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Approval of the Psy.D. Dissertation

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Neural Effects of a Cognitive-Behavioral Social Skills Treatment on Gaze Processing in Children with Autism Spectrum Disorder

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ABSTRACT

NEURAL EFFECTS OF A COGNITIVE-BEHAVIORAL SOCIAL SKILLS TREATMENT ON GAZE PROCESSING IN CHILDREN WITH AUTISM SPECTRUM DISORDER

Karim Ibrahim, Doctor of Psychology, 2016

Dissertation Chaired by John Mehm, Ph.D.
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Social deficits are a hallmark of autism spectrum disorder (ASD) and have been associated with underactivity in brain regions important for social cognition. Social skills training using a cognitive-behavioral (CBT) approach has been shown to improve social behavior in children with ASD. However, little is known about the neural response to treatment. In the present study, we used functional MRI to examine the neural correlates of gaze processing in ASD following a CBT-based social skills group.

Verbally fluent children (ages 8-11) were randomized to CBT or a facilitated play comparison group. Behavioral assessments and fMRI were conducted at baseline, endpoint (12 weeks), and at a 3-month follow-up. While undergoing fMRI, children viewed images of emotionally expressive faces with either a direct or averted gaze. Regression analyses were conducted to evaluate the relationship between changes in brain activity and baseline participant characteristics, and to evaluate neural predictors and moderators of changes in social cognition and behavior.

Following treatment, the CBT group showed greater activity in the medial prefrontal cortex (MPFC) and ventrolateral prefrontal cortex (VLPFC) relative to

baseline. In contrast, the comparison group did not show any regions of increased activity post-intervention. When directly comparing the two groups, the CBT group showed greater increases in the MPFC, implicated in mentalizing, relative to comparison. Greater increases in MPFC and VLPFC activity following treatment were associated with older baseline age for the CBT group. Baseline activity in the FG predicted response to treatment. Specifically, children with greater baseline activation of the FG demonstrated improvements on measures of social competence including the social awareness subscale of the Social Responsiveness Scale and a social cognition composite.

Findings suggest that a cognitive-behavioral approach to social skills treatment may increase activity in social brain networks in verbally fluent children with ASD. In addition, children who demonstrated a more typical neural response to faces at baseline (i.e., increased FG activity) were responders to treatment. This study contributes to our understanding of the plasticity of networks involved in social cognition and neural biomarkers of treatment response.

NEURAL EFFECTS OF A COGNITIVE-BEHAVIORAL SOCIAL SKILLS TREATMENT ON GAZE PROCESSING IN CHILDREN WITH AUTISM SPECTRUM DISORDER

by

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DEDICATION

To every child with autism and their families—

Whose guidance and perseverance made this work possible, bringing encouragement and energy to each line written and analysis performed. It is my expectation that this research should, in some manner, bring light and hope to you and your families. You are our teachers as we strive to learn more about autism in anticipation of discovering a cure or treatment. For your patience during this arduous process, I thank you.

To Eric—

Your diligence and strength are commendable and inspiring. I will always remember what you have taught me.

To my family—

For all the beauty that you have brought to my life and all the journeys that you have walked alongside me—including this one.

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My first clinical experience was with Michael Powers, and it was captivating to observe his clinical expertise and thought process in working with children who have developmental disabilities. Michael is a brilliant clinician, who meets each patient with enthusiasm and energy. He has continually urged me to think critically and broadly, and to pursue a line of research inquiry that bridges the clinical and research worlds to benefit

the patient. His mentorship, advice, and friendship have been a vital part of my graduate experience.

I would also like to thank Jennifer Zarcone, who has played a pivotal role in fostering my enthusiasm and aptitude for scientific research. Her mentorship and friendship have propelled me during my graduate education, and her support during challenging moments was crucial in moving past obstacles. She has taught me the essence of research, and has been the pillars of my education and research. I feel privileged to be mentored by Jennifer, and am thankful for her longstanding camaraderie. She is an exceptional scientist, mentor, and friend.

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CHAPTER I

INTRODUCTION

Autism spectrum disorder (ASD) is a developmental disorder defined by a pervasive impairment in social functioning and communication, and the presence of repetitive, restricted and stereotypical behaviors and interests (American Psychiatric Association, 2013). Common behavioral symptoms include deficits in visual engagement (Jones & Klin, 2013), decreased ability to recognize emotion from faces and voices (Hobson, Ouston, & Lee, 1989; Rutherford, Baron-Cohen, & Wheelwright, 2002), and difficulty understanding the thoughts and intentions of others or theory of mind (Baron-Cohen, Leslie, & Frith, 1985; Senju, Southgate, White, & Frith, 2009). Further, impairments in social behavior impair functioning across many domains for individuals with ASD.

There is evidence that the core social deficits of ASD may be associated with atypical activity in regions of the brain involved in social cognition (Di Martino et al., 2009; Frith, 2001). In particular, data from neuroimaging studies have shown that activity in 'social brain' regions are hypoactive during tasks tapping into mentalizing (Kana, Keller, Cherkassky, Minshew, & Just, 2009; Lombardo, Chakrabarti, Bullmore, & Baron-Cohen, 2011; Pinkham, Hopfinger, Pelphrey, Piven, & Penn, 2008; Wang, Lee, Sigman, & Dapretto, 2007), face processing (Dalton et al., 2005; Hadjikhani, Joseph, Snyder, & Tager-Flusberg, 2007) and gaze processing (Davies, Dapretto, Sigman, Sepeta, & Bookheimer, 2011; Georgescu et al., 2013). Given that aberrant activation of regions implicated in social cognition is present during tasks requiring the evaluation of gaze and mentalizing abilities, it is possible that these two domains of deficits are linked in ASD.

That is, impairments in social cognition and gaze processing. However, activity of 'social brain' networks can be increased by enhancing the salience of social stimuli, suggesting the plasticity of networks involved in social cognition (Dalton et al., 2005; Pierce & Redcay, 2008; Wang et al., 2007). For example, Wang and colleagues (2007) showed that activation of the medial prefrontal cortex, implicated in mentalizing, increased when children with ASD were provided with explicit instructions to attend to social cues such as facial expression and tone of voice. Neuroimaging studies of treatment outcomes have also shown that neural networks implicated in social cognition are sensitive to change following both cognitive (Bolte et al., 2015) and behavioral interventions (Ventola et al., 2015).

Behavioral interventions for treating core ASD deficits integrating social skills training with a cognitive-behavioral approach have been shown to be effective in improving social competence for children with ASD (Reichow, Steiner, & Volkmar, 2012; Weitlauf et al., 2014). However, there is a need for a greater understanding of the neural mechanisms underlying behavioral change in response to treatment (Kasari, Shire, Factor, & McCracken, 2014). More work is also needed to provide randomized controlled trials with larger sample sizes and comparative treatment groups.

This study is part of a randomized, comparative trial that was conducted to evaluate the efficacy of a 12-week, social skills group for school-aged children with ASD (Soorya et al., 2015). Using a cognitive-behavioral approach, three skill areas were addressed that target ASD impairments: Nonverbal communication, Emotion recognition, and Theory of mind Training (Seaver-NETT program) (Soorya et al., 2015). Children in the cognitive-behavioral group showed significant gains in social behavior relative to

children in a facilitated play group. This was the largest randomized controlled trial conducted to date of group social skills training for ASD. Of interest is how social skills training alters activity in 'social brain' networks implicated in ASD.

In the present study, we investigated the neural effects of a group social skills intervention on gaze processing using functional magnetic resonance imaging (fMRI). A previously validated paradigm was used that taps into the targeted domains of emotion and processing faces with direct and averted gaze (Davies et al., 2011). We also examined maintenance data from a 3-month follow-up, and neural moderators and predictors of treatment response.

In this chapter, an overview of ASD is provided along with a review of social behavior and cognition deficits as well as the early symptoms of ASD. This is followed by a review of behavioral interventions addressing social deficits in ASD with particular attention to the studies employing a cognitive-behavioral approach to social skills groups. The chapter concludes with a detailed review of the neural bases of social cognition and gaze processing impairments in ASD, and aims of the current study.

Background

Social impairments are a primary deficit in ASD (American Psychiatric Association, 2013). Impairments in social communication and interaction may include diminished use of gestures and social gaze, difficulty coordinating social attention with others or joint attention, and failure to orient to spontaneous social stimuli (Dahlgren & Gillberg, 1989; Dawson et al., 2004; Loveland & Landry, 1986; Mundy, Sigman, & Kasari, 1990; Ornitz, Guthrie, & Farley, 1977). There is also strong evidence that genetic factors may be implicated in ASD where 10% to 20% of cases are accounted for by a

defined mutation, genetic syndrome, or *de novo* Copy Number Variation (see review by Abrahams & Geschwind, 2008).

Current revisions for ASD in the DSM-5 merged previously separate disorders into a single condition with different levels of symptom severity. Thus, ASD now encompasses the previous DSM-IV Autistic Disorder, Asperger's Disorder, Childhood Disintegrative Disorder, and Pervasive Developmental Disorder-Not Otherwise Specified (Table 1). The revised, single diagnostic category has been shown to have greater validity and to more accurately represent ASD symptoms (Frazier et al., 2012; Lecavalier, Gadow, DeVincent, Houts, & Edwards, 2009; Mandy, Charman, & Skuse, 2012).

About 70% of children with ASD meet criteria for other psychiatric disorders (Simonoff et al., 2008). The prevalence rate of comorbid disorders among children with ASD ranges from 27% to 42% for anxiety-related disorders, from 23% to 31% for Attention Deficit-Hyperactivity Disorder, from 7% to 30% for disruptive behavior disorders, and from 1% to 12% for mood disorders (Leyfer et al., 2006; Simonoff et al., 2008; van Steensel, Bogels, & de Bruin, 2013). In addition, behavioral problems are present in nearly 50% of children with ASD including aggression, noncompliance, tantrums, and self-injury (Farmer et al., 2015; Hartley, Sikora, & McCoy, 2008; Mazurek, Kanne, & Wodka, 2013), and sleep disorders are present in 50% to 86% of

Table 1

DSM-5 Criteria for Autism Spectrum Disorder

Must meet criteria A, B, C, and D:

A. Persistent deficits in social communication and social interaction across contexts, not accounted for by general developmental delays, and manifest by all 3 of the following:

1. Deficits in social-emotional reciprocity; ranging from abnormal social approach and failure of normal back and forth conversation through reduced sharing of interests, emotions, and affect and response to total lack of initiation of social interaction,
2. Deficits in nonverbal communicative behaviors used for social interaction; ranging from poorly integrated verbal and nonverbal communication, through abnormalities in eye contact and body language, or deficits in understanding and use of nonverbal communication, to total lack of facial expression or gestures.
3. Deficits in developing and maintaining relationships, appropriate to developmental level (beyond those with caregivers); ranging from difficulties adjusting behavior to suit different social contexts through difficulties in sharing imaginative play and in making friends to an apparent absence of interest in people

B. Restricted, repetitive patterns of behavior, interests, or activities as manifested by at least two of the following:

1. Stereotyped or repetitive speech, motor movements, or use of objects; (such as simple motor stereotypies, echolalia, repetitive use of objects, or idiosyncratic phrases)
2. Excessive adherence to routines, ritualized patterns of verbal or nonverbal behavior, or excessive resistance to change; (such as motoric rituals, insistence on same route or food, repetitive questioning or extreme distress at small changes).
3. Highly restricted, fixated interests that are abnormal in intensity or focus; (such as strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interests).
4. Hyper-or hypo-reactivity to sensory input or unusual interest in sensory aspects of environment; (such as apparent indifference to pain/heat/cold, adverse response to specific sounds or textures, excessive smelling or touching of objects, fascination with lights or spinning objects).

C. Symptoms must be present in early childhood (but may not become fully manifest until social demands exceed limited capacities)

D. Symptoms together limit and impair everyday functioning.

Note. Adapted from: Diagnostic and Statistical Manual of Mental Disorders, Fifth edition by the American Psychiatric Association (2013), Washington, DC: American Psychiatric Association, p. 50.

children with ASD (Doo & Wing, 2006; Liu, Hubbard, Fabes, & Adam, 2006; Mannion, Leader, & Healy, 2013; also see review by Richdale & Schreck, 2009).

