A MULTI-STUDY EXAMINATION OF ADHD, EARLY ADVERSITY, AND NEURAL DEVELOPMENT

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ABSTRACT

Sarah F. Furlong: A Multi-Study Examination of ADHD, Early Adversity, and Neural Development
(Under the direction of Margaret A. Sheridan)

This integrative dissertation examines neural correlates of attention-deficit/hyperactivity disorder (ADHD) and adversity from a developmental psychopathology framework. In this context, the development of ADHD symptoms is viewed from an equifinality perspective in which both ADHD of unknown or neurobiological origin and ADHD secondary to neglect are considered. The three studies capitalize on advanced neuroimaging techniques, including traditional and novel methods of analyzing electroencephalography (EEG) data as well as the application of structural covariance network analyses to a novel population. Study 1 assessed potential neural correlates of ADHD symptom stability by testing several EEG metrics in early childhood as predictors of ADHD symptom stability in late childhood and early adolescence. While this work did not reveal any significant neural predictors of ADHD symptom stability, it highlighted the importance of family and environmental factors, including parent psychopathology and socioeconomic status, in the maintenance of clinically impairing ADHD symptoms. Study 2 examined the impact of environmental factors on neural correlates of ADHD in early childhood and revealed relative alpha power as a correlate of ADHD symptoms in early childhood independent of family conflict and socioeconomic status. Lastly, Study 3 evaluated the impact of early-life psychosocial deprivation in the form of institutionalization on the development of neural structure and the associated risk for ADHD. The complete body of work expands upon prior research by adding to the understanding of the neural mechanisms that

underlie the development of ADHD in populations with and without early-life adversity. The dissertation culminates in an integrated discussion of the findings, clinical implications, and limitations of the current body of work, as well as future directions for this program of research.

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TABLE OF CONTENTS

LIST OF FIGURES xii

LIST OF TABLES xiii

LIST OF ABBREVIATIONS xiv

LIST OF SYMBOLS xvi

Integrative Introduction 1

ADHD and Neglect as an Example of Equifinality 2

ADHD, Neglect, and Neural Development 4

Neural Correlates of ADHD 4

Neural Impacts of Environmental Factors 4

Summary of Previous Work and Limitations 5

Summary of the Present Studies 6

Study 1: Neural Correlates of Stability of ADHD Symptoms 6

Study 2: Neural Correlates of ADHD and Exposure to Adversity 7

Study 3: The Impact of Institutionalization on Neural Structure and Risk for ADHD 7

REFERENCES 9

STUDY 1: Do Neural Correlates of ADHD in Early Childhood Predict Stability of Symptoms in Late Childhood and Early Adolescence: A Longitudinal Study 19

Reasons for Poor Diagnostic Accuracy and Instability of Diagnosis 20

Limitations of Current Diagnostic Methods 20

Under-Diagnosis of Certain Populations 21
A Possible Solution: Continuous, Not Categorical, Models of ADHD 22
Neural Predictors of ADHD Symptom Stability 23
Current Study 29
Hypotheses 30
Methods 30
Participants 30
ADHD Symptoms at Baseline 32
ADHD Symptoms at Follow-Up 32
Child Internalizing Psychopathology at Baseline 32
Parent Psychopathology at Baseline 32
Socioeconomic Status at Baseline 32
Procedure 33
EEG Acquisition 33
EEG Preprocessing 34
Analytic Plan 35
Relative Alpha Power Analysis 36
Slope and Offset of the Aperiodic 1/f-like Component of the Power Spectrum 36
Connectivity Analysis 37
Statistical Methods 39
Results 41
ADHD Symptom Stability and EEG Metrics 41
Model with Global Efficiency and Slope 41
Model with Local Efficiency and Offset 41

ADHD Symptom Stability and Previously Identified Predictors 42
Combined Models 42
Discussion 43
Null Findings with EEG Metrics 43
Parent Psychopathology 45
Parent Depression 45
Parent ADHD 46
Socioeconomic Status 46
Limitations 47
Conclusions 48
REFERENCES 49
STUDY 2: Neural Correlates of ADHD and Exposure to Adversity: A Resting State EEG Study 77
Continuous Model of ADHD 79
Hypotheses 80
Methods 81
Participants 81
ADHD Symptoms 81
Family SES 82
Family Conflict 82
Testing for Potential Covariates 83
Procedure 83
EEG Acquisition 83
EEG Preprocessing 85

Data Analysis 86
Results 89
Family SES 89
Family Conflict 89
Interaction of ADHD Symptoms and Poverty 90
Interaction of ADHD Symptoms and Family Conflict 90
ADHD Symptoms Controlling for Family Environment 90
Removal of Subjects Without Clear Alpha Peaks 91
Discussion 91
Environmental Variables 93
Absence of Alpha Peaks: Relation to Environmental Variables? 94
Limitations 95
Conclusions 95
REFERENCES 97
STUDY 3: The Long-Term Impact of Institutionalization on Neural Structure: An Examination of Developmental Trajectories of Structural Covariance in the Bucharest Early Intervention Project 112
Neglect and Institutional Care 113
Methodological Design in Studies of Previously Institutionalized Children 115
Effects of Institutionalization on Brain Structure 117
Institutionalization, ADHD, and Brain Structure 118
Structural Covariance 119
Methodological Advantages of Structural Covariance Analysis 120
Structural Covariance and Child Maltreatment 120
Current Study 122

Hypotheses 122
Methods 123
Participants 123
Participants at 9 Years 124
Participants at 16 Years 124
Participants with MRI Data at Both Timepoints 125
Procedure 125
MRI Acquisition at 9 Years 125
MRI Acquisition at 16 Years 125
MRI Preprocessing 126
ADHD Symptoms 126
Construction of Structural Cortical Networks 127
Network Costs 127
Graph Theoretical Metrics 128
Subject-Based Maturational Coupling Approach 129
Statistical Analysis Plan 130
Group-Level Structural Covariance Approach 130
Subject-Based Maturational Coupling Approach 130
Results 131
Structural Covariance 131
Age 9 131
Age 16 133
Subject-Based Maturational Coupling 134
Group Differences in Network Organization of sbMC 134

Institutionalization, ADHD Symptoms, and sbMC: Statistical Mediation 134
Discussion 135
Structural Covariance at Age 9 135
Structural Covariance at Age 16 137
Subject-Based Maturational Coupling 138
Limitations 139
Conclusions 139
REFERENCES 141
Integrative Discussion 165
Clinical Implications 169
Future Directions for Research 170
Conclusions 172
REFERENCES 173

LIST OF FIGURES

Figure 1.1. Distribution of Change in ADHD Symptoms from Baseline to Follow-up 76

Figure 2.1. Distribution of ADHD Symptoms 110

Figure 2.2. The Association of Total ADHD Symptoms and Parietal Alpha Power 111

Figure 3.1. Modularity of structural covariance at 9 years 159

Figure 3.2. Global Efficiency of Structural Covariance at 9 years 160

Figure 3.3. Local Efficiency of Structural Covariance at 9 years 161

Figure 3.4. Modularity of Structural Covariance at 16 years 162

Figure 3.5. Global Efficiency of Structural Covariance at 16 years 163

Figure 3.6. Local Efficiency of Structural Covariance at 16 years 164

LIST OF TABLES

Table 1.1. Sample Demographics 73

Table 1.2. Bivariate Correlations of Variables of Interest 74

Table 2.1. Sample Demographics 107

Table 2.2 Bivariate Correlations of Variables of Interest 108

Table 2.3. Bivariate Correlations of Age, Sex, and EEG Power in Alpha and Theta ROIs 109

Table 3.1. Group Demographics: 9-year Data Collection Sample 156

Table 3.2. Group Demographics: 16-year Data Collection Sample 157

Table 3.3. Group Demographics: Participants with MRI data at both Timepoints 158

LIST OF ABBREVIATIONS

ADHD	Attention-deficit/hyperactivity Disorder
Ag/AgCl-	Silver/Silver Chloride
ANOVA	Analysis of Variance
ASRS	Adult ADHD Self-Report Scale
BCT	Brain Connectivity Toolbox
BDI-II	Beck Depression Inventory, 2nd Edition
BEIP	Bucharest Early Intervention Project
CAUG	Care as Usual Group
CBCL	Achenbach Child Behavior Checklist
CSF	Cerebrospinal Fluid
CTS	Conflict Tactics Scale
DISC-IV	Diagnostic Structured Interview Schedule
DSM	Diagnostic and Statistical Manual of Mental Disorders
EEG	Electroencephalography
ERA	English and Romanian Adoptees
FCG	Foster Care Group
FDR	False Discovery Rate
fNIRS	Functional Near-Infrared Spectroscopy
FPL	Federal Poverty Line
HBQ	MacArthur Health and Behavior Questionnaire
Hz	Hertz
ICA	Independent Component Analysis

KCl	Potassium Chloride
MARA	Multiple Artifact Rejection Algorithm
MCI	Maturational Coupling Index
MRI	Magnetic Resonance Imaging
ms	milliseconds
NIG	Never Institutionalized Group
PAF	Peak Alpha Frequency
PIQ	Performance Intelligence Quotient
PSD	Power Spectral Density
RCT	Randomized Control Trial
RDoC	Research Domain Criteria
ROI	Region of Interest
sbMC	Subject-Based Maturational Coupling
SD	Standard Deviation
SES	Socioeconomic Status
T	Tesla
TD	Typically developing
TE	Echo Time
TI	Inversion Time
TR	Repetition Time
WPLI	Weighted Phase Lag Index
WPPSI-III	Wechsler Preschool and Primary Scale of Intelligence, Third Edition

LIST OF SYMBOLS

α	Alpha
ß	Regression Coefficient
Δ	Delta (Change)
F	F-Statistic
N	Sample Size
p	Probability Value
θ	Theta
t	*t*-statistic

Integrative Introduction

Although children might have different causal or contributing factors to their symptom presentation, studying children with similar symptoms and behaviors might prove useful for informing clinical work in the future. For example, in clinical settings, each child presents with a unique developmental history and various early life experiences. Often these different developmental pathways can lead to similar presentations, a concept known as equifinality (Cicchetti & Rogosch, 1996; Rutter & Sroufe, 2000; Sroufe, 2009). From a clinical perspective, diagnostic considerations are one aspect of determining an appropriate intervention; however, identifying presenting concerns and symptoms regardless of Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2013) diagnosis is frequently the primary focus. Consistent with a developmental psychopathology approach, it has been recommended that psychotherapists utilize different therapeutic approaches in flexible combinations based upon what is determined to be the best fit for the child. This often involves a component of trial and error, but typically the therapist works to identify current symptoms and develop an intervention plan based upon those symptoms. For instance, one might utilize different aspects of several therapeutic styles in conjunction with one another when appropriate and treatment manuals that have been developed for specific disorders have been found to be effective across several disorders. For example, behavioral parent training models were initially developed for children with oppositional, defiant, and conduct problem behaviors, but subsequent research has shown that it is also effective when adapted for children with attention-deficit/hyperactivity disorder (ADHD), autism, and intellectual disabilities (Cartwright-Hatton et al., 2005; McMahon

& Forehand, 2005; Strayhorn & Weidman, 1989). In sum, treatments are effective when targeting symptoms rather than limiting treatments to specific diagnostic groupings. Given this, developing a deeper understanding of the neural underpinnings of the same symptoms arising from different etiologies might prove to be fruitful for advancing clinical approaches.

ADHD and Neglect as an Example of Equifinality

One particular case in which the concept of equifinality applies is that of ADHD of unknown or neurobiological origin and ADHD secondary to neglect. ADHD is a highly prevalent neurodevelopmental disorder characterized by age-inappropriate levels of inattention, hyperactivity, and impulsivity. Importantly, individuals with ADHD often experience deficits in executive function, such as reduced working memory capacity, impaired response inhibition, and diminished planning abilities (Barkley, 1997; Brocki et al., 2008; Corbett et al., 2009; Martinussen et al., 2005; Tenenbaum et al., 2019; Willcutt et al., 2005). Consequently, in relation to these deficits, individuals with ADHD experience impairments in emotion regulation and social functioning (Bunford et al., 2015; Christiansen et al., 2019; Maedgen & Carlson, 2000; Morris et al., 2020; Tenenbaum et al., 2019; Uekermann et al., 2010; Wehmeier et al., 2010). In turn, these impairments are risk factors for poor academic outcomes, substance use, risky sexual behavior, and anti-social behaviors (Barbaresi et al., 2007, 2013; Kofler et al., 2011; Lee et al., 2011; Loe & Feldman, 2007; Wehmeier et al., 2010; Wilens et al., 2011).

While ADHD is often conceptualized as a neurobiological disorder with a strong genetic component, both genes and the environment impact the neural development underlying ADHD (Curatolo et al., 2010). Specifically, experiences of deprivation during childhood (i.e., the lack of expected cognitive stimulation and social learning experiences) are associated with impairments similar to those observed in children with ADHD, such as deficits in attention, concentration,

and executive function (McLaughlin, Sheridan, & Lambert, 2014; McLaughlin et al., 2017; Sheridan et al., 2017; Sheridan & McLaughlin, 2014). Neglect, a profound form of deprivation and the most prevalent form of childhood maltreatment, is defined as failure of the caregiver to provide for the child's physical and emotional health as well as educational needs and protection from harm (Gilbert et al., 2009; Leeb et al., 2008; Straus & Kantor, 2005). Institutional rearing is an extreme form of neglect, where children are raised without an invested caregiver to provide for these needs. Institutional rearing is characterized by high ratios of children to caregivers, limited access to language and cognitive stimulation, regimented caregiving, and low caregiver investment (Bick et al., 2015; Dubowitz et al., 2002; Hanson et al., 2015; McLaughlin et al., 2017; Sheridan et al., 2012; Tottenham et al., 2010; Walker et al., 2011). Institutionalization, similar to other forms of neglect, has been associated with increased rates of impaired attention, concentration, and executive functions, such that previously institutionalized children display higher rates of ADHD than the typical population (Kreppner et al., 2001; Stevens et al., 2008; Zeanah et al., 2009).

Altogether, children with ADHD due to unknown origin and children with ADHD secondary to institutionalization display similar traits and experience overlapping impairments. As such, these two populations are representative of the concept of equifinality, and thus, should be studied in conjunction with one another to inform understanding about children in both categories. Crucially, despite differing circumstances leading to the development of ADHD symptoms, children in both situations can benefit from the same interventions that target ADHD symptoms. Therefore, the enclosed work explores the neural underpinnings of children with ADHD and children with experiences of institutionalization in order to further understand the neural mechanisms underlying these developmental pathways.

ADHD, Neglect, and Neural Development

Neural Correlates of ADHD

In an effort to understand the neural mechanisms underlying the typical impairments experience by individuals with ADHD, numerous studies have applied neuroimaging to this population. Previous research using electroencephalography (EEG) has identified multiple aspects of the EEG power spectrum that are associated with ADHD, including theta/beta ratio, increased alpha band power, increased theta band power, broadband power of the entire signal, and the slope of the change in power with change in frequency (Arns et al., 2013; Barry et al., 2003; Hale et al., 2009, 2010; Koehler et al., 2009; Loo & Makeig, 2012; Robertson et al., 2019; Snyder & Hall, 2006; Tye et al., 2014). In addition, findings from multiple neuroimaging modalities suggest that dysfunctional connectivity is present across networks that are associated with higher-level cognitive functions in individuals with ADHD (Beare et al., 2017; Cao et al., 2013; Castellanos & Proal, 2012; Halperin & Schulz, 2006; Henry & Cohen, 2019; Liston et al., 2011; Rubia et al., 2014; Wang et al., 2009).

Neural Impacts of Environmental Factors

Understanding the neural mechanisms underlying the association of institutionalization with increased ADHD symptoms is critical for developing adequate and timely interventions and policies to better serve children living in neglectful environments. Prior work has identified that previously institutionalized children have widespread changes to their neural structure, indicated by findings of these children having decreased white matter volume, decreased gray matter volume, decreased total brain volume, widespread decreases in cortical thickness, and alterations in white matter microstructure throughout the brain (Bick et al., 2015; Eluvathingal et al., 2006; Herzberg et al., 2018; Mackes et al., 2020; Mehta et al., 2009; Rutter & Sonuga-Barke, 2010;

Sheridan et al., 2012). Other evidence has found that institutionalization is associated with deviations in specific neural structures (Eluvathingal et al., 2006; Mackes et al., 2020; Mehta et al., 2009; Sheridan et al., 2012; Tottenham et al., 2010). Moreover, recent work has indicated that early institutionalization alters risk for ADHD through its impact on neural structure; there is evidence that structural brain differences mediate the association of institutionalization and psychopathology (Bick et al., 2017; McLaughlin et al., 2010; McLaughlin, Sheridan, Winter, et al., 2014; Tibu et al., 2015).

Summary of Previous Work and Limitations

In summary, previous work has examined neural structure and function in two populations that are at risk for similar impairments: individuals with ADHD and individuals that have experienced early childhood deprivation. Evidence from past work indicates that both atypical neurodevelopment in ADHD and atypical development due to environmental disruptions are associated with deficits in attention, concentration, working memory, and behavioral regulation. Moreover, recent work indicates that neural structure and function mediates the association of environmental deprivation with increased rates of ADHD (Machlin et al., 2019; McLaughlin et al., 2010; McLaughlin, Sheridan, Winter, et al., 2014; Tibu et al., 2016). Critically, in order to contribute to overall knowledge of children at risk for ADHD symptomatology, neglect, or both, it is necessary to first deepen our understanding of neurodevelopment in these at-risk populations. Gaps remain in our understanding of 1) the neural correlates of ADHD symptom stability, 2) the impact of environmental factors on neural correlates of ADHD in early childhood, and 3) the impact of early-life deprivation on the development of neural structure and associated risk for ADHD. The next section highlights the

limitations in each of these areas and summarizes how the present work aimed to address those gaps.

Summary of the Present Studies

Study 1: Neural Correlates of Stability of ADHD Symptoms

While recent research has identified neural correlates of ADHD in early childhood as a step toward improving diagnostic accuracy and characterizing neurodevelopment in ADHD, questions remain regarding stability of ADHD diagnosis. Of note, ADHD diagnosis in early childhood (3-7 years old) is highly unstable, with rates of remission or partial remission ranging from 21-50% (Bunte et al., 2014; Campbell & Ewing, 1990; Hill & Schoener, 1996; Law et al., 2014; McGee et al., 1991; Tandon et al., 2011; Teegarden & Burns, 1999). As yet predicting this change in symptoms of ADHD over time is difficult to predict and explain (August et al., 1999; Bunte et al., 2014; Morrow et al., 2012; Pingault et al., 2011). Thus, Study 1 aims to fill the current gaps in the literature by assessing if several EEG metrics that have been previously associated with ADHD in childhood are predictive of stability of ADHD symptom severity from early to middle childhood. Importantly, no previous research could be found that has assessed if neural metrics in early childhood are predictive of ADHD symptom stability later in childhood. This study 1) utilizes the strengths of a longitudinal study to assess for prospective associations of neural function in early childhood with ADHD symptoms in middle childhood and 2) applies advanced neural metrics beyond those typically examined in relation to ADHD. Given that EEG is a relatively safe, low-cost, and easy to administer neuroimaging method, and is thus more directly applicable to clinical settings, this work has implications for improving clinical outcomes as well as contributing to the broader scientific understanding of developmental trajectories of neural development in ADHD.

Study 2: Neural Correlates of ADHD and Exposure to Adversity

The second study examines associations between early adversity exposure, ADHD symptoms, and neural function in early childhood. Of note, this work builds upon emerging research that intimates that early adverse experiences contribute to increased risk of ADHD and are associated with related changes in neural function. Importantly, EEG lends itself particularly well to the study of ADHD, as EEG metrics are able to characterize both developmental changes and arousal/attention (Banaschewski & Brandeis, 2007). Despite this, there is inconsistency with regard to which frequency band is altered in individuals with ADHD. Previous work has suggested that the use of fixed frequency bands in the calculation of EEG metrics might account for variability in findings (Robertson et al., 2019; Saad et al., 2018). Therefore, in this paper we calculate individual frequency bands based upon individual peak alpha frequency. Thus, this paper 1) enhances previous work by applying a methodological approach to address inconsistences in the literature and 2) expands the knowledge base of the associations of exposure to adversity, ADHD symptoms, and neural function in early childhood.

Study 3: The Impact of Institutionalization on Neural Structure and Risk for ADHD

The focus of the third study is on developing an enhanced characterization of the impacts of early childhood experiences of institutionalization on brain structure in late childhood and adolescence. This study is highly innovative, in that it aims to build upon previous literature by applying structural covariance methodology to data collected as part of the Bucharest Early Intervention Project (BEIP). The BEIP is unique in that it utilizes a randomized control trial (RCT) design in order to assess foster care as an intervention for institutionalization. This work contributes to the literature in several ways.

First, this study harnesses the unique RCT design of the BEIP in order to assess the extent to which the detrimental consequences of institutionalization on neural structural covariance can be mitigated by placement in an enriched environment (foster care). Second, at the time of writing, there are no previous studies that have examined structural covariance during middle and late childhood in a sample of previously institutionalized children. Further, this work includes measurements from the same sample at two different timepoints, when the previously institutionalized children were approximately 9 and 16 years old. Therefore, Study 3 applies graph theoretical methods to structural covariance networks in order to develop a nuanced characterization of the changes in structural brain network development across timepoints in a previously institutionalized sample. Lastly, in order to understand the association of institutionalization with ADHD, Study 3 includes an analysis that tests the association of structural brain network development and ADHD symptoms in children with previous exposure to institutionalization.

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STUDY 1: Do Neural Correlates of ADHD in Early Childhood Predict Stability of Symptoms in Late Childhood and Early Adolescence: A Longitudinal Study

Attention-deficit/hyperactivity disorder (ADHD) is a highly prevalent neurodevelopmental disorder, affecting approximately 6% of children globally (Polanczyk et al., 2007; Polanczyk et al., 2014; Thomas et al., 2015). Children with ADHD display age-inappropriate levels of impulsivity, hyperactivity, and inattention. Further, ADHD is associated with deficits in executive function, such as reduced working memory capacity, impaired response inhibition, and diminished planning abilities (Barkley, 1997; Brocki et al., 2008; Corbett et al., 2009; Martinussen et al., 2005; Tenenbaum et al., 2019; Willcutt et al., 2005), and impairments in emotion regulation and social functioning (Bunford et al., 2015; Christiansen et al., 2019; Maedgen & Carlson, 2000; Morris et al., 2020; Tenenbaum et al., 2019; Uekermann et al., 2010; Wehmeier et al., 2010). As a result, children with ADHD are at an increased risk for numerous negative life outcomes, including poor academic achievement, increased risk of substance use, risky behaviors, poor marital relationships, family dysfunction, and overall decreased quality of life later in childhood and into adulthood years (Barbaresi et al., 2007, 2013; Daley & Birchwood, 2010; Kofler et al., 2011; Lee et al., 2011; Loe & Feldman, 2007; Wehmeier et al., 2010; Wilens et al., 2011). Emerging evidence suggests that ADHD symptoms, and not simply diagnostic status, are associated with negative outcomes later in life (Cheung et al., 2015; Du Rietz et al., 2017; Elkins et al., 2019; Selinus et al., 2015). Consequently, ADHD is increasingly viewed as a dimensional rather than categorical disorder (Marcus & Barry, 2011; Mohamed et al., 2015; Philip Shaw et al., 2011), suggesting that future work should employ

continuous measures of ADHD symptoms rather than focusing on categorical diagnostic status. Importantly, early intervention has the potential to shift the negative developmental trajectories associated with childhood ADHD symptoms. However, this potential has not been fully realized because diagnosis of ADHD in early childhood (3-7 years old) is highly unstable, with rates of remission or partial remission ranging from 21-50% (Bunte et al., 2014; Campbell & Ewing, 1990; Hill & Schoener, 1996; Law et al., 2014; McGee et al., 1991; Tandon et al., 2011; Teegarden & Burns, 1999), and is characterized by poor diagnostic accuracy and over-diagnosis (Danielson et al., 2017; Polanczyk et al., 2007, 2014; Visser et al., 2014; Willcutt, 2012).

