits are highly sensitive to variations in the early environment. Although we have already discussed several future directions, we next highlight two important themes to be investigated in future studies.

Systems perspective. The human brain develops as an integrated system, across circuits, across biological systems, within the growing individual. An important future direction is to better integrate the impact of early adversity at the “systems” level. Delineation of the impacts of early experience on separable frontal circuits (e.g. fronto-limbic versus frontal-striatal) is an important step in documenting specificity and/or convergence of effects. This approach is also compatible with existing frameworks for characterizing the dimensions of early adverse environments (Humphreys & Zeanah, 2014; Sheridan & McLaughlin, 2014), in which certain forms of adversity may have stronger impacts on dorsal versus ventral frontal systems. In tandem, considering how

early experience disrupts thalamocortical connectivity, potentially resulting in cascading impacts on frontal lobe development, is critical in determining how broader subcortical-frontal systems are sensitive to the early environment. Characterization of the impacts of early experience must also go beyond “early” infancy to include the prenatal period. Prenatal risk factors are likely over-represented in populations of children who experience postnatal adversity. The impacts of prenatal experience on long-term physiology are well-known in epidemiology (Godfrey & Barker, 2001). Emerging research indicates that adverse prenatal experiences including drug or alcohol exposure (Archibald et al., 2001; Sowell et al., 2008; Warner et al., 2006), maternal stress (Lebel et al., 2015; Sarkar et al., 2014), and more subtle variations in the prenatal environment that result in differences in the normal range of birth weight (Raznahan, Greenstein, Lee, Clasen, & Giedd, 2012) shape long-term measures of brain development. Last, it is necessary to move beyond an exclusive focus on the brain. Understanding interactions between multiple biological systems sensitive to adversity, including physical growth and maturation rate, immunological functioning, and epigenetic modifications will more clearly illuminate how broader biological development is shaped by early experience.

Role of individual differences. The current studies described the impact of early adversity at the group level rather than characterizing individual differences in resilience, the variability of outcomes in individuals following past or concurrent adversity (Masten, 2001). Recent theories rooted in evolutionary biology have posited that high sensitivity to the environment may be selected for across evolution. Within this framework, individuals vary not only in sensitivity to risk, but more broadly in sensitivity to both

positive and negative features of the environment (Belsky & Pluess, 2009; Boyce & Ellis, 2005). While these models are attractive and have demonstrated utility in explaining individual differences in how children respond to manipulations of the environment via interventions (e.g. Bakermans-Kranenburg, Van IJzendoorn, Pijlman, Mesman, & Juffer, 2008), modern conceptualizations of the brain dictate that all individuals are sensitive to the environment and that sensitivity continues across the entire lifespan. Experience-dependent brain development (reviewed in Chapter 1), for example, is a well-defined form of plasticity across the lifespan, supported by continued generation and retention of synapses (Greenough, Black, & Wallace, 1987) and myelination of connections (Lovden et al., 2010). Furthermore, there is not necessarily a special privilege for early plasticity. Rapid changes in brain structure and function can be induced by relatively mundane experiences (i.e. musical instrument training, learning to juggle) in both young children and older adults (Busch, Schuierer, Bogdahn, & May, 2004; Schlaug et al., 2009). Understanding individual differences in sensitivity to the environment is an important direction for future research; however, in tandem, we must also continue to characterize how different neural systems are more or less sensitive to the environment across different windows of development.

Broader Impacts/Implications for Translation

The public health and/or policy implications of our findings are quite clear. Early disparities in prefrontal cortex development, observable even within the first year of life, may persist across the lifespan. Fortunately, multiple pathways exist to target interventions to promote typical development of prefrontal cortex in children at risk.

Training attentional control in young infants fundamentally alters the way children experience and interact with their world; this training has been demonstrated to be effective in infants within the first year of life (Wass, Porayska-Pomsta, & Johnson, 2011; Wass, Scerif, & Johnson, 2012) and shows transfer across cognitive domains (Wass et al., 2012). Sensitive parenting has been linked to better EF development in younger children (Bernier, Calkins, & Bell, 2016; Bernier, Carlson, Deschenes, & Matte-Gagne, 2012; Bernier, Carlson, & Whipple, 2010), and longitudinally to adolescent structural development of prefrontal cortex (Whittle et al., 2014). Interventions that target the development of sensitive, responsive caregiving in parents of young at-risk infants may positively shape early prefrontal cortex development. However, the possibility of intervention should not diminish the potential severity of long-term deficits induced by environmental disparity (e.g. see DiPietro, 2000). The impact of adverse experience on prefrontal cortex development is non-linear; infants at the highest levels of risk are disproportionately affected. Broader social policy changes are ultimately needed to diminish the impacts of early adverse environments on long-term disparities in brain development.

Evidence for how early experience and early interventions impact the developing brain and prefrontal cortex at the mechanistic level is still quite scarce. But waiting to intervene until the preschool or early school years may lead us to miss out an important window of opportunity when prefrontal circuits organize and are especially sensitive to the environment. Intervention programs may produce a higher return on investment by moving much earlier in development: to the toddler, infant, or even prenatal periods (see

Doyle, Harmon, Heckman, & Tremblay, 2009 for a discussion on timing of intervention).

However, there is also little evidence to suggest that differences in prefrontal cortex development induced by early experience are immutable; the human brain remains sensitive to the environment across the lifespan. The effective translation of topics such as “positive” versus “toxic” stress (Shonkoff et al., 2012) to policy makers provides a compelling argument that similar dissemination of these messages is possible. We challenge advocates for children’s well being to craft a similar message, highlighting that brain development disparities begin early in infancy but that neural systems remain open to change.

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APPENDIX for Study 1a

Supplemental Methods

Infant Eye-Tracking Tasks

Reversal learning. In this eye-tracking task, an attention-getting stimulus was used prior to the first trial and between all subsequent trials to orient infants' attention to the center of the screen. All stimuli were presented on a black background. The white outline of two 11.5 x 6.75 inches rectangles, spaced 12 inches apart, remained centered on the screen for the entire trial duration and represented the potential locations of the visual reward. The task consisted of two phases: a pre-switch or "learning" phase (9 trials) followed by a post-switch or "reversal" phase (9 trials). For the pre-switch trials, infants were presented with a central visual cue, a brief delay period, and then a visual reward. The visual cue consisted of a looming, red star, presented for 1100 ms and ranging in size from approximately 1.25 to 3.5 inches square. During the following 900 ms delay period no visual stimuli appeared. The visual cue and subsequent delay were accompanied by a repeating chime sound to maintain infant attention towards the visual display. Last, the visual reward (4 second long video clips of animated animal puppets with background music) consistently appeared on the same side of the screen within the white rectangle. The initial location (left vs. right side of the screen) of the visual reward was counterbalanced across infants. Infants were expected to learn that the reward stimulus appeared in a specific location. In the post-switch phase of the experiment, the trial structure was identical but the location of the visual reward changed such that infants were now required to direct their gaze to the opposite side of the screen.

Infant looking direction was monitored online using the experimenter's key presses to replace invalid trials. Invalid trials included those in which the infant looked away (>500 ms) from the central visual cue and trials in which the infant failed to make a directional look after the disappearance of the central visual cue (i.e. infant never looked to the visual reward). Infant eye movements were subsequently coded offline to confirm latency and directionality of all eye movements. This offline coded data was used to determine outcome measures of interest, including anticipatory looking. An anticipatory look was defined as an initial eye movement to the correct side of the screen after the end of the central visual cue and within the first 250 ms of the visual reward. If infants were able to learn that the visual reward had a predictable location, they would be expected to increase their anticipatory looks to the side of the screen where the visual reward reliably appeared. Perseverative eye movements were coded using similar latency criteria (but looks to the previously correct side) during the reversal phase of the task.

Reliability was assessed on a randomly selected sample of 10% of the videos coded by each trained rater for number of looks classified as anticipatory. Across raters, the correlation for number of anticipatory looks ranged from $r = .85$ to $r = .95$. The agreement between raters at the per-trial level for looks classified as anticipatory was >80% for each coder.