Prevalence estimates of ASD have been increasing steadily over the last decade (see Table 2). Recent statistics from the Centers for Disease Control and Prevention (CDC) estimate an ASD prevalence of 1 out of every 68 children (14.7 per 1,000) in the U.S.A. with a male to female ratio of 4:1 (CDC, 2014), though this ratio approaches 1:1 for more severe cases of ASD (Fombonne, 2005; Rivet & Matson, 2011). Current prevalence estimates represent a 29% increase from 2008 in the U.S.A. (CDC, 2012).

Table 2

Prevalence Estimates of Autism Spectrum Disorders in the U.S. from 2000-2010

	Prevalence	
Year	per 1,000 children	1 in X children
2000	6.7	1 in 150
2002	6.6	1 in 150
2004	8.0	1 in 125
2006	9.0	1 in 110
2008	11.3	1 in 88
2010	14.7	1 in 68

Note. Adapted from the CDC (2014).

Overall increases in ASD prevalence rates have been reported both nationally and globally, with a current global prevalence rate of 7.6 per 1,000 (Baxter et al., 2015). It is challenging to ascertain the cause of such elevations, which may be attributed to improved community awareness and screening, increased documentation of developmental evaluation records, and the widening of diagnostic criteria (Elsabbagh et

al., 2012). For example, in the U.S., variation by state in ASD prevalence rates has been shown to be associated with educational spending, where a higher proportion of children diagnosed with ASD was correlated with greater education-related spending per pupil (Mandell & Palmer, 2005). Mandell and Palmer (2005) propose that the availability of better trained staff may lead to a greater awareness of ASD symptoms and referral for services. Prevalence rate estimates may also be influenced by the type of epidemiological data collected, which often tends to be from high-income developed countries (Elsabbagh et al., 2012), though one study found limited regional variation in ASD prevalence estimates (Baxter et al., 2015).

Deficits in Social Behavior and Cognition in ASD

A hallmark of ASD is a deficit in social and communication abilities that appears early in development (American Psychiatric Association, 2013). Leo Kanner (1943) first described the features of ASD in a paper detailing the account of 11 children who presented with a deficit in 'affective contact', which he reported as the "inability to relate themselves in the ordinary way to people and situations from the beginning of life" (p. 242). In this early paper, Kanner (1943) noted that the common primary pathology among the 11 children was an inability to relate to others or an 'autistic aloneness' in addition to other observed symptoms including language delays, an inability to develop social relationships, insistence on sameness, difficulty with the use language for social interchange, lack of reciprocity, and sensory sensitivities to everyday noises. In 1944, Hans Asperger published an account of four cases of "autistic psychopathy" describing children similar to those in Kanner's case description in terms of impairments in speech and non-verbal communication, and difficulty with social functioning. Later research

that was instrumental in identifying the early onset of autism symptoms included retrospective studies of home movies made during infancy of children later diagnosed with ASD and prospective studies examining infant siblings of children diagnosed with ASD.

Identifying the Early Onset of Social Deficits

Several retrospective studies were conducted that sought to understand the early onset of social impairments by examining home videos of infants prior to an ASD diagnosis. Data from these retrospective studies demonstrated that infants later diagnosed with ASD displayed reduced social orienting behaviors such as attending to faces and following another's pointing gesture (Osterling & Dawson, 1994; Werner, Dawson, Osterling, & Dinno, 2000). Early social behavior symptoms identified in home video studies that could distinguish children later diagnosed with ASD from typically developing children included impairments in joint attention (Mars, Mauk, & Dowrick, 1998; Osterling, Dawson, & Munson, 2002), diminished social gaze (Adrien et al., 1991; Adrien et al., 1993; Werner & Dawson, 2005), lack of a social smile (Adrien et al., 1991; Adrien et al., 1993), and reduced orienting toward social stimuli (e.g., looking at faces, orienting to name) (Baranek, 1999; Osterling & Dawson, 1994; Osterling et al., 2002; Werner & Dawson, 2005; Werner et al., 2000). Some studies reported a worsening of symptoms by the second year of life, particularly for impairments in social behavior (e.g., orienting to name and looking at the face of another person) and for impairments in goal-directed actions (Adrien et al., 1993; Losche, 1990; Werner & Dawson, 2005).

There is also evidence that diminished attention to social stimuli could be associated with a lack of preferential attention to biological motion early in development

in children with ASD (Annaz, Campbell, Coleman, Milne, & Swettenham, 2012; Klin, Lin, Gorrindo, Ramsay, & Jones, 2009; Klin, Shultz, & Jones, 2015). Responsiveness to biological motion serves a social-communicative role, as preferential attention to biological movement may provide the basis for social perception processes (Pavlova, 2012). Specifically, attention to biological movement may be involved in the interpretation of goal-directed actions of others and has been shown to be associated with activation of brain regions implicated in social behavior—in particular, the superior temporal sulcus (Frith & Frith, 1999; Pelphrey, Morris, & McCarthy, 2004; Shultz, Lee, Pelphrey, & McCarthy, 2011). In an elegant study by Klin and colleagues (2009), point light displays were used in upright and inverted orientations to examine whether preferential attention to biological motion is altered in children with ASD by 2 years of age. The ASD group showed no preferential attention to biological motion, although when a physical contingency was present such as clapping during the point light display, the ASD group showed significant preferential viewing, indicating a preference for non-social over social stimuli. This effect has also been shown in older children with ASD 3 to 7 years of age where they did not preferentially attend to point-light displays of biological motion compared to a scrambled animation; instead, greater preferential attention was found for a non-social stimulus (object animation) compared to biological movement (Annaz et al., 2012).

Studies have also been conducted that focused on the presence of autistic symptoms in younger siblings of children with ASD who do not have a diagnosis. These 'infant sibling' studies have contributed to our understanding of the early identification of ASD symptoms (see review by Rogers, 2009). Evidence from prospective familial

studies suggest that infants with at least one older sibling with ASD have an increased risk of later developing the disorder where the reported recurrence risk ranges from 3% to 18.7% (Chakrabarti & Fombonne, 2001; Jorde et al., 1991; Ozonoff et al., 2011; also see review by Wade, Prime, & Madigan, 2015). As early as the first or second years of life, infant siblings of children with ASD have been shown to demonstrate difficulties or abnormalities in social behavior including orienting to name, initiation of and response to joint attention (i.e., the use of gaze or gestures such as pointing to communicate about an object), imitation, and social affect (Cassel et al., 2007; see review by Wade et al., 2015; Zwaigenbaum et al., 2005). Delays in language development have also been found in siblings of children with ASD with poorer performance on measures of expressive and receptive language relative to siblings of typically developing children (Iverson & Wozniak, 2007; Yirmiya, Gamliel, Shaked, & Sigman, 2007; Zwaigenbaum et al., 2005). In addition, there is evidence that delays in communication and language may be associated with delays in motor development among infant siblings of children with ASD, which have been shown to manifest as early 3 to 6 months of age (Bhat, Galloway, & Landa, 2012; Landa & Garrett-Mayer, 2006; LeBarton & Iverson, 2013).

Overall, ASD is a complex disorder with a genetic component that negatively affects the developmental trajectory of children from a young age. Retrospective home video studies of children later diagnosed with ASD were precedents for later research by elucidating the early onset of symptoms in the domains of social behavior and communication. Prospective studies of infant siblings of children with ASD have also contributed to our understanding of the early emergence of symptoms. Another area of investigation involves the nature of social cognition deficits in ASD, particularly related

to the perception of others' mental states or theory of mind and the processing of eye gaze.

Theory of Mind Impairments in ASD

Many studies have found atypical performance during tasks tapping into social cognition in ASD, particularly 'theory of mind' or the ability to attribute mental states to oneself and others (Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001a; Brent, Rios, Happé, & Charman, 2004; Broekhof et al., 2015; Happe, 1993). The concept of theory of mind was introduced by Premack and Woodruff (1978) to predict and explain complex social behavior. The first evidence of mentalizing impairments in ASD comes from data showing that children with ASD fail the Sally-Anne false-belief task compared to preschool-age neurotypical children and a clinical group of children with Down syndrome of similar verbal abilities (Baron-Cohen et al., 1985). False-belief tests such as the Sally-Anne task assess the ability to comprehend the protagonist's mistake about an object due to its manipulation (e.g., moved or removed item). In order to assess the comprehension of false beliefs, one character (Sally) places a marble in a basket and leaves the room. In her absence, another character (Anne) moves the marble to a separate box and children are asked where Sally will look for her marble. Children are scored on their understanding that Sally's actions will be based on what she believes to be true (false-belief); that is, Sally will look in the basket, rather than the box, for the marble.

There is also evidence that some individuals with ASD, particularly those with higher verbal processing skills, are able to pass advanced mentalizing tasks (Bowler, 1992; Happe, 1993; O'Nions et al., 2014; Ozonoff, Pennington, & Rogers, 1991; Ozonoff, Rogers, & Pennington, 1991; for a review, see Senju, 2013). Second-order

theory of mind represents a type of higher-order mentalizing, which involves reasoning about what one person thinks about another person's thoughts. Senju and colleagues (2009) investigated the ability of adults with ASD to spontaneously understand the mental states of others by incorporating eye-tracking to monitor the anticipation of other's actions. While participants with ASD performed at the same level as the control group on verbally instructed, standard false-belief tests (i.e., Sally-Anne task and Strange Stories task), the ASD group did not show anticipatory looking behavior to the correct location of the character's actions on the basis of her false-beliefs compared to the control group (Senju et al., 2009). According to Senju and colleagues (2009), these findings suggest that people with ASD do not spontaneously attribute mental states to others, although they are able to do so during tasks with explicit instructions—perhaps, through relying upon cognitive strengths such as compensatory learning strategies. Overall, individuals with high-functioning ASD may have deficits predominately in implicit or intuitive mentalizing abilities, though they can succeed in understanding complex social scenarios by using logical inferences (Frith, 2004).

A particular area of difficulty for people with ASD is the understanding of others' intentions based on social information gathered from the eyes or gaze cues (Baron-Cohen, Campbell, Karmiloff-Smith, & Grant, 1995; see review by Nomi & Uddin, 2015b). In one of the earliest studies examining mentalization based on the eye region, Baron-Cohen et al. (1997) presented individuals with ASD with images of eyes depicting various emotional expressions and asked them to select the emotion conveyed. The ASD group performed poorly on this task relative to healthy controls. These findings were also replicated in a later study by the same group (Baron-Cohen et al., 2001a).

A review of behavioral studies investigating theory of mind in ASD suggest that impairments in gaze and face processing, such as deriving meaning from the eyes, may contribute to deficits in mentalizing and atypical perception of social cues (Itier & Batty, 2009). Several studies have sought to gain an understanding of the nature of gaze processing deficits in ASD, particularly as related to mentalizing abilities, both on a behavioral and neural level. We now turn to a pathology in eye and gaze processing that may be central to understanding the social interaction deficits observed in ASD.

Gaze Processing Impairments in ASD

Eye gaze is an essential aspect of social behavior and cognition that facilitates the expression of intimacy, threat, mutual attention, and interest (Csibra & Gergely, 2006; Kleinke, 1986). Sensitivity to gaze has been shown to emerge early in development (see review by Itier & Batty, 2009). As early as the first months of life, newborns show a preference for faces with direct gaze over those with averted gaze or closed eyes (Batki, Baron-Cohen, Wheelwright, Connellan, & Ahluwalia, 2000; Farroni, Csibra, Simion, & Johnson, 2002; Farroni, Massaccesi, Menon, & Johnson, 2007; Urakawa, Takamoto, Ishikawa, Ono, & Nishijo, 2014). By 4 months of age, enhanced neural processing for faces with mutual gaze appears (Farroni et al., 2002; Farroni, Johnson, & Csibra, 2004; Grossmann et al., 2008; Hoehl et al., 2009; Rigato, Farroni, & Johnson, 2010; Urakawa et al., 2014). During the first year, distinct neural mechanisms for the discrimination of facial expressions have been shown to emerge (Jessen & Grossmann, 2015; Rigato et al., 2010; Vanderwert et al., 2015). The ability to combine social information from emotional expressions and gaze direction in order to infer another person's goal appears

between 1 and 2 years of age (see reviews by Hoehl et al., 2009; Saxe, Carey, & Kanwisher, 2004).