Reasons for Poor Diagnostic Accuracy and Instability of Diagnosis

Limitations of Current Diagnostic Methods

Currently, the gold standard for ADHD diagnosis based on Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria involves collecting both parent report and teacher report via questionnaires and structured interviews that assess behaviors at home and at school (American Psychiatric Association, 2013). In early childhood, defined in this paper as before age 8, parental report can be less accurate (Pineda et al., 1999; Smidts & Oosterlaan, 2007). Increased physical activity levels are normative in early childhood, and overall physical activity and impulsivity decreases with age (Nader, Bradley, Houts, McRitchie, & O'Brien, 2008; Ortega et al., 2013; Taylor, Williams, Farmer, & Taylor, 2013). Thus, it can be difficult to distinguish typical activity levels from hyperactivity and impulsivity symptoms of ADHD in young children. Further, it is often difficult to acquire both parent and teacher report and to have reporters complete both questionnaires and structured interviews, resulting in increased instability of diagnosis in community samples of preschool aged children relative to clinic referred samples (Farris et al., 2011; Tandon et al., 2011). This variation in diagnostic methodology across

settings and providers might account for discrepancies in diagnostic rates compared to prevalence rates and the instability of ADHD diagnosis in early childhood (Polanczyk et al., 2007; Polanczyk et al., 2014). Even in research using highly-trained clinicians and multiple informants, there is still instability of ADHD diagnosis. For example, one such study utilized skilled clinicians to diagnose ADHD in early childhood and found that 30% of children remitted their diagnosis by late childhood (Law et al., 2014). This work did indicate that stability in diagnosis might be associated with increased internalizing and externalizing psychopathology in early childhood, parental history of psychopathology, and family socioeconomic status (Law et al., 2014). While these predictors might help improve stability of ADHD diagnosis, they also predict psychopathology broadly.

Under-Diagnosis of Certain Populations

While substantial evidence indicates that ADHD is over-diagnosed in childhood, the rates of diagnosis for specific populations are significantly lower than the prevalence rates for ADHD in childhood. These discrepancies might further contribute to the instability of ADHD diagnosis.

Females. The prevalence rate of ADHD in adult females is higher than for female children; indicating that ADHD is under-diagnosed in girls (Pinkhardt et al., 2009). Further, it has also been suggested that the under-diagnosis of ADHD in girls might be due to later developmental onset of impairing symptoms, different manifestations in females, and DSM criteria that has been primarily geared towards typical presentations of ADHD in males (although this has begun to shift with updates to the DSM; Gaub & Carlson, 1997; Mahone, 2012; Quinn, 2008; Ramtekkar et al., 2010; Skogli et al., 2013; Taylor & Keltner, 2002).

Ethnic and Racial Minorities. Although evidence indicates that, based upon teacher-report in kindergarten, African American children do not display ADHD-related behaviors in the

classroom less frequently than Caucasian children, African American children in kindergarten in the United States are 70% less likely to receive an ADHD diagnosis than Caucasian children in Kindergarten (Morgan et al., 2013, 2014). In addition, Hispanic children appear to be under-diagnosed in comparison to non-Hispanic Caucasian children, although after controlling for what language was primarily spoken in the home, this disparity between rates of diagnosis becomes statistically non-significant (Morgan et al., 2014). Moreover, previous work has identified that from kindergarten through 8th grade, persistent and sizeable discrepancies exist when comparing diagnostic rates of ADHD in racial and ethnic minorities to Caucasian children: African American children are 69% less likely to receive an ADHD diagnosis, Hispanic children are 50% less likely to receive an ADHD diagnosis, and children of other races or ethnicities are 46% less likely to receive an ADHD diagnosis (Morgan et al., 2013). In sum, the evidence suggests that diagnosis of ADHD is not standard across different populations, and this inaccuracy in diagnosis might be additionally contributing to the overall instability of ADHD diagnosis from early childhood into later childhood. Overall, the problems with diagnosis of ADHD are related to both the specific assessment methods themselves (e.g., the challenges to accurate parent-report) as well as the lack of dimensional considerations in broader theoretical views that underlie research approaches to improving assessment and treatment of ADHD.

A Possible Solution: Continuous, Not Categorical, Models of ADHD

In response to limitations conferred by traditional DSM-based approaches across all disorder types, the Research Domain Criteria (RDoC) approach has been viewed as a possible solution to the gaps remaining in clinical psychological and neuroscience research (Cuthbert & Insel, 2013; Insel et al., 2010). Moreover, ADHD is characterized by heterogeneous behaviors and symptoms and it has been posited that moving away from DSM-based categorical

approaches has the potential to improve clinical assessment, prediction of treatment response, and development of treatments (Musser & Raiker, 2019). Further, previous work has highlighted the importance of examining developmental trajectories at the neural level across disorders, but especially in regard to ADHD (Casey et al., 2014). In particular, research on typical neurodevelopmental trajectories and that of children with ADHD evidences that the early differences in children with and without ADHD and the heterogeneous presentations and outcomes are related to delayed cortical development in children with ADHD (Shaw et al., 2007; Shaw et al., 2011). Therefore, a shift towards a dimensional, continuous model of ADHD might prove beneficial in future research.

Neural Predictors of ADHD Symptom Stability

In addition to shifting towards a continuous model of ADHD, an objective, brain-based marker of ADHD symptoms holds promise for addressing limitations of current ADHD assessment methods and improving understanding of risk for continued impairment and associated risks from early childhood into late childhood and early adolescence. Importantly, neural measures do not require children to report their internal states or complete complex tasks, and global neural measures capture aggregate information about a child's functioning, and require no self-awareness, fine motor skill, or complex task completion to acquire. Moreover, it has been posited that in conjunction with existing psychological measures, the use of neural metrics to predict clinical outcomes and future behavior represent one fruitful avenue for improving understanding of neural development and psychopathology (Banaschewski & Brandeis, 2007; Berkman & Falk, 2013).

In this spirit, previous work examining neural predictors of clinical and behavioral outcomes provide evidence that neural markers in youth are predictive of future substance use,

mood, and energy regulation (Banaschewski & Brandeis, 2007; Bertocci et al., 2016, 2017; Brumback et al., 2016) and of future cognitive impairment in preterm infants (Woodward et al., 2012). Previous work has also identified that neural markers are predictive of treatment outcomes for a range of psychological disorders, such as depression (Fu et al., 2013; Mayberg, 2003; McGrath et al., 2013; Olbrich & Arns, 2013; Pizzagalli, 2011; Siegle et al., 2006), anxiety (Doehrmann et al., 2013; Hahn et al., 2015; Lueken et al., 2016), post-traumatic stress disorder (Cisler et al., 2016; Zantvoord et al., 2013), substance use disorder (Paulus et al., 2005), and schizophrenia (Kumari et al., 2009). Thus, brain-based predictors may prove useful as a complementary metric to typical psychological measures.

In particular, Electroencephalography (EEG) has potential to function as a brain-based predictor of ADHD symptom stability when utilized in complement to other measures. In part, this is due to EEG lending itself particularly well to the study of ADHD, as EEG metrics are able to characterize both developmental changes and arousal/attention (Banaschewski & Brandeis, 2007). This has resulted in a plethora of research examining EEG correlates of ADHD symptoms and diagnosis during childhood and adolescence (McVoy et al., 2019). Furthermore, EEG is more directly applicable to clinic settings than other modalities, such as functional Magnetic Resonance Imaging (MRI), as it is a safe, low-cost, and easy to administer neuroimaging method relative to other methods. While efficacious psychopharmaceutical and behavioral interventions exist, clinical outcomes could be improved by increasing understanding of and predictive capabilities for who is likely to experience a reduction of symptoms and who is likely to experience persistence of ADHD symptoms. Critically, this knowledge would help identify who is likely at a higher risk for continued ADHD symptoms and the associated negative outcomes in later childhood, adolescence, and adulthood.

Electroencephalography and Neural Correlates of Childhood ADHD. There is extensive literature examining a variety of potential neural correlates of ADHD in childhood. Neural correlates of ADHD have been identified across several different methodological approaches to EEG data analysis. As such, three primary approaches are reviewed in regards to previously identified correlates of ADHD, and are included in the current analysis.

Relative Oscillatory Power. A substantial portion of previous studies on the neural correlates of ADHD has focused on measuring relative oscillatory power, which is defined as the amount that each frequency band contributes to the overall EEG signal relative to the contributions from the other frequency bands. A majority of prior research has focused on the theta/beta ratio as a primary marker of ADHD, with studies indicating that children with ADHD display relatively greater power in the low frequency theta range (approximately 4-8 Hz) and relatively reduced power in the high frequency beta range (approximately 13-21 Hz; Arns et al., 2013; Barry et al., 2003; Loo & Makeig, 2012; Monastra et al., 1999; Snyder & Hall, 2006). However, the utility of reduced theta/beta ratio as a marker for ADHD has been questioned due to failed replications and decreasing effect sizes over time (Arns et al., 2013; Loo & Makeig, 2012; Saad et al., 2018). Additional work with older children indicates that ADHD diagnostic status is associated with increased relative power in the alpha frequency band (approximately 8-13 Hz; Barry et al., 2003; Hale et al., 2009, 2010; Koehler et al., 2009; Robbie et al., 2016) and increased relative power in the theta frequency band (Barry et al., 2003; Koehler et al., 2009; Tye et al., 2014). Recent work with the same sample that was examined in the current study has demonstrated that increased alpha band relative power differentiates children with ADHD from children without ADHD and is associated with increased total ADHD symptom severity (Robertson et al., 2019; Furlong, et al., 2021). Further, activity in the alpha and theta bands has

been associated with cognitive functions that are often impaired in ADHD: the alpha band is associated with visual attention, inhibition, control of alertness, response to task requirements, and flexible updating (Lu et al., 2017; Romei et al., 2012; Sadaghiani et al., 2012), and the theta band has been implicated in cognitive control, selective attention, orienting of attention, response inhibition, and working memory (Başar et al., 2001; Caplan et al., 2000; Cavanagh & Frank, 2014; Jensen & Tesche, 2002; Liu et al., 2014; Raghavachari et al., 2001). Due to ample evidence identifying neural correlates of ADHD within the alpha band in other samples as well as the current sample, and other evidence questioning the theta/beta ratio as a marker for ADHD, in the current study we examined relative power in the alpha band in early childhood as a predictor of ADHD symptom stability in later childhood.

Alternative Measures of the EEG Power Spectrum. In addition to the rhythmic oscillatory power that occurs in narrow frequency band ranges, recent evidence suggests that peaks of oscillatory power are a subset of the useful information captured in a broadband aperiodic signal that reveals diminished power with increasing frequency (Gao, 2015; He, 2014). The slope of the aperiodic signal, which measures the rate of decline in power with increasing frequency, is associated with cognitive state, aging, executive function, and synaptic excitatory/inhibitory balance (Gao et al., 2017; Podvalny et al., 2015; Voytek et al., 2015). In addition, it has been suggested that the broadband power of the signal, referred to as the offset, reflects the firing rate of neurons (Manning et al., 2009). A recent study that utilized the same sample as the present work found that in early childhood (ages 3-7) medication-naïve children with ADHD had steeper slopes and increased offsets compared with typically developing children (Robertson et al., 2019). Given these recent findings, in the current work we tested

whether slope and offset in early childhood predict stability of ADHD symptoms in later childhood.

Neural Network Connectivity. The third primary approach to the analysis of EEG data involves the measurement of the synchronization of oscillatory activity between pairs of electrodes within a specific frequency band. Broadly, evidence across neuroimaging modalities suggests that for individuals with ADHD, neural network dysfunction is present across networks that are associated with higher-level cognitive functions (Casey et al., 2007; Castellanos & Proal, 2012; Castellanos & Tannock, 2002; Halperin & Schulz, 2006; Henry & Cohen, 2019; Konrad & Eickhoff, 2010; Liston et al., 2011; Nigg & Casey, 2005; Qiu et al., 2011; Rubia et al., 2014). In the past 5-10 years, there has been an exponential growth of studies that apply complex analytic methods to examine which aspects of neural connectivity are disrupted in individuals with ADHD. Graph theoretical methods, in particular, have proven to be useful for furthering understanding of neural connectivity in typically and atypically developing populations (Fornito et al., 2015; Meunier et al., 2010; Petersen & Sporns, 2015; Sporns & Betzel, 2016; Vértes & Bullmore, 2015) and characterizing differences in functional connectivity between older children with and without ADHD (Henry & Cohen, 2019). In these prior studies, children with ADHD had increased modularity, decreased global efficiency, and increased local efficiency, suggesting that in late childhood and adolescence, children with ADHD have increased segregation and decreased integration compared to typically developing children (Beare et al., 2017; Cao et al., 2013; Henry & Cohen, 2019; Lin et al., 2014; Wang et al., 2009). Segregation measures the extent to which a network is communicating locally, and integration refers to the extent to which there is global communication across networks. Increased segregation suggests that local information is not being processed effectively due to hyper-connectivity within subnetworks,

potentially reducing processing speed for lower-level cognitive functions. Decreased integration indicates that a network is displaying inefficient long-range communication, which is crucial for higher-level cognitive functions, such as those that are often impaired in individuals with ADHD, that require frontal regions to coordinate with other areas (Baum et al., 2017; Marek et al., 2015). Overall, previous work with children 8 years old and older has suggested that dysfunctional integration and segregation of brain connectivity, as characterized by modularity, local efficiency, and global efficiency, are neural correlates of ADHD.

Despite evidence supporting the utility of the application of graph theoretical methods to the study of connectivity in young children with ADHD, studies examining EEG connectivity in children with ADHD have primarily examined measures of coherence, which is a measure of the synchronicity of oscillating brain activity that underlies functional brain networks (Bowyer, 2016). Further, the majority of studies of EEG coherence have focused on middle and later childhood. Previous studies of older children with ADHD have found differences in coherence in theta and delta (Ahmadlou & Adeli, 2010), while others found differences only in theta (Alba et al., 2016), while still others found differences in each frequency band (Barry et al., 2002, 2011). Other research found differences between controls and older children with ADHD in theta and beta frequency bands (Clarke et al., 2007), and still other findings demonstrated differences in alpha and theta (Robbie et al., 2016). The only existing study examining EEG coherence in children as young as 4 years-old with ADHD did not include age as a factor in their analyses, so their findings do not necessarily demonstrate differences in coherence patterns in young children with ADHD, only that there are differences between children with and without ADHD who are 4-15 years old (González et al., 2013). One reason for the inconsistency in EEG coherence findings is that coherence does not characterize the nuances of neural connectivity to the extent

that a graph theoretical approach can. However, minimal work has applied graph theoretical methods to early childhood (ages 3-7 years) ADHD. Previous work in the same sample as the current study identified that increased global efficiency in the alpha frequency band is associated with increased inattentive symptoms in early childhood (Furlong et al., 2020). Therefore, we examined global efficiency in the alpha band as a predictor of ADHD symptoms stability. Additionally, while evidence in this sample did not indicate that modularity or local efficiency were associated with ADHD symptoms in early childhood, we examined both of these measures in the alpha band due to findings in other work with older children with ADHD implicating these metrics in ADHD symptomatology.

Current Study

The current study aims to fill the current gaps in the literature by assessing if several EEG metrics that have been previously associated with ADHD in childhood are predictive of stability of ADHD symptom severity. There is currently no previous research that has examined if neural metrics in early childhood are predictive of ADHD symptom stability. To fill this gap, we tested several different neural correlates of ADHD as potential predictors of symptom-level stability: relative alpha power; modularity, global efficiency, and local efficiency in the alpha band; spectral slope; and offset. Given evidence that ADHD symptoms, and not diagnostic status, are associated with negative outcomes later in life (Cheung et al., 2015; Du Rietz et al., 2017; Elkins et al., 2019; Selinus et al., 2015), and that ADHD is increasingly viewed as a dimensional rather than categorical disorder (Marcus & Barry, 2011; Mohamed et al., 2015; Shaw et al., 2011), we assessed whether baseline EEG metrics in early childhood are predictive of ADHD symptoms at a second timepoint, while controlling for baseline ADHD symptoms. Thus, the current study harnesses the strengths of a longitudinal study to assess for prospective associations of neural

function in early childhood with ADHD symptoms in late childhood and early adolescence, defined in this study as 8-14 years.

Hypotheses

We predicted that if persistent ADHD symptoms later in childhood are related to neural markers of ADHD in early childhood, stability of ADHD symptoms would be associated with increased relative alpha power, steeper slopes, and greater offsets in early childhood. Further, given that increased global efficiency in alpha has been associated with increased ADHD symptoms in early childhood, we predicted that children with persistent and elevated ADHD symptoms would exhibit increased global efficiency in the alpha band in early childhood. Of note, these hypotheses were based upon previous research that focused on neural correlates of early childhood ADHD. Given that the maturational changes that occur from early to late childhood and early adolescence in regard to ADHD symptoms are unclear, the present analyses were exploratory to some extent.

Methods

Participants

The sample included N=147 children who were followed up from an initial study visit when they were between ages 3 and 7 years old. The sample includes N=27 children that had previously taken ADHD medication and completed a 24-hr medication washout period before baseline data collection. At baseline, these children were identified from a larger sample of 197 typically developing children and children with ADHD. Inclusion criteria included having no history of: chromosomal abnormalities recorded in the medical record such as fragile X or down syndrome, prenatal substance exposure as reported in medical records or by caregivers, presence of autism spectrum disorder, lack of English language comprehension, and non-stimulant psychotropic medication use, including previous or current use of non-stimulant ADHD

medications. Of the original 197 children, N=25 children were not included due to not meeting the inclusion criteria, N=16 children had unusable EEG data and were not included in analyses, and N = 10 children did not complete the diagnostic structure interview at baseline. Thus, N = 146 children met inclusion criteria at baseline, completed baseline diagnostic structured interviews, and had useable EEG data at baseline.

For the current analyses, the families that participated at baseline were contacted to complete a follow-up study visit. The follow-up data began when the oldest children were older than 8, which occurred on average 2.9 years after the initial study visit. Of the N =146 children with useable data at the baseline timepoint, N = 3 declined to participate, N = 27 were not able to be contacted due to change in contact information since the baseline study visit, and N = 116 participants completed the follow-up study visit. The diagnostic interview data for N = 4 subjects was lost due to computer difficulties, resulting in N = 112 participants included in the present analyses for a retention rate of 77%. Of the 112 participants included in the follow-up analyses, N = 19 participants were taking stimulant medications for ADHD prior to the baseline visit when their EEG data was collected. These participants completed a 24-hour washout prior to their baseline visit and we controlled for medication history in all analyses. See Table 1.1 for demographic variables.

For the first wave of the study, participants were recruited from community events, schools, a database of families who had expressed interest in research compiled by the Labs of Cognitive Neuroscience at Boston Children's Hospital, and from a database of participants who were seen for ADHD treatment at Boston Children's Hospital. For the follow-up visit, participants were contacted via phone or email once their children were 8 years old or older. All study procedures were approved by the Institutional Review Board at Boston Children's Hospital

and the University of North Carolina at Chapel Hill. The primary caregiver of each child participant provided informed consent and each child provided verbal assent.

ADHD Symptoms at Baseline

To measure ADHD symptoms at the first timepoint, caregivers reported symptoms of ADHD on the Diagnostic Structured Interview Schedule (DISC-IV; Shaffer et al., 2000; Mean = 9.57, SD = 7.74, range = 0-23).

ADHD Symptoms at Follow-Up

To measure ADHD symptoms at the follow-up, caregivers reported symptoms of ADHD on the DISC-IV via phone (Mean = 7.38, SD = 6.7, range = 0-20). There was a significant difference in the ADHD symptoms at baseline compared to follow-up, $t(111) = 4.55$, $p < 0.01$. For the distribution of change in ADHD symptoms from baseline to follow-up, see Figure 1.1.

Child Internalizing Psychopathology at Baseline

Internalizing symptoms at baseline were measured using the internalizing symptoms t-score from the Achenbach Child Behavior Checklist (CBCL; Achenbach, 1991; Mean = 51.21, SD = 11.73, range = 29-86).

Parent Psychopathology at Baseline

We assessed for both parent depressive and ADHD symptoms at the baseline visit. Parent depressive symptoms were measured using the Beck Depression Inventory, 2nd Edition (BDI-II; Beck et al., 1996; Mean = 6.53, SD = 7.63, range = 0-43). Parent ADHD symptoms were measured using the Adult ADHD Self-Report Scale (ASRS; Kessler et al., 2005; Mean = 43.06, SD = 12.76, range = 18-75).

Socioeconomic Status at Baseline

To measure socioeconomic status, we used income to needs ratio. Income to needs ratio is calculated by dividing the total family income by the federal poverty threshold. Federal poverty threshold was determined based on the household's size in the year the data was collected. Thus, an income to needs ratio of one would indicate that a family is living at the poverty threshold. Income to needs ratio was calculated based upon reported family income, from all sources, on the MacArthur questionnaire (Adler, Epel, Castellazzo, & Ickovics, 2000) and the number of individuals who were a part of a participant's household relying on that income (Mean = 4.47, SD = 2.38, range = 0.08 – 10.12).

Procedure

EEG Acquisition

At the initial timepoint, children completed a resting state EEG recording. Resting state EEG data were collected for a total of three and a half minutes each for eyes-open and eyes-closed conditions. The recordings were collected over seven intervals, during which the participants alternated between 30 seconds of eyes-open data collection, 15 second breaks, and 30 seconds of eyes-closed data collection (Vuga et al., 2008). This approach, previously utilized by Vuga et al., was chosen due to the young age of the children participating in the study and to maximize the amount of data collected without artifact. During the eyes-open condition, the participants were instructed to sit as still as possible while directing their attention toward a cartoon image of open eyes. During the eyes-closed condition, participants were instructed to sit quietly and calmly with their eyes closed. A research assistant accompanied each child for the duration of EEG data collection to maintain motivation and cooperation during data acquisition. Consistent with most of the literature examining EEG metrics as correlates of ADHD (Bresnahan et al., 1999; Callaway, 1983; Snyder et al., 2008) and as an indicator of neurodevelopment (Bell,

1998; Benninger et al., 1984; Lazzaro et al., 1998), in this paper we present data from the eyes-open condition only. Additionally, previous analyses of the baseline data from this sample have not found differences between the eyes-open and eyes-closed conditions (Furlong et al., 2020).

EEG recordings were collected using a 128 HydroCel Sensor Net System (EGI, Inc, Eugene, OR). The net was comprised of an elastic tension structure forming a geodesic tessellation of the head surface. At each vertex is a sensor pedestal housing an Ag/AgCl- coated, carbon-filled plastic electrode and sponge. Prior to fitting the cap on the participant, the net was soaked in an electrolyte solution (6cc KCl/liter distilled water) in order to facilitate electrical contact between the scalp and the electrode. The child's head was measured and marked in the center using a wax pencil to ensure proper placement across participants. Once placed over the scalp, impedance for each electrode was checked using NetStation software. To decrease impedance, electrodes were re-wet with the electrolyte solution and firmly placed in close contact with the scalp (moving aside hair). The process of attempting to decrease impedance continued until less than 10% of the 128 electrodes had impedances greater than 50 mV. EEG data was acquired using NetAmps 200 Amplifiers and the NetStation software. The data were amplified, filtered (bandpass 0.1 to 100.0 Hz), and sampled at an effective rate of 250 Hz. They were digitized with a 12-bit National Instruments Board (National Instruments Corp., Woburn, MA).