Habituation. In this eye-tracking task, an attention-getting stimulus was used prior to the first trial and between all subsequent trials to orient infants' attention to the center of the screen. Stimuli included two Caucasian female faces, which were selected to be highly dissimilar in physical appearance. Faces were approximately 13.5 inches tall

and were presented on a black background. For each infant, one face (counterbalanced across infants) served as the habituation stimulus and the other as the novel, test stimulus.

During the habituation portion of the experiment the face stimulus was presented for up to 15 seconds per trial or until the infant looked away for more than 1000 ms. Infant looking time was calculated online using the experimenter's key presses; if the infant had multiple, short looks (i.e. <1000 ms) away from the screen over the course of the trial, the cumulative looking duration over the entire trial was used. The habituation criterion was based on a sliding-window design. The criterion was met when the infant's average look duration over three consecutive trials was less than 50% of his/her average look duration from the first three trials of the experiment. As such, the minimum number of trials to reach habituation was 4. A maximum of 21 trials to reach habituation was allowed.

Once the infant had reached the habituation criterion, the test phase of the experiment began. First each infant viewed an extended, new attention-getting stimulus for approximately 15-20 seconds to impose a delay that would increase the working memory demands of the task. Infants then completed six additional trials, three in which the now-familiar habituation face was presented and three trials in which the novel face was presented. Trial order (familiar vs. novel) was randomized across infants. Each stimulus in the test phase of the experiment was presented for up to 10 seconds per trial or until the infant looked away for more than 800 ms. Cumulative looking duration over the entire trial was again used if the infant had multiple short looks (i.e. <800 ms) away from the screen. The original attention-getting stimulus was presented between trials to

orient infants' attention to the center of the screen. Throughout the habituation and test phase of the experiment, trials in which the infant immediately looked away following the presentation of the face (i.e. <500 ms of looking-time) were marked as invalid and replaced. Infant eye movements were subsequently coded offline to confirm looking duration for habituation and test trials.

Because the accuracy of the original experimenter's key presses was important in correctly setting the habituation criterion for each infant, reliability of the offline, hand-coded data was assessed for a randomly selected sample of 10% of videos against the original experimenter's computer coding. Correlations for total looking-time measures between the computer and hand-coded data were >.95.

Processing speed/attention shifting. In this eye-tracking task, all stimuli were presented on a black background. An attention-getting stimulus was used prior to the first trial and between all subsequent trials to orient infants' attention to the center of the screen. Infants were presented with a central fixation stimulus followed by a peripheral target stimulus. The central fixation stimulus was a looming fuchsia letter 'X', ranging in size from approximately 1.25 to 3.5 inches square, accompanied by a chime sound to hold infants' attention. The central fixation stimulus was presented for a variable duration of either 1200 or 1800 ms and disappeared upon presentation of the target stimulus. Two durations were selected to avoid anticipatory eye movements to the subsequent target stimulus. The set of peripheral target stimuli consisted of static images, approximately 5.5 inches square, of colorful line-drawings (red flower, orange star, teal spiral, blue butterfly) presented at the left edge or right edge of the screen relative to the

original central fixation stimulus. The target stimulus remained visible for up to 1200 ms or until the infant had looked away for more than 500 ms.

Infant looking behaviors were tracked online using the experimenter's key presses to enable the replacement of invalid trials. Trials were discarded and replaced if the experimenter indicated that the infant looked away prior to the onset of the peripheral target or if the infant failed to make an eye movement toward the target within the 1200 ms window following target onset. Trials continued until the infant became too fussy to continue or completed a maximum of 24 valid trials.

Infant eye movements were subsequently coded offline to confirm direction and latency of all eye movements. This offline coded data was used to determine the latency of the infant's first look following the onset of the target in all trials. Trials that were flagged by the experimenter as invalid were discarded as well as any additional trials that were judged to be invalid by the offline coding. Latency data were initially filtered to exclude latencies <200 ms, as these likely reflected anticipatory looks, or those greater than 2.5 standard deviations above the individual's mean. The remaining data was then averaged to calculate each infant's mean latency to orient (i.e. reaction time) to the peripheral target. Shift rate, or the number of eye movements (e.g. central stimulus to left side of the screen = 1 shift) across each trial, was also calculated for all valid trials and averaged. Infants were required to have a minimum of 10 valid trials, following data filtering, for their data to be considered an accurate measure of the individual's orienting speed.

Reliability was assessed on a sample of 10% of videos coded by each trained rater. The difference in the overall average latency to orient toward the peripheral target between raters was <50 ms for all double-coded videos; specifically, the average difference between raters was 16 ms (range = 2 - 36 ms).

A not B. In this reaching version of the classic A not B task, infants were seated on their caregivers' lap across from the experimenter. The experimenter called the infant's attention to a small attractive toy (e.g. rattle, squeaky animal, etc). If the infant's attention was lost during hiding of the toy, the experimenter attempted to regain it by tapping the toy on the table and calling the infant's name. Toys were also exchanged by the experimenter if the infant lost interest in the task. Correct reaches were rewarded with applause and verbal praise from the experimenter and the opportunity for the infant to briefly manipulate the toy. When the infant reached incorrectly, s/he was allowed to continue searching, but was not permitted to play with the toy. If necessary, the experimenter showed the infant where the toy had been hidden.

Infants first completed a pre-test to assess basic object permanence skills. The infant's attention was called to the center of the table and the toy was hidden under one of two identical covers (blue washcloths). Infants were required to find the item under both the left cover and the right cover over the course of four trials (where the toy alternated sides) to advance to the A not B task. Infants who were unable to complete the pre-test were given a simpler task: to locate an item hidden under one cover on at least two out of three total trials. Those infants who were successful advanced to the A not B task. The remaining infants were given the easiest pre-test task: to locate an item partially hidden

under one cover on at least two out of three total trials.

Infants that successfully completed a portion of the pre-test moved on to the classic A not B task. The A not B test apparatus consisted of a white, wooden box which measured 31 inches long, 11 inches wide, and 11 inches deep. The box contained two square wells that were each 5.5 inches across, separated by 12 inches from their interior edges. White fabric cloths that could be easily lifted by the infant covered the two wells. After calling the infant's attention to the toy over the center of the testing apparatus, the experimenter hid the toy in the appropriate well and pushed the testing apparatus forward to allow the infant to search. Initial side of hiding was counterbalanced across infants.

Infants were given up to five trials to find the toy hidden at the A location. After two consecutive, successful retrievals of the toy from the A location, the toy was then hidden in the opposite well (the B location). Of note, in many A not B tasks the toy reverses location only once. Here the toy reversed location for each new set of trials (each time the A not B error was assessed), so the 'A' and 'B' location refer not to physical locations but to 'repeat' vs. 'reversal' conditions. Young infants frequently make the error of returning to search at location A, known as the A not B error. Infants who made the A not B error were administered one additional set of trials to again test for the A not B error. Those that were able to pass the A not B trial advanced to the delay condition.

During the delay condition the toy was hidden as before but infants were not allowed to immediately search for the toy; instead the experimenter clapped her hands, called the infants name, and counted to divert the infant's attention from the hiding

location. After the delay was completed, the testing apparatus was pushed forward to allow the infant to search.

Testing was stopped after an infant failed two A not B trials at a particular delay length (or if the A not B error was not able to be assessed because the infant was unable to find the toy at the A location on two consecutive trials out of five possible for a given delay length). Delay length increased by 3 seconds for each successful trial set and 9 seconds was set as the ceiling delay length tested.

Data were coded offline by trained raters using the overhead video feed for correct reaches. A reach was operationalized as physically touching the cover in an intentional manner. The first cover that the infant reached to on a trial was counted, even if s/he immediately after reached to the correct location. Each infant was assigned a score equivalent to the highest level of the task s/he successfully completed (similar to Bell & Fox, 1997). The scale included:

0. object partially covered with one cloth
1. object completely covered with one cloth
2. object hidden under one of two cloths
3. Search (A) trials with 0 second delay
4. Switch (B) trials with 0 second delay
5. Search (A) trials with 3 second delay
6. Switch (B) trials with 3 second delay
7. Search (A) trials with 6 second delay
8. Switch (B) trials with 6 second delay

9. Search (A) trials with 9 second delay

10. Switch (B) trials with 9 second delay

Infants were also assigned a score based on whether they were able to complete the 0 second switch trial.