It is well established that deficits in eye contact and gaze fixation patterns are common social impairments in ASD (Kanner, 1943; Klin, Jones, Schultz, Volkmar, & Cohen, 2002; see review by Senju & Johnson, 2009). Eye tracking studies have suggested that, relative to typically developing comparison groups, individuals with ASD show atypical visual scanpaths and fixation patterns characterized by reduced fixation on the eyes and a greater fixation on the nose and mouth (Dalton et al., 2005; Jones, Carr, & Klin, 2008). Results from eye-tracking studies propose that atypical fixation patterns may result from the active avoidance of eye gaze (Kliemann, Dziobek, Hatri, Baudewig, & Heekeren, 2012; Kliemann, Dziobek, Hatri, Steimke, & Heekeren, 2010; Tottenham et al., 2014), which could be due to negatively valenced hyperarousal when viewing a face with a mutual gaze.

Reduced attention to faces, specifically to the eyes, has been shown to occur early in development in ASD (Jones et al., 2008; Jones & Klin, 2013). Children with ASD as young as 2 years of age have been shown to fixate less on the eye region and more on the mouth relative to typically developing (TD) and developmentally delayed children (Jones et al., 2008). In a prospective study of 2- to 6-month-old infants later diagnosed with ASD, Jones and Klin (2013) demonstrated that at 2 months of age, eye fixation occurs at average levels compared to TD infants before declining to approximately half that of the TD group by 24 months of age. Importantly, these deficits in social eye gaze have significant consequences for the development of children with ASD. Specifically, mutual gaze, gaze following, and language acquisition are parts of a progressively more complex

social interaction that may be related to mentalizing abilities, which has its beginnings in eye contact with others (for a review, see Emery, 2000).

Several studies have shown that people with ASD exhibit atypical responses to gaze cues (for review see Senju, 2013; also see Senju & Johnson, 2009). In particular, slower reaction times and poorer accuracy has been reported during active viewing tasks when individuals with ASD are required to detect faces with a mutual gaze relative to an averted gaze (Dalton et al., 2005; Senju, Yaguchi, Tojo, & Hasegawa, 2003; Wallace, Coleman, Pascalis, & Bailey, 2006). One study showed that verbally fluent children with ASD were less accurate at imitating an actor's action when the gaze was direct versus averted (Vivanti et al., 2011). There is also evidence that children with ASD do not derive a benefit as typically developing children do from direct gaze cues. Direct gaze is a salient stimulus and studies have shown a greater sensitivity for mutual compared to averted gaze (Anstis, Mayhew, & Morley, 1969; von Grunau & Anston, 1995), or a gaze facilitation effect in typically developing children. Results suggest that individuals with ASD fail to exhibit a gaze facilitation effect when viewing emotional expressions (Akechi et al., 2009) and neutral expressions (Senju et al., 2003) with direct relative to averted gaze. However, one study did not find differences in performance between the ASD and typically developing group during a visual search paradigm of direct vs. averted gaze when viewing faces as well as the eye region only (Senju, Kikuchi, Hasegawa, Tojo, & Osanai, 2008). Senju and colleagues (2008) suggest that some individuals with ASD may rely upon alternative cognitive mechanisms to interpret social information rather than configural processing of faces.

Deficits in processing gaze in ASD may also be linked to broader deficits associated with social cognition such as the interpretation of the mental states and intentions of others (Baron-Cohen et al., 1995; Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001b). People with ASD are able to discriminate or perceive the direction of gaze and perform well on theory of mind tasks when attention is drawn to social cues and mental states (Bowler, 1992; Frith, 2004; for a review see Senju, 2013). However, the main difficulty may lie in the ability to spontaneously mentalize and extract relevant information from the eye region that is essential for social communication (Baron-Cohen et al., 1995; Baron-Cohen et al., 1997; Nation & Penny, 2008; Ristic et al., 2005; Senju et al., 2009).

Overall, it is well established that deficits in social behavior and social cognition attributed to autism have an early onset and are impairing for individuals with ASD. While deficits in processing gaze are common among individuals with ASD, few studies have focused on the neural bases of these impairments, especially as related to deficits in social perception processes such as mentalizing. More work is needed to understand the neural correlates of gaze processing impairments implicated in ASD.

Neural Correlates of Gaze and Social Cognition Impairments in ASD

Brain Regions Involved in Gaze Processing

On a neural systems level, fMRI studies have shown that processing gaze involves activation of occipito-temporal regions, particularly the banks along the superior temporal sulcus (STS) and the amygdala (see review by Allison, Puce, & McCarthy, 2000). Lesion studies have demonstrated that damage or removal of the STS region in macaques results in impairments in the ability to discriminate gaze direction (Eacott,

Heywood, Gross, & Cowey, 1993). Similar impairments in gaze processing are also found in humans with damage to the STS (Akiyama, Kato, Muramatsu, Saito, Nakachi, et al., 2006; Akiyama, Kato, Muramatsu, Saito, Umeda, et al., 2006) and support the notion that the STS plays a critical role in discriminating gaze direction. Several neuroimaging studies have shown that the STS is activated during the perception of gaze (Engell & Haxby, 2007; Hoffman & Haxby, 2000; Hooker et al., 2003; Puce, Allison, Bentin, Gore, & McCarthy, 1998; Wicker, Michel, Henaff, & Decety, 1998; Wicker, Perrett, Baron-Cohen, & Decety, 2003) and is sensitive to the detection of shifts in gaze (Pelphrey, Singerman, Allison, & McCarthy, 2003; Pelphrey, Viola, & McCarthy, 2004). In particular, the anterior region of the STS is associated with the coding of different gaze directions (Carlin, Calder, Kriegeskorte, Nili, & Rowe, 2011), while the posterior region of the STS is sensitive to intentionality conveyed by gaze or shifts in gaze (for a review, see Nummenmaa & Calder, 2009; Pelphrey, Morris, et al., 2004; Pelphrey, Singerman, et al., 2003). More broadly, the STS has also been implicated in the perception of biological motion (Pelphrey, Mitchell, et al., 2003; Pelphrey, Morris, Michelich, Allison, & McCarthy, 2005; Puce et al., 1998), especially when intentionality is signaled (Pelphrey, Morris, et al., 2004).

The amygdala also plays a central role in gaze processing (Adams, Gordon, Baird, Ambady, & Kleck, 2003; Kawashima et al., 1999; Sato, Yoshikawa, Kochiyama, & Matsumura, 2004). Bilateral damage to the amygdala has been associated with deficits in judgments of gaze direction and emotional expressions (Young et al., 1995), and suggests a role of the amygdala in modulating the perception of gaze. Some neuroimaging studies have found activation of the amygdala when viewing faces with a direct gaze relative to

an averted gaze (George, Driver, & Dolan, 2001; Kawashima et al., 1999; Sato et al., 2004). In contrast, other studies have reported amygdalar activation when viewing an averted compared to a direct gaze (Hooker et al., 2003; Wicker et al., 2003) as well as activation regardless of gaze direction (Adams et al., 2003; Wicker et al., 1998). A recent study using direct recordings from the amygdala of neurosurgical patients found significant activation of the amygdala when processing the identity of faces, but not when processing different gaze directions (Mormann et al., 2015). Based on these results, Mormann and colleagues (2015) suggest that the amygdala may play a role in the processing of identity rather than gaze. However, inconsistencies in gaze tasks used across studies make it difficult to interpret these discrepancies in amygdala activation. While these data demonstrate that the amygdala is involved in processing gaze, it is unclear if the amygdala response is modulated by gaze direction, identity, or the emotion elicited by a particular stimulus (Itier & Batty, 2009).

Activation of a ventral occipito-temporal region called the fusiform gyrus (FG), associated with face processing in general (Kanwisher, McDermott, & Chun, 1997), has been found in several gaze studies (Boyarskaya, Sebastian, Bauermann, Hecht, & Tuscher, 2015; Calder et al., 2002; George et al., 2001; Hooker et al., 2003; Madipakkam, Rothkirch, Guggenmos, Heinz, & Sterzer, 2015; Mosconi, Mack, McCarthy, & Pelphrey, 2005; Pageler et al., 2003; Wicker et al., 1998; Zurcher, Rogier, et al., 2013). However, there is evidence that the FG response may be mediated by invariant aspects of faces and identity rather than changeable facial features such as eye gaze (George et al., 1999; for a review, see Haxby, Hoffman, & Gobbini, 2000; Hoffman & Haxby, 2000; LaBar, Crupain, Voyvodic, & McCarthy, 2003; Sergent, Ohta, &

MacDonald, 1992). While the FG may contribute to gaze processing, it may not be directly involved in gaze discrimination. Deficits in the region of the FG are characteristic of prosopagnosia (De Renzi, Faglioni, Grossi, & Nichelli, 1991; Jonas et al., 2015) and result in impairments in face recognition while leaving the ability to judge gaze direction intact (Campbell, Heywood, Cowey, Regard, & Landis, 1990; Duchaine, Jenkins, Germine, & Calder, 2009). Thus, involvement of the FG during the perception of gaze could reflect enhanced attention to faces with gaze shifts or mutual gaze (Nummenmaa & Calder, 2009). Overall, it is uncertain if FG response is modulated by shifts in gaze since results are inconsistent across fMRI studies,.

There is also evidence that the perception of gaze recruits a wider network of frontal regions that are known to be associated with social cognition (Itier & Batty, 2009), particularly the medial prefrontal cortex (MPFC) and inferior frontal gyrus (IFG) (Nummenmaa & Calder, 2009). Involvement of the MPFC, implicated in theory of mind processes (Amodio & Frith, 2006), has been reported in neuroimaging studies examining gaze direction while viewing faces with emotional expressions (Hooker et al., 2003; Schilbach et al., 2006; Wicker et al., 2003), neutral expressions (Calder et al., 2002; Conty, N'Diaye, Tijus, & George, 2007; Kampe, Frith, & Frith, 2003; Wicker et al., 1998), and during gaze shift tasks (Mosconi et al., 2005; Williams, Waiter, Perra, Perrett, & Whiten, 2005). Some studies have also reported MPFC activation when viewing faces with a direct gaze (Bristow, Rees, & Frith, 2007; Conty et al., 2007; Georgescu et al., 2013; Kampe et al., 2003; Schilbach et al., 2006; von dem Hagen, Stoyanova, Rowe, Baron-Cohen, & Calder, 2014). However, several gaze processing studies have not found MPFC activation when viewing facial expressions (Davies et al., 2011; Engell &

Haxby, 2007; George et al., 2001; Hoffman & Haxby, 2000; Pitskel et al., 2011; Zurcher, Rogier, et al., 2013) as well as when viewing shifts in gaze (Dichter & Belger, 2007; Greene et al., 2011; Hietanen, Nummenmaa, Nyman, Parkkola, & Hamalainen, 2006; Kato et al., 2001; Pelphrey, Morris, & McCarthy, 2005; Vaidya et al., 2011). Activation of the IFG, implicated in emotion regulation and processing negative affect (Engell & Haxby, 2007; Hariri, Bookheimer, & Mazziotta, 2000; Kim et al., 2004; Ogai et al., 2003), has been found when participants viewed faces with different gaze directions (Davies et al., 2011; Engell & Haxby, 2007; Pitskel et al., 2011; Wicker et al., 1998; Zurcher, Rogier, et al., 2013) as well as during gaze shifts and cueing paradigms (Dichter & Belger, 2007; Engell et al., 2010; Greene et al., 2011; Hooker et al., 2003; Mosconi et al., 2005; Vaidya et al., 2011), with activation predominately in the right hemisphere. In summary, the involvement of mentalizing and emotion processing regions during gaze tasks could indicate the evaluation of meaning and intentionality from eye gaze.

Neuroimaging studies have contributed to our understanding of the involvement of neural networks in processing faces and gaze in typically developing individuals (Itier & Batty, 2009; Senju & Johnson, 2009). In contrast, atypical neural activity has been shown in ASD in areas implicated in social cognition or 'social brain' networks during gaze direction and gaze cueing tasks (Itier & Batty, 2009; Nomi & Uddin, 2015b). However, additional research is needed to fully comprehend the neural bases of eye gaze processing deficits in ASD. The following section reviews the autism neuroimaging literature relevant to deficits in gaze processing and social cognition more broadly.