EEG Preprocessing

Using NetStation, EEG data were re-referenced using an average reference (Liu et al., 2015) that was applied after excluding the most radial channels, including those in close proximity to the eye, as those channels are most prone to artifact and were not used in subsequent analyses (Umilta' et al., 2012). Using an average reference has been shown to yield

low re-referencing errors when using high-density EEG data. Electrodes were removed if they contained artifacts outside of a +/- 80 mV range and were replaced with data interpolated from the remaining electrodes. Any remaining artifacts were left in the data to be removed during an independent component analysis (ICA; Luck, 2014). For each participant, the best 2-4 30-second segments of eyes-open and eyes-closed resting state data was exported to MATLAB (The MathWorks Inc., Natick, MA) for further analysis.

Independent Component Analysis. In order to further remove noise contributions to the signal, we conducted an ICA. First, we ran a high pass filter at 1 Hz (Winkler, Debener, Müller, & Tangermann, 2015), and then conducted the ICA using the infomax ICA algorithm implemented in EEGLAB (Delorme & Makeig, 2004; Onton & Makeig, 2006). Further, to reduce highly correlated signal from nearby electrodes, we down-sampled to the 10-10 international electrode system, resulting in 71 electrode channels (Onton & Makeig, 2006). Next, we utilized the Multiple Artifact Rejection Algorithm (MARA), an open-source EEGLAB machine-learning plug-in that automatizes the process of labeling components for artifact rejection (Winkler et al., 2011, 2014). For the components that accounted for more than 1% of the variance, a trained researcher (SF) reviewed the decisions made by MARA. The remaining components were classified solely based on MARA's calculated probabilities, where those assigned a probability greater than 0.50 were marked as artifact. The components marked as artifact were then subtracted from the overall signal to create a cleaned signal that was used for further analysis.

Analytic Plan

In accordance with previous literature that has identified multiple different neural correlates of ADHD in early childhood, we included three different methodological approaches

in the analytic plan. The first approach tested if relative power in the alpha band at baseline was associated with stability of ADHD symptoms at the follow-up. Second, in order to assess if differences in the aperiodic components of the EEG power spectrum in early childhood are associated with stability of ADHD symptoms in later childhood, we tested if altered slope and offset of the aperiodic 1/f-like component of the power spectrum at baseline were associated with stability of ADHD symptoms at the follow-up. Lastly, we tested if modularity, global efficiency, and local efficiency in the alpha band were associated with stability of ADHD symptoms at the follow-up. First, we outline the steps to calculate each EEG metric of interest, and then the planned statistical tests are described.

Relative Alpha Power Analysis

Power spectral density (PSD) was estimated using Welch's method with a Hamming window length of 1 second, and 50% overlap (Gao et al. 2017). Next, to account for differences in the amplitude of the EEG signal due to noise including skull thickness and electrode impedance, we calculated relative power by dividing the power within the alpha band (8-12 Hz) by the total power (Gasser et al. 1982; Kappenman and Luck 2010). Lastly, the average relative alpha power across electrodes was included in statistical analyses.

Slope and Offset of the Aperiodic 1/f-like Component of the Power Spectrum

We used the FOOOF toolbox (Haller et al. 2018) to calculate the slope and offset of the PSD between 4 and 50 Hz. First, we modeled the aperiodic slope, then found the oscillatory peaks and fit them with Gaussians. Then the Gaussians were subtracted iteratively until all peaks were removed. We then refit the aperiodic slope of the power spectrum with the peaks removed using an exponential function in semi-log power space. This procedure provides an estimate for

each EEG channel of two key aperiodic features of the power spectrum: slope and offset. The average slope and offset across all electrodes were used in the statistical models.

Connectivity Analysis

To perform the connectivity analysis, the preprocessed data was exported from EEGLAB into FieldTrip (Oostenveld et al., 2011).

Weighted Phase Lag Index. To control for the innate problem of volume conduction in EEG data, we utilized Weighted Phase Lag Index (WPLI), a synchronization measure that does not rely on correlations or partial correlations and has been applied to functional connectivity analyses in EEG data (see Ortiz et al., 2012 for an application of WPLI; see Vinck, Oostenveld, van Wingerden, Battaglia, & Pennartz, 2011 for a detailed review). WPLI measures the asymmetry in the distribution of the phase differences obtained from the instantaneous phases of the two time series, and critically, in WPLI the contribution of the observed phase leads and lags is weighted by the magnitude of the imaginary component of the cross-spectrum. WPLI was calculated as defined by Vinck and colleagues (see Vinck et al., 2011), and is expressed as an absolute value between 0 (random phase difference: minimum strength of functional connectivity), and 1 (constant phase difference: maximum strength of functional connectivity) (Tóth et al., 2017). WPLI was calculated for each pair of electrodes for every participant using FieldTrip, resulting in WPLI matrices (71 electrodes x 71 electrodes, with WPLI values in each cell) for all participants. Once the WPLI matrices were created, graph theoretical methods were applied to analyze characteristics of the networks.

Graph Theoretical Metrics. Using graph theoretical methods, the network of interest is divided into nodes and edges. In the current study the nodes were the electrodes and the edges were defined as the WPLI value for each pair of electrodes. There are a multitude of measures to

examine within graph theory; based on previous work, we examined three graph theoretical measures, modularity, global efficiency, and local efficiency. These measures were calculated using the Brain Connectivity Toolbox (BCT) (Rubinov & Sporns, 2010).

Modularity. Modularity is the ratio of the number of within-module connections to the number of expected within-module connections in a random network (Cohen & D'Esposito, 2016; Rubinov & Sporns, 2010; Sporns, 2013). The extent of modularity (measured from 0 to 1) can be described as a spectrum ranging from more integrated to more segregated (Sporns, 2013). Segregation refers to strong interconnectivity within modules, which results in efficient local processing. Integration refers to increased connections across modules, which represents global processing. Modularity was calculated using the BCT algorithm (see Rubinov & Sporns, 2010). We used the Louvain Method for community detection, which maximizes network modularity (De Meo et al., 2011). The structure (and thus modularity) of the network is determined by subdividing the network into groups of nodes, with a maximally possible number of within-group edges, and a minimally possible number of between-group edges (Rubinov & Sporns, 2010).

Global Efficiency. In order to evaluate the association of integration of the neural networks in early childhood with persistent ADHD symptoms, we examined global efficiency, which measures the efficiency of information transfer among all pairs of nodes (electrodes in this case) in the graph, and thus reflects the efficiency of interaction across the whole graph (de Pasquale et al., 2016; Rubinov & Sporns, 2010). Global efficiency was calculated using the BCT algorithm (see de Pasquale et al., 2016; Rubinov & Sporns, 2010).

Local Efficiency. To assess whether the extent of segregation of neural networks in early childhood is associated with persistent ADHD symptoms, we calculated local efficiency, which

measures the efficiency of information transfer limited to neighboring nodes (i.e. nodes with a direct connection to the node of interest) (Cohen & D'Esposito, 2016; Rubinov & Sporns, 2010; Sporns, 2013). Local efficiency was calculated using the BCT algorithm (see Latora & Marchiori, 2001; Rubinov & Sporns, 2010).

Network Costs. In network analyses it is appropriate to threshold the network in order to analyze a sparse network that most closely represents the density of connection of human and non-human nervous systems, by focusing on the strongest functional connections in the network (Achard & Bullmore, 2007). All graph theoretical analyses were conducted over a range of costs (10-30%, in 5% increments) to ensure that any results were not due to a specific threshold. The range of thresholds was chosen based upon the range of values that have been shown to produce graphs with small world characteristics (Bullmore & Bassett, 2011). Modularity, global efficiency, and local efficiency were calculated using matrices created with weighted thresholds (e.g., the edge values were maintained after each threshold was performed).

Statistical Methods

Statistical tests were conducted using R version 3.5.3 (R Core Team, 2013).

First-Order Associations. As a first step, we calculated the first-order correlations of the variables of interest in order to assess for multicollinearity among predictors. This was important given the aim of the study to test different EEG metrics as predictors of ADHD symptom stability in the same model. Variables with a correlation value of 0.8 or greater were considered to be collinear and were not included in the same models. Global efficiency and local efficiency were correlated at $r = 0.84$ and slope and offset were correlated at $r = 0.89$. Thus, global and local efficiency were not included in the same regression models and slope and offset were not

included in the same regression models. See Table 1.2 for results of the correlations between all variables of interest and covariates.

Symptom Stability: Linear Regression Models.

ADHD Symptom Stability and EEG Metrics. The first set of linear regression models assessed if brain metrics at the baseline visit predicted stability of symptoms. As such, the first models included ADHD symptoms at follow-up as the dependent variable, the EEG metrics as predictors, and sex, ADHD symptoms at baseline, medication history, and change in age as covariates. Given that global efficiency and local efficiency were collinear and slope and offset were collinear, the first model included relative alpha power, modularity, global efficiency, and slope as the EEG predictors. In an additional model to confirm the results with the collinear variables, the EEG predictors included relative alpha power, modularity, local efficiency, and offset.

ADHD Symptom Stability and Previously Identified Predictors. The second set of models tested if non-brain metrics that have been previously identified as being predictive of ADHD diagnostic stability were predictive of symptom stability in this sample. Thus, a linear regression model was conducted which included ADHD symptoms at follow-up as the dependent variable, parent depression symptoms, parent ADHD symptoms, SES, and child internalizing symptoms as the predictors, and sex, baseline ADHD symptoms, medication history, and change in age as covariates.

Combined Models. In the third step of the regression models, we included both brain metrics and non-brain metrics from baseline to assess if the brain metrics improved the predictive relationship of the non-brain metrics with ADHD symptom stability at follow-up. In all of the regression models, ADHD symptoms at baseline, change in age between timepoints,

history of stimulant medications, and sex were included as covariates. Consistent with the previous models, the regression models included total ADHD symptoms at the follow-up as the dependent variable.

Results

ADHD Symptom Stability and EEG Metrics

Model with Global Efficiency and Slope

Controlling for baseline ADHD symptoms, sex, history of ADHD stimulant use, and change in age, modularity ($\beta = -0.07$, $p = 0.26$), global efficiency ($\beta = 0.00$, $p = 0.98$), slope ($\beta = -0.07$, $p = 0.61$), and relative alpha power ($\beta = -0.07$, $p = 0.34$) were not significantly associated with total ADHD symptoms at follow-up. Sex ($\beta = -0.06$, $p = 0.36$), change in age ($\beta = -0.09$, $p = 0.15$), and history of ADHD stimulant use ($\beta = 0.09$, $p = 0.22$) were not associated with ADHD symptoms at follow-up. Baseline ADHD symptoms were significantly associated with total ADHD symptoms at follow-up ($\beta = 0.71$, $p < 0.01$). Results were the same across all thresholds applied for the graph metrics.

Model with Local Efficiency and Offset

Controlling for baseline ADHD symptoms, sex, history of ADHD stimulant use, and change in age, modularity ($\beta = -0.09$, $p = 0.17$), local efficiency ($\beta = -0.07$, $p = 0.35$), offset ($\beta = -0.05$, $p = 0.51$), and relative alpha power ($\beta = -0.03$, $p = 0.68$) were not significantly associated with total ADHD symptoms at follow-up. Sex ($\beta = -0.05$, $p = 0.47$), change in age ($\beta = -0.08$, $p = 0.20$), and history of ADHD stimulant use ($\beta = 0.09$, $p = 0.25$) were not associated with ADHD symptoms at follow-up. Baseline ADHD symptoms were significantly associated with total ADHD symptoms at follow-up ($\beta = 0.72$, $p < 0.01$). Results were the same across all thresholds applied for the graph metrics.

ADHD Symptom Stability and Previously Identified Predictors

Controlling for baseline ADHD symptoms, sex, history of ADHD stimulant use, and change in age, parent depression was significantly associated with total ADHD symptoms at follow-up ($\beta = 0.17$, $p = 0.03$). There was a trending association of income to needs ratio ($\beta = 0.13$, $p = 0.06$) with ADHD symptoms at follow-up. Parent ADHD symptoms ($\beta = 0.01$, $p = 0.87$) and baseline internalizing symptoms ($\beta = 0.03$, $p = 0.75$) were not associated with ADHD symptoms at follow-up. Sex ($\beta = -0.06$, $p = 0.34$), change in age ($\beta = -0.11$, $p = 0.09$), and history of ADHD stimulant use ($\beta = 0.05$, $p = 0.52$) were not associated with ADHD symptoms at follow-up. Baseline ADHD symptoms were significantly associated with total ADHD symptoms at follow-up ($\beta = 0.68$, $p < 0.01$).

Combined Models

The original analytic plan was to combine significant predictors from the brain-based metrics models with the significant predictors from the non-brain metrics model to test whether any brain-based metrics are a useful tool when used in conjunction with other metrics. Given that no brain-based metrics were significantly associated with follow-up ADHD symptoms when included in the same model with each other, each EEG metric was tested as a predictor in a model with the significant and trending predictors from the non-brain-based metrics model. Thus, the following models included follow-up ADHD symptoms as the dependent variable, parent depression, income to needs ratio, and an EEG metric as predictors, and baseline ADHD symptoms, sex, history of ADHD stimulant use, and change in age as covariates. In the combined models, modularity ($\beta = -0.03$, $p = 0.60$), global efficiency ($\beta = -0.03$, $p = 0.67$), local efficiency ($\beta = -0.07$, $p = 0.25$), slope ($\beta = -0.05$, $p = 0.45$), offset ($\beta = -0.06$, $p = 0.36$), and relative alpha power ($\beta = -0.10$, $p = 0.11$) were not associated with total ADHD symptoms at

follow-up. Parent depression ($\beta = 0.17$, $p = 0.01$) and baseline ADHD symptoms ($\beta = 0.70$, $p < 0.01$) remained significantly associated with total ADHD symptoms at follow-up. Again, sex, change in age, and history of ADHD stimulant use were not associated with ADHD symptoms at follow-up (all p's > 0.07).

Discussion

In this paper we explored different predictors of ADHD symptom stability, with a focus on 1) evaluating if neural metrics in early childhood prospectively predicted ADHD symptoms in later childhood and 2) assessing whether neural metrics contributed to predictive models when used in conjunction with non-neural metrics. In contrast to our hypotheses, none of the six EEG metrics predicted ADHD symptoms at the follow-up visit. Parental depression at baseline was a significant predictor of ADHD symptoms at follow-up and baseline income to needs ratio had a trend-level association with ADHD symptoms at follow-up.

Null Findings with EEG Metrics

While we expected to find an association of the EEG metrics with ADHD symptoms at follow-up, there are a number of reasons that the models did not reveal a significant association. First, the neural metrics of focus in this study were EEG metrics; however, it is possible that these measures capture an aspect of the neural mechanisms related to inattention and hyperactivity in early childhood but are reflective of state variables of inattention and hyperactivity rather than trait variables. From this perspective, EEG metrics would reflect fluctuations in attention and activity that are present at the time of the EEG recording, but not trait variables of attention, distractibility, and hyperactivity that would predict continued ADHD symptoms later in childhood and adolescence. In fact, previous work has found that 40% of the variance of EEG asymmetry is due to occasion-specific fluctuations (Hagemann et al., 2002). In

regard to ADHD, this possibility is further supported by the susceptibility of the EEG signal to medication effects which have been documented even after a one-time acute dose of methylphenidate (Song et al., 2005). Other neural measures, such as structural MRI might tap more directly into the neural mechanisms associated with stability of ADHD symptoms across childhood. Additionally, in this study we considered total ADHD symptoms at baseline and follow-up, but individuals with ADHD can present with varied presentations (primarily inattentive, primarily hyperactive/impulsive, and combined presentation). Thus, it is possible that the EEG metrics would be predictive of inattentive or hyperactive/impulsive symptoms at the follow-up, but not both. In fact, previous work has identified that increased global efficiency is associated with increased inattentive, but not hyperactive symptoms, in early childhood (Furlong et al., 2020). Based on those previous findings, it is plausible that EEG metrics, or global efficiency at least, could be predictive of inattentive symptoms but not total ADHD symptoms in late childhood and early adolescence. Lastly, the concept of multifinality suggests that people with similar early experiences can present with varied outcomes later in life. Researchers have proposed that multifinality can be understood through distal and proximal risk factors, such that distal risk factors precede and cause proximal risk factors, which in turn lead to the development of psychopathology (Nolen-Hoeksema & Watkins, 2011). In this framework, an early experience, such as emotional abuse, might lead to rumination via a variety of possible mechanisms, and rumination in turn can lead to depression, anxiety, substance use disorder, or an eating disorder, depending on a multitude of possible moderators (Nolen-Hoeksema & Watkins, 2011). If this concept is applied to neurodevelopment, it is conceivable that similar neural patterns in early childhood could lead to a diverse set of outcomes via the varied experiences

each individual undergoes from early childhood to adolescence, thus resulting in the EEG metrics not predicting ADHD symptoms at follow-up in this study.

Parent Psychopathology

Parent Depression

In the present study, parent depressive symptoms at baseline were associated with their children's ADHD symptoms in later childhood and early adolescence. Parent depression has been associated with child development outcomes across a number of domains, including cognitive (Liu et al., 2017) and social-emotional development (Huang et al., 2014). Previous work has found that children of parents with depression have an increased likelihood of ADHD (Cheung et al., 2018; Cunningham & Boyle, 2002) as well as heightened risk for psychopathology more broadly (Beck, 1999; Cummings & Davies, 1994; Humphreys et al., 2012; Ringoot et al., 2015). Intervention research also highlights the bidirectional relationship of parent depression and child psychopathology, with findings that behavioral parent training interventions for childhood disorders result in reductions of parental stress and depressive symptoms (Anastopoulos et al., 1993; Colalillo & Johnston, 2016; Gerdes et al., 2012; Iida et al., 2018) and treatment of parental depression improves the mental health of their children (Cuijpers et al., 2015). Taken together, there is substantial evidence linking parental depression and child psychopathology, and thus, it is not surprising that parental depression significantly predicted child ADHD symptoms at follow-up. This adds to the existing evidence that prevention and intervention efforts should focus on both the needs of the child and the parents, as well as the family system as a whole.

Parent ADHD

Surprisingly, in the current findings, parent ADHD symptoms at baseline were not associated with the children's ADHD symptoms at follow-up. Previous research has identified that parental ADHD symptoms are associated with an increased risk for child ADHD and child psychopathology more broadly (Breaux et al., 2017; Humphreys et al., 2012). It is possible that those findings are not replicated in this study due to adults with ADHD being potentially inaccurate reporters of their own ADHD symptoms, as there are often discrepancies between adult patients' self-reports and observer-reports (typically completed by a parent or significant other) and as it is unclear which type of source is more valid it has been suggested that clinicians use a combination of sources for adult ADHD evaluation (Marshall et al., 2021). Additionally, it is possible that in this study parent depression was accounting for parent psychopathology more generally, and that the association of parent depression with child ADHD symptoms at follow-up represents the general risk for psychopathology associated with family psychiatric history (Caspi et al., 2014). This interpretation would suggest that parent psychopathology in general, rather than parental depression specifically, is associated with childhood ADHD symptom stability. This view integrates the findings within this sample with findings in other studies that have found an association of parent ADHD and child ADHD.

Socioeconomic Status

We found that there was a trend-level relationship of SES and ADHD symptoms at follow-up, suggesting that environmental factors might play a role in the longitudinal course of ADHD symptoms across childhood. In fact, children from low SES families have increased rates of ADHD (Rowland et al., 2018; Russell et al., 2016; Scahill et al., 1999; St Sauver et al., 2004). While the association of SES and ADHD symptom stability was not significant in this sample,

this trending result, along with previous research that identified that SES predicts diagnostic stability of ADHD (Law et al., 2014), suggests that SES should be considered in future studies that explore the neural mechanisms of the developmental course of ADHD.

Limitations

There are several limitations to the current study. First, the length of EEG data collected in this sample was shorter than in other studies. This could have limited the power of the EEG metrics to predict ADHD symptom stability because the measure of EEG metrics would be less stable than if a more typical approach had been used. However, the data collection procedures were selected based on the young age of the participants and their success in acquiring EEG data with similarly aged children in previous studies (Vuga et al., 2008). Regarding the longitudinal nature of the study, it is possible that various factors in the intervening years led to different outcomes. For example, if the children in the sample received behavioral or medical interventions between the baseline visit and the follow-up, the neural signal at baseline would not predict later outcomes. Future work should examine the EEG metrics as predictors of later ADHD symptoms in a group of children who did receive interventions between study visits compared to children who did not. Regarding the impact of parent psychopathology, this study did not account for parent psychopathology at follow-up, which could impact the actual and perceived functioning of the children at follow-up. Lastly, future work should explore the relationship of SES and ADHD symptom stability in a sample that was collected to assess for the impact of severe poverty, as this study did not specifically recruit for low SES families.

This study was designed to assess the stability of ADHD symptoms across childhood from a dimensional and transdiagnostic perspective, which is in line with the evidence supporting the application of transdiagnostic RDoC approaches. However, to better understand

the neurodevelopment underlying the instability of ADHD in early childhood, future work to address this specific question might be improved by applying a diagnostic approach that groups children into the following: 1) children who met diagnostic criteria for ADHD at baseline and maintained the diagnosis at follow-up, 2) children who met diagnostic criteria for ADHD at baseline and remitted the diagnosis at follow-up, 3) children who did not meet diagnostic criteria for ADHD at baseline but did meet criteria at follow-up, and 4) children who did not meet diagnostic criteria for ADHD at either timepoint. This approach, which might benefit from a machine learning analysis, would allow for evaluation of neural metrics in association with specific types of outcomes, rather than stability of ADHD symptoms which is more general.

Conclusions

In conclusion, we demonstrate that parent psychopathology, and parent depression in particular, is associated with stability of ADHD symptoms from early childhood to later childhood and early adolescence. However, we did not find evidence to support EEG metrics as predictors of ADHD symptom stability despite previous evidence identifying neural correlates of ADHD using the same EEG metrics examined in this study. Overall, this work highlights the importance of continuing to examine the roles of parent psychopathology and family SES in the development and progression of ADHD. Clinically, these results suggest that interventions should consider targeting both child ADHD symptoms and parent depression given the links with later ADHD symptoms. Future work that attempts to elucidate if other neural metrics are predictive of ADHD symptoms stability when applied in conjunction with non-neural measures should include parent psychopathology and SES.

