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Brain Connectivity Changes Associated with One Year of Behavioral Therapy for Young Children with Autism Spectrum Disorder (ASD)

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Brain Connectivity Changes Associated with One Year of Behavioral Therapy for Young Children with Autism Spectrum Disorder (ASD)

by

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Although much of the current literature in autism spectrum disorders (ASD) has focused on illuminating their biological underpinnings or identifying effective treatment approaches, very little research has integrated these two areas of study and examined the neurobiological outcomes associated with various autism interventions. The proposed study will use functional connectivity magnetic resonance imaging (fcMRI) to measure changes in resting state connectivity associated with an intensive behavioral intervention for young children with ASD. Independent component analysis and *t*-tests will be used to determine if 20 children receiving a behavioral intervention experience greater changes in connectivity than 20 children (matched for sex and developmental age) in a control group receiving treatment as usual (TAU).

Table of Contents

Introduction

Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder characterized by social and communication deficits, as well as restricted or repetitive patterns of behavior. ASD is thought to be around five times more common among boys than girls, and to be etiologically linked to some combination of both genetic and environmental influences (Boyle et al., 2011; Hallmayer et al., 2011). At present, there is no definitive test for ASD; diagnoses are made on the basis of observable behavioral symptoms, and often not until age 4 or later (Centers for Disease Control [CDC], 2012). As a result, individuals with ASD comprise a heterogeneous group with widely varying degrees of impairment, ranging from mild social challenges to severe intellectual disability.

The prevalence of ASD has steadily risen over the past half century, and the Centers for Disease Control (2012) now estimate that approximately 1 in 88 children born in the United States today will be diagnosed with ASD. This number nearly doubles the estimated prevalence of 1 in 150 just a decade ago (CDC, 2002). Considering the average lifetime cost of care for one individual with ASD, researchers recently determined that ASD costs the nation approximately $137 billion each year (Mandell & Knapp, 2011)—a number calculated using a previous estimated prevalence rate of 1 in 110 (CDC, 2009), which suggests that the figure is almost certainly an underestimate. Taken together, it is apparent that ASD has become a public health crisis with a staggering cost to society. Not surprisingly, the rising prevalence of ASD has generated a corresponding increase in ASD research (see Singh, Illes, Lazzeroni, & Hallmayer, 2009)

as scientists, practitioners, and parents seek answers about potential causes of and treatments for ASD.

Over the past two decades, brain imaging methods have become a popular and promising tool in the study of ASD, and researchers have used a variety of approaches to identify which brain structures and processes may be disordered in the autistic brain (Amaral, Schumann, & Nordahl, 2008). Although ASD diagnoses are made on the basis of behavioral observations rather than biological markers, early researchers predicted the disorder had biological bases in the brain, and more specifically, expected to find abnormalities in the brain regions responsible for ASD's core behavioral deficits. Consistent with predictions, a myriad of anatomical and functional differences have since been discovered in the brains of individuals with ASD. For instance, research suggests that young children with ASD have greater total brain volume than typically developing children (Aylward et al., 2002; Piven et al., 1995), including increases in white matter volume (Courchesne et al., 2001; Herbert et al., 2003; Sparks et al., 2002) and number of neurons (Courchesne et al., 2011), which suggests a possible flaw in the brain's mechanisms for neural pruning.

Functionally, these differences in brain development are thought to play a role in some or all of the behavioral excesses and deficits seen in ASD. The cerebellum, for example, has emerged as the most consistent site of neural abnormality in ASD (Allen, 2005). This is significant given that it is also one of the most widely connected brain structures (Allen et al., 2005; Clower, West, Lynch, & Strick, 2001; Middleton & Strick, 2001), and that some cerebellar abnormalities have been identified retrospectively from

the prenatal ultrasounds of children later diagnosed with ASD (Allen & Brinster, 2012). Similarly, notable impairments in neural development and connectivity have been found in regions related to emotion, social cognition, and language development (e.g., Allen, 2011; Belmonte et al., 2004; Lee et al., 2009; Monk et al., 2009). As connectivity has emerged as a useful measure of brain functioning, the discovery of aberrant connectivity patterns in individuals with ASD has become a crucial explanation for some ASD's characteristic symptoms and behaviors. Thus, although ASD may be phenotypically heterogeneous, it has been consistently linked to various abnormalities during early brain development. Ultimately, it clear that these early differences in brain development have a long-lasting impact on the developmental trajectories of individuals with ASD.

In contrast to neurobiological research, another large portion of the present ASD literature is devoted to identifying the most efficacious ASD interventions. Dozens of approaches are currently used in the treatment of ASD, varying greatly in terms of their resource requirements (e.g., time, money, training), theoretical orientation (e.g., behavioral, biomedical, psychosocial), and the extent of their empirical support. Despite the fact that behavioral interventions are well established and appear to have the most pronounced effects on outcomes when compared to other interventions (e.g., Zachor & Itzchak, 2010), they also tend to be much more resource-intensive, leading many schools and community-based service providers to opt for the cheaper and more practical 'eclectic' approaches. These eclectic interventions typically incorporate a variety of strategies, including some that may not be widely supported by empirical evidence. As a

result, many researchers are interested in determining if behavioral interventions are, in fact, the best known treatment for ASD, and if so, by how much and why.

Despite the explosive growth of ASD research, especially in the areas of treatment and neurobiology, there are very few studies to date that have examined the neurobiological impact of treatment for individuals with ASD. This dearth of research is surprising given that the study of brain changes associated with intervention has become a prominent area of focus for numerous interventions for a variety of other disorders. For instance, researchers have used neuroimaging methods to show that the use of antipsychotic medication is associated with structural brain changes in schizophrenia (Tomelleri et al., 2009), magnetic seizure therapy impacts regional brain glucose metabolism in major depression (Hoy et al., 2012), and comprehensive reading instruction is linked to changes in brain activation in children with dyslexia (Aylward et al., 2003). Further, researchers have hailed the use of imaging methods in examining how therapy changes the brain (e.g., Linden, 2006), and have even specifically suggested using brain connectivity measures to assess autistic disorders and evaluate treatment effects (Coben & Myers, 2008; Vissers, Cohen, & Guerts, 2012).

In sum, it is clear that more information is needed about how ASD interventions affect the brain, including which neural mechanisms underlie effective treatments, as well as the developmental implications of early brain change. If more is understood about the nature of brain change in ASD and the factors influencing these changes, it is likely that this information could be used in the future to improve treatment outcomes (Vissers, Cohen, & Guerts, 2012). For the purpose of this integrative analysis, reviews of the

relevant literature in brain connectivity and ASD treatment will be provided in the sections that follow.

Integrative Analysis

Brain Connectivity

Definition. Brain connectivity can be broadly conceptualized as the structural and functional patterns of communication between brain regions. Structural connectivity refers to the anatomical connections between brain regions based on known axonal projections. Functional connectivity, on the other hand, describes the temporal connections, also known as coherence, between brain regions. Fundamentally a statistical concept, functional connectivity captures deviations from statistical independence in patterns of brain activation. More specifically, it can be estimated by analyzing the correlation or covariance of regional activations in the brain (Sporns, 2007).