Functional Abnormalities in Gaze and Social Cognition in ASD

Gaze processing. Numerous studies have sought to comprehend the neural bases of social perception impairments, though relatively few studies have focused on the neural correlates of gaze processing in ASD. Studies investigating the perception of gaze direction in ASD have utilized both passive and active paradigms. Passive tasks have involved passively viewing faces with different gaze directions displaying emotional expressions (Davies et al., 2011; Zurcher, Rogier, et al., 2013) and neutral expressions (Pitskel et al., 2011). Active paradigms have consisted of viewing animated videos of neutral faces displaying direct and averted gaze while making judgments of gender categorization (von dem Hagen et al., 2014) or likeability ratings (Georgescu et al., 2013). Behavioral findings from gaze direction studies using active paradigms show similar performance in accuracy (Pelphrey, Morris, & McCarthy, 2005; von dem Hagen et al., 2014; Wicker et al., 2008) and reaction time (Greene et al., 2011; Kliemann et al., 2012; Pelphrey, Morris, & McCarthy, 2005).

In spite of comparable performance at the behavioral level, neuroimaging studies suggest atypical neural activity in fronto-temporal and parietal regions implicated in social cognition in ASD. The right temporoparietal junction (TPJ), associated with mentalization (Lombardo et al., 2011), has been found to be underactivated in individuals with ASD during gaze processing tasks involving neutral faces with alternating gaze (Georgescu et al., 2013; Pitskel et al., 2011; von dem Hagen et al., 2014). While hypoactivation of the FG is often reported during the perception of emotion (Corbett et al., 2009; Critchley et al., 2000; Dalton et al., 2005; Pierce, Muller, Ambrose, Allen, & Courchesne, 2001; Piggot et al., 2004; Wang, Dapretto, Hariri, Sigman, & Bookheimer,

2004), particularly when viewing faces with negative affect (Pelphrey, Morris, McCarthy, & Labar, 2007; Perlman, Hudac, Pegors, Minshew, & Pelphrey, 2011), individuals with ASD show no differences in FG activation when processing changeable aspects of faces such as gaze. Other studies have found that high-functioning children and adults with ASD underactivate the amygdala during the perception of gaze when emotional expressions are involved (Kliemann et al., 2012; Tottenham et al., 2014; von dem Hagen et al., 2014) and during complex social tasks when making mentalistic inferences from the eye region and faces (Baron-Cohen et al., 1999b; Pinkham et al., 2008). Finally, reduced activation of the ventrolateral prefrontal cortex (VLPFC) has been reported during the perception of gaze (Davies et al., 2011; Zurcher, Donnelly, et al., 2013; Zurcher, Rogier, et al., 2013), which could result from a reduced salience of gaze cues. In an elegant study by Davies and colleagues (2011), children with ASD viewed emotionally expressive faces (e.g., angry, fearful, happy or neutral) with either a direct or averted gaze. Relative to a typically developing group, the ASD group showed hypoactivity in the VLFPC when viewing faces with a direct gaze and negative emotions. Taken together, the data suggest aberrant neural processing of gaze in ASD, which may be associated with broader deficits in social perception.

Results from neuroimaging studies suggest atypical differential activation when viewing faces with direct and averted gaze. There is evidence that individuals with ASD show greater activation in 'social brain' regions (e.g., TPJ, MPFC, FG, and amygdala) for averted compared to direct gaze, while TD individuals show the opposite pattern (Nomi & Uddin, 2015b). When individuals with ASD attend to direct vs. averted gaze, hypoactivation has been reported in regions including in the posterior STS (Georgescu et

al., 2013), IFG (Davies et al., 2011; Pitskel et al., 2011), and anterior insula (Pitskel et al., 2011) compared with TD individuals. Two studies reported equivalent activation for faces with a direct and averted gaze for the ASD group, in contrast to the TD group that showed greater activation in frontal and temporal regions for direct vs. averted gaze (Davies et al., 2011; von dem Hagen et al., 2014). These findings may indicate that individuals with ASD lack sensitivity to gaze direction cues given the results indicating differential neural response in TD groups.

Taken together, studies in ASD have consistently shown functional abnormalities during gaze tasks within regions of the 'social brain'. Deficits in processing gaze may be associated with impairments in mentalizing—specifically, in the ability to extract pertinent information for social communication from the face and eye region (see reviews by: Itier & Batty, 2009; Nation & Penny, 2008). In support of this notion, some gaze studies have found hypoactivation of the MPFC, involved in theory of mind processes (see reviews by: Amodio & Frith, 2006; Frith & Frith, 1999; Frith & Frith, 2006; Frith, 2001; Gallagher & Frith, 2003; Saxe et al., 2004; Van Overwalle, 2011), when individuals with ASD were prompted to attend to the eye region (Georgescu et al., 2013; von dem Hagen et al., 2014). Aberrant MPFC activity has also been reported during complex mentalizing tasks when high-functioning children and adults with ASD are prompted to infer the feeling states and intentions of others during social stories (Happe et al., 1996; O'Nions et al., 2014; Wang et al., 2007), view animations (Castelli, Frith, Happe, & Frith, 2002; Kana et al., 2009), and make evaluative judgments of a person's emotional state (Baron-Cohen et al., 1999a; Kana, Patriquin, Black, Channell, & Wicker, 2015; Kennedy & Courchesne, 2008; Pierce, Haist, Sedaghat, & Courchesne, 2004;

Silani et al., 2008). Given that the MPFC is involved in top-down biasing of information as socially relevant (Frith & Frith, 2012), atypical activation of this region during mentalizing and gaze tasks may indicate that broader deficits in social cognition could be linked to deficits in gaze processing in ASD, particularly in deriving the goal-directed intentions or saliency from gaze cues.

Social cognition. Many studies have sought to understand the neural bases of social deficits in ASD. Neuroimaging data suggest that impairments in social perception processes may be linked to hypoactivity of regions implicated in social cognition during the perception of faces and mental states (see meta-analysis by Di Martino et al., 2009; Dichter, 2012; Frith, 2001; also see Philip et al., 2012).

Aberrant activity in prefrontal and temporal areas has been shown when individuals with ASD view faces with different expressions. Underactivation of the FG is commonly found when individuals with ASD view faces with neutral and emotional expressions (for a review, see Grelotti, Gauthier, & Schultz, 2002; Nomi & Uddin, 2015b). Several studies have also found abnormal activation of the STS (Hadjikhani et al., 2007; Pelphrey et al., 2007; Pierce et al., 2004; Pierce et al., 2001) and VLPFC (Bookheimer, Wang, Scott, Sigman, & Dapretto, 2008; Davies et al., 2011; Hadjikhani et al., 2007; Ogai et al., 2003) during the perception of faces in ASD. When attention is drawn to affect, individuals with ASD have been shown to underactivate the amygdala (Baron-Cohen et al., 1999b; Corbett et al., 2009; Critchley et al., 2000). Given that the amygdala is associated with processing salient information from faces (Adolphs, 2010; Davis & Whalen, 2001; Fitzgerald, Angstadt, Jelsone, Nathan, & Phan, 2006),

hypoactivation of this region during face processing tasks may indicate decreased salience of social cues in ASD.

Data from neuroimaging studies suggest that emotion perception impairments in ASD are more pronounced during implicit rather than explicit processing of affect from faces (Bolte et al., 2015; Castelli et al., 2002; Kana et al., 2015; Piggot et al., 2004; Silani et al., 2008; Wang et al., 2004). Implicit processing of emotional information is considered to be automatic or unconscious, while explicit processing involves the deliberate evaluation of social stimuli using cognitive strategies. Two studies investigating the neural substrates of affect in ASD have found reduced activation of social brain regions, specifically the MPFC and STS, during implicit processing of emotional expressions (i.e., object judgments, gender categorization), with no differential activation between TD and ASD groups for explicit processing (i.e., labeling affect) (Bolte et al., 2015; Kana et al., 2015). Other studies have found hypoactivation of temporal regions involved in salience detection and face perception including the amygdala (Bolte et al., 2015; Critchley et al., 2000; Wang et al., 2004) and FG (Bolte et al., 2015; Piggot et al., 2004; Wang et al., 2004), respectively, during implicit tasks of emotion matching and gender categorization compared to explicit tasks of affect labeling. These fMRI results suggest that explicit emotional processing may be less impaired than implicit processing in verbally fluent people with ASD, possibly due to reliance upon cognitive strengths.

During theory of mind tasks, aberrant activation has been found in fronto-temporal regions implicated in social cognition. Hypoactivation of the right TPJ was reported during mental state attribution tasks when viewing animated shapes (Castelli et

al., 2002) and making self-reflective judgments (Lombardo et al., 2011). During mentalizing tasks, individuals with ASD have also been shown to underactivate the VLPFC (Kana et al., 2009; Pinkham et al., 2008) and STS (Saitovitch et al., 2012; Zilbovicius et al., 2006). Moreover, aberrant STS activity may have effects on a range of social deficits associated with ASD due to its connections with other areas of the 'social brain' including the FG, prefrontal regions, and amygdala (see review by Saitovitch et al., 2012; Zilbovicius et al., 2006). Of interest is how underactivity in regions of the social brain can be enhanced in individuals with ASD, particularly by using behavioral approaches to increase the saliency of social cues in the environment.

Neural Mechanisms of Plasticity: Enhancing Activity in Social Brain Networks

Data from neuroimaging studies offer promising results suggesting the plasticity of neural networks in response to experience and learning in ASD. There is emerging evidence that regions of the 'social brain' network can exhibit more typical patterns of activity when the salience of core social information is increased for people with ASD. Studies have examined hypotheses related to social deficits and change in neural activity by fixating gaze on a particular facial feature such as the eyes, providing verbal prompts as well as explicit performance demands to attend to social stimuli, and through cognitive training.

When cognitive processing is enabled, such as viewing a familiar or personally significant face, increased activation has been shown in temporal regions, particularly the FG and amygdala (Pierce et al., 2004; Pierce & Redcay, 2008). Equivalent activation of the FG has been reported in ASD and TD groups when increasing the relevance of facial features through challenging task demands such as identity matching of inverted faces vs.

upright faces (Bookheimer et al., 2008) or by viewing familiar vs. stranger faces (Pierce & Redcay, 2008). Altering gaze fixation patterns in ASD by cueing visual attention to the face and eye region have also shown comparable activity in the FG (Hadjikhani et al., 2004; Hadjikhani et al., 2007; Perlman et al., 2011) and amygdala (Kliemann et al., 2012; Tottenham et al., 2014) relative to controls. In a study that examined gaze manipulation to enhance activity of the face processing network, Perlman and colleagues (2011) found that activation of the right FG increased to levels equivalent to that of a TD group when the scanpath of adults with ASD was manipulated to focus on the eye region. Taken together, these results suggest that directing gaze or enhancing visual fixation to salient features of a face may modulate activity of face processing networks and possibly normalize activation of face and emotion sensitive regions to approach levels equivalent to typically developing comparison groups.

Similarly, when attention to social cues is increased through prompting, activity in the MPFC—a central node in the mentalizing network—has been found to approach typical patterns in children and adults with ASD. In a previous study, we used a mentalizing task of irony scenarios to examine the neural circuitry underlying impairments in interpreting communicative intent (Wang et al., 2007). Prompts to attend to social cues were provided in the form of neutral instructions (i.e., "pay attention") or explicit instructions (i.e., "pay attention to the facial expression" or "tone of voice"). In the absence of explicit instructions, the ASD group showed hypoactivity in the MPFC for ironic vs. non-ironic cartoons relative to the TD group. However, when explicit social prompts were given, the ASD group showed a significant increase in MPFC activity that closely resembled patterns of activity in the TD group. In line with these findings,

Zurcher and colleagues (2013) reported that directing visual attention towards the eyes through prompting and altering facial features (i.e., inverting eyes and mouth) increased activity in the MPFC in adults with ASD that was equivalent to a TD group. Another study found that MPFC activation increased following cognitive training for emotion recognition in adults with ASD relative to an ASD control group (Bolte et al., 2015). Overall, these results suggest that activity in social cognitive regions can be increased when attention is drawn to salient social cues and emphasizes the effect of training-induced plasticity of social brain networks.