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Table 1.1. Sample Demographics

	n	%
Female	41	36.6
Handedness (R)	101	90.2
Race		
White	78	69.6
Black/African American	17	15.2
Asian	3	2.7
Native American or Alaska Native	0	0.0
Native Hawaiian or Pacific Islander	0	0.0
Other/Multiracial	14	12.5
Hispanic/Latino	10	8.9

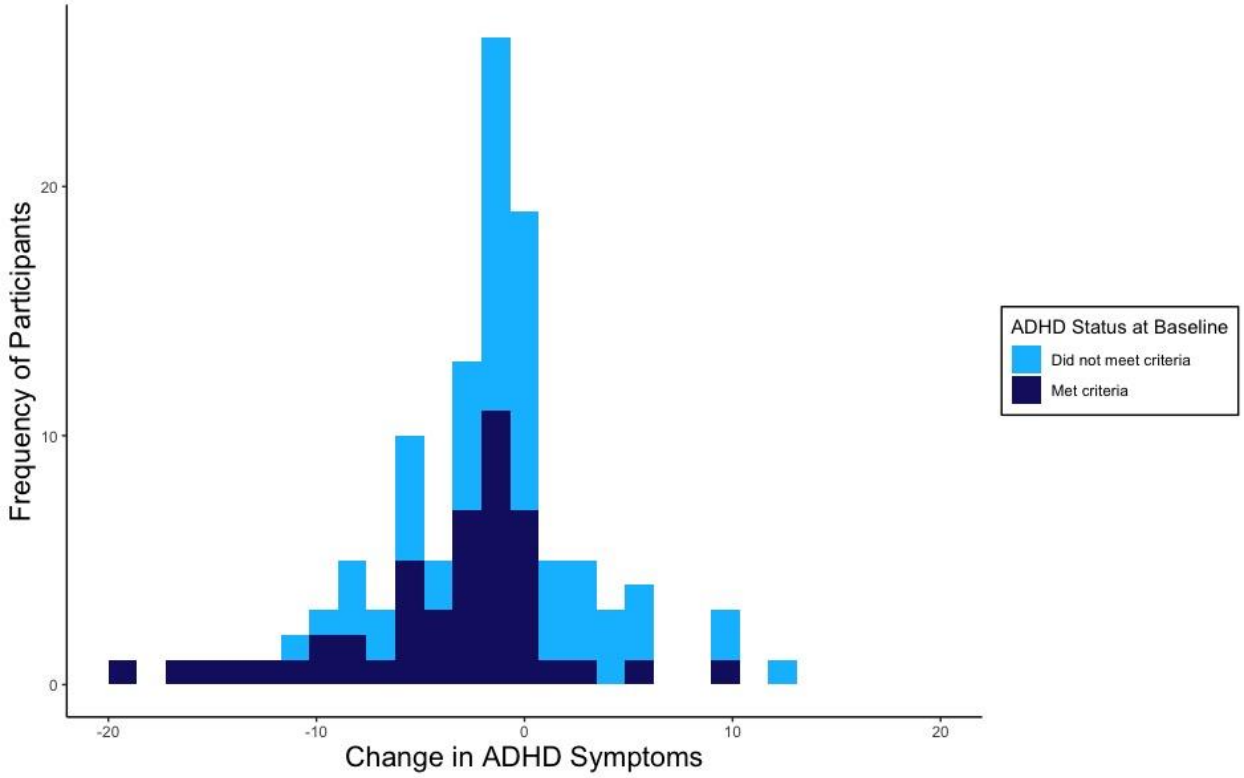
Note. N = 112. At baseline, participants were on average 5.96 years old (SD = 1.12). At follow-up, participants were on average 8.87 years old (SD = 1.14). The average amount of time between visits was 2.92 years (SD = 1.59).

Table 1.2. Bivariate Correlations of Variables of Interest

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1. Modularity	--	-0.27*	-0.33*	-0.05	0.04	-0.08	0.05	-0.05	-0.03	-0.05	-0.04	-0.01	0.15	0.07	0.00
2. Global Efficiency		--	0.84*	0.25*	0.22*	0.48*	0.17	0.10	0.17	0.06	0.10	-0.01	-0.06	0.06	-0.04
3. Local Efficiency			--	0.17	0.11	0.50*	0.02	-0.06	0.05	0.09	0.06	-0.01	-0.07	0.13	-0.07
4. Slope				--	0.89*	0.40*	0.03	-0.07	0.06	0.05	0.11	0.01	0.11	0.03	-0.24*
5. Offset					--	0.40*	0.08	-0.06	0.03	0.00	0.13	-0.05	0.28*	-0.06	-0.25*
6. Relative Alpha Power						--	0.05	-0.05	0.03	0.05	0.14	0.02	0.01	-0.08	-0.09
7. Baseline ADHD Sx							--	0.76*	0.54*	0.36*	0.33*	-0.28*	-0.01	-0.18	0.50*
8. Follow-up ADHD Sx								--	0.49*	0.33*	0.37*	-0.10	-0.12	-0.19*	0.48*
9. Baseline Internalizing Sx									--	0.44*	0.45*	-0.18	-0.05	-0.07	0.37*
10. Parent ADHD										--	0.53*	-0.09	0.07	-0.05	0.18*
11. Parent Depression											--	-0.16	0.08	-0.10	0.17
12. SES												--	-0.09	0.06	-0.11
13. Δ Age													--	-0.08	-0.18
14. Sex														--	-0.15
15. Stimulant Use															--

Note. Table displays results of bivariate correlations of variables of interest. Variables with a correlation value of 0.8 or greater were considered to be collinear and were not included in the same models. Global efficiency and local efficiency were collinear and slope and offset were collinear, so they were included in separate models. ADHD symptoms were measured using the DISC-IV. Internalizing symptoms were measured using the Achenbach Child Behavior Checklist internalizing symptoms t-score. Parent ADHD symptoms were assessed using the Adult ADHD Self-Report Scale and parent depression symptoms were assessed using the Beck Depression Inventory. Sx = Symptoms. *$p < 0.05$

Figure 1.1. Distribution of Change in ADHD Symptoms from Baseline to Follow-up



Note. Histogram plot of the distribution of change in ADHD symptoms for the entire sample. Children who met diagnostic criteria for ADHD at baseline are shown in navy blue and the children who did not meet diagnostic criteria for ADHD at baseline are shown in the light blue.

STUDY 2: Neural Correlates of ADHD and Exposure to Adversity: A Resting State EEG Study

Attention-deficit/hyperactivity disorder (ADHD) is a highly prevalent neurodevelopmental disorder characterized by age-inappropriate levels of inattention, hyperactivity, and impulsivity. Previous studies estimate that the prevalence rate (rate of occurrence) of ADHD is approximately 6% worldwide (Polanczyk et al., 2007; Polanczyk et al., 2014; Thomas et al., 2015). Having an ADHD diagnosis is associated with numerous negative life outcomes, including but not limited to poor academic achievement, increased risk of substance use, risky driving behaviors, poor marital relationships, and family dysfunction later in life (Barbaresi et al., 2007, 2013; Daley & Birchwood, 2010; Kofler et al., 2011; Lee et al., 2011; Loe & Feldman, 2007; Wehmeier et al., 2010; Wilens et al., 2011). Because ADHD is diagnosed in childhood, it often precedes these negative life events, lending this association to a unidirectional interpretation that ADHD leads to future adversity exposure. This interpretation is supported by longitudinal studies which have followed children with ADHD from early childhood through adulthood (Barbaresi et al., 2007).

However, other data indicates that, particularly in early childhood, the association between adversity exposure and ADHD may be bidirectional or transactional in nature (Law et al., 2014). While heritability for ADHD is high (Bornovalova et al., 2010; Hicks et al., 2004; Silberg et al., 2012) and evocative gene-environment correlations have been associated with development of ADHD symptoms (Bornovalova et al., 2014; Harold et al., 2013; Sellers et al., 2019), there is emerging evidence suggesting that environmental factors independently impact

the development of inattention, impulsivity, hyperactivity, and executive functions, particularly when these environmental factors are present early in childhood. Specifically, an increasing body of research indicates that environments characterized by lack of cognitive stimulation are associated with decreased inhibitory control and general executive function (Machlin, Miller, et al., 2019; Rosen et al., 2018, 2019; Sheridan et al., 2017), cognitive functions that are commonly impaired in individuals with ADHD (Barkley, 1997; Toplak et al., 2008). Given this emerging evidence, it is possible that early adversity shapes risk for ADHD through its impact on neural structure and function. Indeed, children exposed to extreme neglect, such as institutionalization, have higher rates of ADHD, and this appears to be mediated by the impact of institutionalizations on neural structure and executive function (McLaughlin et al., 2010, 2014; Tibu et al., 2015). Relatedly, children in the United States who are exposed to a more mild form of adversity, low socioeconomic status (SES), also have increased rates of ADHD (Rowland et al., 2018; Russell et al., 2016; Scahill et al., 1999; St Sauver et al., 2004) and recent work indicates that this association may also be mediated by neural structure (Machlin, McLaughlin, et al., 2019). However, this potential pathway has been less well studied, particularly in early childhood, when these associations are likely first emerging.

Here we examine associations between early adversity exposure, ADHD symptoms, and neural function in early childhood. To measure neural function, we employ resting state electroencephalogram (EEG), as there is substantial literature examining resting state EEG oscillatory power in individuals with ADHD across the lifespan. The majority of studies examining quantitative EEG metrics and psychopathology in childhood have focused on ADHD (McVoy et al., 2019). Despite ample research, there is some inconsistency in which frequency band is altered in individuals with ADHD. A majority of previous work has focused on the

theta/beta ratio as one primary marker of ADHD, with studies indicating that children with ADHD display relatively greater power in the low frequency theta range (approximately 4-8 Hz) and relatively reduced power in the high frequency beta range (approximately 13-21 Hz; Arns et al., 2013; Barry et al., 2003; Loo & Makeig, 2012; Monastra et al., 1999; Snyder & Hall, 2006). However, the utility of reduced theta/beta ratio as a marker for ADHD has been questioned due to failed replications and decreasing effect sizes over time (Arns et al., 2013; Loo & Makeig, 2012; Saad et al., 2018). Furthermore, other studies have found differences in both children and adults with ADHD when compared to typically developing (TD) controls in the alpha frequency band (approximately 8-13 Hz; Barry et al., 2003; Hale et al., 2009, 2010; Koehler et al., 2009; Robbie et al., 2016, Robertson et al., 2019) and theta frequency band (Barry et al., 2003; Koehler et al., 2009; Tye et al., 2014). It has been proposed that the use of fixed frequency bands in the calculation of EEG metrics, including the theta/beta ratio, might account for variability in findings (Robertson et al., 2019; Saad et al., 2018). Thus, in this paper we calculate individual frequency bands based upon individual peak alpha frequency. For the current study, we chose to focus on relative power in the alpha and theta bands due to ample evidence identifying neural correlates of ADHD within those two bands as well as previous findings that reductions in power within the alpha frequency band and increases in power within the theta frequency band partially account for the impact of adversity, specifically deprivation, on symptoms of inattention and hyperactivity (McLaughlin et al., 2010).

Continuous Model of ADHD

In addition to the reasons discussed above, the variability in past findings might be related to limitations of categorical models of ADHD that do not reflect the heterogeneous behaviors and symptoms that characterize ADHD (Musser & Raiker, 2019; Shaw et al., 2011).

Therefore, in the current paper, we utilize a continuous model of ADHD consistent with Research Domain Criteria (RDoC) approaches and the diverse neurodevelopmental patterns of children with ADHD (Casey et al., 2014; Cuthbert & Insel, 2013; Insel et al., 2010; Musser & Raiker, 2019). Of note, in a previous paper using the same sample, we analyzed the data from a traditional, categorical approach to ADHD (Robertson et al., 2019). In that paper, we reported differences between children with and without ADHD in mean alpha power as well as in the slope of the 1/f power spectrum for 12 midline electrodes. Those 12 electrodes were selected to be consistent with other papers examining the slope of the 1/f power spectrum. The current paper extends upon that work in two ways: 1) including data from the entire scalp instead of 12 midline electrodes, and 2) assessing total symptoms of ADHD across all participants. In sum, a continuous measure of ADHD is particularly useful because the presence of hyperactive and inattentive behaviors is normative in early childhood and ADHD is conceptualized as contiguous with the normative developmental continuum.

Hypotheses

Given previous work linking relative power and ADHD, we expect relative power in the alpha and theta bands to be associated with increased ADHD symptoms. We expect family adversity to be associated with both symptoms of ADHD and relative power in the alpha band. We examine these associations using two forms of family adversity: family SES and family conflict. Given previous theoretical (Sheridan & McLaughlin, 2014; Sheridan & McLaughlin, 2016) and empirical (Machlin, McLaughlin, et al., 2019; Miller et al., 2018) work pointing to the link between family SES and cognitive stimulation in predicting externalizing psychopathology, we expect family SES to have a selective association with ADHD symptoms and neural correlates after controlling for family conflict.

Methods

Participants

A sample of N =100 children, (3 years, 0 months -7 years, 3 months) were identified from a larger sample of 197 children as described in Robertson, et al., 2019. Inclusion criteria included having no history of: chromosomal abnormalities recorded in the medical record such as fragile X or down syndrome, prenatal substance exposure as reported in medical records or by caregivers, presence of autism spectrum disorder, lack of English language comprehension, psychotropic medication use, including previous or current use of ADHD medications. The larger sample included children that did not meet inclusion criteria (N = 51) or had unusable EEG data (N = 18). Additionally, to be consistent with Robertson, et al., N = 28 participants were excluded as they were not selected as age/gender matches in that study. See Table 2.1 for demographic variables. Lastly, N = 4 subjects did not have DISC-IV data available and N = 2 did not have CTS data available and were excluded from the analyses.

This data was collected as part of an ongoing longitudinal study of stability of diagnosis in young children with ADHD. Participants were recruited from community events, schools, a database of families who had expressed interest in research compiled by the Labs of Cognitive Neuroscience at Boston Children's Hospital, and from a database of participants who were seen for ADHD treatment at Boston Children's Hospital. All study procedures were approved by the Institutional Review Board at Boston Children's Hospital in compliance with the Helsinki Declaration. The primary caregiver of each child participant provided informed written consent and each child provided verbal assent.

ADHD Symptoms

To measure ADHD symptoms, caregivers reported symptoms of ADHD on the Diagnostic Structured Interview Schedule – young child version (DISC-IV; Shaffer et al., 2000; Mean = 10.25, SD = 7.44, range = 0-23). See Figure 2.1 for the distribution of total ADHD symptoms across the sample.

Family SES

To identify family socioeconomic status, we use income to needs ratio. Income to needs ratio is calculated by dividing the total family income by the federal poverty threshold. Federal poverty threshold was determined based on the household's size in the year the data was collected. Thus, an income to needs ratio of one would indicate that a family is living at the poverty threshold. Income to needs ratio was calculated based upon reported family income, from all sources, on the MacArthur questionnaire (Adler, Epel, Castellazzo, & Ickovics, 2000) and the number of individuals who were a part of a participant's household relying on that income (Mean = 4.27, SD = 2.48, range = 0.13 – 10.12).

Family Conflict

Family conflict was measured using the Conflict Tactics Scale (CTS), a parent-report measure (Straus, 1979). The CTS is comprised of 17 scored items that can be divided into three subscales: reasoning (3 items), verbal aggression (7 items total; 6 scored items), and violence (8 items). The reasoning scale reflects adaptive or positive conflict resolution strategies, whereas the other scales reflect maladaptive conflict tactics and negative family interactions. Items on the verbal aggression scale include interactions such as "insulted or swore at each other" and items on the violence scales include behaviors such as "slapped another family member" or "threatened another family member with a knife or gun." On the CTS, parents respond to each item by selecting one of five categories that represent how often that item occurred in their

family in the past year. Possible answers are never, rarely, sometimes, often, and very often. Items are scored on a 1-5 scale with 1-point increments, with higher total scores indicating higher levels of family conflict in the home in the past year. The total sum of the verbal aggression and violence scales was used in the present study, with a maximum possible score of 70 (Mean = 20.44, SD = 5.92, range = 14-44, alpha = 0.88).

Testing for Potential Covariates

To control for potential confounds, bivariate correlations were used to test for significant associations between the variables of interest (income to needs ratio, family conflict, ADHD symptoms) and potential confounders: IQ, age, gender. Age was measured in months of age at the time of participation (Mean = 67.73 months, SD = 14.63, range = 36-88 months). Gender was indicated as male or female by parent report. The Wechsler Preschool and Primary Scale of Intelligence, Third Edition (WPPSI-III) performance intelligence quotient (PIQ) composite was used as a measure of IQ (Wechsler, 2002) (Mean = 108.55, SD = 16.9, range = 75-137). Age, gender, and IQ were not associated with the variables of interest, and thus were not included in subsequent analyses. See Table 2.2 for bivariate correlations.

Procedure

EEG Acquisition

Children completed a resting state EEG recording. Resting state EEG data were collected for a total of three and a half minutes each for eyes-open and eyes-closed conditions. The recordings were collected over seven intervals, during which the participants alternated between 30 seconds of eyes-open data collection, 15 second breaks, and 30 seconds of eyes-closed data collection (Vuga et al., 2008). This approach, previously utilized by Vuga et al., was chosen due to the young age of the children participating in the study and to maximize the amount of data

collected without artifact. During the eyes-open condition, the participants were instructed to sit as still as possible while directing their attention toward a cartoon image of open eyes. During the eyes-closed condition, participants were instructed to sit quietly and calmly with their eyes closed. A research assistant accompanied each child for the duration of EEG data collection to maintain motivation and cooperation during data acquisition. Consistent with most of the literature examining EEG metrics as correlates of ADHD (Bresnahan et al., 1999; Callaway, 1983; Snyder et al., 2008) and as an indicator of neurodevelopment (Bell, 1998; Benninger et al., 1984; Lazzaro et al., 1998), we present data from the eyes-open condition only.

EEG recordings were collected using a 128 HydroCel Sensor Net System (EGI, Inc, Eugene, OR). The net was comprised of an elastic tension structure forming a geodesic tessellation of the head surface. At each vertex is a sensor pedestal housing an Ag/AgCl- coated, carbon-filled plastic electrode and sponge. Prior to fitting the cap on the participant, the net was soaked in an electrolyte solution (6cc KCl/liter distilled water) in order to facilitate electrical contact between the scalp and the electrode. The child's head was measured and marked in the center using a wax pencil to ensure proper placement across participants. Once placed over the scalp, impedance for each electrode was checked using NetStation software. To decrease impedance, electrodes were re-wet with the electrolyte solution and firmly placed in close contact with the scalp (moving aside hair). The process of attempting to decrease impedance continued until less than 10% of the 128 electrodes had impedances greater than 50 mV. EEG data was acquired using NetAmps 200 Amplifiers and the NetStation software. The data were amplified, filtered (bandpass 0.1 to 100.0 Hz), and sampled at an effective rate of 250 Hz. They were digitized with a 12-bit National Instruments Board (National Instruments Corp., Woburn, MA).

EEG Preprocessing

Using NetStation, EEG data were re-referenced using an average reference (Liu et al., 2015) that was applied after excluding the most radial channels, including those in close proximity to the eye, as these channels were most prone to artifact and were not used in subsequent analyses (Umilta' et al., 2012). Using an average reference has been shown to yield low re-referencing errors when using high-density EEG data. Electrodes were removed if they contained artifacts outside of a +/- 80 mV range and were replaced with data interpolated from the remaining electrodes. Any remaining artifacts were left in the data to be removed during an independent component analysis (ICA; Luck, 2014). For each participant, the best 2-4 30-second segments of eyes open resting state data was exported to MATLAB (MathWorks Inc., Natick MA) for further analysis. All subjects had 1-2 minutes of data. The average amount of data exported for all participants was 114.98 seconds (SD = 15.65).

Independent Component Analysis. In order to further remove noise contributions to the signal, we conducted an ICA (Bell & Sejnowski, 1995; Delorme et al., 2007; Jung et al., 2001). In Matlab, prior to conducting an ICA, we ran a high pass filter at 1 Hz (Winkler, Debener, Müller, & Tangermann, 2015) and conducted the ICA using the infomax ICA algorithm implemented in EEGLAB (Delorme & Makeig, 2004; Onton & Makeig, 2006). Further, to reduce highly correlated signal from nearby electrodes and address issues related to interpolating channels and referencing prior to the ICA, we down-sampled to the 10-10 international electrode system (for more on why down-sampling was chosen instead of using a principal components analysis prior to the ICA, see Artoni et al., 2018), resulting in 71 electrode channels (Onton & Makeig, 2006). Next, we utilized the Multiple Artifact Rejection Algorithm (MARA), an open-source EEGLAB machine-learning plug-in that automatizes the process of labeling components

for artifact rejection (Winkler et al., 2011, 2014). A trained researcher (SF) reviewed the decisions made by MARA for the first 12 components, which were the components that accounted for more than 1% of the variance. In the rare instances when it differed from MARA's classification, the experimenter's classification by visual inspection was used. The remaining 59 components were classified solely based on MARA's calculated probabilities, those assigned a probability greater than 0.50 were marked as artifact, and their time series were subtracted from the overall signal creating a cleaned signal that is used for further analysis.

Motion Confounds. Given that ADHD has hyperactivity as a central symptom, we sought to ensure that our results were not due to children with increased ADHD symptoms having increased artifacts due to motion. The ICA analysis functions to remove signal generated from motion (i.e., eye blinks, facial muscle movements) and retain neural signal (Bell & Sejnowski, 1995; Delorme et al., 2007; Jung et al., 2001), thus, the number of components removed can serve as a measure of the amount of motion artifact for each participant. We assessed the number of components removed during ICA in association with symptoms of ADHD. The total number of ADHD symptoms was not associated with the total number of components removed ($r = -0.10$, $p = 0.35$).

Data Analysis

First, we calculated individual frequency bands based upon each individual's alpha peak alpha frequency. Then, subsequent analyses examined relative power in alpha and theta using the frequency bands derived from individualized peak alpha frequency.

Individualized Peak Alpha Frequency. Power spectral density (PSD) was estimated using Welch's method with a Hamming window length of 1 second, and 50% overlap (Gao et al. 2017). Each participant's peak alpha frequency (PAF) was determined through visual inspection

of the plot of the power spectrum, which was then used to estimate individualized narrow-band power (Doppelmayr et al. 1998) across all electrodes. We assessed PAF at 12 midline electrodes across the frontal, central, parietal and occipital regions (FCZ, FZ, F3, F4, C3, C4, CZ, P3, P4, PZ, O1, O2), which is consistent with the research base for this method (Doppelmayr et al., 1998). PAF detection was performed through visual inspection of the plot of the power spectrum within the predefined alpha band of 5.5–13 Hz (Klimesch 1999; Marshall et al. 2002), and defined as the average point of highest amplitude within that range for the 12 channels tested. Two researchers (MMR and MK[1]) independently identified the peak within the alpha range to the nearest 0.25 Hz with 83% agreement. In the instances where the researchers differed in their classifications, most frequently a result of split peaks, or minimal deviation from the aperiodic background scaling, the PAF was re-evaluated to ensure accurate selection. If researchers could not agree upon a dominant peak upon re-evaluation, split peaks were averaged together to estimate PAF, whereas those with minimal deviation from background scaling were regarded as having no PAF and were excluded from calculation of group PAF averages. Of 100 participants, 91 had a clear alpha peak. Those with and without alpha peaks did not differ in regards to age ($t(98)=0.53$, $p = 0.60$), data length ($t(98)=1.09$, $p = 0.28$), gender ($t(98)=1.95$, $p = 0.05$), or the total number of components removed ($t(98)=1.63$, $p = 0.11$). Individualized frequency bands were calculated as a percentage of the PAF as follows: theta [PAF × 0.4 – PAF × 0.6] and alpha [PAF × 0.6 – PAF × 1.2]. This approach accounts for observations that frequency bandwidths vary based on PAF (Doppelmayr et al. 1998). For the nine participants with no clear alpha peak, we instead calculated individualized frequency bands using the average PAF for the entire sample, which was 8.64. The individualized frequency bands were then applied to signal across

[1]MMR is Madeline M. Robertson; MK is Michelle Kim. Thank you to both of them for their contributions.

all electrodes. Next, to account for differences in the amplitude of the EEG signal due to noise including skull thickness and electrode impedance, we calculated relative power by dividing the power within each band by the total power, which was defined as 1-60 Hz (Gasser et al. 1982; Kappenman and Luck 2010).