Reliability was assessed on a sample of 30% of videos coded by each trained rater. Raters were in agreement for the highest level achieved by the infant on 94% of videos.

Problem solving. Infants were asked to complete a sequence of steps to uncover and retrieve a hidden toy. Infants were seated on their parents' lap, with task materials presented by the experimenter, seated directly across from the infant-parent dyad, on a 22.5 x 14 inch blue tray, oriented perpendicularly to the infant. Parents were instructed that they could talk to their infant but that they should not direct him/her in retrieving the toy; parents were also asked not to touch the task materials. All infants first completed a familiarization trial where they were given 30 seconds to explore the materials used during the task (i.e. cloth, barrier, and cover).

During task trials, the experimenter called the infant's attention to a small attractive toy (e.g. rattle, squeaky animal, etc). If the infant's attention was lost during hiding of the toy, the experimenter attempted to regain it by tapping the toy on the tray and calling the infant's name. Toys were also exchanged by the experimenter if the infant lost interest in the task. Solved problems were rewarded with applause and verbal praise from the experimenter. When the infant failed to solve the problem prior to the time limit (30 seconds), s/he was allowed to continue or was helped by the experimenter.

To maintain task motivation, infants were allowed to manipulate the toy for approximately 20 seconds after each trial. Sequences that were tested included a one-step, two-step, and three-step problems.

In one-step problems, a 12 x 12 inch blue cloth was placed on the tray. The toy was placed at the far end of the cloth. The infant was required to pull the cloth in order to retrieve the toy. In the two-step problems, the cloth and toy were arranged identically to the one-step problem on the tray. In addition, an opaque 9 x 4 x 6 inch foam barrier was then placed directly in front of the cloth. Infants therefore had to remove the barrier prior to being able to pull the cloth and retrieve the toy. In the three-step problems, the cloth and toy were again arranged identically to the one-step problem on the tray. A transparent plastic cover (6 x 6 x 3 inches) was set directly over the toy, on top of the cloth. The barrier was placed in front of the cloth as in the two-step problems. To retrieve the toy, infants had to remove the barrier, pull the cloth, and lift the transparent cover.

Infants attempted three trials at each level of the task. Testing was terminated if the infant was unable to complete at least one trial within the time limit at a given level of the task. The time limit for all trials was 30 seconds, beginning from when the infant first made contact with the cloth (one-step problem) or the barrier (2- and three-step problems) and ending when the infant touched the toy. If the toy became inaccessible during the trial (e.g. fell off the edge of the table), the trial was re-administered.

Data were coded offline using the overhead video feed by two trained raters based on a coding scheme adapted from Willatts et al. (1998) for evidence of intentional

behavior and latency to solve each problem. Infants were considered to have ‘solved’ the problem if they picked up the toy within the 30 second time limit. See Appendix Table 1 for an example scoring rubric for the three-step problem.

Reliability was assessed on an overlapping sample of 10% of the videos coded by the two raters. The correlation across raters for total intentionality scores was $r = .99$. The correlations across raters for the one-step, two-step, and three-step problem latencies were above $r = .95$.

Appendix Table 1

Example Scoring Rubric for Three-Step Problem in Problem Solving Task

<u>Step</u>	<u>No intention (0)</u>	<u>Possible intention (1)</u>	<u>Intention (2)</u>
<i>Barrier</i>			
Barrier behavior	Play; barrier not removed	Hesitant removal*	Removal of barrier
Fixation	Fixate away from tray setup	Fixate mostly on barrier	Fixate toward tray setup
Cloth retrieval	Ignore cloth	Attempt to grasp cloth	Pick up cloth
<i>Cloth</i>			
Cloth behavior	Play; no attempt to grasp cloth	Hesitant pulling	Pull cloth
Fixation	Fixate away from cover	Fixate briefly away** from cover	Fixate on cover continuously
Cover retrieval	Ignore cover	Attempt to grasp cover	Pick up cover
<i>Cover</i>			
Cover behavior	Play; no attempt to remove cover	Hesitant removal	Removed cover
Fixation	Fixate away from toy	Fixate briefly away from toy	Fixate on toy continuously
Toy retrieval	Ignore toy	Attempt to grasp toy	Pick up toy

Notes.

*"Hesitant" = infant successfully completes the step but with a 2 second or longer break in goal-directed activity (e.g. contacts the barrier and then removes hands for over 2 seconds)

**Fixates "briefly away": infant fixates mostly on the relevant task item, but looks away for brief periods (<2 seconds per individual look-away). Look aways of greater than 2 seconds result in the '0' non-intentional score.

Attention flexibility. Infants completed a semi-structured, free play with toys task. Infants were seated on their parents' lap and presented with a single toy (a colorful, inchworm rattle with small moveable parts) on top of a 22.5 x 14 inch blue tray. The experimenter was seated crosswise from the infant and parent. Parents were instructed that they could talk to their infant and should allow their infant to play with the toy freely, but were asked not to touch the toy. Infants were given two minutes to explore the toy and it was returned by the experimenter if it became out of reach.

Data were coded offline using the video feed that was focused directly toward the infant's face as described in Clearfield and Jedd (2013). Two measures of attentive behaviors (focused attention toward toys and focused attention toward people) and two measures of inattention (quiet disengagement and inattention) were operationalized. Focused attention toward toys was defined as visual attention toward a toy, often including a focused face and/or examining behaviors. Focused attention toward people was defined as visual attention with a social focus, directed at either the parent or the caregiver. Quiet disengagement was defined as the infant making physical contact with a toy, but not visually looking at the toy, reflecting haptic exploration for toys. The last measure, inattention, was defined as looking off task and not touching the toy (e.g. looking at the ceiling, playing with the toy presentation tray, etc).

All data were coded by trained raters for the total duration and number of epochs of each type of attention and inattention event that occurred during the two minute period. The two types of focused attention were selected as outcome measures of infants; for each type of focused attention, average length of attention bouts across the entire two

minute period was calculated.

Reliability was assessed on a randomly selected sample of 10% of videos coded by each trained rater for the number of attention shifts and duration of attention shifts. Across raters, the correlation for number of attention shifts was as follows: attention toward toys ($r = .84$ to $r = .94$), attention toward people ($r = .84$ to $r = .99$), quiet disengagement ($r = .83$ to $r = .99$), and inattention ($r = .88$ to $r = .99$). Across raters, the correlation for the duration of attention types was as follows: attention toward toys ($r > .99$), attention toward people ($r = .76$ to $r = .96$), quiet disengagement ($r = .83$ to $r = .99$), and inattention ($r = .90$ to $r = .99$).

APPENDIX for Study 3

Supplemental Methods

Participants: 56-Direction DTI Data

A partially overlapping sample of 24 PI children (18 females, 6 males, $M_{age} = 13.17$ years, $SD = .60$, range = 12.20 - 14.09 years) and 28 controls (23 females, 5 males, $M_{age} = 12.80$ years, $SD = .46$, range = 12.12 - 13.92 years) successfully completed a higher-quality, 56-direction DTI sequence (TR = 8600 ms, TE = 90 ms, FOV = 256 mm, 2 mm slice thickness), covering 64 slices with a b-value of 1000. Demographic and adoption-related characteristics for the sample of children that provided 56-direction DTI data are included in Appendix Tables 1 and 2.

Data from an additional 19 PI children and 25 comparison children were excluded from the final sample of 56-direction DTI data for the following reasons: structural MRI scan anomaly (1 PI, 3 control), neuroimaging data collection errors (2 control), and excess motion in DTI data (18 PI, 20 control).