Neuroimaging studies of treatment-related neural changes in children and adults with ASD are rare, but offer initial evidence that neural networks are sensitive to change (Ventola, Oosting, Anderson, & Pelphrey, 2013). Alterations in neural activity have been demonstrated in young children with ASD in response to ABA-based early intensive behavioral interventions including ESDM (Dawson et al., 2012) and Pivotal Response Treatment (PRT), a naturalistic intervention approach (Ventola et al., 2015; Voos et al., 2013). In a recent study, Ventola et al. (2015) examined the neural outcomes of PRT for 10 preschool-aged children with ASD. Following treatment, neural responses of children in the PRT group were more similar to those of the TD group in the reward system network including the ventral striatum and putamen, and in subcortical regions associated with relaying information and regulating the flow of stimulation including the amygdala, thalamus, and hippocampus. Changes on a neural level have also been shown in adolescents with ASD following the Program for the Education and Enrichment of Relational Skills (Van Hecke et al., 2015), a naturalistic social skills treatment focused on friendship training. For adults with ASD, one study found treatment-related neural

changes following an 8-week computerized cognitive training program to enhance attention to facial features and affect recognition (Bolte et al., 2015). Bolte and colleagues (2015) reported increased activation in 'social brain' regions including the MPFC, FG, amygdala and posterior STS pre- to post-intervention for the ASD group that received cognitive training compared to a control ASD group.

Taken together, there is compelling evidence that by directing attention to salient social cues and through the use of cognitive approaches, activity in 'social brain' regions is sensitive to change. This information could contribute to the development of personalized interventions and the discovery of biomarkers to guide treatment delivery and predict treatment response. While several studies have sought to understand gaze fixation patterns in ASD and the manipulation of gaze towards the face and eyes, few studies are intervention-based. Even though results from the existing intervention studies offer preliminary evidence on the neural substrates of treatment response, more work is needed to provide randomized controlled trials that incorporate a comparative, active treatment group to fully understand the specificity of treatment effects. This would offer a greater understanding of the underlying neural mechanisms of treatment response for core social deficits in ASD (see review by Kasari et al., 2014).

Given the pervasive nature of social deficits in ASD, a related area of research involves the development and identification of effective behavioral interventions for targeting core social deficits and associated symptoms or conditions. A specific type of intervention addressing core deficits or 'social skills training' often addresses areas of difficulty including making eye contact, theory of mind, and emotion recognition and

regulation among children with ASD. In the next section, we describe behavioral interventions targeting social deficits.

Behavioral Interventions for ASD

According to the 2013 goals of the Interagency Autism Coordinating Committee (IACC), a theme in current research is to "[investigate and develop] interventions that are effective for reducing both core and associated symptoms, for building adaptive skills, and for maximizing quality of life and health for people with ASD" (p. 53). Empirically supported treatments for ASD include early intensive behavioral interventions that are based on Applied Behavioral Analysis (ABA), which involves discrete trial training that is focused on obtaining specific, desired responses by breaking skills down and using a progressive, structured approach (Lovaas, Koegel, Simmons, & Long, 1973; Vismara & Rogers, 2010). Two well-established ABA-based early interventions include the University of California Los Angeles/Lovaas method (Lovaas et al., 1973) and the Early Start Denver Model (ESDM), which was developed by Rogers and Dawson (2010) and uses a naturalistic approach to promote skill acquisition. While early intensive behavioral interventions may have moderate effects on cognitive abilities, language, and adaptive living skills, the evidence is mixed for their impact on ASD core symptoms and severity (see review by Weitlauf et al., 2014).

For school-aged children with ASD, the use of social skills groups has been shown to promote the acquisition of social communication skills in the context of peer interactions (Dawson & Burner, 2011; Williams White, Keonig, & Scahill, 2007). Social skills training is based upon behavioral and social learning techniques, and involves teaching and practicing specific social skills in naturalistic as well as in hypothetical

situations (Spence, 2003). Common skill areas addressed include perspective taking, initiating and maintaining conversations, non-verbal communication, interpretation of non-literal language, and social problem solving (see review by Bellini & Peters, 2008; Cappadocia & Weiss, 2011). A recent meta-analysis by Reichow and colleagues (2012) offers support for the role of social skills groups in improving social competence and friendship quality, as well as decreasing feelings of loneliness for individuals with ASD. In addition, social skills interventions that incorporate a parent component (e.g., psychoeducation, parent training, or supportive psychotherapy) have shown improvements on measures of social competence (Cappadocia & Weiss, 2011).

Overall, the development of targeted and personalized intervention is a key long-term goal of autism research according to the IACC 2013 strategic plan. Further, the identification of the active ingredients of an intervention is an integral part of developing a personalized medicine approach for children with ASD. Studies investigating outcomes sensitive to intervention components, such as delivery or dose of treatment, will help to elucidate for whom a particular treatment approach is most beneficial. While there are different types of approaches targeting social deficits in ASD and identifying a best fit treatment for a specific child with ASD remains a challenge, one intervention that has promising results involves the use of a cognitive-behavioral approach for social skills training. Interventions using a cognitive-behavioral approach integrate the teaching of social perception processes with behavioral strategies to reinforce the acquisition of skills.

Cognitive-Behavioral Interventions for ASD Social Deficits

Cognitive-behavioral therapy (CBT) is an evidence-based treatment that teaches

emotion regulation and problem-solving skills (Beck, 2011). Interventions that use a cognitive-behavioral approach typically place an emphasis on structured strategies, learning principles, and social strategies that could lead to changes in thinking, feeling, and behavior (Kendall, 2006). In the format of outpatient psychotherapy, CBT has been used extensively and has received empirical support for the treatment of child mental health conditions broadly (James, James, Cowdrey, Soler, & Choke, 2015; Sukhodolsky, Smith, McCauley, Ibrahim, & Piasecka, 2016; Walkup et al., 2008). A cognitive-behavioral approach has also been used with children who have ASD to target associated behaviors and conditions including aggression (Scarpa & Reyes, 2011; Sofronoff, Attwood, Hinton, & Levin, 2007), obsessive-compulsive behavior (Elliott & Fitzsimons, 2014; Lehmkuhl, Storch, Bodfish, & Geffken, 2008; Murray, Jassi, Mataix-Cols, Barrow, & Krebs, 2015; Vause, Neil, Jaksic, Jackiewicz, & Feldman, 2015), and anxiety (McNally Keehn, Lincoln, Brown, & Chavira, 2013; Storch et al., 2015; Wood et al., 2015). However, more work is needed to understand the efficacy of a cognitive-behavioral approach for treating core social deficits in ASD.

Few studies have been conducted that used a control or comparison group design to explore the efficacy of cognitive-behavioral interventions (CBI) when integrated within social skills groups. CBIs typically provide a multifaceted approach for treating social deficits related to social competence and cognition. A basic assumption of CBIs is that social perception processes can be taught cognitively and influence behavior (Hart & Morgan, 1993). This principle is optimized in social skills interventions by using both "top-down" and "bottom-up" approaches. In combination, these approaches provide strategies for learning and scaffolding social skills, and for building an implicit awareness

of social cues through social problem solving and training in social perception (Spence, 2003). The existing studies examining CBIs in the format of social skills groups have reported gains in social functioning among individuals with ASD (DeRosier, Swick, Davis, McMillen, & Matthews, 2011; Lopata et al., 2010; Soorya et al., 2015), including greater social knowledge (Koning, Magill-Evans, Volden, & Dick, 2013; Lopata et al., 2010) and increases in social problem solving abilities (Solomon, Goodlin-Jones, & Anders, 2004). However, data is limited in terms of the number of CBI social skills studies providing independent or blinded evaluations of outcome measures, the use of standardized measures for social outcomes, and data on maintenance.

Studies investigating CBIs for social deficits using a control or comparative group examined outcomes related to social behavior and social cognition processes. For social behavior, three randomized controlled trials (RCTs) measured outcomes using the SRS (Constantino, 2005), a standardized measure of ASD symptoms and severity of social impairment, and reported significant post-treatment gains for the CBI group compared to either a control or comparative group (DeRosier et al., 2011; Lopata et al., 2010; Soorya et al., 2015). One study did not find significant changes in SRS scores at endpoint for children with ASD relative to a control group, though only boys were included in this study (Koning et al., 2013). One RCT did not assess social behavior outcomes (Baghdadli et al., 2013) and another RCT reported gains in social problem solving on a standardized measure (Solomon et al., 2004).

For social cognition, no significant change was reported in emotion recognition abilities following treatment in three CBI RCTs (Baghdadli et al., 2013; Lopata et al., 2010; Soorya et al., 2015), although one RCT found significant gains in the recognition

of adult and child facial expressions post-treatment for the CBI group (Solomon et al., 2004). In line with these results, a meta-analysis of social skills groups for ASD showed a lack of significant differences between treatment and control groups in relation to emotion recognition outcomes in the context of social skills training (Reichow et al., 2012). Another area of focus for CBIs in the domain of social cognition is theory of mind or mentalizing abilities. However, most CBI RCTs did not measure mentalizing skills using well-validated child-assessments of social cognition, which limits the available data on social cognition outcomes from CBIs. Of the CBI studies reviewed here, two RCTs examined mentalizing outcomes using validated measures and both reported a lack of significant gains in mentalizing (Solomon et al., 2004; Soorya et al., 2015). In addition, a recent meta-analysis found a lack of generalization of mentalizing skills to novel contexts following interventions that address theory of mind impairments in ASD (Fletcher-Watson, McConnell, Manola, & McConachie, 2014).

While there are various tools for assessing social abilities, the lack of consensus on appropriate measures for social cognition and social behavior makes it difficult to compare and generalize outcomes across studies. Discrepant results related to social behavior and social cognition outcomes make it difficult to ascertain the impact of CBI-based studies on these domains. In addition, the number of CBI-based studies addressing social skills deficits that have incorporated a randomized, controlled design is limited. The majority of studies used pre-post intervention designs (Bauminger, 2002; Bauminger, 2007; Cotugno, 2009; Crooke, Hendrix, & Rachman, 2008; Lopata, Thomeer, Volker, & Nida, 2006; Lopata, Thomeer, Volker, Nida, & Lee, 2008; Stichter et al., 2010; Tse, Strulovitch, Tagalakis, Meng, & Fombonne, 2007), which hinders any understanding of

an intervention's efficacy due to methodological limitations, such as the lack of a control group. To date, only five CBI studies employed an RCT approach.

While evidence supports the use of social skills groups for improving social competence among individuals with ASD (Reichow et al., 2012), CBI-studies using an RCT approach range in sample size from 14 to 69 and only three were comparative treatment trials. Thus, there is still a need for more RCTs with adequate sample size and with a comparative treatment group (for a review and recommendations, see Kasari et al., 2014), which is important for controlling for nonspecific therapeutic factors such as attention and parent perceptions of the credibility of a treatment (for a systematic review, see Jensen, Weersing, Hoagwood, & Goldman, 2005). To the best of our knowledge, three CBI studies employed a comparative treatment group (Baghdadli et al., 2013; DeRosier et al., 2011; Soorya et al., 2015). In one of the largest CBI comparative trials conducted using standardized measures of social behavior, DeRosier and colleagues (2011) adapted a social skills intervention for youths ages 8 to 12 with ASD (SS-GRIN-HFA) that addressed communication, working with others, friendship skills, and community-based activities to promote generalization. Compared to children with ASD who received an unmodified version of the intervention, improvements in social competence were reported based on the SRS. However, the lack of dual treatment outcomes for social behavior and cognition makes it difficult to fully understand changes that may have occurred in social perception after treatment.

In the largest CBI randomized, comparative trial to date of social skills groups, Soorya and colleagues (2015) examined dual treatment outcomes of social behavior and cognition. Children with ASD were randomized to a CBI condition that addressed

Nonverbal communication, Emotion recognition, and Theory of Mind Training (Seaver-NETT) or a facilitated play group. Children in the CBI group improved significantly on a social behavior composite measure relative to the comparison group at endpoint, though changes on a social cognition composite did not reach statistical significance. Verbal IQ was found to moderate changes in social behavior, where higher verbal IQ scores were associated with significant gains in social behavior for the CBI group only. Age approached significance as a moderator of social behavior outcomes for the CBI group, where older age was associated with greater improvement in social behavior outcomes.