Region of Interest Analysis. Given the extent to which EEG signal is shared across electrodes and to reduce the number of comparisons, a region of interest (ROI) analysis was conducted to test for group differences between regions of brain signal. To do this, electrodes were grouped a priori into frontal (Fz, F1, F2, F3, F4, F5, F6, F7, F8), central (C1, C2, C3, C4, C5, C6, C7), and parietal (Pz, P3, P4, P7, P8) regions in accordance with previous studies of children with ADHD (Tye et al., 2014). Average relative power in alpha and theta was calculated for each region and then included in statistical models.

Statistical Methods. Data were analyzed using R version 3.5.3 (R Core Team, 2013). Bivariate correlations were conducted to test if age or sex was associated with relative power in alpha or theta in any of the ROIs. Neither age nor sex were associated with alpha or theta power in any of the ROIs (see Table 2.3), and thus age and sex were not included in the following statistical models. First, multiple linear regression models were used to test the associations of ADHD symptoms with relative power in alpha and theta and subsequently to test if either family SES or family conflict were associated with relative power in alpha and theta within the three ROIs. Next, additional models assessed if there was an association of ADHD symptoms with relative power in alpha and theta when controlling for the family environment (family SES and family conflict). Finally, regression models were included to test if there was an association of the interaction of ADHD symptoms and SES with relative power or if there was an association of

the interaction of ADHD symptoms and family conflict with relative power. Between-group comparisons of the ROIs were False Discovery Rate (FDR) corrected to $p < 0.05$.

Results

First, we tested if total ADHD symptom severity was associated with relative power in alpha and theta in frontal, central, and parietal ROIs. Standardized beta values are reported for all regression models. Alpha power in the parietal region of interest was positively associated with ADHD symptoms ($\beta = 0.24$, $p = 0.02$, see Figure 2.2). Frontal and central alpha power were only associated with total ADHD symptoms at the trend level (frontal, $\beta = 0.19$, $p = 0.07$, central, $\beta = 0.19$, $p = 0.06$). Parietal alpha power was associated with ADHD symptoms at the trend level after FDR correction. ADHD symptoms were not significantly associated with theta relative power in frontal ($p = 0.10$), central ($p = 0.44$), or parietal regions of interest ($p = 0.50$).

Family SES

Income to needs was negatively associated with ADHD symptom severity such that where income to needs ratio increased ADHD symptom severity decreased ($\beta = -0.31$, $p = .01$). Income to needs was not associated with frontal ($\beta = -0.03$, $p = 0.75$), central ($\beta = -0.04$, $p = 0.71$), or parietal ($\beta = 0.01$, $p = 0.93$) alpha relative power; nor was it associated with frontal ($\beta = -0.01$, $p = 0.92$), central ($\beta = -0.05$, $p = 0.66$), or parietal ($\beta = -0.06$, $p = 0.60$) theta relative power.

Family Conflict

Family conflict was positively associated with ADHD symptom severity such that where conflict increased ADHD symptom severity increased ($\beta = .24$, $p = .02$). The next set of models tested the relationship of family conflict and alpha and theta power. In these models, parent report of family conflict was not related to frontal ($\beta = -0.02$, $p = 0.84$), central ($\beta = -0.02$, $p =$

0.84), or parietal (β = -0.02, p = 0.83) alpha relative power; nor was it related to frontal (β = -0.02, p = 0.83), central (β = -0.06, p = 0.56), or parietal (β = -0.07, p = 0.48) theta relative power.

Interaction of ADHD Symptoms and Poverty

Next, we examined the possibility that poverty enhances the association between ADHD symptoms and oscillatory power in alpha and/or theta. We did not observe a significant interaction between ADHD and poverty in association with frontal (β = 0.19, p = 0.30), central (β = 0.07, p = 0.53), or parietal (β = 0.08, p = 0.42) alpha relative power or with frontal (β = 0.01, p = 0.16), central (β = 0.16, p = 0.17), or parietal (β = 0.16, p = 0.20) theta relative power.

Interaction of ADHD Symptoms and Family Conflict

Next, we examined the possibility that family conflict enhances the association between ADHD symptoms and oscillatory power in alpha and/or theta bands. We did not observe a significant interaction between ADHD and family conflict in association with frontal (β = 0.04, p = 0.83), central (β = 0.03, p = 0.78), or parietal (β = 0.01, p = 0.91) alpha relative power or with frontal (β = 0.16, p = 0.23), central (β = 0.16, p = 0.24), or parietal (β = 0.04, p = 0.71) theta relative power.

ADHD Symptoms Controlling for Family Environment

Finally, given the significant association of ADHD symptoms but not family environment variables with alpha relative power, we next assessed the association between ADHD symptoms and relative power controlling for poverty and family conflict. Symptoms of ADHD were positively associated with parietal (β = 0.29, p = 0.02) relative power in the alpha band but remained non-significant for frontal (β = 0.20, p = 0.10) and central (β = 0.21, p = 0.08) alpha power. This finding remained significant after FDR correction. ADHD symptoms were not

associated with frontal (β = 0.14, p = 0.25), central (β = 0.04, p = 0.75), or parietal (β = -0.001, p = 0.99) theta power while controlling for the family environment.

Removal of Subjects Without Clear Alpha Peaks

While the participants without alpha peaks did not differ from the other participants on a number of metrics, to test for robustness of the findings, analyses were run after removing those N=9 participants from the sample. After removing those participants, results remained the same except for one difference: frontal and central alpha were significantly associated with ADHD symptoms (frontal, β = 0.22, p = 0.04, central, β = 0.22, $p < 0.05$), whereas when the children without alpha peaks were included in the analyses frontal and central alpha power were only associated with ADHD symptoms at a trend level. These findings remained significant after FDR correction. All other results remained the same after removal of the participants without alpha peaks, including that when controlling for family environment only parietal alpha power was significantly associated with ADHD symptoms (β = 0.34, p = 0.01). This finding also remained significant after FDR correction.

Discussion

The aim of this paper was to explore the potential impact of two environmental factors, family conflict and income to needs ratio, on a possible neural correlate of ADHD diagnosis, relative frequency band power in alpha and theta measured during resting state EEG. A secondary aim of the paper was to identify potential interactions between ADHD and family environment in predicting EEG relative power. Consistent with previous findings, we show that increased ADHD symptoms are associated with increased relative alpha band power. Interestingly, in analyses that include the entire sample, we do not observe that environmental variables are associated with this aspect of the EEG signal as was predicted, nor do these

variables interact with ADHD symptoms to predict neural signal. Of note, associations between total ADHD symptoms and relative alpha power over parietal cortex was robust to controls for both family SES and family conflict.

This analysis represents a useful incremental improvement over previous work. The findings from this paper indicate that increased alpha power is associated with increased ADHD symptom severity. Previous evidence has suggested that differences in power in the alpha and theta bands might be used as diagnostic markers of ADHD (Barry et al., 2003; Hale et al., 2009, 2010; Koehler et al., 2009; Robbie et al., 2016; Tye et al., 2014) and activity in the alpha band has previously been associated with functions that are typically disrupted in individuals with ADHD, including inhibitory control (Başar et al., 2001; Klimesch, 2012). With one exception, an analysis using the current dataset (Robertson, et al., 2019), these findings are for children in middle childhood, adolescence, and adults. Here we extend these findings into early childhood using a continuous model of ADHD, and show that in early childhood, these findings appear to be localized over parietal cortex. Importantly, this work has implications for understanding early brain development in the context of the widely-varied developmental trajectories that are particularly present in early childhood. The use of a continuous model highlights that neural development should be considered on a spectrum in relation to behavioral development in early childhood. This approach might prove useful for researchers, clinicians, and educators that are interesting in understand child development in a non-binary framework.

In addition, we demonstrate that associations between ADHD symptoms and relative alpha power over parietal cortex are robust to controls for family SES and family conflict. There is a growing body of literature indicating that metrics in the alpha band have potential for improving both diagnostic tools as well as mechanistic understanding of neural signatures that

underlie ADHD symptomatology and this work extends previous findings into early childhood and demonstrates robustness of these associations to some novel control variables.

Environmental Variables

While we did observe significant associations between family SES and conflict with ADHD symptoms, we did not observe any association between family SES or family conflict and EEG relative power. Previous work linking adversity exposure to ADHD through neural structure and function has identified that the part of the brain impacted by these factors are primarily subcortical (Machlin, McLaughlin, et al., 2019; McLaughlin et al., 2014). The EEG signal is primarily the result of coordinated firing of assemblies of pyramidal neurons oriented in geometrically specific ways, these synchronized assemblies in subcortical structures generally are not large enough to be measurable at the surface due to the distance required for the signal to travel and evidence that signal from subcortical structure may be more prone to noise contamination (Jackson & Bolger, 2014). Thus, resting state EEG is not thought to capture changes in subcortical function and this may partially explain differences between our observations and previous work. Crucially, this suggests that resting state EEG might have potential to serve as a metric of ADHD symptom severity regardless of other factors impacting a child's presentation. However, regarding mechanistic understanding of the neural underpinnings of the nuances of behavior in early childhood, our findings suggest that methods that can examine both subcortical and cortical structures and functions should be utilized.

Previous work identifying links between adversity, EEG relative power, and ADHD symptoms examined these associations in children in middle childhood who had been exposed to institutionalization, a profound and pervasive example of deprivation (McLaughlin et al., 2014). Thus, another possible explanation for the lack of associations of family conflict and SES with

EEG in the current study is that those impacts might not be seen in EEG at the developmental timepoint employed in this study or with the level of exposure which we examine here.

Absence of Alpha Peaks: Relation to Environmental Variables?

In supplemental analyses that were included to test the robustness of the findings, a difference in results was revealed when removing the participants that did not have a clear alpha peak. It is important to note that while it is common in the literature for some participants to not have a clear alpha peak, there is no consensus on the implications of not having an alpha peak nor on how to interpret findings in relation to individuals without an alpha peak. In the current study, the removal of the children without alpha peaks revealed a significant association of alpha power at all three ROIs and that when including environmental factors in the model only parietal alpha power remained significantly associated with ADHD symptoms. One possibility for this finding is that the children without clear alpha peaks actually have substantially lower alpha power and thus skew the findings and hide evidence of an impact of environmental variables on the relationship of ADHD symptoms and EEG power. Moreover, when comparing the children with and without peaks, the children without peaks have significantly reduced income to needs ratio values compared to the children with peaks ($p<0.05$). This suggests that the children without clear alpha peaks in the current sample have an overrepresentation of children from lower resourced households compared to the overall sample, which in turn could partially explain the slightly different finding when the children without peaks are removed from the analyses. However, it is important to limit conclusions drawn from a small sample (N=9), particularly when individuals without clear alpha peaks have not been thoroughly examined outside of being included as a small part of a larger sample in many studies.

Limitations

There are several limitations of the present work. Of note, the length of data was fairly short in comparison to other studies collected in older children and adolescents. Regarding the measures of environmental adversity, only two measures were used, and it is possible that other measures would impact resting state EEG power in the alpha or theta bands including direct measures of deprivation instead of the use of socioeconomic status (Machlin, McLaughlin, et al., 2019; Machlin, Miller, et al., 2019; Sheridan et al., 2017; Sheridan & McLaughlin, 2014). Furthermore, the population in the study was not recruited as part of a study on maltreated children or children living below the poverty threshold, thus resulting in a limited range of scores on the CTS. It is possible that family conflict does impact the neural signal associated with ADHD, but that the level of family conflict that would produce an identifiable change in the neural signal is severe and was not fully represented in the current sample. Therefore, future research should examine these questions in a sample with more severe instances of adversity, which might in turn impact the neural correlates of ADHD.

Conclusions

In summary, we demonstrate the application of individual alpha peak frequency bands to EEG data collected with young children (ages 3-7 years old). Using this approach, we identified that increased ADHD symptom severity was associated with increased alpha power over parietal regions. These findings are consistent with other literature in children with ADHD. In addition, the association between ADHD symptoms and EEG relative power were robust to controls for family environment, captured via family SES and family conflict. Future work should evaluate whether these findings extend to older children and adults in a longitudinal study, are replicated with a greater length of data and number of subjects, if children with severe adversity exposure

have differential neural signals in association with ADHD symptomatology, and if relative alpha power measured in individual alpha peak frequency bands is normalized after stimulant treatment for ADHD.

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Table 2.1. Sample Demographics

	n	%
Female	28	29.8
Handedness (R)	82	87.2
Race		
White	61	64.8
Black/African American	12	12.8
Asian	2	2.1
Other/Multiracial	17	18.1
Did not report	2	2.1
Hispanic/Latino	11	11.7

Note. N = 94. Participants were on average 67.73 months old (SD = 14.63).

Table 2.2 Bivariate Correlations of Variables of Interest

	Age	PIQ	Sex	Total ADHD Symptoms	Income to Needs	CTS Total
Age	--	-0.09	0.22*	-0.07	0.16	0.11
PIQ		--	0.06	-0.08	0.18	-0.06
Sex			--	-0.14	0.06	-0.09
Total ADHD Symptoms				--	-0.31**	0.24*
Income to Needs					--	-0.24*
CTS total						--

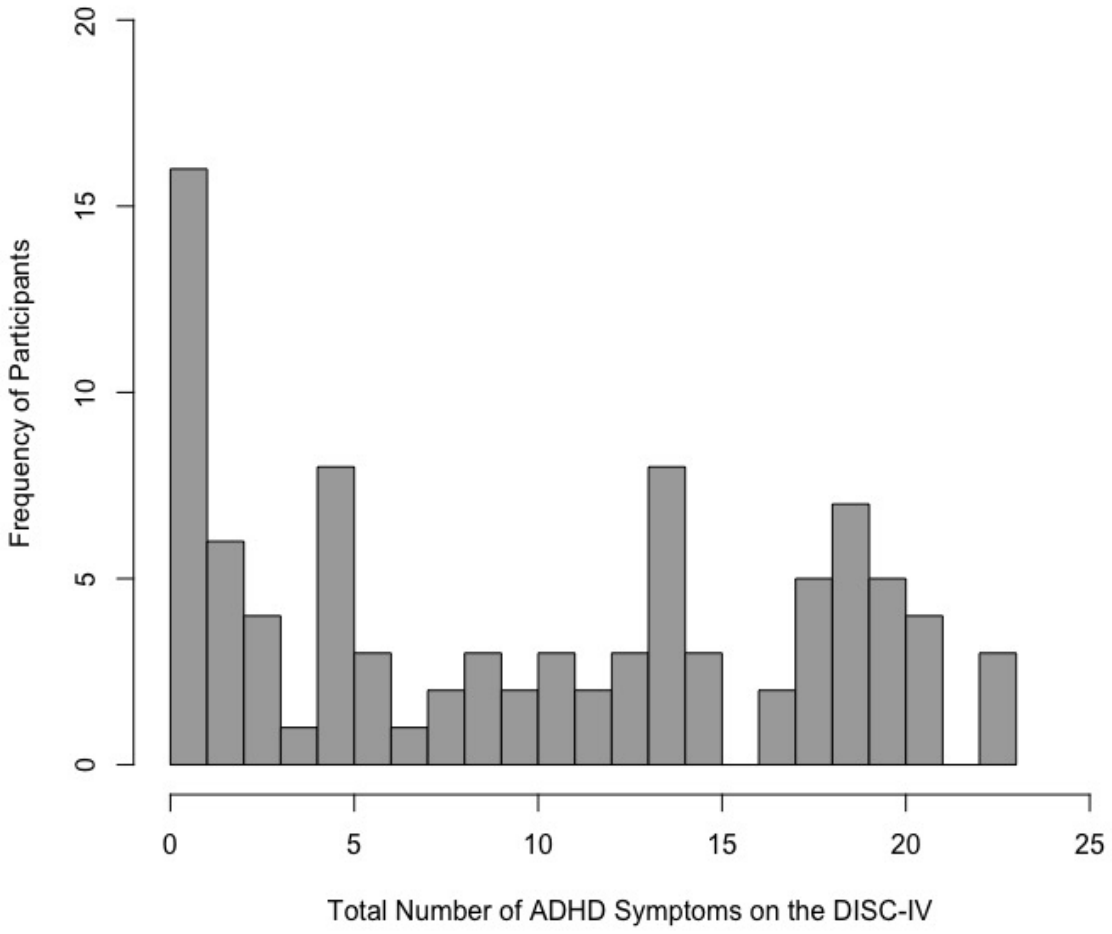
Note. Table displays results of bivariate correlations of variables of interest (total ADHD symptoms, income to needs ratio, and family conflict measured on the CTS) and potential confounds (age, IQ, and sex). None of the potential confounds were significantly correlated with the variables of interest, thus, they were not included in the subsequent analyses. *$p < 0.05$

Table 2.3. Bivariate Correlations of Age, Sex, and EEG Power in Alpha and Theta ROIs

	Age	Sex
Frontal α	0.11 (0.25)	-0.03 (0.80)
Central α	0.14 (0.18)	-0.09 (0.39)
Parietal α	0.16 (0.11)	-0.05 (0.59)
Frontal θ	-0.05 (0.59)	-0.03 (0.74)
Central θ	-0.05 (0.61)	-0.06 (0.53)
Parietal θ	-0.10 (0.34)	-0.09 (0.36)

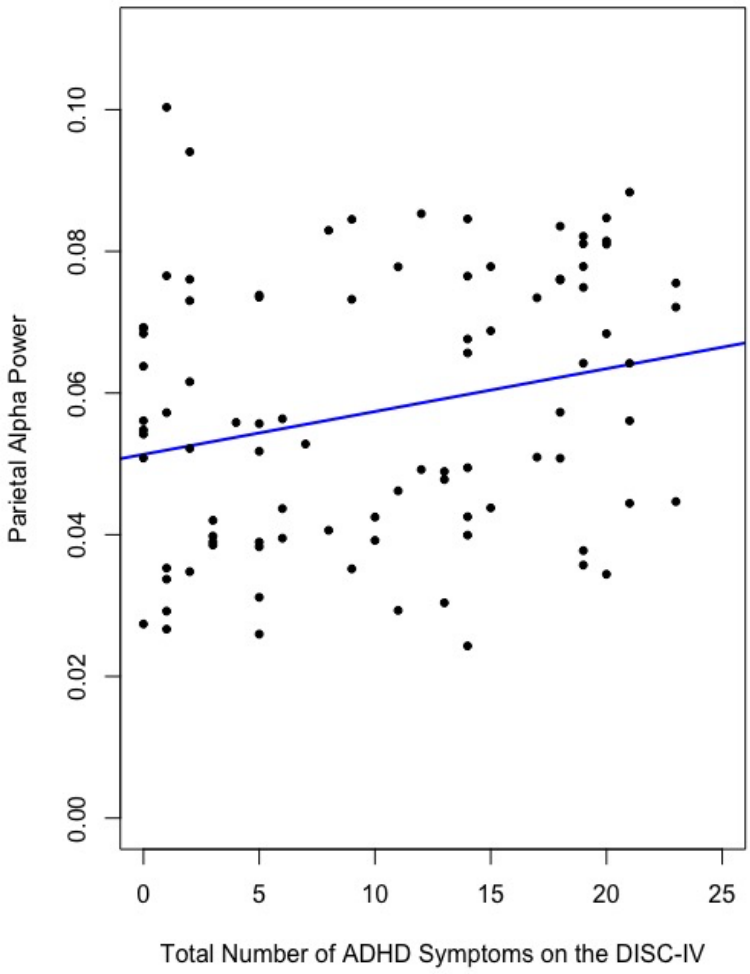
Note. Table displays results of bivariate correlations that tested if age or sex were associated with relative power in alpha or theta at any of the ROIs (α: alpha band; θ: theta band). Values are displayed as the correlation coefficient with p-values in parentheses. Neither age nor sex were significantly correlated with the variables of interest, thus, they were not included in the subsequent analyses. *$p < 0.05$

Figure 2.1. Distribution of ADHD Symptoms



Note. Histogram containing the frequency of participants having each possible value of total ADHD symptoms. ADHD: attention-deficit/hyperactivity disorder; DISC-IV: Diagnostic Structured Interview Schedule – young child version.

Figure 2.2. The Association of Total ADHD Symptoms and Parietal Alpha Power



Note. A plot of the relationship of total ADHD symptoms and relative alpha power over parietal regions. There was a significant association, such that increased ADHD symptom severity was associated with increased parietal alpha power. ADHD: attention-deficit/hyperactivity disorder; DISC-IV: Diagnostic Structured Interview Schedule – young child version.

STUDY 3: The Long-Term Impact of Institutionalization on Neural Structure: An Examination of Developmental Trajectories of Structural Covariance in the Bucharest Early Intervention Project

The process of typical neural development depends profoundly on a wide variety of experiences and environmental inputs, particularly during sensitive periods (McLaughlin et al., 2017). Sensitive periods exist for lower-level sensory functions (and have been suggested to also exist for higher-level behaviors and complex cognition) and these domains that require environmental inputs are considered to be *experience-expectant* (Bick & Nelson, 2016; Greenough et al., 1987; McLaughlin et al., 2017). Consequently, disruptions to the expected environment (i.e., experiences of childhood adversity), can lead to profound deviations of behavioral, cognitive, and neural development. In particular, exposure to adverse experiences in early childhood confers an increased risk for psychopathology, language delays, cognitive deficits, and reduced academic achievement (Benjet et al., 2010; Black et al., 2008; Green et al., 2010; Leventhal & Brooks-Gunn, 2000; McLaughlin et al., 2010). While some prior research has focused on cumulative risk models of adversity by examining the associations of total number of adverse experiences with psychopathology and other deleterious outcomes (Anda et al., 2005; Dube et al., 2003), more recent evidence indicates that different forms of adversity have differential impacts on cognitive and emotional development (Busso et al., 2016, 2017; Lambert et al., 2016; Machlin et al., 2019; Miller et al., 2018). Based on this work, a recent model has, in comparison to cumulative risk models of adversity, posited that childhood adversity can be differentiated into two underlying dimensions, deprivation (i.e., the lack of expected cognitive

stimulation and social learning experiences) and threat (i.e., experiences reflecting harm or threat of harm to the child), that impact development in unique ways (McLaughlin, Sheridan, & Lambert, 2014; McLaughlin & Sheridan, 2016; Sheridan et al., 2017; Sheridan & McLaughlin, 2014). Thus far, evidence indicates that experiences of deprivation during childhood are associated with poor executive functioning, deficits in cognition, and associated changes in neural structure and function, whereas experiences of threat are associated with heighted emotional reactivity, difficulty with emotion regulation, and associated changes in neural structure and function (McLaughlin & Lambert, 2017; Sheridan et al., 2017). As such, this growing literature emphasizes the importance of examining unique aspects of childhood adversity along these two dimensions in order to further understanding of the neurodevelopmental mechanisms that underlie the negative impacts of adverse experiences.

Neglect and Institutional Care

The most prevalent form of childhood maltreatment is neglect, which involves failure of the caregiver to provide for the child's physical and emotional health as well as educational needs and protection from harm (Gilbert et al., 2009; Leeb et al., 2008; Straus & Kantor, 2005). Recent work found that 75% of reported maltreatment cases in 2017 included reports of neglect ("Child Trends," 2019; Finkelhor et al., 2014). In comparison, 9% of maltreatment cases included reports of sexual abuse and 18% included reports of physical abuse ("Child Trends," 2019; Finkelhor et al., 2014). Additionally, while some environmental factors, such as poverty, are not necessarily indicative of neglect (i.e., a child living in poverty can experience typical exposures to cognitive stimulation and social inputs), they can serve as a risk factor for increased likelihood of deprivation in exposure to enriching cognitive and social environments (Sheridan & McLaughlin, 2014). Critically, an estimated 21.1% of all children in the United States (15.5

million children) live in households with incomes below the federal poverty line (FPL), and approximately 42.9% of children in the United States (over 31.5 million children) live below the FPL or live in low-income households (i.e., incomes up to 200% of the FPL; AAP Council on Community Pediatrics, 2016; Pascoe et al., 2016). Further, it is estimated that 6.8 million children live in deep poverty (i.e. incomes below 50% of the FPL; AAP Council on Community Pediatrics, 2016; Pascoe et al., 2016). As such, millions of children in the United States are at increased risk for experiencing deprivation of expected social and cognitive input. While all forms of child maltreatment are harmful, neglect is the most prevalent, and it is a critical public health concern to further understand the impact of neglect on child development.