Data Processing: 56-Direction DTI Data

Processing for the 56-direction DTI data was equivalent to that described in the main paper. The one exception was that we were forced to also relax the relative motion criterion for the B0 images to <1.5 mm to retain an adequate amount of participants in this smaller data set.

Tract of Interest Analyses: 56-Direction DTI Data

An identical analysis plan to the 12-direction data set was employed. However, age at adoption group analyses and age at adoption correlation analyses were not performed in the 56-direction data set due to the reduced sample size.

Appendix Table 1

Demographics of Youth with 56-Direction DTI Data

	PI Adolescents <i>N</i> = 24	Non-Adopted Controls <i>N</i> = 28
<i>Sample Characteristics</i>		
Age in years, <i>M</i> (<i>SD</i>)	13.17 (.60)	12.80 (.49)*
Male, <i>n</i> (%)	6 (25.0)	5 (17.9)
Two Parent Household, <i>n</i> (%)	18 (75.0)	25 (89.3)
IQ score, <i>M</i> (<i>SD</i>); range	107.33 (12.30) 88-128	117.07 (6.62)* 99-130
Pubertal score, <i>M</i> (<i>SD</i>); range	2.65 (.86) 1.20-3.80	2.35 (.71) 1.00-3.60
<i>Primary Caregiver Education</i>		
High school degree or GED, <i>n</i> (%)	1 (4.2)	1 (3.6)
Some college, <i>n</i> (%)	1 (4.2)	1 (3.6)
Associate degree, <i>n</i> (%)	3 (12.5)	1 (3.6)
Bachelor's degree, <i>n</i> (%)	11 (45.8)	15 (53.6)
Master's degree, <i>n</i> (%)	7 (29.2)	7 (25.0)
Doctoral or professional degree, <i>n</i> (%)	1 (4.2)	3 (10.7)
<i>Annual Household Income^a</i>		
Income, <i>M</i> (<i>SD</i>); range	\$107,696 (\$98,164); \$30,000-\$500,000	\$115,667 (\$48,326); \$20,000-\$200,000
≤ \$50,000, <i>n</i> (%)	4 (17.4)	2 (8.0)

\$51,000 - \$100,000, <i>n</i> (%)	13 (56.5)	9 (37.5)
\$101,000 - \$150,000, <i>n</i> (%)	4 (17.4)	7 (29.2)
$\geq \$151,000$, <i>n</i> (%)	2 (8.7)	6 (25.0)

Notes. ^aNot all families provided full demographic data; percentages thus reflect the percent of total responses. * $p < .05$.

Appendix Table 2

Adoption History of Post-Institutionalized Youth with 56-Direction DTI Data

PI Youth	
<i>N = 24</i>	
<i>Adoption History</i>	
<hr/>	
Age at adoption in months, <i>M (SD)</i> ; range	18.08 (16.39) 8-72
Institutional care in months, <i>M (SD)</i> ; range	17.31 (14.87) 8-60
Percent of care in institution, <i>M (SD)</i> ; range	97.02 (4.95) 83-100
Time since adoption in years, <i>M (SD)</i> ; range	11.66 (1.56) 6.78-13.38
<hr/>	
<i>Country of Origin</i>	
<hr/>	
China, <i>n (%)</i>	7 (29.2)
Ecuador, <i>n (%)</i>	1 (4.2)
India, <i>n (%)</i>	4 (16.7)
Russia, <i>n (%)</i>	10 (41.7)
Ukraine, <i>n (%)</i>	1 (4.2)
Vietnam, <i>n (%)</i>	1 (4.2)
<hr/>	

Supplemental Results

Outline of Results

The following analyses are included in the Supplemental Results and are numbered as follows:

1. Group differences in TBSS: Adoption group comparisons (12-direction data):
These analyses include the TBSS comparison of earlier- and later-adopted PI children to the non-adopted control group. Only the PI vs. non-adopted controls contrasts were shown in the main paper.
2. Tract of interest analyses (56-direction data): These analyses duplicate the tract of interest analyses presented in the main paper, but use the 56-direction data set.
3. Tract of interest analyses: correction for total white matter volume: These analyses test whether previously detected effects in all tract of interest analyses remain significant after correcting for individual differences in total white matter volume.
 - a. Group differences in scalar metrics of white matter organization (12- and 56-direction data): These analyses represent the PI vs. control group differences.
 - b. Age at adoption group analyses (12-direction data): These analyses represent the PI-EA vs. PI-LA vs. control analyses.
 - c. Age at adoption correlational analyses (12-direction data): These analyses were performed within the truncated (<24 months of age at adoption) PI group.

4. Ethnic subgroup analyses (12-direction data): These analyses determine whether lower FA observed in the PI-EA group is driven by differences between the groups in ethnicity.

1. Group Differences in TBSS: Adoption Group Comparisons

TBSS results from the 12-direction DTI data set for the comparisons of earlier- and later-adopted PI children to controls are described below and visualized in Appendix Figures 1-4. TBSS results are consistent with TOI analyses demonstrating that the impact of institutional care on white matter organization was strongest within earlier- adopted (<12 months of age) adolescents.

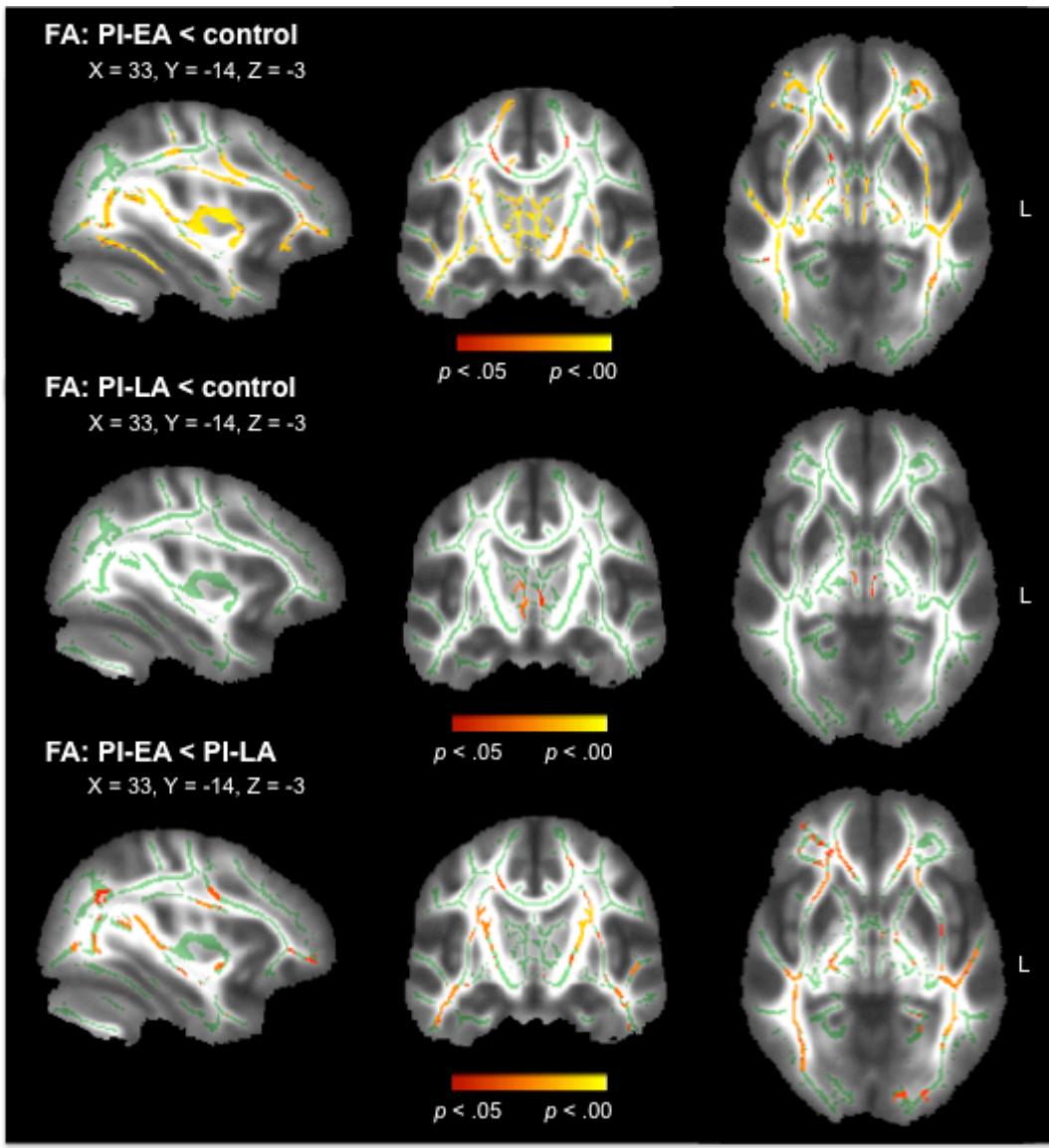
Group differences in FA were driven by the PI-EA group, who showed broad reductions in FA in comparison to both non-adopted controls and later-adopted children. Reductions in FA in later-adopted children vs. controls were restricted to subcortical portions of the thalamic radiations. All other pair-wise comparisons were non-significant.