Methods of measurement. Mapping the structural and functional connectivity of the human brain, also called the "human connectome", has been a major interest and challenge of neuroscience since connectivity was first conceptualized (Biswal et al., 2010). Several methods have become prominent in the analysis of connectivity, including positron emission tomography (PET), electroencephalography (EEG), magnetoencephalography (MEG), and magnetic resonance imaging (MRI; Horwitz & Horovitz, 2012). Additionally, novel techniques for analyzing connectivity data are frequently being developed, tested, and adapted.

In particular, MRI has emerged as an excellent tool in connectivity research because it can be used to reveal both the anatomy of network connections as well as the functional coherence between networks. Techniques such as diffusion tensor imaging (DTI) and diffusion spectrum imaging (DSI), for example, are commonly used in the

assessment of structural connectivity from MRI. In contrast, the analysis of blood-oxygen level-dependent (BOLD) signal fluctuations between regions is a commonly used approach in the assessment of functional connectivity (for a review, see Fox and Raichle, 2007).

Independent component analysis (ICA) has become an increasingly popular technique in the measurement of whole-brain and regional functional connectivity. ICA is an exploratory, data-driven approach that decomposes complex imaging data into temporally coherent networks within the brain (Comon, 1994; de Marco, Devauchelle, & Berquin, 2009; Eichele, Calhoun, & Debener, 2009). This is accomplished by maximizing the statistical independence (i.e., minimizing mutual information and maximizing non-Gaussianity) of the estimated network components (Hyvärinen, Karhunen, & Oja, 2001; Stone, 2004). When applying ICA to fMRI, the independent source signals are interpreted as networks of similar BOLD activity (McKeown et al., 1998). ICA can be revealing when brain activation is difficult to predict beforehand, such as when internal shifts of activation are not time-locked to an easily identified sensory or motor event (i.e., during resting state scans). It is also able to separate out artifacts that are embedded in the data, which is important given that movement during brain scans may lead to spurious connectivity patterns (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012; Van Dijk, Sabuncu, & Buckner, 2012). Hence, ICA has become an especially useful approach to the measurement of functional connectivity in populations where movement during scanning or compliance with active tasks may present

challenges (Assaf et al., 2010), including young children (Supekar, Musen, & Menon, 2009; Supekar et al., 2010) and individuals with ASD (Assaf et al., 2010).

Significance. Over the past decade connectivity has emerged as an important indicator of local and global functioning in the brain, where normal patterns of connectivity reflect healthy mental functioning (Castellanos et al., 2010) and abnormal patterns of connectivity reflect psychopathology, brain trauma, or maldevelopment (e.g., Bleich-Cohen, 2012; McAllister, Sparling, Flashman, & Saykin, 2001; Stevens et al., 2012). Connectivity research also indicates that the development of social, emotional, and cognitive functions is accompanied by changes in the magnitude and extent of activation in the brain regions and networks responsible for those functions (e.g., Blakemore, 2008; Jolles, van Buchem, Crone, & Rombouts, 2011; Luna, Padmanabhan, & O'Hearn, 2010). In recent years, identifying patterns of both typical and atypical connectivity has become critical to understanding how neural networks process information and how the brain changes over time.

Typical Connectivity Development

Before atypical connectivity development could be reliably recognized, it was first necessary to identify how connectivity develops in typically developing children. Jolles and colleagues (2011) were interested in investigating whole-brain functional connectivity in children and young adults to determine whether patterns of functionally connected regions, the size of those regions, or the strength of functional connectivity between regions changed over time. When compared to young adults, they found that children had increased functional connectivity in networks associated with complex

cognitive or emotional functions, including the default-mode network (DMN), the dorsal attention system, and the executive control system. In a similar vein, Perlman and Pelphrey (2011) found that amygdala activation increased in adults but decreased in children during recovery from a frustrating experience, suggesting excessive connectivity among children in regions important to affective regulation. Together, these findings suggest that regional hyperconnectivity may be a sign of neural immaturity within a given network, and that this connectivity is adaptively reduced over time during normal development.

To examine the relationship between functional connectivity and language development, Veroude, Norris, Shumska, Gullberg, and Indefrey (2010) investigated how naturalistic language exposure impacts resting state connectivity among adults learning a new language. In comparison to participants who were unable to recognize target words (*non-learners*), the authors found that participants who were able to successfully recognize words they had learned previously (*learners*) had different patterns of connectivity in brain regions related to language acquisition. More specifically, learners showed stronger functional connectivity before the word recognition task in regions important to phonological rehearsal, and showed stronger connectivity after the word recognition task in regions important to the storage of phonological forms. These findings illustrate how connectivity appears plays a role in the learning processes.

Overall, research indicates that connectivity formation and strengthening occurs throughout development, and therefore infants generally have far fewer and weaker connections than adults (Jolles et al., 2011; Supekar, Musen, & Menon, 2009). Although

changes in connectivity are known to occur throughout childhood and adolescence (e.g., Fair et al., 2009; Kelly et al., 2009; Supekar et al., 2010), the greatest changes appear to take place during periods of rapid brain development, namely early childhood (Jolles et al., 2011). As such, it appears that efforts to reorganize and strengthen connectivity in children with developmental disorders should begin as early as possible, preferably before a child is school-aged, while the brain is still rapidly developing. Research has made it increasingly clear that early intervention plays an important role in improving developmental trajectories (for a review see Dunst, 2007).

Atypical Connectivity Development

Many disorders have been linked to atypical connectivity in the brain regions implicated in their symptoms or impairments. For example, Konrad and Eickhoff (2010) reported numerous findings that suggest a predominant network dysfunction within the default-mode network (DMN), a large network of brain regions associated with passive mental processes, among children with ADHD. These findings include disruptions in functional connectivity identified during resting and task states, as well as disruptions in structural connectivity identified using diffusion tensor imaging. In another example, Cerullo and colleagues (2012) found that during the transition from a manic or mixed episode to a depressive episode, individuals with bipolar I disorder experienced distinct changes in cortical-amygdala functional connectivity. Abnormal activation in corticolimbic regions, which are responsible for regulating emotions, might help to explain the affective lability that is characteristic of bipolar I disorder. Similarly, Yan and colleagues (2012) found that individuals with schizophrenia had abnormal functional

connectivity in the cognitive division of the anterior cingulate cortex (ACC), which is known for its role in cognitive control. This finding might help to explain the cognitive impairments that are core to schizophrenia, including the loss of executive control processes.

Taken together, connectivity research across a variety of psychological and neurodevelopmental disorders suggests that aberrant connectivity development may underlie and help to explain the emotional, behavioral, and cognitive symptoms that are characteristic of a given disorder. Importantly, findings such as these have eventually led researchers to explore the effects of treatment on connectivity.