Institutional care is a severe form of neglect that can be studied to increase knowledge of the impairments to typical developmental sequalae that occur in response to experiences of deprivation. Institutional rearing represents a severe violation of the expected environment due to children in these environments typically experiencing high ratios of children to caregivers, limited access to language and cognitive stimulation, regimented caregiving, and low caregiver investment (Bick et al., 2015; Dubowitz et al., 2002; Hanson et al., 2015; McLaughlin et al., 2017; Sheridan et al., 2012; Tottenham et al., 2010; Walker et al., 2011). Ample evidence exists that institutionalization is associated with numerous cognitive delays, memory deficits, learning difficulties, and impairments in language development, such that these children experience higher rates of academic difficulties and school adjustment problems (Bick & Nelson, 2016; Bos et al., 2009; Johnson et al., 2010; Nelson et al., 2007; Pechtel & Pizzagalli, 2011). Consequently, children who have experienced early institutionalization are at higher risk of developing psychopathology, including attention-deficit/hyperactivity disorder (ADHD), experience higher rates of interpersonal problems, and are at increased risk for engagement in antisocial activities

(Bos et al., 2011; Cohen et al., 2001; Dennison et al., 2019; Eaves et al., 2010; Hanson et al., 2015; Humphreys & Zeanah, 2015; Jaffee, 2017; Zeanah et al., 2009). Importantly, despite the evidence that children who experience early institutionalization face numerous developmental deficits across a wide range of domains, it remains common practice to place children into these settings, and it has been estimated that approximately 8 million children worldwide are currently in institutional care (Desmond et al., 2020; Jacobs & The Congressional Coalition on Adoption Institute (CCAI), 2011; Walker et al., 2011). As such, it is crucial to further the research basis for understanding the long-term outcomes for children who experience institutionalization and what mechanisms underlie those outcomes, both in order to inform policy regarding the care of institutionalized children, and to deepen understanding of development in the context of neglect. One explanation of the association of institutionalization with increased rates of psychopathology and cognitive deficits is that institutionalization hinders the development of neural structures during sensitive periods in childhood, and in turn, the neural effects of institutionalization underlie the previously identified increased risks for developing psychopathology and cognitive impairments. Understanding the neural mechanisms underlying this association is critical for developing adequate and timely interventions and policies to better serve children living in neglectful environments.

Methodological Design in Studies of Previously Institutionalized Children

While it is unethical to manipulate the environments that children are raised in, several research teams have utilized samples of internationally adopted children to examine the impact of early life neglect on development. However, the majority of these studies are limited in their ability to draw causal inference, as they are quasi-experimental in nature and are confounded by lack of information about the previously institutionalized children's experiences before adoption,

among other factors. This makes it difficult to identify matched samples that reduce confounding variables and limits the strength of these studies. Several studies, including the English and Romanian Adoptees (ERA) study and the International Adoption Project at the University of Minnesota, have worked with samples of previously institutionalized, internationally adopted children who were living in the United States or the United Kingdom, and compared those to typically developing children (Herzberg et al., 2018; Mackes et al., 2020; Mehta et al., 2009; Silvers et al., 2016; Tottenham et al., 2010; Tottenham, 2013). These studies have often utilized rigorous observational designs, including longitudinal designs that have contributed substantially to the body of research on institutionalization (Schaefer, 2018).

The Bucharest Early Intervention Project (BEIP) is the first and only known randomized control trial (RCT) to examine foster care as an intervention for early institutionalization by comparing foster care to continued institutional care. This approach is unique and has profound implications for the study of previously institutionalized children. In the BEIP, 136 children between the ages of 6 and 31 months of age living in institutions in Bucharest, Romania were randomly assigned to either a foster care intervention (foster care group, FCG) or to remain in the institution (care-as-usual group, CAUG). Additionally, children in Romania who were never institutionalized have been included in the BEIP as controls (never institutionalized group, NIG). The use of the RCT approach allows for both the evaluation of the efficacy of foster care as an intervention for institutionalization in early childhood, but also the ability to identify causal effects of severe early-life deprivation on numerous aspects of development (Schaefer, 2018; Zeanah et al., 2003). The children in the BEIP have been followed for approximately 20 years at the time of writing, leading to invaluable causal evidence regarding the impact of severe, early psychosocial deprivation.

Effects of Institutionalization on Brain Structure

Evidence from multiple studies indicates the previously institutionalized children have widespread changes to their neural structure, indicated by findings of these children having decreased white matter volume, decreased gray matter volume, decreased total brain volume, widespread decreases in cortical thickness, and alterations in white matter microstructure throughout the brain (Bick et al., 2015; Eluvathingal et al., 2006; Herzberg et al., 2018; Mackes et al., 2020; McLaughlin, Sheridan, Winter, et al., 2014; Mehta et al., 2009; Rutter & Sonuga-Barke, 2010; Sheridan et al., 2012). While this suggests that institutionalization is associated with widespread alterations in brain structure, other evidence has found that institutionalization is associated with deviations in specific neural structures, including decreased volume of the left hippocampus and increased volume of the right amygdala (Mehta et al., 2009), decreased right inferior frontal surface area and volume and increased right inferior temporal lobe thickness, surface area, and volume (Mackes et al., 2020), increased amygdala volume in late (>15 months) adopted children (Tottenham et al., 2010), decreased fractional anisotropy values in the left uncinate fasciculus (Eluvathingal et al., 2006), and decreased anterior and posterior corpus callosum volume (Sheridan et al., 2012). Lastly, other work reported no differences in overall cortical volume, amygdala volume, hippocampal volume, or caudate volume in children who were previously institutionalized (Tottenham et al., 2010). Taken together, the evidence from previous work predominantly (although inconsistently) reports alterations to brain structure in previously institutionalized children; however, there is marked differences in the particular findings across studies, both in terms of findings supporting alterations to the whole brain versus primarily to specific neural structures, and in terms of which measures differ and in which direction compared to controls. Overall, previous findings suggest that social deprivation might

impact both specific neural structures in the brain as well as global neural structure. Critically, multiple studies from the BEIP indicate that randomization into foster care remediates some of the neurodevelopmental deficits associated with early institutionalization, suggesting plasticity of some aspects of neural development and supporting policies that promote foster care placements instead of institutionalization (Bick et al., 2017; Bick et al., 2015; Sheridan et al., 2012).

In summary, ample evidence suggests that early severe psychosocial deprivation, in the form of institutionalization, is associated with numerous deleterious impacts on neural structure in childhood and adulthood. Despite the growing body of evidence, there are still remaining questions concerning the different findings regarding changes in brain volume in specific regions not replicating across studies and inconsistencies in detection of global neural differences. Possible explanations for these differences include the use of different samples and ages at measurement, but also the utility and variety of the methodological approaches. Given that neural regions that develop on similar trajectories tend to covary in cortical thickness and surface area (Alexander-Bloch et al., 2013), the application of structural covariance analyses to this population holds promise for deepening the characterization of the nuanced structural brain changes conferred by early deprivation and the mitigation of those differences by foster care intervention.

Institutionalization, ADHD, and Brain Structure

Of note, institutionalization, along with other experiences of neglect, during childhood is associated with impairments similar to those observed in children with ADHD, such as deficits in attention, concentration, and executive functions (McLaughlin et al., 2017; McLaughlin, Sheridan, & Lambert, 2014; Sheridan et al., 2017; Sheridan & McLaughlin, 2014). Unsurprisingly, previously institutionalized children display higher rates of ADHD than the

typical population (Kreppner et al., 2001; Stevens et al., 2008; Zeanah et al., 2009). Importantly, there is evidence that these structural brain differences mediate the association of institutionalization and ADHD (Bick et al., 2017; McLaughlin, Sheridan, Winter, et al., 2014). However, given the limited studies on this association, the current work explored the relationship of institutionalization, brain structure development, and ADHD by examining if structural brain network development mediates the relationship of institutionalization and ADHD.

Structural Covariance

Structural covariance analysis involves the measurement of covarying interindividual differences in neural anatomy across groups, and has been posited to improve conceptual understanding of the fine tuning of neural structure that occurs across development (Alexander-Bloch et al., 2013; Bethlehem et al., 2017; Evans, 2013; Khundrakpam et al., 2013). Furthermore, it has been suggested that axonal connections forming and reforming over the course of development underlie the synchronization of maturational change between brain regions, and thus structural covariance is thought to function as a structural marker of early functional co-activations of regions that are known to develop together (Alexander-Bloch et al., 2013; Khundrakpam et al., 2013; Mackes, 2019; Raznahan et al., 2011). Evidence from human and animal models supports that there is an impact of genetic influences on covariation of brain regions and structural brain development (Badea et al., 2009; Chen et al., 2011, 2012; Jha et al., 2018; Schmitt et al., 2008, 2009, 2010, 2018). However, other evidence suggests that environmental factors and learning also have a role in the development of brain structure (Bermudez et al., 2009; Draganski et al., 2004; Driemeyer et al., 2008; Evans, 2013; Haier et al., 2009; Karpati et al., 2018; Schmitt et al., 2018). Evidence of altered structural covariance in ADHD (Bethlehem et al., 2017; Li et al., 2015), autism spectrum disorder (Balardin et al., 2015;

Bethlehem et al., 2017; Duan et al., 2020; Sharda et al., 2016), obsessive compulsive disorder (Subirà et al., 2016), and conduct disorder (Fairchild et al., 2016) highlights the importance of neural structure for understanding atypical functioning and suggests that biological and environmental factors might both impact structural covariance.

Methodological Advantages of Structural Covariance Analysis

There are several advantages to the structural covariance methodological approach. First, this approach is relatively insensitive to the noisy components present in task-based and resting-state functional magnetic resonance imaging (MRI; Sun et al., 2018). Second, early experience of deprivation is likely to disrupt the coordinated development of brain networks and not only specific regions, such that altered structural covariance has the ability to investigate the network properties of the brain from a maturational perspective that incorporates entire networks instead of single brain structures (Bethlehem et al., 2017; Mackes, 2019). Lastly, structural covariance can capture the lasting impact of deprivation that occurs during early sensitive periods, which are characterized by the neural maturation thought to result in covariation of structural brain development (Ismail et al., 2017).

Structural Covariance and Child Maltreatment

While only a few studies exist that have examined structural covariance in association with childhood maltreatment, they provide evidence that childhood maltreatment is associated with alterations in structural covariance (Mackes, 2019; Sun et al., 2018; Teicher et al., 2014). Two studies could be found that examined structural covariance in adolescents who reported previous experiences of all types of maltreatment (Sun et al., 2018) and adults who reported previous experiences of abuse (Teicher et al., 2014). Both studies found that history of abuse in childhood was associated with decreased centrality (a measure of connectedness) among regions

that are important for emotion regulation, self-awareness, and internal emotional perception (Sun et al., 2018; Teicher et al., 2014). Together, evidence from both studies indicates that there are alterations in structural covariance that are related broadly to maltreatment. However, this work on maltreatment and structural covariance is limited by the use of retrospective report of maltreatment, and by the association of maltreatment and structural covariance being confounded by the participants' genetic risk for psychopathology and genetic influences on brain development. Moreover, this work does not specifically examine the impact of early psychosocial deprivation on structural covariance networks in the brain.

One novel study recently aimed to address these limitations by examining structural covariance in adults who were followed up as part of the ERA study. Institutional deprivation was associated with altered structural covariance in right frontal-temporal regions in adulthood, with some pairs of regions having decreased covariance and some having increased covariance (Mackes, 2019). While highly innovative, there are several limitations to this study as well. First, the ERA study measured structural covariance at one timepoint in adulthood, leaving questions regarding the developmental trajectories of structural covariance in previously institutionalized children. In addition, graph theoretical metrics were not applied to the structural covariance networks in the ERA study, making it difficult to 1) compare the findings to those of previous structural covariance studies that used graph theoretical metrics to assess topological characteristics of the structural networks, and 2) characterize the disruptions to the structural covariance networks at a more nuanced level. Most importantly, these previous studies are not able to test for causal inferences due to study design and sample selection. Critically, the RCT design of the BEIP allows for causal inferences to be made regarding the effects of institutionalization on structural brain development.

Current Study

The current study aims to fill gaps in the literature by applying structural covariance methodology to data collected as part of the BEIP. There is currently no previous research that has examined structural covariance during middle and late childhood in a sample of previously institutionalized children. Importantly, the extent to which the detrimental effects of institutionalization on neural structural covariance can be mitigated by placement into an enriched environment (foster care) has never been examined, but the present work is able to do so because of the RCT design of the BEIP. Additionally, this work includes measurements from the same sample at two different timepoints, when the children were approximately 9 and 16 years old, which allows this work to further characterize the developmental trajectories of structural brain network development in this population. Further, in order to assess for the extent to which the impact of institutionalization is related to structural brain development and ADHD, we conducted a mediation analysis in order to test the association of structural brain network development and ADHD symptoms in children with previous exposure to institutionalization. Lastly, the current work applies graph theoretical methods to the structural covariance networks in order to further characterize structural brain network development in previously institutionalized children and the relationship of institutionalization with structural brain networks and ADHD.

Hypotheses

Broadly, previous work indicates that institutional deprivation is associated with alterations in structural covariance in adulthood. However, previous work did not utilize graph theoretical analyses to characterize these network differences, and reported increases and decreases in covariance depending on which pair of regions were evaluated. Thus, it was difficult

to predict what differences would be present in the graph theoretical metrics in previously institutionalized children beyond hypothesizing that children in the CAUG would have impaired network efficiency when compared to the FCG and the NIG. This would indicate that institutionalization disrupts the development of regions that typically develop synchronously. Further previous evidence indicates that global structural covariance network properties change throughout development, with increasing integration and decreasing segregation from early childhood to late childhood and decreasing integration and increasing segregation from late childhood into early adolescence and further into late adolescence. Thus, we expected that if children in the FCG demonstrate normalization of their brain structure at age 9, the FCG would exhibit increased integration and decreased segregation compared to the CAUG and similar levels of integration and segregation compared to the NIG. We also expected the FCG to have normalization of structural covariance at age 16, and given the nonlinear trajectory of structural brain development, we expected the FCG to have decreased integration and increased segregation compared to the CAUG at age 16 and again display similar levels of integration and segregation to the NIG. Lastly, exploratory analyses utilize participants with data at both timepoints to further characterize the network organization of structural brain development in children in the CAUG and FCG in comparison to each other and the NIG, as well as to assess for the relationship of ADHD symptoms with institutionalization status and brain development.

Methods

Participants

As part of the ongoing BEIP, structural MRI scans were acquired for 85 participants when the children were approximately 9 years old, and for 115 participants when the children were approximately 16 years old. Participants included children who were randomly selected to

remain in institutional care (CAUG), children who were randomized out of institutions into foster care (FCG), and children who had never been in institutional care (NIG). All study procedures were approved by the local commissions on child protection in Bucharest, the Romanian ministry of health, and the institutional review boards of the home institutions of the three primary investigators. A complete description of procedures used in the BEIP has been published previously, and previous literature has discussed the ways in which ethical integrity was maintained in the BEIP (Nelson et al., 2007; Zeanah et al., 2003, 2006, 2006, 2009, 2012).

Participants at 9 Years

At the 9-year data collection timepoint, 86 children completed MRIs. Four participants were excluded from all analyses because poor scan quality prevented proper segmentation of cortical and subcortical gray/white matter boundaries (two CAUG, one FCG, and one NIG), and one child was excluded from all analyses because of frank neurological abnormality (FCG). The total sample of useable data at 9 years included N = 81 children. In terms of group status, there were N = 32 CAUG children (16 females; M = 9.68 years, SD = 0.77), N = 27 FCG children (13 females; M = 9.85 years, SD = 0.68), and N = 22 NIG children (13 females; M = 9.79, SD = 0.94). There were no differences in age across the three groups at the 9-year data collection ($F = 0.36$, $p = 0.70$). There was no difference in age between boys and girls, $t(78.99) = -1.34$, $p = 0.17$. See Table 3.1 for group demographics for the 9-year data collection timepoint.

Participants at 16 Years

At the 16-year data collection timepoint, N = 115 children completed MRIs. The total sample at 16 years included N = 41 CAUG children (19 females; M = 16.65 years, SD = 0.49), N = 41 FCG children (21 females; M = 16.57 years, SD = 0.52), and N = 33 NIG children (19 females; M = 16.85 years, SD = 0.48). There were no differences in age across the three groups

at the 16-year data collection (F = 3.14, p = 0.05). There was no difference in age between boys and girls, $t(110.97) = -0.18$, p = 0.86. See Table 3.2 for group demographics for the 16-year data collection timepoint.

Participants with MRI Data at Both Timepoints

For the exploratory subject-based maturational coupling analyses, the subset of children with MRI data at both timepoints (N = 62) were included. The sample of children with data at both timepoints included N = 27 CAUG children (13 females), N = 23 FCG children (10 females), and N = 12 NIG children (5 females). See Table 3.3 for demographics and distribution of ADHD symptoms for the children with MRI data at both timepoints.

Procedure

MRI Acquisition at 9 Years

At the 9-year timepoint, structural magnetic resonance images were acquired at Regina Maria Health Center (Bucharest, Romania) on a Siemens Magnetom Avanto 1.5T Syngo System. Images were obtained using a transverse magnetization-prepared rapid gradient-echo three-dimensional sequence (TE = 2.98 ms, TI = 1,000 ms, flip angle = 8°, 176 slices with 1 × 1 × 1 mm isometric voxels) with a 16-channel head coil. The TR for this sequence varied between 1,650 and 1,910 ms. Five subjects were acquired in the sagittal plane; one was acquired in the coronal plane. Acquisition parameters did not differ by group membership nor were they associated with scan quality; thus, all scans are considered together.

MRI Acquisition at 16 Years

At the 16-year timepoint, structural magnetic resonance images were also acquired on a Siemens Magnetom Avanto 1.5T Syngo System in Bucharest, Romania. Images were obtained using a transverse magnetization-prepared rapid gradient-echo three-dimensional sequence (TE =

3.61ms, TI = 1,000ms, TR = 2,400ms, flip angle = 8°, 176 slices with 1.3 × 1.3 × 1.2 mm isometric voxels) with a 16-channel head coil.

MRI Preprocessing

T1-weighted images were analyzed in FreeSurfer (http://surfer.nmr.mgh.harvard.edu), which performs automated cortical reconstruction and segmentation of the brain to identify subcortical gray matter structures and estimate cortical thickness (Fischl et al., 2002, 2004). The results were inspected and manually edited for all participants to optimize accurate placement of gray/white and gray/Cerebrospinal Fluid (CSF) borders. For all participants, research assistants highly trained in FreeSurfer editing provided manual edits using control points and white matter or brain volume edits as needed. Each brain was rerun through recon-all following edits, inspected again, and edited again if indicated. After reconstruction, the cortex was parcellated based on the structure of gyri and sulci using the Destrieux atlas (Destrieux et al., 2010). Next, intensity and continuity information sere used to generate measurements of cortical thickness, calculated as the closest distance from the gray/white boundary to the gray/CSF boundary at each vertex on the tessellated surface (Fischl & Dale, 2000). The cortical thickness measurements are used to construct the structural brain networks.

ADHD Symptoms

The MacArthur Health and Behavior Questionnaire (HBQ; Essex et al., 2002) was completed by the parent of each child at age 16. The HBQ assesses for emotional and behavioral problems and has been previously used in studies with children in preschool through adolescence. Symptoms of ADHD from the HBQ are used in exploratory analyses of institutionalization, brain structure, and ADHD. These analyses are described in more detail later.

Construction of Structural Cortical Networks

For group level analyses, the two timepoints were considered separately. For each timepoint, the following steps were conducted to construct structural covariance networks. Using graph theoretical methods, the network of interest is divided into nodes and edges. In the current study the nodes are the brain regions and the edges are defined as the statistical similarity of cortical thickness between two brain regions (He et al., 2007). To be consistent with previous work (Khundrakpam et al., 2017; Nie et al., 2014), we utilized linear regression to remove effects of sex and mean overall cortical thickness and to calculate across-subject correlations between each pair of brain regions across each group of participants from the remaining residuals. This produced a correlation matrix where each cell represents the correlation of cortical thickness of each pair of regions. The Destrieux atlas results in 146 regions, and thus this step resulted in 146 x 146 correlation matrices for each group. In order to compare graph theoretical metrics between groups, a nonparametric permutation test with 1000 repetitions was conducted (Griffiths et al., 2016).

Network Costs

In network analyses it is appropriate to threshold the network in order to analyze a sparse network that most closely represents the density of connection of human and non-human nervous systems, by focusing on the strongest connections in the network (Achard & Bullmore, 2007; Alexander-Bloch et al., 2013; Bullmore & Sporns, 2009). Applying multiple thresholds ensures that any results are not due to a specific threshold. To be consistent with other studies examining structural covariance networks, all analyses were conducted across a range of thresholds, from 0 to 0.2 (van den Heuvel et al., 2015). These thresholds are applied such that for each pair of regions with a correlation value greater than the given correlation threshold (either 0, 0.1, or 0.2),

the value was retained. For each pair of regions with a correlation value below the given correlation threshold, the value was set to 0. Results reported in this paper are for matrices created with weighted thresholds (e.g., the edge values were maintained after each threshold was performed). Next, using the Brain Connectivity Toolbox (BCT; Rubinov & Sporns, 2010), graph theoretical metrics were calculated for each group in order to analyze topological characteristics of the structural networks.

Graph Theoretical Metrics

There are a multitude of measures to examine within graph theory; based on previous work assessing developmental trajectories of summary metrics of global network topological properties (Khundrakpam et al., 2013), we focused on the following measures: modularity, global efficiency, and local efficiency.

Modularity. Modularity is the ratio of the number of within-module connections to the number of expected within-module connections in a random network (Cohen & D'Esposito, 2016; Rubinov & Sporns, 2010; Sporns, 2013). The extent of modularity (measured from 0 to 1) can be described as a spectrum ranging from more integrated to more segregated (Sporns, 2013). Segregation refers to strong interconnectivity within modules, which results in efficient local processing. Integration refers to increased connections across modules, which represents global processing. Modularity was calculated using the BCT algorithm (see Rubinov & Sporns, 2010). We used the Louvain Method for community detection, which maximizes network modularity (De Meo et al., 2011). The structure (and thus modularity) of the network is determined by subdividing the network into groups of nodes, with a maximally possible number of within-group edges, and a minimally possible number of between-group edges (Rubinov & Sporns, 2010).

Global Efficiency. In order to further evaluate differences in the integration of the neural networks of children in the CAUG, FCG, and NIG, we examined global efficiency, which measures the efficiency of information transfer among all pairs of nodes (electrodes in this case) in the graph, and thus reflects the efficiency of interaction across the whole graph (de Pasquale et al., 2016; Rubinov & Sporns, 2010). Global efficiency was also calculated using the BCT algorithm (see de Pasquale et al., 2016; Rubinov & Sporns, 2010).

Local Efficiency. To further assess for and characterize differences in the segregation of neural networks of children in the CAUG, FCG, and NIG, we calculate local efficiency, which measures the efficiency of information transfer limited to neighboring nodes (i.e. nodes with a direct connection to the node of interest; Cohen & D'Esposito, 2016; Rubinov & Sporns, 2010; Sporns, 2013). Local efficiency was calculated using the BCT algorithm (see Latora & Marchiori, 2001; Rubinov & Sporns, 2010).