The lack of generalization data from CBI-based studies makes it difficult to ascertain the gains in social skills to other naturalistic environments beyond the research or clinic setting. To address this concern, some studies have examined generalization using naturalistic settings. One study assessed the generalization of skills using an interaction task with a peer confederate and reported improvements following treatment (Koning et al., 2013). DeRosier et al. (2011) incorporated community-based activities to promote the generalization of skills to naturalistic environments, though no specific assessment was used to examine changes in social behavior within other settings.

Overall, social skills interventions are a promising treatment for social deficits related to ASD (Bellini & Peters, 2008; Kasari et al., 2014; Krasny, Williams, Provencal, & Ozonoff, 2003; Williams White et al., 2007). Further, there is evidence to support the use of a cognitive-behavioral approach to social skills training that may promote positive gains in social competence and improve the quality of social interactions for individuals with ASD (Cappadocia & Weiss, 2011). A greater understanding of the neural mechanisms of treatment-related changes in social functioning would provide both

exciting and critically important information for understanding the potential of interventions to activate different networks and for identifying biomarkers of treatment response. Combined, information about neural substrates and biomarkers of treatment response could be valuable for ascertaining subgroups of children with ASD for whom a particular treatment approach would be most advantageous (Kasari et al., 2014). Given the challenge in addressing social cognition impairments through behavioral interventions, results from neuroimaging studies could also provide insights into our understanding of networks involved in social perception to inform treatments targeting deficits in social cognition.

Study Aims and Hypotheses

The current study investigates the neural effects of social skills groups for children with ASD and builds upon prior research by addressing methodological limitations. Given the support for social skills groups to improve social competence (for a meta-analysis, see Reichow et al., 2012; Weitlauf et al., 2014), a randomized, comparative trial was conducted as part of a larger study to evaluate the efficacy of a group cognitive-behavioral treatment for social deficits in school-aged children with ASD. The 12-session CBI curriculum addressed 3 skill areas known to be impaired in ASD: Nonverbal communication, Emotion recognition, and Theory of mind Training (Seaver-NETT; Soorya et al., 2015). Results from the clinical outcomes of this study showed that children in the CBI group made significant gains in social behavior compared to a child-directed play group (comparison) (Soorya et al., 2015). This was the largest randomized comparative trial conducted to date of a social skills intervention for

ASD. Of interest is how social skills training alters activity in 'social brain' networks implicated in ASD.

The primary aim of this study was to investigate the neural effects of a cognitive-behavioral approach to treating social deficits on networks implicated in processing gaze and emotion. We sought to understand the neural mechanisms of response to social skills training by employing an fMRI approach and a previously validated face processing task of emotional expressions with direct and averted gaze (Davies et al., 2011). Based on our prior findings of increased MPFC activity when explicit instructions to attend to social cues were given to children with ASD (Wang et al., 2007) as well as data from neuroimaging studies that suggest plasticity of networks in ASD when social information is signaled, we hypothesized that children randomized to the CBT group would show increased activity in regions important for social cognition following treatment. Based on the research described earlier, candidate regions for showing treatment effects at endpoint (i.e., increased activation) were areas of the brain implicated in social perception processes including the VLPFC and MPFC. Using the same task tapping into gaze and face processing, children with ASD showed hypoactivation in the VLPFC when viewing negative emotions relative to a TD group (Davies et al., 2011). Thus, we predicted that the cognitive-behavioral group would show increased activation in the VLPFC relative to the comparison group pre- to post-treatment. In contrast, we predicted that children randomized to the comparison group would show little to no change in activity in these 'social brain' networks relative to the CBT group at endpoint. In the larger clinical sample, children in the cognitive-behavioral group made significant gains on a composite measure of social behavior post-intervention relative to the comparison

group (Soorya et al., 2015). Thus, we focused our analyses on composite measures used in the larger clinical study addressing social behavior and cognition. Given that maintenance data is greatly needed, we also sought to examine changes in brain activity at a 3-month follow-up.

A second aim was to identify neural predictors and moderators of treatment response. We also evaluated baseline participant characteristics including age as potential moderators of changes in brain activity. In the larger clinical trial, age and verbal IQ moderated the treatment response for the cognitive-behavioral group (Soorya et al., 2015), whereby higher baseline verbal ability was associated with greater improvements in social behavior. Given this finding, we predicted an association between similar characteristics, particularly age and verbal abilities, and change in activity within 'social brain' regions relevant to this gaze task (e.g., MPFC, VLPFC).

CHAPTER II

METHODS

Participants

Participants were recruited from the Mount Sinai Medical Center and affiliate institutions, autism parent support groups, advertisements in local papers, and referrals from the Seaver Autism Center clinic. Each participant's parent(s) provided informed consent according to specifications by the Institutional Review Board at the Ichan School of Medicine at Mount Sinai (see Appendix A). Each child provided assent. The current study draws on data collected from a larger project examining the effect of a 12-week randomized CBT intervention targeting social behavior and the neural correlates of social cognition (Soorya et al., 2015). Permission to analyze this data was obtained from the University of Hartford's Human Subjects Committee (see Appendix B).

Sixty-nine verbally fluent children with ASD (age range: 8-12; $M = 9.9$ years; $SD = 1.2$ years; 57 male and 12 female) were randomized to either a 12-week CBT social skills group (treatment) or a facilitated play group (comparison) (Soorya et al., 2015). Inclusion criteria were as follows: (1) 8 to 11 years of age at the time of consent; (2) meet criteria for ASD according to a psychological interview (DSM-IV), the Autism Diagnostic Observation Schedule–Generic (Lord et al., 2000), and the Autism Diagnostic Interview–Revised (Rutter, Le Couteur, & Lord, 2003); and (3) have a Verbal IQ above 70, as measured by the Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV; Wechsler, 2003). Participants were excluded if they: (1) had a history of psychiatric or neurological disorders other than ASD (e.g., seizure disorder); (2) began any new psychotropic medication or other therapeutic intervention (e.g., behavior, speech) within

30 days prior to the groups that would confound the evaluation of the social skills treatment; (3) had gross structural abnormality present in the brain (e.g., aneurysm); or (4) history of head trauma or loss of consciousness.

Of the 69 children randomized in the clinical trial conducted by Soorya and colleagues (2015), 24 participants have high-quality fMRI data both pre- and post-treatment on the gaze and emotion processing task described below (see fMRI Activation Paradigm for task details and Figure 1 for CONSORT). Our imaging sample included 3 girls and 21 boys. Children were also characterized using the Social Responsiveness Scale (Constantino, 2005) and the Vineland Adaptive Behavior Scales (Sparrow, Cicchetti, & Balla, 2005). Table 3 shows demographic and characterization information for participants. Full inclusion criteria and treatment outcomes are reported by Soorya et al. (2015).

Participants completed fMRI tasks at baseline and following treatment (12-weeks). A total of 13 participants had high-quality fMRI scan data at a 3-month maintenance evaluation (7 in the CBT group and 6 in the comparison group). Full details on participants excluded for the follow-up interval are described below.

For baseline characteristics, *t* tests were used to examine potential differences between the 24 participants randomized to CBT vs. facilitated play, which showed that there were no significant differences between groups in terms of age, IQ, and symptom severity. Independent samples *t* tests were also performed to compare baseline characteristics between participants who were included in and excluded from the final imaging analysis, which showed that there was a marginally significant difference in age between groups, $t(66) = -2.0$, $p = 0.049$. Children included in the final imaging analysis

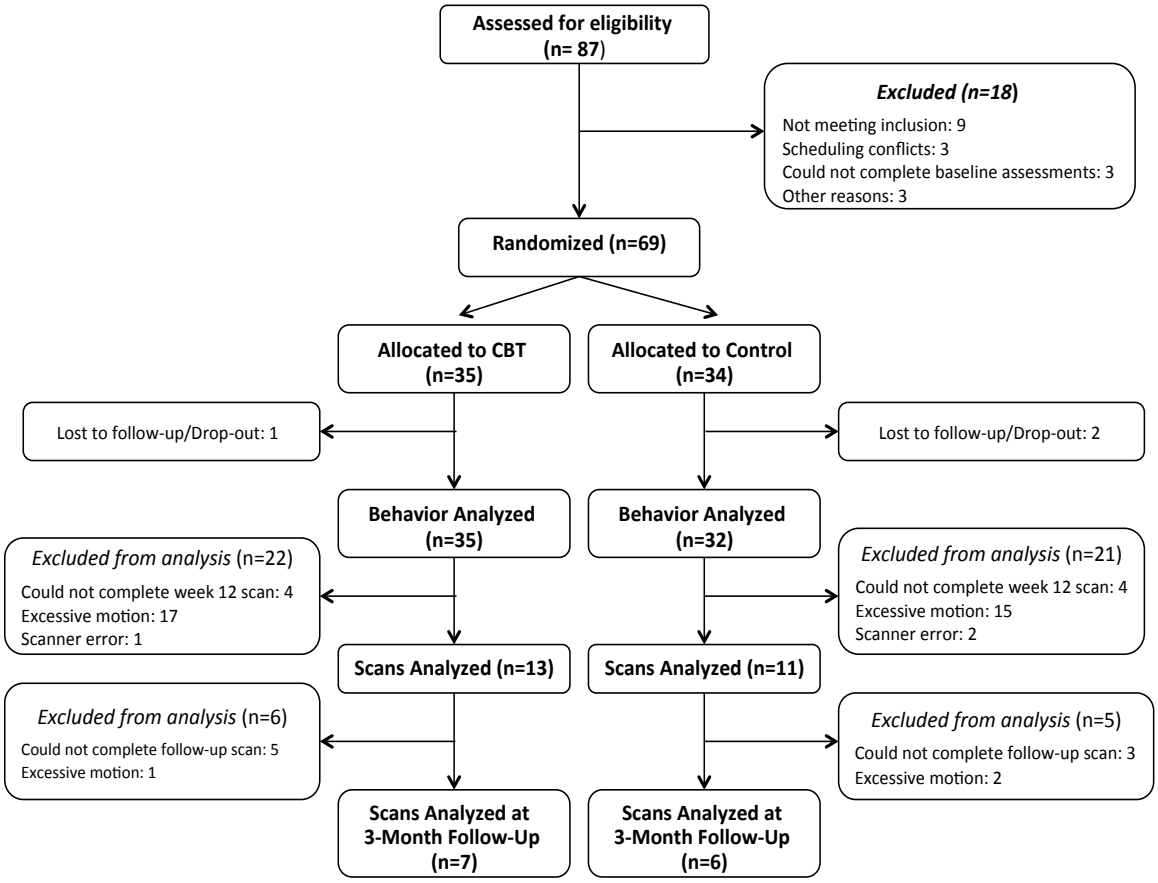

Figure 1. CONSORT diagram displaying the progress of participants through the trial.

(*M* = 10.2 years; *SD* = 1.3) were on average six months older than the excluded participants (*M* = 9.6 years, *SD* = 1.2). Included and excluded participants did not differ significantly in IQ or ASD symptom severity.

Ethnicity data obtained from caregiver reports indicate an ethnically diverse sample for the 24 participants included in the neuroimaging analysis: 13 participants (54%) were Caucasian, 5 (21%) were African-American, 4 (17%) were Hispanic, 1 (4%) was Asian, and 1 (4%) was of mixed ethnicity. Of the 24 participants, 2 (8%) were on stable doses of ADHD stimulant medication, 3 (12%) on ADHD nonstimulant, medication, and 2 (8%) on antidepressant medication.

Table 3

Participant Demographics and Characterization Data

	CBT (*n* = 13) Mean (*SD*)	**Comparison** (*n* = 11) Mean (*SD*)	**Excluded from fMRI analysis** (*n* = 45) Mean (*SD*)
Age in years	10.5 (1.3)	9.9 (1.2)	9.6 (1.2)
Full Scale IQ	103.1 (19.1)	95.5 (20.6)	91.6 (14.9)
Verbal IQ	106.5 (19.1)	96.7 (17.0)	94.6 (13.6)
Nonverbal IQ	105.7 (16.1)	96.4 (15.8)	101.4 (16.3)
Vineland Adaptive Behavior Composite	77.8 (10.9)	76.7 (8.7)	81.3 (10.2)
SRS Total Score	78.5 (12.8)	74.7 (11.4)	82.1 (12.2)
ADOS Module 3 Total	11.1 (4.2)	11.0 (4.6)	11.4 (4.5)

Note. SRS = Social Responsiveness Scale; ADOS =Autism Diagnostic Observation Schedule, ASD cutoff = 7.