ASD and Connectivity

ASD has been consistently linked to atypical connectivity development, including many structural and functional abnormalities within the brain regions thought to be involved in ASD's core deficits (Belmonte et al, 2004; Courchesne et al., 2007; Muller et al, 2011). For example, the prefrontal cortex, which is involved in complex cognitive processes such as executive functioning, personality expression, and the moderation of appropriate social behavior, has been commonly pinpointed as a site of abnormal connectivity among individuals with ASD (Lee et al., 2008). Similarly, evidence suggests there is also disrupted connectivity in brain regions and networks associated with imitation (Shih et al., 2010) and complex social-emotional processing (Ameis et al., 2011; Kennedy & Courchesne, 2008).

Connectivity theory of ASD. One prominent theory in ASD brain research maintains that the aberrant patterns of functional connectivity seen among individuals

with ASD underlie many (if not all) outwardly visible symptoms of ASD (Assaf et al., 2010; Coben & Myers, 2008). Research consistently indicates that the functional connectivity of individuals with ASD differs significantly from that of typically developing individuals, and that these connectivity differences (although variable throughout development) can be observed across all age groups (for a review, see Wass, 2010). Because ASD is known to effect normal developmental processes in the brain, it is plausible that differences in connectivity patterns between typically developing individuals and those with ASD may change or become more pronounced over time (Herbert et al., 2003), again highlighting the need for early interventions.

To better understand how atypical connectivity is implicated in ASD, many studies have aimed to define whole-brain and regional connectivity patterns in greater detail. At present, converging evidence suggests that ASD is marked by patterns of both long-range underconnectivity as well as short-range overconnectivity (Wass, 2010). That is, neural coherence appears to be deficient between distant brain regions, but excessive within individual or adjacent brain regions. However, the nature of connectivity disturbances (i.e. reduced or increased) may vary by region (Kennedy & Courchesne, 2008). Not surprisingly, connectivity dysfunction appears to be most prominent in the regions and networks responsible for some of the adaptive behavioral processes that are commonly impaired among individuals with ASD, such as social cognition and emotion regulation (Ameis et al., 2011).

Connectivity within the default-mode network. The default-mode network (DMN) is the connectivity network that is active during passive, or "task-

negative", resting states. Anatomically, the DMN subsystems include part of the medial temporal lobe (memory), part of the medial prefrontal cortex (theory of mind), and posterior cingulate cortex (integration), as well as the adjacent ventral precuneus and the medial, lateral, and inferior parietal cortex. Some components of the DMN are thought to overlap with components involved in theory of mind, which involves the ability to understand that others have beliefs, desires, and intentions that are different from one's own. There is also evidence of distinct cerebellar contributions to the DMN, namely through the neocerebellum (Allen et al., 2005; Habas et al., 2009).

Activity in the DMN can be observed during a variety of tasks and activities, including daydreaming, envisioning the future, and light (non-REM) sleep (Koike, Kan, Misaki, & Miyauchi, 2011). This network is thought to be important to the performance of certain social-cognitive processes that are commonly impaired in ASD, such as self-referential thought, introspection, perspective taking, and episodic memory. Therefore, aberrant connectivity in sub-regions of the DMN may help to explain some of the social difficulties commonly experienced by individuals with ASD (Assaf et al., 2010; Broyd et al., 2009).

Patterns of hyperconnectivity. Coben and Myers (2008) used EEG to explore the nature of the atypical connectivity patterns seen in ASD. As predicted, the authors discovered patterns of increased connectivity within the frontotemporal and left hemispheric regions, which are important for their role in the comprehension of spoken language (Tyler & Marslen-Wilson, 2008). Similarly, Monk and colleagues (2009) used fMRI to assess connectivity in ASD, and found that restricted and repetitive behavior was

associated with stronger connectivity between the posterior cingulate cortex and the right parahippocampal gyrus, which are components of the default mode network (DMN).

In another study using fMRI, Noonan, Haist, and Müller (2009) compared whole-brain functional connectivity between individuals with ASD and typically developing controls during the performance of a source recognition task. Although the authors found fcMRI patterns to be largely similar across the two groups, task effects on connectivity were generally more extensive for the ASD group. Based on these findings, the authors suggest that ASD is associated with inefficiency in optimizing task performance (Noonan, Haist, & Muller, 2009), such that diffusely increased functional connectivity can be attributed to impaired experience-driven brain mechanisms. This conclusion is consistent with earlier notions that ASD may be linked to flawed mechanisms for synaptic pruning and reorganization (e.g., Courchesne et al., 2001; Herbert et al., 2003).

Patterns of hypoconnectivity. In contrast to their findings of short-range excesses in connectivity, Coben and Myers (2008) also identified patterns of decreased connectivity in the frontal (orbitofrontal), right posterior (occipital/parietal-temporal), frontal-posterior, and left hemispheric regions. These findings are consistent with early examinations of connectivity in ASD which suggest the disorder is marked primarily by patterns of long-range underconnectivity. Additionally, Monk and others identified patterns of decreased connectivity between the posterior cingulate cortex and the right superior frontal gyrus, and were able to link these patterns to poorer social functioning in participants (Monk et al., 2009).

Taken together, there is a myriad of evidence indicating abnormal connectivity development within and between certain brain regions in ASD. Based on the functions controlled by those brain regions, study results demonstrate a clear link between the behavioral symptoms of ASD and measures of brain functioning, namely connectivity. Coben and Myers (2008) concluded from their findings that connectivity disturbances may be the primary dysfunction in ASD. In light of these findings, the authors suggest that ASD interventions should aim to uptrain coherence deficits and downtrain coherence excesses in these regions, perhaps through coherence training or other neurofeedback (Coben & Myers, 2008)

Connectivity as a Correlate of Symptom Improvement

Recently, a growing body of experimental researchers have begun presenting changes in connectivity following treatment as evidence of tangible and meaningful brain change. This assertion presumes the observed neurological changes are caused by the treatment and reflective of the cognitive and behavioral changes associated with the treatment. These interventions have used a variety of methodological techniques (e.g., psychopharmacology, electroconvulsive therapy, deep brain stimulation) to treat numerous psychiatric and neurodevelopmental disorders. For example, Li and others (2012) found that individuals with Alzheimer's disease who were treated with donepezil for 12 weeks experienced improved cognition that correlated with increases in cerebral blood flow and functional connectivity. Similarly, Zaidel and colleagues (2012) found that treatment with donepezil had a significant effect on functional connectivity between right and left dorsolateral prefrontal cortices. Other drugs have also been linked to

changes in functional connectivity during treatment. Stimulant medications, for instance, have been linked to improvements in working memory when used in the treatment of attention-deficit/hyperactivity disorder (ADHD), and have been associated with strengthened connectivity of some frontoparietal regions known to effect working memory (Wong & Stevens, 2012).