Group differences in RD were similarly driven by the PI-EA group, who showed higher RD in comparison to both non-adopted controls and later-adopted children; between group differences largely overlapped with regions that had differed in FA. Later-adopted children did not differ from controls in RD. All other pair-wise comparisons were also non-significant.

Group differences in AD were only present for the PI-EA group vs. controls. Earlier-adopted children had higher AD in the bilateral CST, bilateral cingulum (cingulate portion), forceps major and minor, and the right IFOF and anterior thalamic

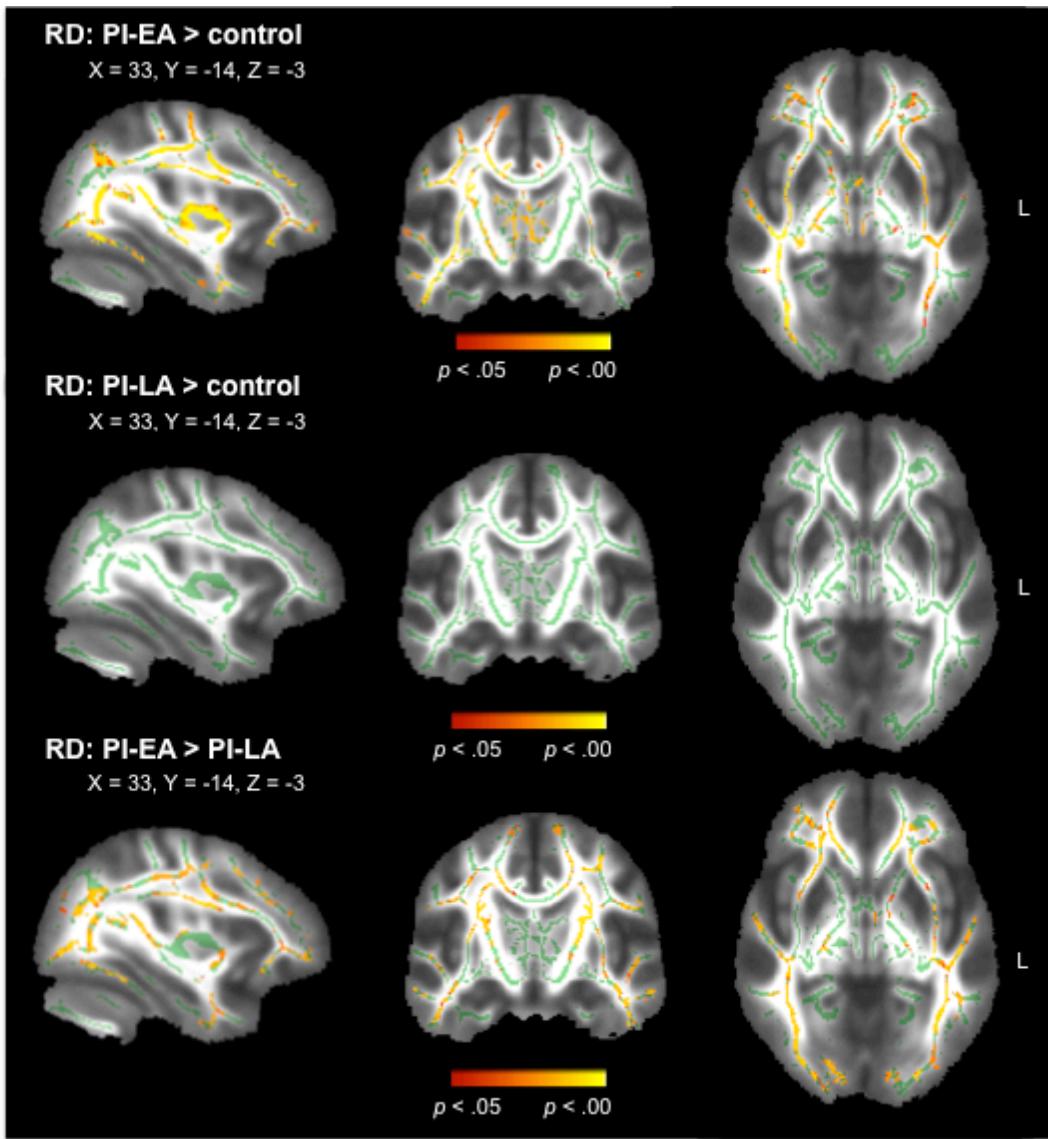
radiations.

Group differences in MD were driven by the PI-EA group, who showed higher MD in comparison to both non-adopted controls and later-adopted children, primarily across posterior regions. Later-adopted children did not differ in from controls in MD. All other pair-wise comparisons were also non-significant.

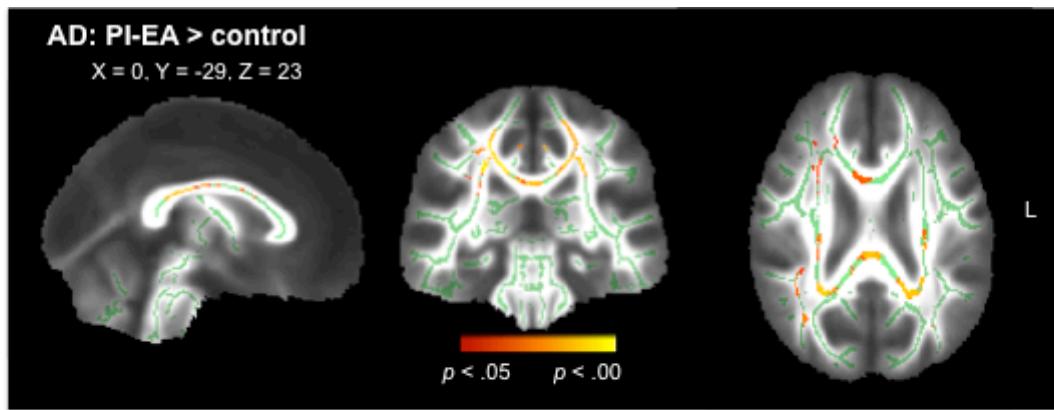


Appendix Figure 1. TBSS group differences in FA. Voxel-wise white matter microstructure differences by adoption group along the derived white matter skeleton (in green). Spatially corrected via multiple comparisons using TFCE at $p < .050$ and overlaid on the group mean FA image. Previously described alterations in FA in PI youth were driven by broad reductions in FA in earlier-adopted PI children. Later-adopted