Subject-Based Maturational Coupling Approach

In order to assess for individual variability in structural brain network development, a novel approach was recently developed by Khundrakpam and colleagues (Khundrakpam et al., 2019). This approach allows for analyses at the individual level in compliment to the previously described structural covariance approaches that allow for group comparisons. This subject-based Maturational Coupling (sbMC) approach first quantifies the similarity of cortical thickness across timepoints between any two pairs of regions. In the sbMC analysis, the slope of cortical thickness change at one region between the two timepoints is compared to the slope of cortical thickness change at a different region between the same timepoints. To do so, the cosine of the angle between the two slopes is calculated between the two timepoints (this aspect is exploratory in that Khundrakpam, et al. utilized three timepoints in the development of the method; the

current work involves a dataset that only has two timepoints). This metric is referred to as the maturational coupling index (MCI). Once the MCI is calculated for every pair of regions, a 146 x 146 maturational coupling matrix can be developed. In this matrix, each cell represents the MCI between each pair of brain regions for that subject. From each subject's maturational coupling matrix, graph theoretical measures can be calculated as described above and utilized in statistical analyses.

Statistical Analysis Plan

Group-Level Structural Covariance Approach

First, to assess for the impact of institutionalization on structural covariance and the ability for foster care to mitigate those effects, we utilized one-way between-subjects analysis of variance (ANOVA) to test for the effect of institutionalization and foster care on modularity, global efficiency, and local efficiency of the structural covariance networks. The aforementioned tests were conducted for the 9-year sample and the 16-year sample separately to characterize differences in structural covariance at each timepoint. Separate models tested for group differences in network metrics across all 3 thresholds for each metric. False discovery rate (FDR) correction was used to control for multiple comparisons within each analysis. Significance was set to $p < 0.05$.

Subject-Based Maturational Coupling Approach

Group Differences in Network Organization of sbMC. In an exploratory analysis using the sbMC approach to examine individual variation, we used ANOVAs to test for differences in modularity, global efficiency, and local efficiency of sbMC between the CAUG, FCG, and NIG. Previous work has followed a similar plan of testing for group differences in both the standard structural covariance approach and using the sbMC individual level approach

(Khundrakpam et al., 2019). Separate models tested for group differences in network metrics across all 3 thresholds for each metric. FDR correction was used to control for multiple comparisons within each analysis. Significance was set to $p < 0.05$.

Institutionalization, ADHD Symptoms, and sbMC: Statistical Mediation. In order to probe the relationship of institutionalization, ADHD symptoms, and sbMC, we utilized statistical mediation. First, we examined if institutionalization predicted ADHD symptoms at 16 years using a linear regression model that included the three groups as predictors (using a dummy variable coding system) and ADHD symptoms at 16 years as the dependent variable, and sex and change in age between timepoints as covariates. Second, in order to probe the second pathway of the mediation model, we used linear regression models that included modularity, global efficiency, and local efficiency as the dependent variables while controlling for sex and change in age. The models were ran at each network threshold, resulting in 9 models. Lastly, we tested the significance of indirect effects of institutionalization on ADHD symptoms at age 16 through sbMC using a bootstrapping approach that provides bias-corrected confidence intervals (Preacher & Hayes, 2008). A significant indirect effect is indicated by confidence intervals that do not include zero.

Results

Structural Covariance

Age 9

Modularity. There was a statistically significant difference in modularity between groups across all three thresholding options after FDR correction (no threshold: $F(2,2997) = 235$, $p < 0.01$; 0.1 threshold: $F(2,2997) = 212.4$, $p < 0.01$; 0.2 threshold: $F(2,2997) = 143.5$, $p < 0.01$). Tukey post hoc tests revealed that the FCG had significantly increased modularity compared to

the CAUG across all three thresholding options ($p < 0.01$), the FCG had significantly increased modularity compared to the NIG across all three thresholding options ($p < 0.01$), and the CAUG had significantly increased modularity compared to the NIG at two of the three thresholding options (no threshold and 0.1 threshold: $p < 0.01$; 0.2 threshold: $p = 0.16$). See Figure 3.1 for a plot of modularity by group and network cost at age 9.

Global Efficiency. There was a statistically significant difference in global efficiency between groups across all three thresholding options after FDR correction (no threshold: $F(2,2997) = 24.4$, $p < 0.01$; 0.1 threshold: $F(2,2997) = 24.4$, $p < 0.01$; 0.2 threshold: $F(2,2997) = 24.37$, $p < 0.01$). Tukey post hoc tests revealed that the CAUG had significantly increased global efficiency compared to the FCG ($p < 0.01$ at all thresholding options) and compared to the NIG ($p < 0.01$ at all thresholding options). There was no statistically significant difference in global efficiency at any thresholding option between the FCG and the NIG ($p = 0.24$ at all thresholding options). See Figure 3.2 for a plot of global efficiency by group and network cost at age 9.

Local Efficiency. There was a statistically significant difference in local efficiency between groups across all three thresholding options after FDR correction (no threshold: $F(2,2997) = 25.47$, $p < 0.01$; 0.1 threshold: $F(2,2997) = 24.18$, $p < 0.01$; 0.2 threshold: $F(2,2997) = 38.93$, $p < 0.01$). Tukey post hoc tests revealed that the CAUG had significantly increased local efficiency compared to the FCG ($p < 0.01$ at all thresholding options) and compared to the NIG ($p < 0.01$ at all thresholding options). There was no statistically significant difference in local efficiency at two of the three thresholding options between the FCG and the NIG (no threshold: $p = 0.43$; 0.1 threshold: $p = 0.07$), but at the 0.2 threshold, the FCG had increased local efficiency compared to the NIG ($p < 0.01$). This result remained significant after FDR;

however, given that this result only occurred at one thresholding option, it may be spurious. See Figure 3.3 for a plot of local efficiency by group and network cost at age 9.

Age 16

Modularity. There was a statistically significant difference in modularity between groups across all three thresholding options after FDR correction (no threshold: $F(2,2997) = 13.44$, $p < 0.01$; 0.1 threshold: $F(2,2997) = 16.14$, $p < 0.01$; 0.2 threshold: $F(2,2997) = 24.41$, $p < 0.01$). Tukey post hoc tests revealed that the NIG had significantly increased modularity compared to the FCG ($p < 0.01$ at all thresholding options) and compared to the CAUG ($p < 0.01$ at all thresholding options). There was no statistically significant difference in modularity at any thresholding option between the FCG and the CAUG ($p > 0.88$ at all thresholding options). See Figure 3.4 for a plot of modularity by group and network cost at age 16.

Global Efficiency. There was a statistically significant difference in global efficiency between groups across all three thresholding options after FDR correction (no threshold: $F(2,2997) = 37$, $p < 0.01$; 0.1 threshold: $F(2,2997) = 37$, $p < 0.01$; 0.2 threshold: $F(2,2997) = 36.62$, $p < 0.01$). Tukey post hoc tests revealed that the NIG had significantly decreased global efficiency compared to the FCG ($p < 0.01$ at all thresholding options) and compared to the CAUG ($p < 0.01$ at all thresholding options). There was no statistically significant difference in global efficiency at any thresholding option between the FCG and the CAUG ($p = 0.91$ at all thresholding options). See Figure 3.5 for a plot of global efficiency by group and network cost at age 16.

Local Efficiency. There was a statistically significant difference in local efficiency between groups across all three thresholding options after FDR correction (no threshold: $F(2,2997) = 34$, $p < 0.01$; 0.1 threshold: $F(2,2997) = 36.72$, $p < 0.01$; 0.2 threshold: $F(2,2997) =$

42.5, $p < 0.01$). Tukey post hoc tests revealed that the NIG had significantly decreased local efficiency compared to the FCG ($p < 0.01$ at all thresholding options) and compared to the CAUG ($p < 0.01$ at all thresholding options). There was no statistically significant difference in local efficiency at any thresholding option between the FCG and the CAUG (no threshold: $p = 0.92$; 0.1 threshold: $p = 0.97$; 0.2 threshold: $p = 0.90$). See Figure 3.6 for a plot of local efficiency by group and network cost at age 16.

Subject-Based Maturational Coupling

Group Differences in Network Organization of sbMC

There were no significant differences in modularity of sbMC between groups across all three thresholding options (no threshold: $F(2,59) = 1.96$, $p = 0.15$; 0.1 threshold: $F(2,59) = 2$, $p = 0.14$; 0.2 threshold: $F(2,59) = 1.91$, $p = 0.16$). There were no significant differences in global efficiency of sbMC between groups across all three thresholding options (no threshold: $F(2,59) = 1.05$, $p = 0.36$; 0.1 threshold: $F(2,59) = 1.05$, $p = 0.36$; 0.2 threshold: $F(2,59) = 1.05$, $p = 0.36$). There were no significant differences in local efficiency of sbMC between groups across all three thresholding options (no threshold: $F(2,59) = 1.11$, $p = 0.34$; 0.1 threshold: $F(2,59) = 1.81$, $p = 0.17$; 0.2 threshold: $F(2,59) = 1.13$, $p = 0.33$).

Institutionalization, ADHD Symptoms, and sbMC: Statistical Mediation

Institutionalization and ADHD Symptoms. There was a significant direct effect of institutionalization on ADHD symptoms at 16 years ($\beta = 0.24$, $p = 0.04$) when controlling for sex and change in age.

Institutionalization and Network Organization of sbMC. There was no significant effect of institutionalization on modularity of sbMC at any threshold ($p > 0.26$ across thresholds). There was no significant effect of institutionalization on global efficiency of sbMC

at any threshold ($p = 0.41$ at all thresholds). There was no significant effect of institutionalization on local efficiency of sbMC at any threshold ($p > 0.35$ across all thresholds).

Network Organization of sbMC and ADHD Symptoms. There was no significant effect of modularity of sbMC on ADHD symptoms at any threshold ($p > 0.39$ across thresholds). There was no significant effect of global efficiency of sbMC on ADHD symptoms at any threshold ($p = 0.91$ at all thresholds). There was no significant effect of local efficiency of sbMC on ADHD symptoms at any threshold ($p > 0.21$ across thresholds).

Indirect Effect of Institutionalization on ADHD Symptoms Through Network Organization of sbMC. There was no significant indirect effect of institutionalization on ADHD symptoms through network organization of sbMC for any of the network metrics across thresholds as all bias-corrected confidence intervals contained 0.

Discussion

Structural Covariance at Age 9

As we hypothesized, when the children were 9 years old, there was a negative impact of institutionalization on network organization, such that the CAUG had increased global and local efficiency compared to the FCG and NIG. Consistent with previous findings from the BEIP that demonstrate that foster care is an effective intervention for institutionalization, the FCG had similar levels of global and local efficiency to the NIG, indicating a normalization of function at 9 years of age. However, regarding modularity of the networks, the benefits of the intervention are not as clear. At age 9, the FCG demonstrated the greatest level of modularity, followed by the CAUG, and the NIG had the lowest modularity. This highlights the varied impacts of institutionalization on the development of structural brain network organization.

Interestingly, while we predicted that there would be a negative impact of institutionalization on brain network organization, the results at age 9 were only partially consistent with hypotheses. The hypotheses were based on findings in typical development that generally suggest increased integration and decreased segregation during later childhood. Instead, the results suggest that the children in the CAUG experienced a hyper-connected network organization, both globally and locally, at age 9. Aberrant topological organization of structural covariance networks has been associated with various disease states and psychological disorders, suggesting the importance of typical network organization for healthy functioning (Buchy et al., 2017; Duan et al., 2020; Kuang et al., 2020; Li et al., 2015; Wang et al., 2016; Yun et al., 2020). A network with increased global and local efficiency is analogous to a research laboratory in which all members meet with each other regularly, which is a poor use of time and resources. In functional networks, increased global efficiency has been suggested to reflect disrupted information transfer across the brain, which is necessary for successful completion of complex cognitive tasks (Ma et al., 2018; Zhang et al., 2015). Increased local efficiency of structural covariance has previously been associated with ADHD diagnosis and the related impulsivity that children with ADHD display (Griffiths et al., 2016). The different levels of modularity across all three groups at the age 9 timepoint highlight the dynamic nature of neurodevelopment across childhood, and indicate that the children in all three groups are following different neurodevelopmental trajectories, such that the FCG is not experiencing a complete normalization of neural structure, but is not displaying the same structural network organization development as the CAUG.

Structural Covariance at Age 16

Critically, between the two timepoints it appears that all groups are experiencing changes in global efficiency, local efficiency, and modularity. While this was not statistically tested in this paper, qualitatively all three groups are decreasing in global efficiency and local efficiency and increasing in modularity from age 9 to age 16. These trends reflect the ongoing developmental maturation of neural structure and highlight that these metrics should be viewed from a dynamic developmental lens, rather than a static perspective viewing the two timepoints as isolated periods of time. This is especially important given that structural covariance aims to measure the maturational development of regions that develop synchronously.

When the children were 16 years old, the CAUG still had significantly increased global and local efficiency compared to the NIG. Unlike at age 9, this effect of institutionalization is also seen in the FCG at age 16, as both groups with previously institutionalized children had significantly increased global and local efficiency compared to the NIG. This extends the finding that previously institutionalized children experience a hyper-connected network, both globally and locally, into adolescence. As mentioned previously, a hyper-connected network might underlie impairments in psychological functioning via dysfunctional organization disrupting short- and long-range neural communication. Moreover, this finding further evidences the strength of the impact of early institutionalization on structural brain network development, as foster care no longer shields against the effects on global and local efficiency. There are several possible explanations for this. First, foster care as an intervention for institutionalization has been shown to ameliorate some, but not all, of the deleterious effects of severe psychosocial deprivation across multiple domains (Stamoulis et al., 2017; Tibu et al., 2016). Second, this finding might reflect the recency of the randomization to foster care at 9 years compared to 16

years, as structural covariance is purported to reflect the history of coactivation of regions over time. Given that as the children aged, the percent of their lives spent experiencing severe neglect in the institutional setting diminishes, there would be less variability in environmental input between age 9 and 16.

Additionally, at age 16, the CAUG and FCG displayed decreased modularity compared to the NIG. This finding suggests that institutionalization hinders the development of specialized networks, and instead results in larger, more poorly organized networks. Reduced modularity compared to typically developing controls has implications for adaptability to changing environmental demands and related goals, which in turn can result in cognitive impairments (Alexander-Bloch et al., 2010). Overall, these results are indicative of the lasting detrimental impact of institutionalization on structural brain network development.

Subject-Based Maturational Coupling

In the second set of analyses, we utilized a novel approach to quantify the network organization of the change in cortical thickness within each brain region. However, there were no significant differences in network organization of change in thickness between groups and despite evidence implicating neural structure as a mediator of the relationship between institutionalization and ADHD symptoms, the mediation model was not significant. This indicates that while other work has shown a mediating effect of brain structure on the relationship of institutionalization and ADHD symptoms, the organization of the correlated changes in thickness does not underlie that relationship. It is possible there were no significant results in the subject-based maturational coupling analyses due to the use of a novel method that has previously only been done using three timepoints. Applying this method with two timepoints was an innovative use of the metrics; however, it is possible that measuring change in thickness

over time and assessing the organization of those changes is not stable when only using two timepoints.

Limitations

This study has several limitations. First, we did not compare structural covariance metrics at each timepoint within each group. This limits the ability to interpret the different findings at the two timepoints. Future work should address this in order to discern if there are different trajectories of change underlying the different structural covariance findings at each timepoint. In an extension of this work, a future paper will use permutation testing to create 1000 samples of matrices for each group with both timepoints included in the permutation at the same time. This will allow for paired t-tests to compare graph metrics within each group at the two timepoints. Relatedly, the current work did not probe if additional environmental changes since the randomization into foster care impacted structural covariance. To test if a decrease in variance of environmental input after age 9 is associated with the different findings at each time point, future work should consider the percent time institutionalized as well as the ratings of caregivers recorded by study personnel. Regarding the subject-based maturational coupling analyses, that method was limited in that it was a novel application of a novel method. Additionally, the subject-based maturational coupling analyses only included subjects with data at both timepoints, which resulted in a small sample size for each group.

Conclusions

In this paper, we present the first examination of structural covariance in a randomized control trial of foster care as an intervention for early-life institutionalization. We demonstrate that across two timepoints, the harmful effects of early psychosocial deprivation (in the form of institutionalization) are chronic and alter the developmental maturation of brain structure well

into adolescence. In addition to examining the impact of institutionalization on structural covariance, we assessed the potential benefits of foster care as an intervention. These effects were present, but did not result in complete normalization of function across metrics or timepoints. Given that the impacts of early deprivation were observed differentially at the different timepoints, the results suggest that institutionalization alters the development of structural neural networks by impairing the ability of brain regions to properly co-activate during development, underscoring the importance of expected social, cognitive, and psychological inputs in early childhood.

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Table 3.1. Group Demographics: 9-year Data Collection Sample

	CAUG (N = 32)	FCG (N = 27)	NIG (N = 22)
Female	50.0 (16)	48.1 (13)	59.1 (13)
Race			
Romanian	43.8 (14)	63.0 (17)	95.5 (21)
Roma	40.6 (13)	25.9 (7)	0.5 (1)
Unknown	15.6 (5)	11.1 (3)	0.0 (0)
Other	0.0 (0)	0.0 (0)	0.0 (0)
Age (years)	9.68 ± 0.77	9.85 ± 0.68	9.79 ± 0.94

Note. Demographics by group for all participants with data at the 9-year data collection. Across groups, N = 81. Values are expressed as percentage of the group, with the raw number in parentheses; age is expressed as mean ± SD.

Table 3.2. Group Demographics: 16-year Data Collection Sample

	CAUG (N = 41)	FCG (N = 41)	NIG (N = 33)
Female	46.3 (19)	51.2 (21)	57.6 (19)
Race			
Romanian	43.9 (18)	58.5 (24)	94.0 (31)
Roma	43.9 (18)	26.8 (11)	6.0 (2)
Unknown	9.8 (4)	14.6 (6)	0.0 (0)
Other	2.4 (1)	0.0 (0)	0.0 (0)
Age (years)	16.65 ± 0.49	16.57 ± 0.52	16.85 ± 0.48

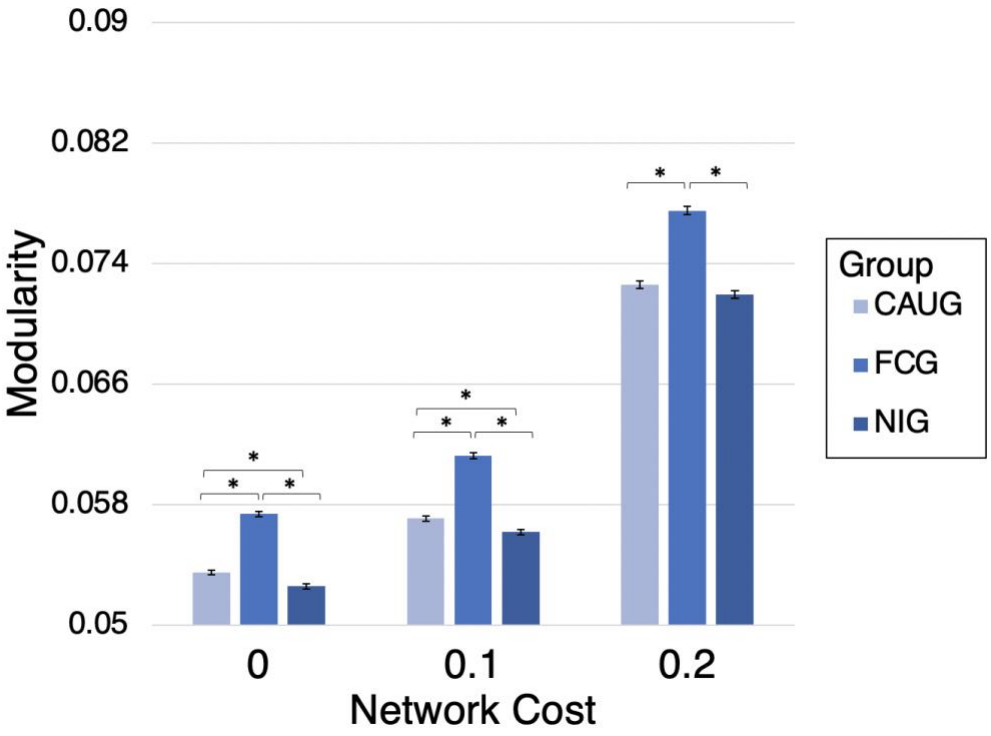
Note. Demographics by group for all participants with data at the 9-year data collection. Across groups, N = 115. Values are expressed as percentage of the group, with the raw number in parentheses; age is expressed as mean ± SD.

Table 3.3. Group Demographics: Participants with MRI data at both Timepoints

	CAUG (N = 27)	FCG (N = 23)	NIG (N = 12)
Female	46.3 (19)	51.2 (21)	57.6 (19)
Race			
Romanian	43.9 (18)	58.5 (24)	94.0 (31)
Roma	43.9 (18)	26.8 (11)	6.0 (2)
Unknown	9.8 (4)	14.6 (6)	0.0 (0)
Other	2.4 (1)	0.0 (0)	0.0 (0)
Age at 9-year timepoint (years)	9.63 ± 0.76	9.87 ± 0.69	10.06 ± 0.83
Age at 16-year timepoints (years)	16.64 ± 0.51	16.67 ± 0.53	16.58 ± 0.44
Δ Age (years)	7.01 ± 0.59	6.80 ± 0.62	6.51 ± 0.76
ADHD Symptoms	0.80 ± 0.44	0.68 ± 0.54	0.40 ± 0.37

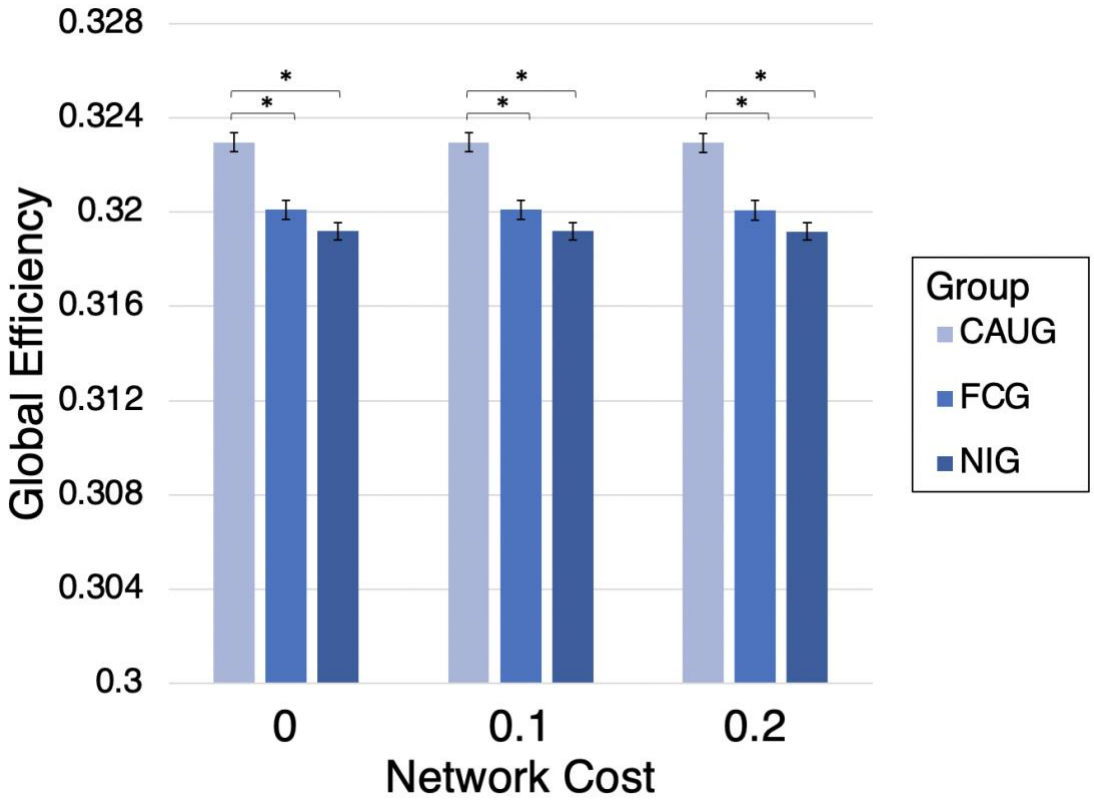
Note. Demographics by group for all participants with data at both the 9-year and 16-year data collection timepoints. Across groups, N = 62. Values are expressed as percentage of the group, with the raw number in parentheses; age and ADHD symptoms are expressed as mean ± SD.