In another study examining connectivity change after treatment, Schweder and colleagues (2010) found evidence that chronic, low-frequency stimulation of the pedunculopontine nucleus normalized pathological connectivity in that region, suggesting neuroplasticity that involves the reorganization of connectivity over time. Likewise, electroconvulsive therapy has also been linked to reduced frontal cortical connectivity when used in the treatment of severe depressive disorder (Perrin et al., 2012). In contrast to studies examining connectivity changes following treatment, Castellanos and others used resting state MEG recording to determine that the reorganization of functional connectivity was correlated with cognitive recovery among individuals with an acquired brain injury. These findings suggest that connectivity reorganization may be one of the neurophysiological mechanisms underlying the brain's plasticity, and provide evidence that changes in connectivity are related to observable behavioral changes (Castellanos et al., 2010).

In sum, there is a strong foundation of evidence indicating that improvements in cognitive and behavioral symptoms may signify and correspond to underlying changes in connectivity, and thus, that efficacious interventions may result in more typical brain connectivity. Surprisingly, there is a paucity of research examining connectivity changes

related to the treatment of ASD (Lee et al., 2009). As a result, it is still unclear whether the behavioral and cognitive changes associated with efficacious ASD interventions are linked to measurable improvements in local and global brain functioning. This gap in the literature is significant given that connectivity might be useful in informing and evaluating interventions (Coben & Myers, 2008), and that changes in patterns of functional connectivity are more likely to occur early in life while cognitive skills are rapidly developing (Lee et al., 2009).

Treatment of ASD

In contrast to the increasingly popular neuroimaging literature, another large portion of the current ASD research is devoted to testing and evaluating new treatment approaches, as well as identifying the most efficacious ASD interventions. Dozens of approaches are currently used in the treatment of ASD, varying greatly in terms of their resource requirements (e.g., time, money, training), theoretical orientation (e.g., psychosocial, behavioral), and the extent of their empirical support. This includes interventions that are provided privately and those that are provided publicly at schools or daycares for little or no additional cost to the family beyond any cost of daily care.

Over the past several decades, interventions from a great number of theoretical paradigms, including behavioral, biomedical, sensory/motor, psychosocial, and educational/generic approaches, have emerged and become popular. Behavioral interventions, which include many techniques that are widely supported by empirical literature, typically focus on teaching new skills and decreasing problematic behaviors by manipulating the antecedents and consequences that precede and follow the behavior.

Examples of common behavioral approaches include applied behavior analysis (ABA), pivotal response training, (PRT), and joint attention interventions. Psychosocial interventions tend to focus on improving one's psychological development in, and interaction with, a social environment. The DIR model (which emphasizes Development, Individual Differences, and Relationships) is one example of a popular psychosocial intervention. Unlike most other theoretical approaches, biomedical intervention models view ASD as a medical pathology, and maintain that the behavioral excesses and deficits can be corrected using treatments that promote brain and body health. Such interventions include special diets (e.g., gluten-free, casein-free), chelation, and the avoidance of vaccinations. Finally, sensory/motor intervention programs view ASD as a disorder of sensory processing and poor motor control, and treatments are designed to limit motor requirements, refine sensation and perception, and maximize sensory input. Examples of sensory/motor interventions include music therapy, sensory integration therapy, and facilitated communication. Educational and generic approaches are usually not grounded in any one theoretical orientation, and thus are often characterized as 'eclectic'. These intervention strategies typically do not designate any systematic, pre-specified techniques for instruction or behavior management.

Early intensive behavioral interventions. Early intensive behavioral interventions (IBIs) for children with ASD have been consistently linked to improvements in intellectual functioning, language development, daily living skills, and social functioning (Eldevik et al., 2009). Language-related outcomes (e.g., IQ, receptive and expressive language, nonverbal communication) show the most pronounced gains,

with an effect size approaching 1.5 (Virués-Ortega, 2010). For the purpose of the proposed study, interventions are considered to be early, intensive, and behavioral in nature if they begin before the age of 4, include 25 or more hours of 1:1 instruction each week, and are based on the principles of behavior analytic theory. The potential effects of these treatments are maximized when implemented continually for at least a year, though longer is preferable (Virués-Ortega, 2010). Although EIBIs are currently viewed as the most effective interventions for ASD, they are usually also very time- and cost-intensive, which severely limits the number of individuals and families for which these therapies are feasible.

Applied behavior analysis. Applied behavior analysis (ABA) therapy is a particularly well-esteemed IBI used in the treatment of ASD. Developed in the late 1960s by Ivar Lovaas (now referred to as the "father" of ABA), ABA therapy is highly systematic, grounded in theory and research, and has a long documented history of being the best known ASD intervention (Virués-Ortega, 2010). Moreover, the prescribed curriculum has been revised and adapted continuously over the years, and the implementation of the treatment is typically closely supervised by a board-certified behavior analyst (Soorya, Carpenter, & Romanczyk, 2011). In comparison to ABA, however, the 'eclectic approach' is more commonly used in schools. This approach, which is essentially an integration of several intervention strategies, requires less one-on-one attention from the teacher, is generally less data-driven, and is cheaper to provide when training and wage costs are considered (Zachor & Itzchak, 2010).

Center for Autism and Related Disorders. In Odom, Boyd, Hall, and Hume's (2010) evaluation of comprehensive treatment models for ASD, they found that although most models were well operationalized, most were weak in measurement of implementation and evidence of efficacy. One of the service providers that earned adequate ratings for operationalization, fidelity, replication, and outcome data has branches in over 30 major cities nationwide, and has become a well known provider of ABA therapy. The Center for Autism and Related Disorders (CARD, Inc.) was founded by a mentee of Lovaas and is generally well-regarded for its evidence of efficacy (Keenan et al., 2006). Importantly, CARD provides financial assistance (funded by a grant from the Department of Assistive and Rehabilitative Services) to those who qualify. As a result, CARD serves children and families from diverse racial, ethnic, economic, and educational backgrounds, including families who may otherwise be unable to afford an intensive intervention.

Responders vs. nonresponders. The positive gains associated with IBIs, and ABA therapy in particular, appear to be more probable for some individuals than for others. More specifically, children fitting the 'responder' profile experience better outcomes from ABA therapy than children fitting the 'nonresponder' profile (Sherer & Schreibman, 2005; Ingersoll, Schreibman, & Stahmer, 2001). According to Sherer and Schreibman (2005), children meeting criteria for the responder profile are characterized as being low in social avoidance, tolerant of being in close proximity to others, and having moderate to high interest in toy play. Additionally, responders are distinguished by low-to-moderate rates of nonverbal self-stimulatory behavior and moderate-to-high rates of verbal self-

stimulatory behavior, as well as relative strengths in joint attention and imitation. Not surprisingly, children with less severe ASD symptoms at baseline also tend to experience more progress in adaptive skills and in cognitive abilities (Zachor & Itzchak, 2010).