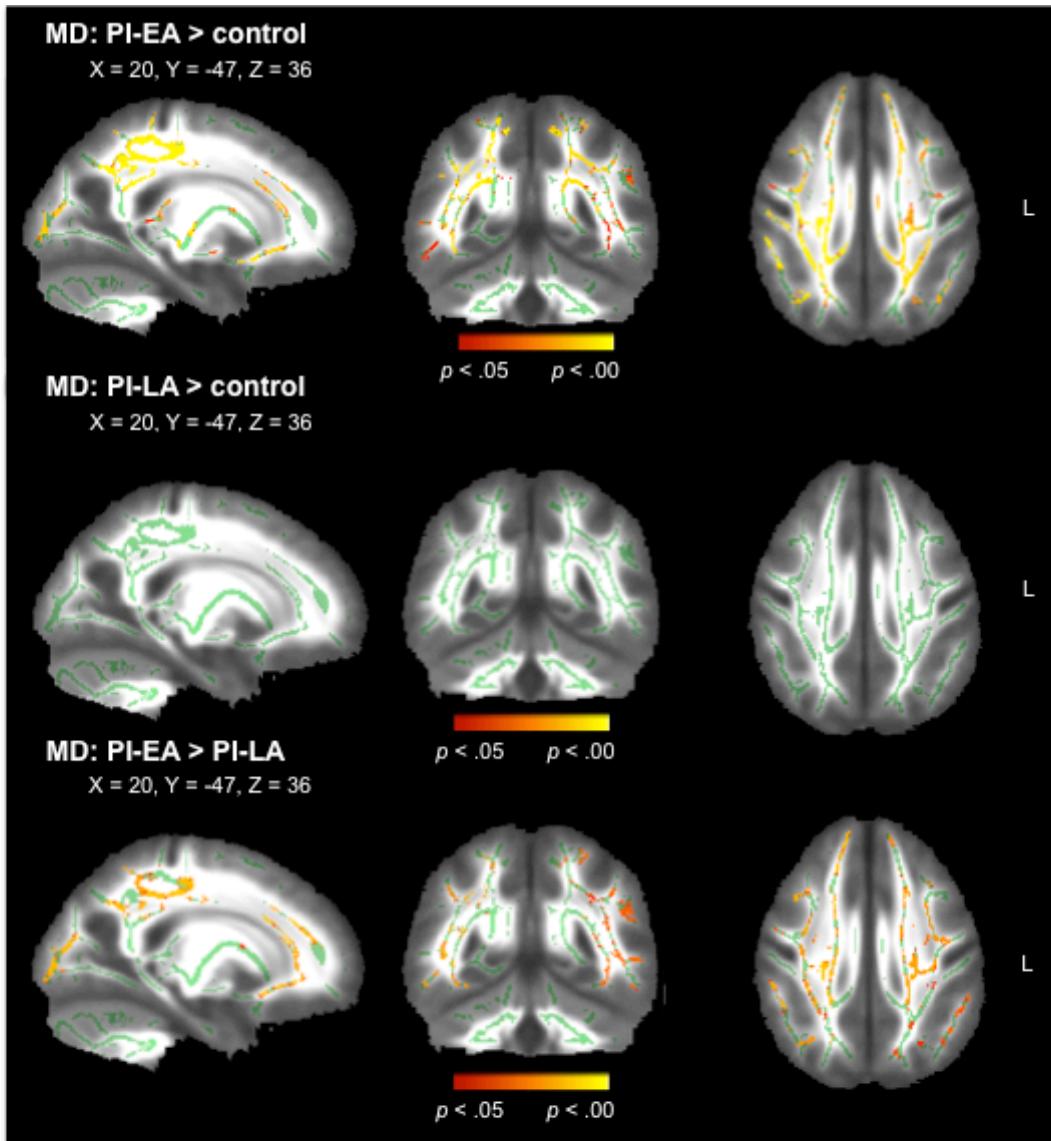
children had reduced FA in comparison to controls only in subcortical portions of the anterior thalamic radiations.



Appendix Figure 2. TBSS group differences in RD. Voxel-wise white matter microstructure differences by adoption group along the derived white matter skeleton (in green). Spatially corrected via multiple comparisons using TFCE at $p < .050$ and overlaid on the group mean FA image. Earlier-adopted children showed higher RD across most regions that differed in FA. Later-adopted children did not differ from non-adopted controls.



Appendix Figure 3. TBSS group differences in AD. Voxel-wise white matter microstructure differences by adoption group along the derived white matter skeleton (in green). Spatially corrected via multiple comparisons using TFCE at $p < .050$ and overlaid on the group mean FA image. Only earlier-adopted PI children showed increased AD vs. non-adopted controls; all other pair-wise comparisons were not significant.



Appendix Figure 4. TBSS group differences in MD. Voxel-wise white matter microstructure differences by adoption group along the derived white matter skeleton (in green). Spatially corrected via multiple comparisons using TFCE at $p < .050$ and overlaid on the group mean FA image. Previously described alterations in MD in PI youth were driven by broad increases in MD in earlier-adopted PI children. Later-adopted children did not differ from non-adopted controls.

2. Tract of Interest Analyses: 56-Direction DTI Data

Age at adoption group analyses and age at adoption correlation analyses were not performed in the 56-direction data set due to the reduced sample size. The following results describe the comparison of the PI vs. control group within TOI in the 12-direction DTI data set. See Inline Supplemental Table 1 from the main paper for details.

Fractional anisotropy (FA). Effects were generally consistent with those reported in the 12-direction data. PI children had reduced FA in the right cingulum (hippocampal portion), bilateral IFOF, right ILF, and right UF.

Radial diffusivity (RD). Only the group difference in the right UF reached statistical significance in the 56-direction data set. Additionally, in the 56-direction data set, PI children had lower RD in the forceps major in comparison to non-adopted controls.

Axial diffusivity (AD). There were few group differences in AD. PI children had lower AD in the right cingulum (hippocampal portion) and in the forceps major.

Mean diffusivity (MD). Differences in MD were generally not statistically significant in the 56-direction data set. However, PI children had lower MD in the forceps major in comparison to non-adopted controls.

3. Tract of Interest Analyses: Correction for Total White Matter Volume

As previously described, PI children showed white matter volume decreases in comparison to controls, following adjustment for age, sex, and total intracranial volume. It is possible that whole brain differences in white matter volume are related to white matter microstructural differences. In TBSS analyses, the use of an internal white matter

skeleton reduces partial volume effects, and as such, group differences in white matter volume are less of a concern. We elected to conduct supplemental TOI analyses with cortical white matter volume as a covariate. We re-ran analyses for significant effects detected in group difference (PI vs. control) and adoption group difference (PI-EA vs. PI-LA vs. controls) models.

Of note, exploratory analyses in the larger, 12-direction DTI data set indicated that the relationship between scalar white matter metrics and whole brain white matter volumes differed across the three study groups (PI-EA, PI-LA, and control children). For example, within the non-adopted controls, most tracts of interest showed statistically significant, positive correlations between fractional anisotropy (FA) and total cortical white matter volume (age and sex adjusted). However, significant relationships between FA and total cortical white matter volume (age and sex adjusted) were largely absent in the PI group (both when all participants were pooled and when participants were divided in PI-EA and PI-LA groups). Since the relationship between this covariate and white matter metric outcomes are not equivalent across groups, these results should be interpreted with some caution; however, they are largely consistent with the uncorrected analyses reported in the main paper.

3a. Group differences in scalar metrics of white matter organization: corrected for total cortical white matter volume. We re-ran analyses only in which significant group difference (PI vs. control) effects were previously detected. Following correction for total white matter volume, effects were generally consistent with those reported in the main paper and in earlier supplemental results (although some effects

were reduced to trend level significance). See Appendix Table 3 for additional details.

Fractional anisotropy (FA). Of the tracts that showed a significant group effect in the 12-direction data set ($PI < control$), the following survived correction: right anterior thalamic radiations, right cingulum (cingulate and hippocampal portions), bilateral IFOF, and right UF. Of the tracts that showed a significant group effect in the 56-direction data set ($PI < control$), only the right UF survived correction.

Radial diffusivity (RD). Of the tracts that showed a significant group effect in the 12-direction data set ($PI > control$), the following survived correction: right cingulum (cingulate portion), bilateral IFOF, right ILF, right SLF, and right UF. Of the tracts that showed a significant group effect in the 56-direction data set, only the forceps survived correction ($PI < control$).