Social Skills Interventions

Participants were randomized to either the social skills treatment group (CBT) or a child-directed play-group (Comparison). The CBT-based social skills program

addressed the following core social-communicative impairments in ASD: Nonverbal communication, Emotion recognition, and Theory of mind Training (Seaver NETT). Participants randomized to the comparison condition received a child-directed, play-based curriculum in which group leaders followed participants' interests and suggestions for games.

Both groups met weekly for 90 minutes and consisted of four to six participants, in addition to two to three therapists (e.g., one psychologist and one or two program assistants in order to maintain a 1:2 therapist to child ratio). Concurrently with child sessions, a parent component was incorporated which was psychoeducational or supportive for the CBT or comparison group, respectively. Behavioral assessments and fMRI tasks (discussed below) were administered at baseline, three months, and at a 3-month follow-up.

Treatment Condition: CBT

Typical session components for the CBT group included the following: (1) circle time or greeting period, (2) skill review, (3) introduction of new target skill, (4) free play, and (5) snack and prizes. A token-exchange system was used in which points were used to earn a weekly reinforcer at the end of each session. Teaching methods included providing concrete steps, role-playing, assigning homework, personalized reinforcement schedules, visual supports, and generalization training.

The CBT social skills program incorporated three, 4-week modules**.** Module 1 focused on nonverbal communication including active listening and social referencing (i.e., following eye gaze and checking facial expressions and gestures of others). Children practiced using their gaze direction, facial expression, and/or gestures to

communicate their intent to others. In addition, sessions addressed synchronization of affect and actions to develop empathy and connection with others (Gustein & Sheely, 2002). Module 2 activities focused on emotion recognition. Skills during Module 2 addressed recognition of emotion in others (e.g., facial expression, tone of voice, and gestures), communication of feelings with others, and appropriate responses during various social situations. Module 3 focused on Theory of Mind training and targeted the ability to comprehend the communicative intent behind non-literal remarks. Module 3 also addressed perspective taking and utilized thought bubbles to visually represent another person's cognition (Kerr & Durkin, 2004; Wellman et al., 2002). During each session, a psychoeducational parent component was incorporated. This consisted of reviewing the homework from the previous week, addressing any concerns or difficulties encountered by parents, and discussing strategies for overcoming those challenges. Parent informational handouts were also provided, along with suggestions for the generalization of skills into the home environment and everyday life.

Comparison Group: Facilitated Play

The comparison group was tailored to incorporate child-led play that was based on the interests of group members. Therapists established "stations" to promote object play (e.g., LEGO and board games), motor/tactile activities (e.g., drawing), and dramatic play. Session components for the control condition included: (1) circle or greeting time; (2) game, activity, or talk time; (3) free play; and (4) snacks and prizes. A token-exchange system was not implemented, though children were allowed to choose a small prize at the end of each session. During each session, a concurrent parent group was provided, which was supportive in nature and facilitated by a therapist.

Measures

Participants were administered behavioral assessments and underwent an fMRI scan at baseline, post-treatment, and at a 3-month follow-up. Parent-rated measures of social behavior were collected in addition to child-based assessments of social cognition, particularly for emotion recognition and theory of mind. For the larger behavioral study, a principal components analysis (PCA) with varimax (orthogonal) rotation was conducted to develop composite scores for the dual treatment targets of social behavior and social cognition (Soorya et al., 2015). PCA was used as a means to reduce the occurrence of type I errors associated with modeling numerous tests separately as well as with multiple comparisons, and to reduce measurement errors. Raw subscale scores of each measure were entered into the factor analysis to develop empirically based groupings. Variables with high factor loadings for subscales were retained. Social behavior and social cognition composites measures were constructed based upon well-validated measures of social relationships, nonverbal communication, empathy, emotion recognition, and perspective taking.

Social behavior composite. The resulting social behavior composite included the following: Diagnostic Analysis of Nonverbal Accuracy-2 (DANVA-2; Nowicki & Duke, 2003), Reading the Mind in the Eyes Test, Child Version, (RMET; Baron-Cohen et al., 2001a), and the mentalizing scale of the Strange Stories Task (Brent, Rios, Happe, & Charman, 2004). Lower scores on the social behavior composite indicate better social relationships, nonverbal communication, and empathy.

Social cognition composite. The resulting social cognition composite included th.e following tests/subscales: Children's Communication Checklist-2 (CCC-2; Bishop,

2003) social relations subscale, CCC-2 nonverbal subscale, and Griffith Empathy Scale (Dadds et al., 2008) total. Higher scores on the social cognition composite indicate better emotion recognition and perspective taking.

fMRI Activation Paradigm

All children underwent an event-related fMRI task where they viewed 160 photographs of emotionally expressive faces, which was adapted from a previously validated task (Davies et al., 2011). While undergoing fMRI, children viewed faces from the NimStim Face Stimulus Set (Tottenham et al., 2009) that depicted expressions of anger, fear, disgust or a neutral expression (see Figure 2). Half of the faces displayed a direct eye gaze towards the participant, while half of the faces were modified to display an averted eye gaze towards the participant's left or right. The order of faces was determined using an optimized random sequence (Wager & Nichols, 2003). Alternate versions of each set of emotions were employed so that participants would not receive identical activation runs at each time point (e.g., baseline, end of treatment, and follow-up). Stimulus faces were presented in a pseudo-random order for 2 s each and were preceded with fixation crosses to the eyes to ensure that children were attending to the eye region. Null events were included in order to increase the statistical efficiency (Dale, 1999), which consisted of fixation crosses situated in the center of a blank screen for 2 s each. Null events were distributed pseudo-randomly throughout each run and were modeled as a separate condition. Participants were instructed to simply observe the faces.

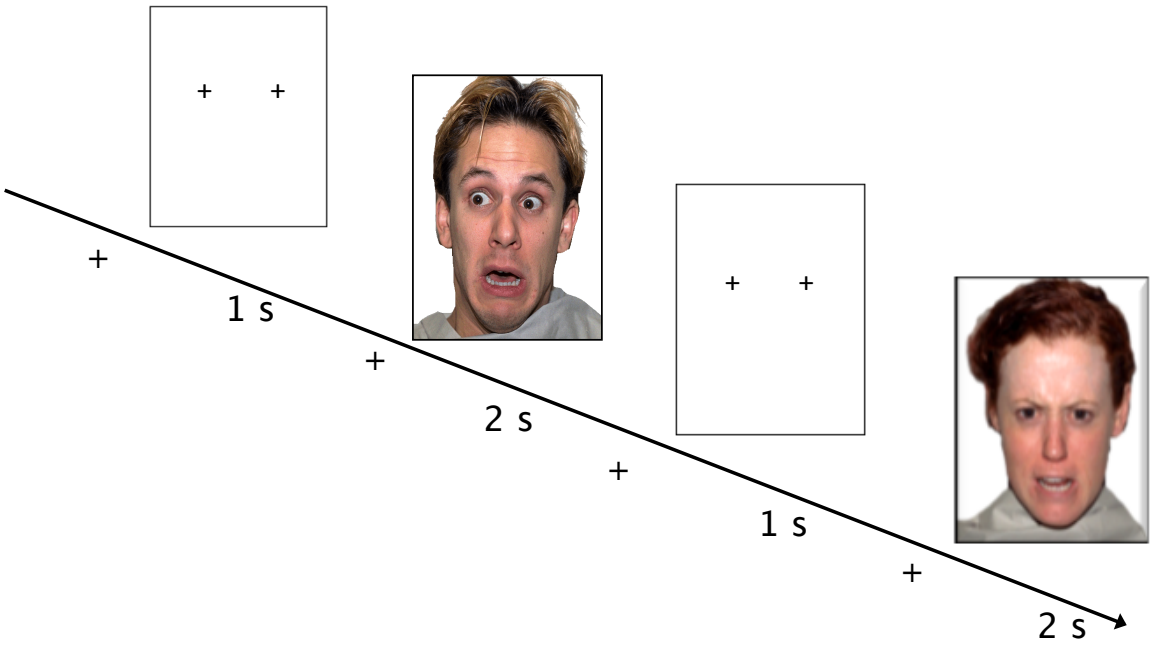

Figure 2. fMRI task sequence and eye gaze paradigm. Stimulus faces were preceded by fixation crosses in which participants viewed 160 photographs of emotional faces. Faces were presented for 2 s each and preceded by 1s fixation crosses. Faces depicted four emotions: fearful, angry, neutral, or disgusted. Faces displayed either a direct or averted eye gaze.

fMRI Data Acquisition Parameters

Imaging was performed using a Siemens Allegra 3 Tesla scanner with an Acoustic Nuclear Magnetic Resonance (ANMR) upgrade for echoplanar images (EPI). A T2-weighted high-resolution anatomical scan was obtained for each participant for co-registration purposes: repetition time (TR), 5000 ms; echo time (TE), 33 ms; matrix size 128 x 128; field of view (FOV), 20 cm. For each participant, 216 interleaved, whole-brain functional volumes were collected in the axial plane parallel to the intercommissural (AC-PC) line using an EPI gradient echo sequence: TR, 2.5 s; TE, 25 ms; slice thickness, 3 mm/1 mm gap; flip angle, 90°; matrix size 64 x 64; FOV, 21 cm.

Statistical Analysis

Behavioral data analysis. Behavioral outcomes for the social behavior and cognition composite measures were analyzed using general linear mixed models (SAS/ STAT software, version 9.4). Mixed models were used to examine the longitudinal effect of treatment condition on composite measures and moderation analyses. Participants were included if at least two time points of valid data were available. All effects are reported as significant at $p < 0.05$.

Neuroimaging analysis. Neuroimaging statistical analyses were conducted with SPM5 (Wellcome Department of Cognitive Neurology, London, England; http://www.fil.ion.ucl.ac.uk/spm). Functional images were realigned to correct for head motion, spatially normalized to Montreal Neurological Institute (MNI) space for intersubject averaging (Woods, Dapretto, Sicotte, Toga, & Mazziotta, 1999), and spatially smoothed using an 8 mm full-width half-maximum Gaussian kernel. For each participant's functional run, any volume that exceeded a difference of 3mm/deg from the

first volume or 2mm/deg between successive volumes were identified and removed (i.e., "scrubbed"). Participants with less than 85% of volumes retained after scrubbing were excluded from the final analysis. For the 24 participants with baseline and 12-week scans analyzed, 5 participants had volumes removed (2 in the CBT group and 3 in the comparison group). For the three-month follow-up, 7 participants were lost to follow-up and 4 participants were excluded due to excessive motion. Of the 13 participants included in the follow-up analysis, 4 participants' runs were subjected to scrubbing. Following motion correction and data scrubbing, we performed independent samples *t* tests to compare subject movement for the CBT vs. comparison groups. There were no significant differences between the CBT and comparison groups for mean amount of head motion (see Table 4). To remove any artifactual signal changes due to head motion, spatial realignment parameters were included as regressors of no interest in the model.

For each participant, condition effects were estimated according to the General Linear Model, using a canonical hemodynamic response function. Functional MRI measures local changes in the proportion of oxygenated blood in the brain (e.g., the Blood Oxygen Level Dependent or BOLD signal). This proportion changes in response to neural activity. Therefore, the BOLD signal or the hemodynamic response indicates the location and magnitude of neural activity.

The effect of time was modeled at the single-subject level and a one-sample *t*-test was applied to examine differences from baseline to endpoint within each group. Between-group differences were examined using a 2-sample independent *t*-test within regions where activation was detected in either group. The threshold for significance was set at a voxel-wise uncorrected $p < 0.01$ (two-tailed), with a cluster threshold of 71

contiguous functional voxels. This yielded an overall corrected threshold of $p < 0.05$, as determined by a Monte Carlo simulation (Forman et al., 1995). An inclusive mask was applied for second-level analyses, which was accomplished by creating an image file for each group at baseline and endpoint consisting of activity across all gaze conditions vs. rest ($p < 0.05$, uncorrected, and 50 contiguous voxels) and combining these images to create the mask. For the post-intervention interval, one sample and two sample *t*-tests were used as described above to examine differences from baseline and endpoint to the 3-month follow-up within each group and for between group differences, respectively. In addition, to examine changes in neural activity that were associated with treatment-related changes on measures of social functioning, we conducted a regression between changes in social behavior and social cognition composite scores (Soorya et al., 2015) and changes in brain activation following treatment.