Although behavioral interventions are well-established and appear to have the most pronounced effects on outcomes (e.g., Zachor & Itzchak, 2010), they also tend to be very resource-intensive, leading many schools and community-based service providers to opt for the cheaper and more practical 'eclectic' approaches. Eclectic interventions typically incorporate a variety of techniques, including some that may not be widely supported by empirical evidence. For these reasons, researchers are interested in testing the prominent belief that behavioral interventions are superior to many other common ASD interventions, as well as determining what makes behavioral interventions superior. To that end, it is imperative that changes in the brain following treatment are better understood, including the putative mechanisms underlying those changes, and how changes in connectivity relate to changes in behavior and cognitive ability.

Proposed Research Study

Statement of Problem

Although much of the current ASD literature has focused on illuminating the biological underpinnings of ASD or identifying effective treatment approaches, very little research has integrated these two areas of study and examined the neurobiological outcomes associated with various ASD interventions. However, if neuroimaging methods can be used to measure the extent and nature of one's impairments, then it follows logically that these same methods could be used to measure the extent and nature of one's improvements after treatment. The paucity of this type of research is surprising, given that a wide variety of intervention strategies are currently used in the treatment of ASD, including some that have not been empirically supported. Clearly, more information is needed about how treatment affects the brain, including which neurological mechanisms underlie effective treatments, and how early brain changes may influence future brain development (i.e., change developmental trajectories). If more is learned about the nature of brain change and the factors influencing these changes, it is likely that interventions will be improved, schools will be forced to adopt more effective intervention approaches, and treatment gains will be maximized.

Statement of Purpose

For the reasons outlined in the review of the literature above, the purpose of the proposed study is to explore the treatment related changes in IQ and functional connectivity for two common ASD interventions. More specifically, this study aims to determine if the cognitive and behavioral changes associated with early, intensive

behavioral interventions (i.e., ABA therapy) for children with ASD also correspond to greater changes in IQ, whole-brain connectivity, and DMN connectivity than changes (if any) associated with a less systematic treatment approach (i.e., treatment as usual [TAU]).

Research Questions and Hypotheses

Research Question 1. Does the mean change in IQ score following treatment differ significantly between treatment groups?

Hypothesis 1. It is expected that the mean change in IQ after treatment will differ significantly between treatment groups, such that children in the ABA therapy group will, on average, experience greater change in IQ than children in the TAU group.

Rationale 1. There is a vast body of evidence supporting the use of behavioral interventions in the treatment of ASD. In comparison to interventions with other theoretical orientations (e.g., psychosocial, biomedical, or eclectic models), behavioral therapies appear to have the most pronounced effects on most outcomes (Virués-Ortega, 2010; Zachor & Itzchak, 2010), with an effect on IQ that is considered large (Eldevik et al., 2009). Eclectic ASD interventions, on the other hand, have much less empirical support and are not known to have a significant effect on IQ (Eikeseth, 2009; Rogers & Vismara, 2008;). Therefore, if children in both groups have approximately equal IQs when they begin treatment (accomplished through a matching procedure), it is plausible that children in the ABA group will experience a greater average change in IQ score group following treatment than children in the TAU group.

Research Question 2. Does the mean change in pre- and post-treatment whole-brain functional connectivity differ significantly between treatment groups?

Hypothesis 2. It is expected that the collective degree of change in whole-brain connectivity after treatment will differ significantly between treatment groups, such that participants in the ABA group will experience greater changes in functional connectivity that participants in the TAU group.

Rationale 2. In a study comparing resting state functional connectivity among individuals with ASD and typically developing controls, Monk and colleagues (2009) discovered that the extent of altered connectivity among participants with ASD corresponded with the presence and severity of core ASD symptoms. In a similar vein, Anderson and others (2011a; 2011b) also found that measures of whole-brain connectivity in participants with ASD were significantly correlated with general ASD symptoms. The results of these studies indicate that the symptoms of ASD may be correlated with and predictive of brain connectivity abnormalities. If that is true, it follows logically that the symptom improvements often seen among children who receive evidence-based behavioral therapies for ASD may be reflective of underlying changes in brain connectivity. Thus, in the proposed study it is expected that participants in the ABA therapy group will experience greater changes in whole-brain connectivity than participants in the TAU group.

Research Question 3. Does the mean change in pre- and post-treatment functional connectivity within the DMN differ significantly between treatment groups?

Hypothesis 3. It is expected that participants in the ABA therapy group will experience a greater mean change in connectivity within components of the DMN than participants in the TAU group.

Rationale 3. Lesion studies provide evidence that observable changes in behavior can be linked to changes in connectivity patterns in the region of a lesion (e.g., Carter et al, 2012). Similarly, a vast number of studies have examined changes in connectivity following interventions for various developmental and neurological disorders (e.g., Alzheimer's disease, attention-deficit/hyperactivity disorder, depression), and results suggest that participants receiving an effective, evidence-based treatment for their disorder typically experience changes in connectivity in the brain regions implicated in their impairments (Li et al., 2012; Scheidegger et al., 2012; Wong & Stevens, 2012). In comparison to the brain connectivity of typically developing individuals, some of the most consistent and pronounced connectivity abnormalities identified in individuals with ASD occur within the DMN. It is now widely believed that aberrant connectivity within the DMN, which is involved in some of the social functions characteristically impaired in ASD, is a hallmark of the disorder. Numerous studies have identified patterns of excesses and deficits in connectivity within the DMN (e.g., Cherkassky et al., 2006; Monk et al., 2009), and these results suggest that weaker connectivity within the DMN is associated with some of the impairments specific to ASD (Weng et al., 2010). Taken together, it follows logically that greater improvements in behavior and cognitive functioning seen among children receiving ABA therapy relative to children receiving TAU likely

corresponds to greater changes in connectivity in the brain regions or networks impaired by ASD, namely the DMN.

Method

The proposed study will use a pretest-posttest control match design. Functional connectivity within the DMN will be measured using magnetic resonance imaging scans from 40 male children with ASD. Study participants will undergo diagnostic confirmation, assessments of overall cognitive abilities, language, and adaptive skills (see measures section below), and magnetic resonance imaging (MRI) scans before and after receiving one year of treatment. Participants will be matched between groups by handedness and pre-treatment scores of overall cognitive ability as measured by the Leiter-R. To ensure treatment fidelity, study investigators will monitor the implementation of both interventions throughout the duration of the study.

Participants

Participants will be recruited via fliers and word of mouth from daycares, preschool programs, and a large, grant-funded ABA therapy provider. Forty males between the ages of 2 and 5 years old with an existing ASD diagnosis will be tracked for 12 months as they receive either 30 hrs./wk. of ABA therapy (treatment group; $n = 20$), or 30 hrs./wk. of treatment as usual (control group; $n = 20$).

Consent and authorizations. Participation in the study will be undertaken with the understanding and written consent of participants' parents, with the approval of the University of Texas Institutional Review Board and in compliance with national legislation and the Code of Ethical Principles for Medical Research Involving Human

Subjects of the World Medical Association. Participants will receive a copy of the consent form, which explains the purpose, risks, and benefits of the research study, and will have the option of receiving the results of the study after its completion. Participants will also be compensated for their time and travel.