Axial diffusivity (AD). Of the tracts that showed a significant group effect in the 12-direction data set, only the right CST ($PI > control$) survived correction. Of the tracts that showed a significant group effect in the 56-direction data set, only the forceps survived correction ($PI < control$).

Mean diffusivity (MD). Of the tracts that showed a significant group effect in the 12-direction data set ($PI > control$), the following survived correction: right CST, right IFOF, right ILF, right SLF, and right UF. Of the tracts that showed a significant group effect in the 56-direction data set, only the forceps survived correction ($PI < control$).

Appendix Table 3

Comparison of Age and Sex Adjusted White Matter Scalar Metrics in Controls and PI Children, Corrected for Individual Differences in White Matter Volume, in Tracts that Differed by Group (12-Direction and 56-Direction DTI Data)

	12-Direction Data				56-Direction Data			
	F	p	η_{partial}^2	PI B (se)	F	p	η_{partial}^2	PI B (se)
L. Anterior Thalamic Radiations								
FA	1.817	.181	.018	-.006 (.004)				
RD	2.865	.094	.028	.945 x 10 ⁻⁵ (.558 x 10 ⁻⁵)				
AD								
MD								
R. Anterior Thalamic Radiations								
FA	5.784	.018*	.055	-.009 (.004)				
RD	2.581	.111	.025	.932 x 10 ⁻⁵ (.580 x 10 ⁻⁵)				
AD								
MD								
R. CST								
FA								
RD								
AD	6.945	.010*	.065	.165 x 10 ⁻⁴ (.629 x 10 ⁻⁵)				
MD	4.231	.042*	.041	.945 x 10 ⁻⁵ (.459 x 10 ⁻⁵)				
L. Cingulum - Cingulate								
FA	1.728	.192	.017	-.009 (.007)				
RD	2.882	.093	.028	.135 x 10 ⁻⁴ (.797 x 10 ⁻⁵)				
AD								

	MD							
R. Cingulum - Cingulate								
FA	6.021	.016*	.057		-.020 (.008)			
RD	5.221	.024*	.050		.172 x 10 ⁻⁴ (.754 x 10 ⁻⁵)			
AD								
MD								
L. Cingulum - Hippocampus								
FA								
RD								
AD	2.324	.131	.023		-.157 x 10 ⁻⁴ (.103 x 10 ⁻⁴)			
MD								
R. Cingulum Hippocampus								
FA	4.957	.028*	.047		-.016 (.007)	1.287	.262	.027
RD	2.450	.121	.024		.118 x 10 ⁻⁴ (.754 x 10 ⁻⁵)			-.011 (.010)
AD	1.929	.168	.019		-.115 x 10 ⁻⁴ (.830 x 10 ⁻⁵)	3.935	.053	.077
MD								-.230 x 10 ⁻⁴ (.116 x 10 ⁻⁴)
L. IFOF								
FA	9.101	.003*	.083		-.013 (.004)	3.806	.057	.075
RD	7.345	.008*	.068		.158 x 10 ⁻⁴ (.582 x 10 ⁻⁵)			-.011 (.006)
AD								
MD								
R. IFOF								
FA	4.129	.045*	.040		-.009 (.004)	2.543	.117	.051
RD	5.386	.022*	.051		.125 x 10 ⁻⁴ (.540 x 10 ⁻⁵)			-.008 (.005)
AD								
MD	4.299	.041*	.041		.976 x 10 ⁻⁵ (.471 x 10 ⁻⁵)			
R. ILF								
FA	3.656	.059	.035		-.008 (.004)	1.344	.252	.028
								-.007 (.006)

	RD	8.387	.005*	.077	.175 x 10 ⁻⁴ (.604 x 10 ⁻⁵)			
	AD							
	MD	8.186	.005*	.076	.163 x 10 ⁻⁴ (.570 x 10 ⁻⁵)			
R. SLF								
	FA							
	RD	6.313	.014*	.059	.138 x 10 ⁻⁴ (.548 x 10 ⁻⁵)			
	AD							
	MD	6.905	.010*	.065	.132 x 10 ⁻⁴ (.503 x 10 ⁻⁵)			
L. UF								
	FA	1.635	.204	.016	-.005 (.004)			
	RD							
	AD							
	MD							
R. UF								
	FA	4.751	.032*	.045	-.011 (.005)	4.207	.046*	.082
	RD	4.830	.030*	.046	.133 x 10 ⁻⁴ (.607 x 10 ⁻⁵)	2.428	.126	.049
	AD							
	MD	3.998	.048*	.038	.103 x 10 ⁻⁴ (.514 x 10 ⁻⁵)			
Forceps Major								
	FA							
	RD				7.503	.009*	.138	-.347 x 10 ⁻⁴ (.123 x 10 ⁻⁴)
	AD				6.946	.011*	.129	-.507 x 10 ⁻⁴ (.193 x 10 ⁻⁴)
	MD				9.270	.004*	.165	-.402 x 10 ⁻⁴ (.132 x 10 ⁻⁴)

Notes. F-values represent the test statistic value for the effect of group status on the DTI parameter of interest, with corresponding *p*-value and effect size. *B* and associated standard errors give the parameter estimates for the contrast of PI vs. controls.

Corticospinal tract (CST), inferior fronto-occipital fasciculus (IFOF), inferior longitudinal fasciculus (ILF), superior longitudinal fasciculus (SLF), uncinate fasciculus (UF).

*Main effect of group status significant at $p < .050$.

3b. Age at adoption group analyses: corrected for total cortical white matter volume. We re-ran analyses only in which significant adoption group effects were previously detected. Following correction for total white matter volume, effects were generally consistent with those reported in the main paper (although some were reduced to trend level). Recall that analyses were only conducted in the 12-direction DTI data set to maintain statistical power. See Appendix Table 4 for additional details.

Fractional anisotropy (FA). Adoption group differences in the right anterior thalamic radiations, right cingulum (cingulate and hippocampal portions), bilateral IFOF, right ILF, and right UF survived corrections for total cortical white matter volume.

Radial diffusivity (RD). All adoption group differences survived corrections for total cortical white matter volume.

Axial diffusivity (RD). There were no adoption group differences in the original data.

Mean diffusivity (MD). Adoption group differences in the bilateral cingulum (cingulate portion) IFOF, SLF (temporal portion), and the right ILF, right SLF, right UF, and forceps major survived corrections for total cortical white matter volume.

Appendix Table 4

Comparison of Age and Sex Adjusted White Matter Scalar Metrics in Controls, PI-EA, and PI-LA Children, Corrected for Individual Differences in White Matter Volume, in Tracts that Differed by Adoption Group (12-Direction DTI Data)

	<i>F</i>	<i>p</i>	η^2	PI-EA <i>B</i> (<i>se</i>)	PI-LA <i>B</i> (<i>se</i>)	EA vs. LA <i>p</i>
L. ATR						
FA	2.580	.081	.050	-.010 (.005)	-.002 (.005)	.072
RD						
MD						
R. ATR						
FA	5.092	.008*	.093	-.013* (.004)	-.005 (.004)	.043
RD	3.174	.046*	.060	.152 x 10 ⁻⁴ * (.648 x 10 ⁻⁵)	.405 x 10 ⁻⁵ (.635 x 10 ⁻⁵)	.057
MD	2.539	.084	.049	.125 x 10 ⁻⁴ (.603 x 10 ⁻⁵)	.317 x 10 ⁻⁵ (.591 x 10 ⁻⁵)	.085
R. CST						
FA						
RD						
MD	2.908	.059	.055	.125 x 10 ⁻⁴ * (.518 x 10 ⁻⁵)	.671 x 10 ⁻⁵ (.508 x 10 ⁻⁵)	.214
L. Cing-C						
FA	2.436	.093	.047	-.015 (.007)	-.003 (.007)	.081
RD	4.592	.012*	.085	.238 x 10 ⁻⁴ * (.880 x 10 ⁻⁵)	.429 x 10 ⁻⁵ (.862 x 10 ⁻⁵)	.015*
MD	5.242	.007*	.096	.223 x 10 ⁻⁴ * (.779 x 10 ⁻⁵)	.376 x 10 ⁻⁵ (.763 x 10 ⁻⁵)	.009*
R. Cing-C						
FA	4.131	.019*	.077	-.027* (.009)	-.014 (.009)	.144
RD	7.678	.001*	.134	.291 x 10 ⁻⁴ * (.818 x 10 ⁻⁵)	.644 x 10 ⁻⁵ (.802 x 10 ⁻⁵)	.002*
MD	5.903	.004*	.107	.193 x 10 ⁻⁴ * (.751 x 10 ⁻⁵)	-.225 x 10 ⁻⁵ (.736 x 10 ⁻⁵)	.002*
L. Cing-H						
FA	2.929	.058	.056	-.012 (.007)	.003 (.007)	.021
RD						
MD						
R. Cing-H						
FA	7.337	.001*	.129	-.026* (.008)	-.006 (.007)	.003*
RD	5.950	.004*	.107	.235 x 10 ⁻⁴ * (.821 x 10 ⁻⁵)	.124 x 10 ⁻⁵ (.804 x 10 ⁻⁵)	.003*
MD						