Figure 3.1. Modularity of structural covariance at 9 years



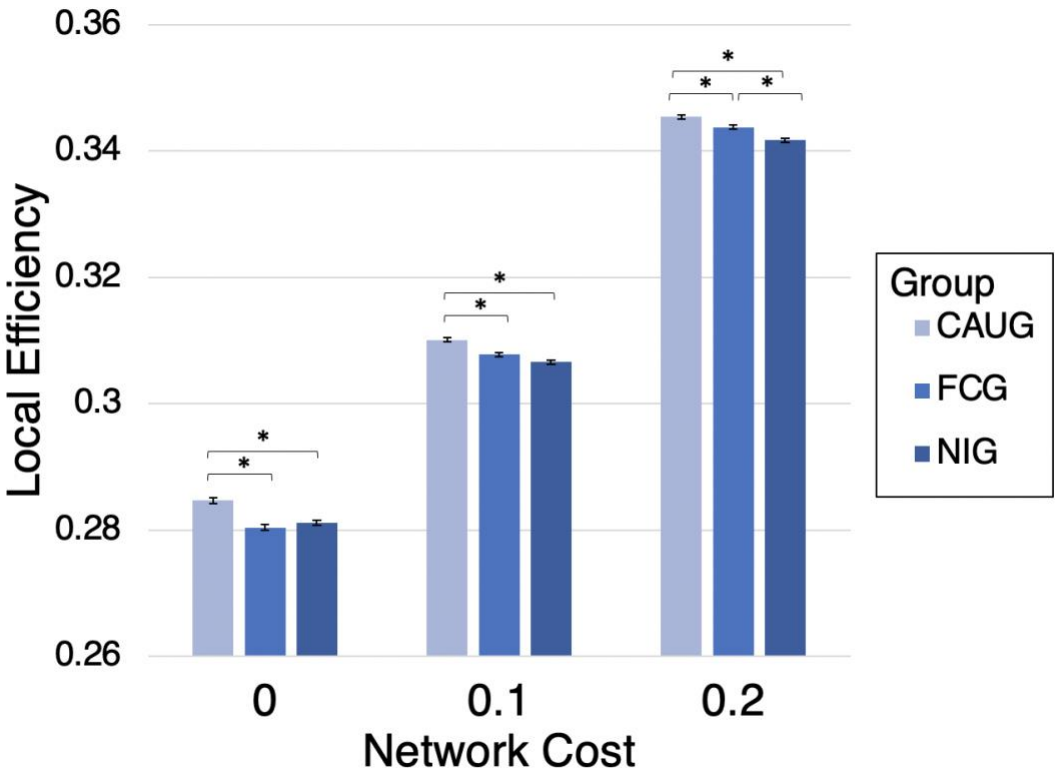
Note. Graph depicts modularity of structural covariance networks by group for each network cost at the 9-year timepoint. *p < 0.05

Figure 3.2. Global Efficiency of Structural Covariance at 9 years



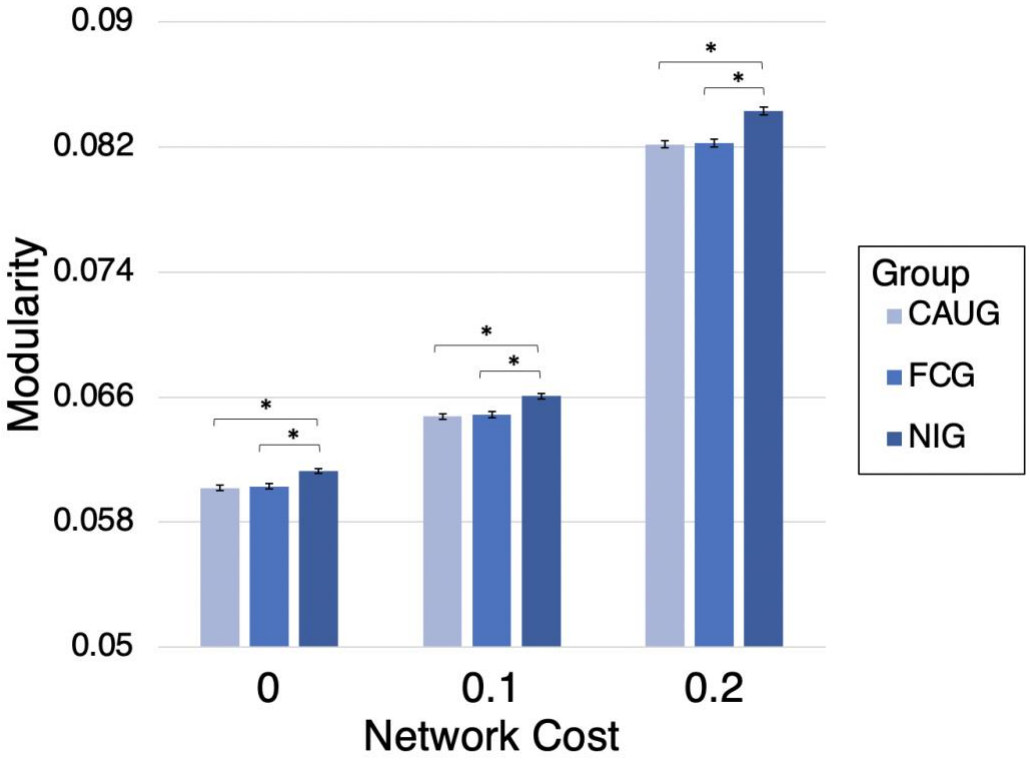
Note. Graph depicts global efficiency of structural covariance networks by group for each network cost at the 9-year timepoint. *p < 0.05

Figure 3.3. Local Efficiency of Structural Covariance at 9 years



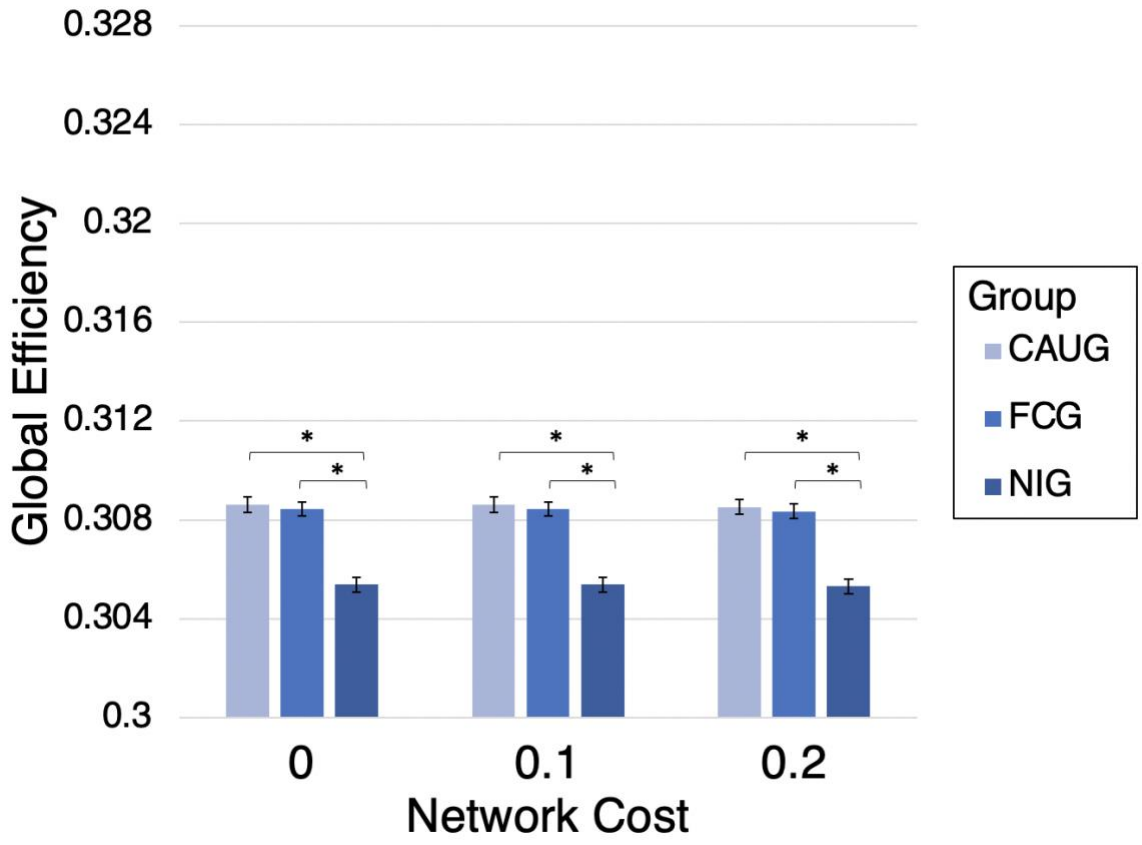
Note. Graph depicts local efficiency of structural covariance networks by group for each network cost at the 9-year timepoint. *p < 0.05

Figure 3.4. Modularity of Structural Covariance at 16 years



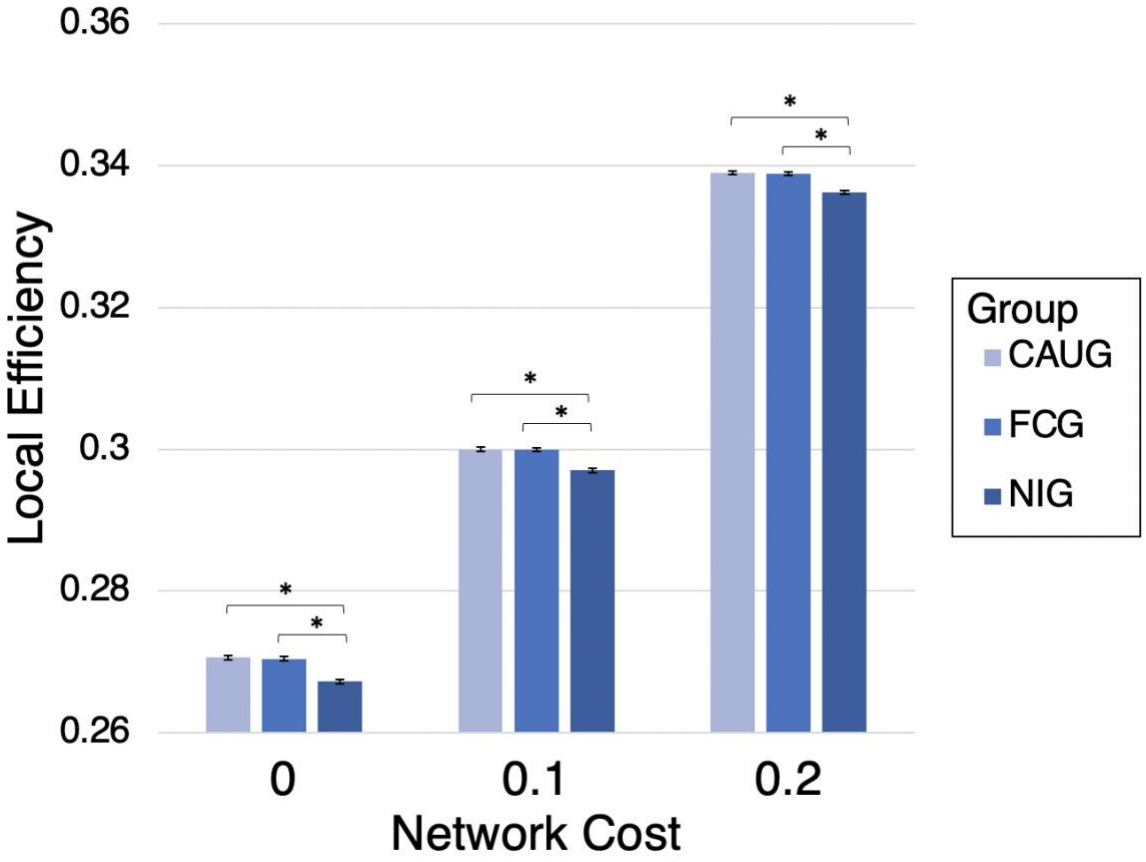
Note. Graph depicts modularity of structural covariance networks by group for each network cost at the 16-year timepoint. *p< 0.05

Figure 3.5. Global Efficiency of Structural Covariance at 16 years



Note. Graph depicts global efficiency of structural covariance networks by group for each network cost at the 16-year timepoint. *p < 0.05

Figure 3.6. Local Efficiency of Structural Covariance at 16 years



Note. Graph depicts local efficiency of structural covariance networks by group for each network cost at the 16-year timepoint. *p < 0.05

Integrative Discussion

This body of work applied a developmental psychopathology approach to the exploration of neural mechanisms that underlie the clinically impairing inattention, hyperactivity, and impulsivity symptoms seen in children with attention-deficit/hyperactivity disorder (ADHD). Specifically, the three studies were conceptualized within the framework of equifinality as it applies to ADHD of unknown or neurobiological origin and ADHD secondary to neglect. As such, the three studies together explored 1) the neural correlates of ADHD symptom stability, 2) the impact of environmental factors on neural correlates of ADHD in early childhood, and 3) the impact of early-life psychosocial deprivation on the development of neural structure and the associated risk for ADHD.

Study 1 assessed whether electroencephalography (EEG) metrics collected in early childhood predicted later ADHD symptom stability. In contrast to our hypotheses, we did not find an association between any of the neural metrics and ADHD symptom stability. However, we replicated and extended findings regarding the importance of parental psychopathology and family factors in the maintenance of childhood ADHD symptomatology. In Study 1, parental depression, and not parental ADHD symptoms, predicted stability of child ADHD symptoms at the follow-up timepoint. Socioeconomic status (SES) also predicted stability of ADHD symptoms at the trend level. The finding regarding parental depression is consistent with other research indicating that parental depression is associated with increased risk for child ADHD (Cheung et al., 2018; Cunningham & Boyle, 2002). However, the finding that parental ADHD

did not predict stability of child ADHD symptoms was surprising given previous work demonstrating that parental ADHD is associated with child ADHD (Breaux et al., 2017). Overall, Study 1 indicates that future research should examine alternative measures of neural function, such as magnetic resonance imaging (MRI), as predictors of symptom stability, and should include parent psychopathology and SES. Future work should also consider examining the EEG metrics in the context of a latent class or machine learning approach in which diagnostic starting points and end points are considered, in contrast to the dimensional perspective utilized in the current work.

Study 2 explored the impact of environmental variables on neural correlates of ADHD in early childhood. Interestingly, neural activity, specifically, relative alpha power, was associated with ADHD symptoms but was not related to or impacted by SES or family conflict. This finding was consistent with the finding in Study 1 that SES diverged from alpha power as a predictor of ADHD symptom stability, as well as with previous literature that has indicated that power in the alpha band is associated with having an ADHD diagnosis (Koehler et al., 2009; Robbie et al., 2016). Additionally, alpha band signal has been associated with functions such as inhibitory control that are often disrupted in individuals with ADHD (Başar et al., 2001; Klimesch, 2012). Study 2 contributes to a growing literature that implicates alpha frequency band signal as a correlate of ADHD and extends previous findings by demonstrating the association of relative alpha power and ADHD from a dimensional symptoms-based framework in early childhood.

Study 3 utilized structural MRI data to assess 1) the impact of severe neglect (institutionalization) on the coordinated structural development of brain regions and 2) whether organization of structural change mediates the relationship of institutionalization and ADHD

symptoms. In Study 3, we presented findings that early psychosocial deprivation results in chronic and harmful alterations to the developmental maturation of brain structure into adolescence. Importantly, foster care functioned as a partially ameliorative intervention, although the benefits were not consistently seen across timepoints or metrics. While the results from Study 3 provide evidence of the impacts of institutionalization on the maturation of brain structure, we did not find that the organization of within region change mediated the relationship between institutionalization and ADHD symptoms.

Taken together, the Study 1 and Study 2 findings suggest that the EEG metrics of interest reflect the functional neural activity that occurs in association with early childhood ADHD, but do not reflect the aspects of neural development that are impacted by environmental and family factors, including parental psychopathology, SES, and family conflict. In Study 1, SES predicted symptom stability at a trend level, which suggested a possible subtle effect of SES on the maintenance of ADHD symptoms. Based on that result, one might expect that SES impacts the neural correlates of ADHD; however, in Study 2 the EEG metrics were not impacted by environmental factors (SES and family conflict) when examined as neural correlates of ADHD in early childhood. Collectively, the findings from Studies 1 and 2 suggest that EEG might not be the best tool for assessing the relationships of ADHD symptoms, family functioning, environmental factors, and symptom stability. However, it is worth considering that the EEG metrics explored in Studies 1 and 2 might reflect a different aspect of neural mechanisms than we originally thought. It is possible that EEG metrics correlate to either the state variables associated with ADHD rather than trait variables, or that they reflect the components of an ADHD presentation that are independent from environmental and family factors. As such, EEG might be considered a useful reflection of ADHD symptoms in early childhood independent of

SES or family conflict, but not an appropriate tool to predict maintenance of ADHD symptoms later in childhood.

Utilizing a unique dataset in Study 3, we conducted the first examination of structural covariance in a randomized control trial of foster care as an intervention for early-life institutionalization. The results of Study 3 add to the continually expanding evidence of the detrimental effects of psychosocial deprivation, and indicate that these effects are chronic, impacting the developmental maturation of brain structure well into the adolescent years. Additionally, while the network organization of maturational coupling did not mediate the relationship of institutionalization and ADHD, other research suggests that brain structure mediates the association of institutionalization and ADHD (Bick et al., 2017; McLaughlin et al., 2014), as well as the association of SES and ADHD (Machlin et al., 2019). In combination, it appears that there are unique impacts of neglect on brain development, and some of those impacts function as a pathway to the development of ADHD. The development of structural covariance appears to be a mechanism that is altered by the experience of early institutionalization, but is not a mediating pathway for the development of ADHD in this population. There are a few possible reasons for this, including that Study 3 applied a novel approach to asses if neural metrics that reflect synchronized developmental change mediate the pathway to ADHD. Thus, when interpreted in light of other studies that implicate brain structure as a mediating path to ADHD in this population, it appears that this mediation does not occur through the specific mechanism of synchronized maturational changes. Despite the Study 3 findings not revealing a new mechanism for understanding the development of ADHD, they reveal new information about adversity, and severe neglect in particular. Of note, Study 3 examined ADHD symptoms when the children were 16 years old. Studies 1 and 2 were focused

on earlier timepoints in childhood, and together these three works underscore the varied developmental pathways at play across childhood and adolescence in relation to ADHD symptomatology.

Clinical Implications

There are several clinical implications stemming from the findings described here. First, this body of work highlights the importance of considering the entire family system, rather than the child and their behaviors or symptoms in isolation. While we are (hopefully) taught as trainees that this is necessary, the type of work included in this program of research highlights how critical it is to consider the child's current presentation in conjunction with possible parental psychopathology as well as family resources. In Study 1 we found a trending relationship of SES and stability of ADHD symptoms as well as a significant relationship of parental depression and stability of ADHD symptoms. Given the longitudinal nature of Study 1, these findings underscore that clinicians should consider following children from low SES backgrounds or with parents with psychopathology more closely over time to manage child functioning. In addition, in Study 3 we demonstrated that early-life institutionalization is associated with ADHD symptoms in adolescence. Therefore, if one clinical takeaway is to be made from this program of research, it is to view the child or adolescent client within the context of their early developmental history, adversity exposures, family, and community.

Secondly, this research highlights the complex developmental pathways that one can follow. At different ages, different variables are associated with psychopathology and future outcomes, and this is something that is yet to be completely understood. As such, a second recommendation stemming from this program of work would be for clinicians to not make

assumptions about how a given child came to present a certain way, nor should they make assumptions about the likely path that child will follow as they continue to develop.

Future Directions for Research

While the current body of research represents important initial steps to being able to fully understand the neural mechanisms underlying the development of ADHD across populations (those with and without early adversity in this case), this research only represents an incremental addition to the current literature and will serve as a starting point for continued research. Ideally, initial future work will ask questions about neural structure and function in the same way across children with ADHD due to unknown or neurobiological origin and children with ADHD secondary to neglect, as this would allow for more direct connections to be drawn about the mechanisms underlying these processes that seemingly result in a form of equifinality. Unfortunately, in the present work, the three studies utilized different neuroimaging methods and analytic tools, all of which were appropriate for the individual studies, but reduced the ability to integrate findings more directly.

There are also several improvements to be made when embarking on related research in the future, such as reconsidering which neural metrics are best able to function as predictors of psychopathology while maintaining the promise of lower cost for future clinical applications. For example, one might consider exploring the application of functional near-infrared spectroscopy (fNIRS) to these questions in order to harness some of the strengths of EEG and functional MRI. For example, fNIRS improves upon the spatial resolution of EEG, although it is limited to cortical areas unlike functional MRI, and maintains the functional mobility of EEG systems, which has allowed for advancements in studies of neurological processes in unconstrainted environments (Scarapicchia et al., 2017). Lastly, fNIRS is relatively inexpensive compared to

functional MRI. Previous work has already begun applying fNIRS to preschool age children (Perlman et al., 2014), suggesting utility for addressing questions of early development, and recent work has demonstrated the use of fNIRS in measuring inter-brain synchrony in mother-child dyads (Miller et al., 2019). As such, future research might consider applying fNIRS to address some of the questions presented in this body of work.

The present body of work additionally demonstrates that while there is promise for using neural metrics to understand mechanisms underlying the development and maintenance of psychopathology, and ADHD in particular, there is ample room for future research to continue exploring this area and to consider alternative mechanisms. The collective body of work highlights that some aspects of neural function are associated with ADHD, while others are not. Given that in the current work brain metrics and adversity were each independently related to ADHD, future research should consider other, non-neural pathways that might link adversity to ADHD.

Moreover, regarding the clinical implications, this work was undertaken with the goal of understanding mechanisms that underlie development of ADHD. While this work on its own warrants consideration and continued exploration, future avenues of research might consider the roles of interventions, such as behavioral parent training, in the developmental course of ADHD and co-morbid disorders. Ultimately, the goal of this mechanistic research would be to improve treatment outcomes and individualization of treatment, but first work needs to be done to connect neural mechanisms research with treatment research, which is not common in early childhood in particular.

Conclusions

While the understanding of the neural mechanisms of the development of ADHD across populations with and without early neglect is still not fully understood, this body of work advanced novel methodologies and applied dimensional approaches to the study of a historically categorically considered disorder. There is ample future work to be conducted in order to move the field forward in its understanding of the mechanisms underlying the development and maintenance of ADHD. The novel aspects of these studies will hopefully lay groundwork upon which future studies may build.

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