Diagnostic confirmation and exclusionary criteria. ASD diagnoses will be confirmed by an ASD specialist using the Autism Diagnostic Observation Schedule-Generic (ADOS-G; Lord et al., 2000) and the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV; American Psychiatric Association, 1994). Additionally, all participants must meet the criteria of 'responders' to early behavioral interventions, as the 'responder' and 'nonresponder' profiles are strong predictors of treatment effectiveness (Sherer & Schreibman, 2005). Children with a history of seizure disorders or hearing problems will be excluded from participation, as well as children who take psychotropic medications.

Matching. Participants who meet criteria for both an ASD diagnosis and the responder profile will be tested to determine pre-intervention scores on various abilities. Pre-treatment scores of overall cognitive ability will be used to match participants for statistical comparisons. Participants will be considered adequate matches if the difference in their IQ scores is no more than 5 points (1/3 standard deviation). Participants will also be matched for handedness, as handedness is a strong indication of the hemispheric location of certain lateralized functions within the brain.

Instrumentation

Diagnostic confirmation. A clinical psychologist will screen all participants using the Autism Diagnostic Observation Schedule (ADOS; Lord et al., 2000) to confirm ASD diagnoses and ensure study eligibility. The ADOS is a semi-structured assessment of communication, social interaction, and play. Current research indicates that the ADOS is a sufficiently valid and reliable instrument for discriminating ASD from non-ASD in children with developmental age equivalents of at least 15 months who are able to walk independently (Gray, Tonge, & Sweeney, 2008). However, research also suggests it may not be a good measure of response to treatment or developmental gains, and thus scores obtained from the ADOS will be used for diagnostic purposes only in the proposed study.

IQ. The Leiter International Performance Scale, Revised (Leiter-R) will be used to measure participants' overall intelligence. The Leiter-R is a completely nonverbal measure that is ideal for use with those who are cognitively or developmentally delayed, including children with ASD. It is appropriate for use with children as young as 2 years old and provides scores for four subscales: Memory, Attention, Reasoning, and Visualization. The Leiter-R IQ score is not significantly influenced by a child's social, family, or educational experience. For the proposed study, participants' global IQ score will be used for matching purposes.

Language abilities. The Psychoeducational Profile (PEP-3), a norm-referenced test designed to assess the skills and behaviors of children with ASD and communicative disabilities, will be used to determine participants' language abilities and motor skills. The PEP-3 is appropriate for use with children who have a developmental

age between 6 months and 7 years, and is especially useful for determining the degree or severity of one's impairments across several domains of functioning. The test is comprised of 10 subtests and yields 3 composite scores (Communication, Motor, and Maladaptive Behaviors). Research indicates the PEP-3 assessment system, including the Caregiver Report, is sufficiently reliable and valid for use as an outcome measure (Chen, Chiang, Tseng, Fu, & Hsieh, 2011; Fu, Chen, Tseng, Chiang, & Hsieh, 2012; Portoghese et al., 2009; Villa et al., 2010).

Handedness. The Edinburgh Handedness Inventory (Oldfield, 1971), a standardized assessment of hand preference, will be obtained for each subject. This inventory consists of a numerical score between –100 and 100, where –100 represents strong left-handedness and 100 represents strong right-handedness.

Adaptive behavior. The Vineland Adaptive Behavior Scales, Second Edition (Vineland-II), a commonly used measure of personal and social skills needed for everyday living, will be completed with parents. The Vineland-II provides index scores across five domains: Communication, Daily Living Skills, Socialization, Motor Skills, and Maladaptive Behavior. Many of the skills and behaviors assessed by the Vineland-II are executed or coordinated by regions within the DMN, making the device an ideal baseline measure for the proposed study.

Image Acquisition

Scanning will be performed on a 3 Tesla GE scanner (General Electric Medical Systems, Milwaukee, WI) at Seton Medical Center of Central Texas as participants sleep following the protocol outlined by Nordahl and colleaguesWhole brain axial slices will

be collected with a gradient-recalled echo-planar imaging (EPI) pulse sequence with the following parameters: TR (repetition time) = 2000 ms; TE (echo time) = 30 ms; flip angle = 90°; field of view (FOV) = 220 mm; matrix = 64 x 64 (3.44mm^2 in-plane resolution); slice thickness = 4 mm; no. of axial slices = 32; no. of volumes = 262. T1-weighted anatomical images will be collected for co-registration with the functional images [FOV = 256 mm; matrix = 256 x 256 (1 mm^2 in-plane resolution); slice thickness = 1 mm; no. of axial slices = 124]. One 9-min scan (262 volumes) will be obtained for each subject.

Procedure

Appointment 1. At the initial appointment, which will occur approximately 2 weeks before the interventions begin, consent will be obtained and participants' ASD diagnoses will be confirmed by a licensed clinical psychologist using the Autism Diagnostic Observation Schedule- Generic (ADOS-G). If a participant meets diagnostic criteria for ASD, the ADOS-G results will be used to determine if he or she fits the profile of a likely 'responder' to ABA treatment based on measures of joint attention, toy play, and verbal ability. Regardless of treatment group, all participants in the proposed study must fit the responder profile, as research has not clearly demonstrated whether responders and nonresponders differ significantly with regards to pre-treatment connectivity. Participants who meet criteria for the study will then undergo an assessment of cognitive and language skills while a parent completes measures of their child's social skills and adaptive behavior. Although overall cognitive ability is the only test score that will be included in the proposed study analyses, other measures of skills and abilities may

prove useful in explaining connectivity trends during future follow-up analyses of the data.

Appointment 2. At the second appointment, which will immediately precede the start of interventions, participants will undergo MRI scans of the brain designed to be sensitive to functional brain connectivity. Scanning will be completed at night during the participants' natural sleep. Participants will be prepared for these night scans using the protocol outlined by Nordahl et al. (2008). Although this protocol requires several weeks of preparation (e.g., playing loud sounds while the child sleeps, exposure trials in the scanner), it has achieved a 93% success rate in similar studies of young children requiring night scans without sedation. This procedure is important given that failed trials are costly and can ultimately be a source of attrition from the study.

Between the second and third appointments, participants will be tracked as they receive ABA therapy or treatment as usual for 12 months. Tracking will be essential to minimizing the time and monetary costs required by the study, and will consist of video review and a brief phone call every three months to ensure that the stipulations of treatment conditions are being satisfied (e.g., sufficient time spent in treatment). More important, tracking will also ensure treatment fidelity, essentially confirming that the independent variable is being manipulated as planned. Participants will be disqualified from the study if, at any time, they no longer meet criteria for eligibility.