L. IFOF						
FA	6.930	.002*	.123	-.018* (.005)	-.009 (.005)	.038
RD	7.493	.001*	.131	.238 x 10 ⁻⁴ * (.640 x 10 ⁻⁵)	.852 x 10 ⁻⁵ (.627 x 10 ⁻⁵)	.009*
MD	6.305	.003*	.113	.184 x 10 ⁻⁴ * (.564 x 10 ⁻⁵)	.457 x 10 ⁻⁵ (.552 x 10 ⁻⁵)	.007*
R. IFOF						
FA	5.217	.007*	.095	-.014* (.005)	-.004 (.004)	.015
RD	7.738	.001*	.135	.210 x 10 ⁻⁴ * (.586 x 10 ⁻⁵)	.483 x 10 ⁻⁵ (.574 x 10 ⁻⁵)	.002*
MD	6.529	.002*	.117	.167 x 10 ⁻⁴ * (.514 x 10 ⁻⁵)	.344 x 10 ⁻⁵ (.504 x 10 ⁻⁵)	.005*
L. ILF						
FA						
RD	3.411	.037*	.064	.133 x 10 ⁻⁴ (.724 x 10 ⁻⁵)	-.285 x 10 ⁻⁵ (.709 x 10 ⁻⁵)	.014*
MD						
R. ILF						
FA	7.797	.001*	.136	-.016* (.005)	-.002 (.005)	.001*
RD	12.514	.000*	.202	.293 x 10 ⁻⁴ * (.639 x 10 ⁻⁵)	.686 x 10 ⁻⁵ (.626 x 10 ⁻⁵)	.000*
MD	9.693	.000*	.164	.256 x 10 ⁻⁴ * (.617 x 10 ⁻⁵)	.788 x 10 ⁻⁵ (.604 x 10 ⁻⁵)	.002*
R. SLF						
FA						
RD	4.314	.016*	.080	.181 x 10 ⁻⁴ * (.617 x 10 ⁻⁵)	.987 x 10 ⁻⁵ (.604 x 10 ⁻⁵)	.138
MD	4.758	.011*	.088	.174 x 10 ⁻⁴ * (.565 x 10 ⁻⁵)	.943 x 10 ⁻⁵ (.553 x 10 ⁻⁵)	.117
L. SLF temporal						
FA						
RD	3.530	.033*	.067	.600 x 10 ⁻⁵ (.103 x 10 ⁻⁴)	-.175 x 10 ⁻⁴ (.101 x 10 ⁻⁴)	.012*
MD	4.093	.020*	.076	.874 x 10 ⁻⁵ (.721 x 10 ⁻⁵)	-.963 x 10 ⁻⁵ (.707 x 10 ⁻⁵)	.005*
R. SLF temporal						
FA						
RD						
MD	3.616	.030*	.068	.127 x 10 ⁻⁴ (.641 x 10 ⁻⁵)	-.185 x 10 ⁻⁵ (.628 x 10 ⁻⁵)	.013*
R. UF						
FA	3.727	.028*	.070	-.015* (.005)	-.007 (.005)	.108
RD	4.555	.013*	.084	.198 x 10 ⁻⁴ * (.676 x 10 ⁻⁵)	.752 x 10 ⁻⁴ (.662 x 10 ⁻⁵)	.045
MD	3.832	.025*	.072	.153 x 10 ⁻⁴ * (.574 x 10 ⁻⁵)	.568 x 10 ⁻⁵ (.562 x 10 ⁻⁵)	.062
Forceps Major						
FA						
RD						
MD	3.311	.041*	.063	-.717 x 10 ⁻⁵ (.112 x 10 ⁻⁴)	-.261 x 10 ⁻⁴ * (.110 x 10 ⁻⁴)	.059
Forceps Minor						
FA	3.067	.051	.058	-.016 (.004)	.001 (.004)	.020*

RD
MD

|

|

Notes. F-values represent the test statistic value for the effect of adoption group on the DTI parameter of interest, with corresponding *p*-value and effect size. *B* and associated standard errors give the parameter estimates for the contrast of PI-EA or PI-LA in comparison to controls, and EA vs. LA *p* represents the contrast between the adjusted means for the earlier and later adopted groups.

Anterior thalamic radiations (ATR), corticospinal tract (CST), cingulum-cingulate bundle (Cing-c), cingulum-hippocampal bundle (Cing-h), inferior fronto-occipital fasciculus (IFOF), inferior longitudinal fasciculus (ILF), superior longitudinal fasciculus (SLF), uncinate fasciculus (UF).

*Main effect of group status significant at $p < .050$ or pair-wise comparison between groups significant at $p < .020$.

3c. Age at adoption correlational analyses: corrected for total cortical white matter volume. These analyses were already provided in Inline Supplemental Table 3. Recall that analyses were only conducted in the 12-direction DTI data set to maintain statistical power.

4. Ethnic Subgroup Analyses

We intentionally included a diverse sample of PI children to be representative of children with a history of orphanage care entering the United States. One potential limitation of this approach is that the non-adopted comparison children are primarily of a different racial background than many of the PI children. A second potential limitation is that due to differences between countries in adoption policies, the earlier- and later-adopted PI groups are also composed of children of different ethnic backgrounds.

To address the first limitation, we examined whether group differences between PI and control children in FA within tracts of interest were present in the 38 Caucasian PI children (14 PI-EA; 24 PI-LA) versus the 30 Caucasian non-adopted children. These analyses were restricted to the 12-direction data set to maintain power. Results indicated that as a group, Caucasian PI children showed reductions in FA in comparison to Caucasian controls in the right cingulum (hippocampal portion; $p < .024$), left IFOF ($p < .012$), and right UF ($p < .029$). Analyses investigating adoption group effects indicated there were similar main effects of group status within these tracts (although the right UF finding was only marginally significant, $p < .073$), with pair-wise differences driven mostly by PI-EA children in comparison to non-adopted controls.

To address the second limitation, we examined effects of age at adoption on FA within tracts of interest in the sample of 33 Asian children (21 PI-EA, 12 PI-LA); there were insufficient non-adopted controls of Asian ancestry to constitute a control group. As before, these analyses were restricted to the 12-direction data set to maintain power. Asian PI-EA children showed reduced FA in comparison to Asian PI-LA children across the following tracts: forceps minor ($p < .024$), bilateral IFOF ($p_{left} < .023$, $p_{right} < .032$), and bilateral ILF ($p_{left} < .021$, $p_{right} < .001$).

In combination, these sub-group analyses within significantly smaller samples sizes demonstrated a similar pattern of results (although across a smaller set of tracts) as discussed in our main report. Specifically, reductions in FA were present for PI children, particularly those who were earlier-adopted, both in the Caucasian and Asian sub-samples. This suggests the non-linear effects of age at adoption detected in FA in the larger sample of children were not driven solely by ethnic differences between the PI and non-adopted comparison children or by ethnic differences between the PI-EA and PI-LA groups.