Appointment 3. The third appointment will take place after the child has completed 12 months of treatment. At this appointment, participants will again undergo MRI scans at night as they sleep, and parents will be reminded in advance to follow the

pre-scan protocol (Nordahl et al., 2008). It is essential that the scans are organized and scheduled within two weeks of the end of the 12th month of treatment. The timing of the second scan is crucial to the validity of the outcome measures, as all participants must receive treatment for the same duration. For obvious reasons, it is unethical to request that parents discontinue treatment, so care must be taken to execute this measurement at the correct time.

Appointment 4. The final appointment will consist of testing and interviews. This appointment should also be scheduled as close as possible to the end of the 12th month of treatment. At this meeting, participants will again undergo cognitive and language testing, and parents will complete the Vineland-II for a second time. Additionally, qualitative data will be gathered about the parents' experiences and opinions concerning their child's treatment, including their perceptions of any possible changes in their children's behavior or level of functioning that may have occurred in the past 12 months. The final appointment will end with an open-ended discussion in which parents can share any information they think may be useful, or ask any questions they may have about the study itself. If desired, parents can elect to receive a summary of the study results and conclusions when the study is completed.

Data Analyses and Expected Results

Preliminary analysis. A power analysis conducted using G*Power software (version 3.0) determined that 27 participants (14 per group) will be needed to detect treatment effects, given the estimated effect size of ABA therapy, desired power, and alpha parameters (d = .30; β = .80; α = .05) for the primary analysis of change in full

scale IQ. Thus, the overall alpha was set at .05 and the probabilities associated with the IQ outcome measure will be statistically significant at $p < .025$ for the two-tailed analyses. A sample of 40 total participants will be collected to account for possible attrition.

Hypothesis 1. To test Hypothesis 1, mean change in IQ score after treatment will be compared between groups. This will be accomplished using a paired samples *t*-test, testing the null hypothesis that there is no difference in IQ change between treatment groups. A main effect of treatment group is expected, such that the mean change in IQ is expected to be significantly larger for the ABA group than the TAU group

Hypothesis 2. To test Hypothesis 2, mean change in whole-brain functional connectivity after treatment will be compared between groups. This will be accomplished using a paired-samples *t*-test, testing the null hypothesis that there is no difference in whole-brain connectivity changes between treatment groups. A main effect of treatment group is expected, such that whole-brain connectivity changes are expected to be significantly greater for the ABA group than the TAU group.

Hypothesis 3. To test Hypothesis 3, connectivity change within the DMN after treatment will be compared between groups. A paired-samples *t*-test will be used to test the null hypothesis that there is no difference in connectivity change in the DMN between treatment group. Changes in connectivity will be calculated using the individual best-fit network components for the DMN, as determined through independent component analysis (ICA). FSL, which includes a comprehensive library of analysis tools for fMRI data (Smith et al., 2004), will be used for connectivity analyses.

Functional connectivity data analysis. An ICA-based approach (using multivariate exploratory linear decomposition into independent components [MELODIC]) will be used in combination with a "dual regression technique" (Biswal et al., 2010; Filippini et al., 2009). Using Randomise implemented in FSL (FMRIB's software library, www.FMRIb.ox.ac.uk/fsl; Smith et al., 2004), this approach allows voxel-wise comparisons of functional connectivity between groups.

Data preprocessing. The following data preparation procedures will be applied: motion correction (Jenkinson et al., 2002), nonbrain removal (Smith, 2002), spatial smoothing using a Gaussian kernel of full-width at half-maximum 4.0 mm, grand-mean intensity normalization of the entire 4D data set by a single multiplicative factor, highpass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma = 50.0 s). This preparation is consistent with the data preprocessing implemented by Jolles and colleagues (2010) to examine whole-brain and regional functional connectivity in children. To register fMRI scans to standard space, functional scans of each individual will be registered to the corresponding high-resolution EPI images, which will be registered to the T1 images, which will be registered to the standard space of typically developing children of the same age (Jenkinson & Smith, 2001; Jenkinson et al., 2002; Supekar et al., 2010).

Stage 1. The dual regression approach includes three stages (Biswal et al., 2010; Fillipini et al., 2009). In the first stage, the data will be decomposed in separate functional networks. To accomplish this, time series of all participants will be temporally concatenated into a single 4D time series, and this time series will be automatically

separated into 25 components using ICA in MELODIC. This technique automatically isolates noise-related signal fluctuations such as head motion (Damoiseaux et al, 2006; Fox & Raichle, 2007), which is an important advantage when scanning young children with ASD. Thirteen components will be selected for whole-brain analyses based on spatial similarity to functional networks described previously (Damoiseaux et al., 2006; Jolles et al., 2011): network A: visual system; network B: sensorimotor system; network C: default-mode network; network D: auditory system; network E: ventral stream; network F: executive control system; network G: dorsal attention system; network H: frontoparietal network (left hemisphere); network I: frontoparietal network (right hemisphere); network J: anterior default-mode network; network K: occipitoparietal network; network L: insula/operculum-cingulate network; and network M: superior parietal network. Other identified components may be related to white matter, cerebrospinal fluid, head movement, and nonneuronal noise.

Stage 2. The second stage of the functional connectivity analyses involves the participant-specific component maps. First, individual time series will be extracted for each component, using the component maps in a (spatial) regression against individual data. The resulting time series matrices will then be entered in a second (temporal) regression against the associated data to estimate spatial component maps for each participant.

Stage 3. In the third and final stage of the analysis, mean change in connectivity within each of the 13 selected functional networks will be calculated and aggregated for each group, resulting in a single value for whole-brain connectivity change for each

group. To do so, the regional resting-state fMRI timeseries will computed for the entire brain by averaging all the voxels within each component at each timepoint in the timeseries (Greicius, Krasnow, Reiss, & Menon, 2003; Greicius, Srivastava, Reiss, & Menon, 2004). Voxel-wise nonparametric permutation testing will be performed using Randomise in FSL (with 5000 permutations; Nichols & Holmes, 2002). All statistical maps will be family-wise error (FWE) corrected using $p < 0.05$, based on the threshold-free cluster enhancement (TFCE) statistic image (Smith & Nichols, 2009). Group comparisons will be masked by group main effects (i.e., voxels that fall within the group map of either group, thresholded at $p < 0.05$, FEW corrected for multiple comparisons using the TFCE technique).

Post-treatment change in the strength of functional connectivity at the whole-brain level will be compared between groups. Changes in the strength of functional connectivity will be examined by using a voxel-wise comparison of correlation values obtained before and after treatment. Functional networks are said to be characterized by strong functional connectivity between components within the network. As such, higher correlation values in a specific area correspond to stronger involvement of that area in the functional network (Jolles et al., 2011).

Connectivity in the DMN. The regional resting-state fMRI timeseries will computed for the DMN by averaging all the voxels within each region at each timepoint in the timeseries (Greicius, Krasnow, Reiss, & Menon, 2003; Greicius, Srivastava, Reiss, & Menon, 2004). Partial correlation will be used as a measure of strength of functional connectivity between brain regions belonging to the DMN. That is, functional

connectivity will be computed as partial correlations controlling for the influence of other DMN nodes and other major large-scale brain networks. Partial correlation measures the degree of association between two regions, controlling for the effect of other regions, and is a widely used procedure in task- and resting-state fMRI (Liu et al., 2008; Salvador et al., 2005; Sun et al., 2008; Supekar et al., 2010).

Discussion

Summary

Despite the rising prevalence of ASD in the general population and in schools, relatively little is known about the neural processes underlying ASD interventions, and why some treatments are so much more efficacious than others. More specifically, there is a dearth of neurological evidence that might help explain the variable efficacy of ASD treatments, namely by determining changes in connectivity that result from a given treatment. This gap in the literature is surprising given that brain imaging techniques have been useful thus far in the evaluation of treatment outcomes (e.g., Wong & Stevens, 2012; Schweder et al., 2010). Although behavioral and neurological investigations of ASDs have managed to progress independently of one another for several decades, it is now apparent to researchers that the two fields must eventually cross paths if ASD is ever to be fully understood or well treated.

The proposed study seeks to address this gap in the literature and explore whether the cognitive and behavioral changes observed following an intervention correspond to meaningful changes in IQ and functional brain connectivity, including connectivity within the default mode network. To do so, the IQ and functional connectivity of forty young children with ASD will be assessed and compared prior to and after they receive one of two interventions (i.e., applied behavior analysis [ABA] therapy and treatment as usual [TAU]). It is expected that the change in IQ experienced by participants receiving ABA therapy will be significantly greater than the change in IQ experienced by participants receiving TAU. It is also expected that change in whole-brain functional

connectivity will be greater for children receiving ABA, and that significantly greater changes in connectivity will also occur in the brain regions known to be affected by ASD, namely the default mode network.

Limitations

There are several important limitations of the proposed study. To begin with, finding participants who are willing to complete scanning at night may be difficult, as this would interfere with the schedules of most families. Similarly, it is possible that there will be a high rate of attrition from the study over time given that participation will require at least four appointments over the course of a year, and possibly more appointments if there are any challenges during scanning. This limitation is a threat to power and may increase the probability of making a Type II error. To address this limitation, the proposed study aims to recruit more participants than are required to detect treatment effects on IQ, and to compensate participants adequately for their time.

A second limitation concerns the use of functional connectivity as an outcome measure for children with ASD. Because some of the methods used to collect and analyze resting state fMRI data are in their infancy relative to other imaging strategies, it is unclear how sensitive current techniques will be at detecting the effects of treatment on connectivity, especially within a population and age group known to be difficult to scan. This limitation is also a threat to power, perhaps increasing the probability of making a Type II error. In consideration of this limitation, the proposed study plans to make comparisons between groups using aggregate data of whole-brain connectivity as well as connectivity within the DMN, as these are where the greatest changes are expected.

Another limitation of the proposed study is that resting connectivity data will be collected while participants sleep. It is possible that participants will wake up and become alarmed or begin moving, which would compromise imaging data. Moreover, sleep is known to alter functional connectivity in many brain networks, including some regions of the default-mode network, where connectivity is typically already decreased among individuals with ASD. Thus, this method of data collection may make it more difficult to detect connectivity patterns in areas with weak degrees of activation, or may limit the generalizability of study results. However, Koike and others (2011) determined that resting state functional connectivity patterns within core DMN regions (i.e., the posterior cingulate cortex, rostral anterior cingulate cortex, and inferior parietal lobule) did not vary greatly from patterns detected during wakeful rest among young adults. In consideration of this limitation, the proposed study will follow that scanning preparation protocol outlined by Nordahl and colleages (2011), which achieved a 93% success rate in acquiring high quality MRI scans of young children with ASD without the use of sedation. This protocol, which includes scanning simulations and familiarizing the child to scanner sounds at night, is designed to comfortably acclimate young children (including those with special sensory needs) to the scanning experience. Although there are still major methodological limitations in analyzing connectivity measures derived from noninvasive in vivo neuroimaging (for a review, see Vissers, Cohen, & Guerts, 2012), most researchers agree that the use of these methods is critical to understanding the etiology and treatment of neurodevelopmental disorders.

Finally, participants in the proposed study will not be randomly assigned to treatment conditions for ethical and practical reasons, which may pose a threat to the internal validity of the study. That is, it is possible that post-treatment differences in IQ and connectivity between groups could be attributed to variables other than treatment type, such as diet, access to healthcare, or parents' level of education. However, the screening and matching procedures for the proposed study are intended to ensure that participants in both groups are similar in ways that may be important to study outcomes (e.g., overall intelligence, sex, handedness). Further, care will also be taken to ensure that there are no significant differences in socioeconomic status (SES) between groups, including the selection of an ABA provider that is grant funded and awards need-based financial assistance to low-income families.

Implications and Future Directions

For mental health practitioners, the brain bases of behavior have become a major focus in recent years. This is not surprising given that researchers are finally beginning to understand brain connectivity and the role it plays in the development of cognitive, social, and emotional functioning. If hypotheses for the proposed study are confirmed, the results of this study could be extremely useful to individuals and families affected by ASD, as well as the educators and clinicians who work with this population. These data could provide neurobiological evidence that ABA therapy is superior to the eclectic approaches often used in schools and daycares, which would suggest that efficacious therapies for ASD work by reorganizing brain connectivity and making it more like that of typically developing individuals. Results could also potentially be used to demonstrate

methodological convergence between measures of brain connectivity and measures of IQ, language skills, and adaptive behavior in children with ASD. Practitioners would have another piece of the ASD puzzle, so to speak, to inform their approaches to intervention.

If more is known about factors affecting brain change, it is likely that treatment decisions could likely be improved, and the effects of treatment could be maximized. For example, if results indicate ABA therapy to significant changes in whole-brain connectivity but not DMN, different treatment options could be implemented in addition to ABA therapy to bolster emotional gains. Likewise, it is plausible that connectivity research will reveal that specific components of different interventions could be combined to create a stronger, more comprehensive treatment effect. Future research should aim to determine whether tailored interventions are able to elicit connectivity change within targeted brain regions.

In sum, the implications surrounding the study of brain changes associated with interventions are great, especially for neurodevelopmental disorders such as autism spectrum disorder. Presumably, those ASD intervention strategies associated with positive outcomes may alter individuals' developmental trajectories by creating neural pathways and communication networks that are more comparable to those of typically developing individuals. In addition, it is also plausible that treatments informed by neurological measures, such as coherence between regions of the brain, will be more effective in addressing the cognitive and behavioral impairments specific to each individual. Finally, identifying disparities between common interventions on measures of connectivity change may serve an evaluative purpose to teachers and parents trying to

determine which intervention to implement with a child. For these reasons, and those outlined in the review of relevant literature, more research is certainly warranted in the investigation of the relationship between ASD interventions and brain connectivity.

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