Table 4

Mean Amount of Head Movement for CBT and Comparison Groups

	Interval	Translational motion (mm) mean (SE)	Rotational motion (deg) mean (SE)
CBT	Baseline	0.289 (0.0422)	0.331 (0.0387)
	Endpoint	0.363 (0.0823)	0.359 (0.0733)
Comparison	Baseline	0.246 (0.0382)	0.341 (0.0705)
	Endpoint	0.377 (0.0791)	0.401 (0.0706)

Note. Based on $n = 13$ participants in the CBT group and $n = 11$ participants in the comparison group.

Moderators of neural treatment outcomes. Regression analyses were conducted to evaluate the relationship between participant characteristics and changes in brain activity pre- to post-intervention. Participant characteristics used in the regression analysis included chronological age and verbal abilities. Verbal abilities were measured by verbal IQ composite scores.

Neural predictors and moderators of treatment outcomes. Regression analyses were also conducted to evaluate the relationship between baseline brain activity and changes in social cognition and behavior. We examined baseline neural activity as a predictor and moderator of treatment response across both groups and within each group, respectively.

CHAPTER III

RESULTS

Behavioral Results

Consistent with the larger behavioral study (Soorya et al., 2015), for participants retained in the neuroimaging analyses (n = 24), results of linear mixed model regression analyses showed a significant group by time interaction for the social behavior composite. This reflected a significant improvement in ratings of social competence for the CBT group following treatment (p = 0.0189), whereas the comparison group did not show significant change (Figure 3). There were no significant main effects or interactions for the social cognition composite. There were also no significant correlations with baseline participant characteristics, including verbal IQ and age, and changes in social behavior and cognition composite scores. However, for the larger clinical trial, verbal IQ moderated improvements on the social behavior composite for the CBT group (Soorya et al., 2015). That is, children who had greater verbal processing abilities showed the greatest gains in social behavior (i.e., a decrease in the social behavior composite score) following treatment. In addition, age approached significance as a moderator of social behavior in the larger clinical cohort.

For the follow-up interval (n = 24), linear mixed model analyses indicated no significant group x time interaction effect for social behavior and social cognition composite scores. Overall, the significant gains made in social behavior outcomes at endpoint were not maintained at the 3-month follow-up.

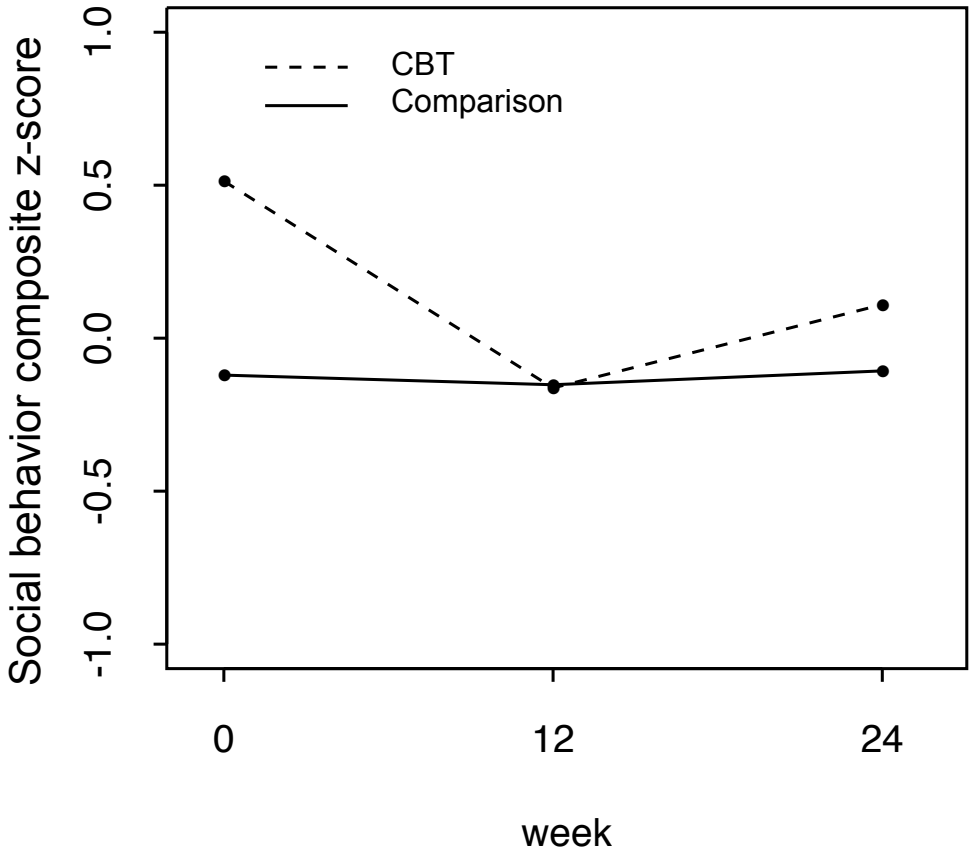

Figure 3. Changes in social behavior scores for CBT and comparison groups following treatment. A significant Group x Time interaction was found for the social behavior composite immediately following treatment (week 12). There was no significant Group x Time interaction at follow-up (week 24) for the social behavior composite. Decreasing scores on the social behavior composite measure reflect an improvement in performance.

Neuroimaging Results

Within-Group Effects

We first examined changes in brain activity from pre- to post-treatment within each group. Following treatment, children in the CBT group showed greater activity in prefrontal networks implicated in Theory of Mind and emotion regulation including the MPFC and VLPFC, respectively, relative to baseline for both direct and averted gaze conditions (see Figure 4). Greater activity was also observed in regions associated with visual and emotion processing (e.g., occipital cortex, cingulate gyrus), frontotemporal networks (e.g., precentral and postcentral gyri, right middle temporal gyrus), and subcortical regions including the left caudate, bilateral putamen, and right thalamus. In contrast, children in the comparison group (n = 11) did not show any significant changes in activity at endpoint. Peak coordinates are shown in Table 5.

Between-Group Effects

Our core hypotheses centered on identifying the neural effects of CBT relative to a comparative play group in areas implicated in social cognition. Therefore, we examined changes in brain activity between both groups (N = 24) following treatment (CBT vs. comparison for pre- vs. post-treatment). When viewing faces with a direct and averted gaze, children in the CBT group showed greater changes in activity relative to the comparison group in regions associated with reasoning about others' intentions (MPFC), emotion processing (e.g., cingulate gyrus, insula), and frontal networks (e.g., left middle frontal gyrus) (see Figure 5). Peak coordinates are shown in Table 6. In contrast, there were no significant areas of greater change in activity for the Comparison versus CBT contrast.

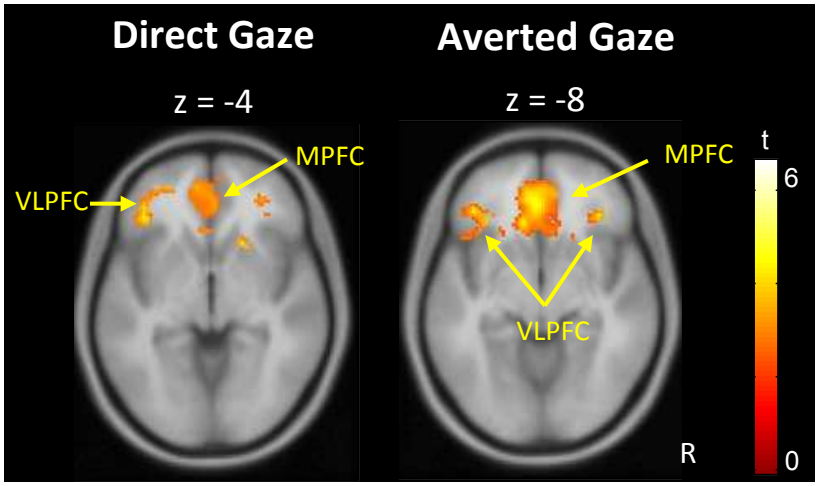

Figure 4. Within group changes in activity for the CBT group following treatment. Children in the CBT group showed greater activity in the MPFC and VLPFC relative to baseline when viewing faces with a direct gaze (left) and averted gaze (right) following treatment. In contrast, children in the comparison group did not show any regions of increased activity post- versus pre-treatment. Images are thresholded at $t > 2.68$, volume = 568 mm^3, $p < 0.05$, corrected.

Table 5

Peaks of Activation While Viewing Faces With a Direct Gaze and Averted Gaze for CBT (post > pre)

Region	BA	H	Direct Gaze				Averted Gaze				Averted > Direct			
			x	*y*	*z*	*t*	*x*	*y*	*z*	*t*	*x*	*y*	*z*	*t*
MPFC	9	L	-2	56	36	5.27	-12	58	34	3.92				
	9	R					14	44	18	5.15				
	8	L	-12	42	46	5.24								
	10	R	14	54	14	5.15	10	62	14	4.21				
	10	L	-10	44	-12	4.08	-12	50	8	3.16				
	11	L	-2	38	-10	3.78	-2	40	-10	5.72				
	11	R					10	40	-14	4.54				
VLPFC	47	L	-40	34	-4	4.30	-38	32	-4	5.80				
	47	R					36	34	-8	4.65				
Anterior cingulate gyrus	32	L	-10	32	28	3.74								
	32	R	8	30	24	3.90	10	42	6	3.80				
	24	L	-8	38	14	4.20	-10	36	14	5.45				
	24	R	8	28	14	3.99	8	30	8	3.83				
Posterior cingulate gyrus	23	L					-12	-34	32	5.73				
	23	R					4	-58	16	3.72				
	31	L					-24	-36	30	3.69				
		L					-28	10	18	4.49	-34	20	26	3.29
Insula	44	L					-42	14	12	4.32				
Inferior frontal gyrus	6	L	-34	4	56	6.55								
Middle frontal gyrus	8	L	-26	22	46	5.04								
	9	L					-42	34	26	3.50				
	10	L	-34	48	2	4.81	-32	56	6	3.37				
	10	R	40	54	8	5.52								
Superior frontal gyrus	6	L	-12	16	62	4.23	-12	16	62	6.61				
	9	R	24	48	34	4.96								

(continued)

Table 5 (continued)

			Direct Gaze				Averted Gaze				Averted > Direct			
Region	BA	H	*x*	*y*	*z*	*t*	*x*	*y*	*z*	*t*	*x*	*y*	*z*	*t*
Precentral gyrus	4	L					-32	-16	46	7.52	-30	-16	44	3.73
	6	L									-38	-12	36	3.78
Postcentral gyrus	1	L					-52	-22	54	3.15				
Precuneus	7	L	-10	-54	72	5.27	-10	-56	72	5.65				
	7	R	2	-52	64	3.64	2	-52	64	3.30				
Middle temporal gyrus	39	R	38	-66	30	4.22	40	-64	28	4.30				
Globus pallidus		L					-16	4	4	4.62				
Putamen		L					-24	10	0	4.32				
		R	20	18	-2	4.11	20	18	-2	4.55				
Caudate							-8	24	-2	4.6				
Thalamus		R					26	-26	6	3.59				
Cuneus	18	R	2	-94	20	3.99								
Middle occipital gyrus	18	L					-18	-98	16	3.80				
	18	L	-18	-98	16	3.56	22	-86	16	5.22				
Superior occipital gyrus	19	R	32	-88	24	4.15	32	-88	24	4.92				
	19	L					-22	-88	30	4.29				
Cerebellum		L	-24	-80	-24	3.26	-20	-80	-22	3.99				

Note: BA = probable Brodmann area; H = hemisphere; L and R = left and right hemispheres, respectively; *x*, *y*, and *z* = the Montreal Neurological Institute coordinates corresponding to the left-right, anterior-posterior, and inferior-superior axes, respectively; *t* = the highest *t*-score within a region. The threshold of significance was set at $p < 0.05$ corrected for multiple comparisons at the cluster level and $p < 0.01$ corrected for multiple comparisons at the voxel level.

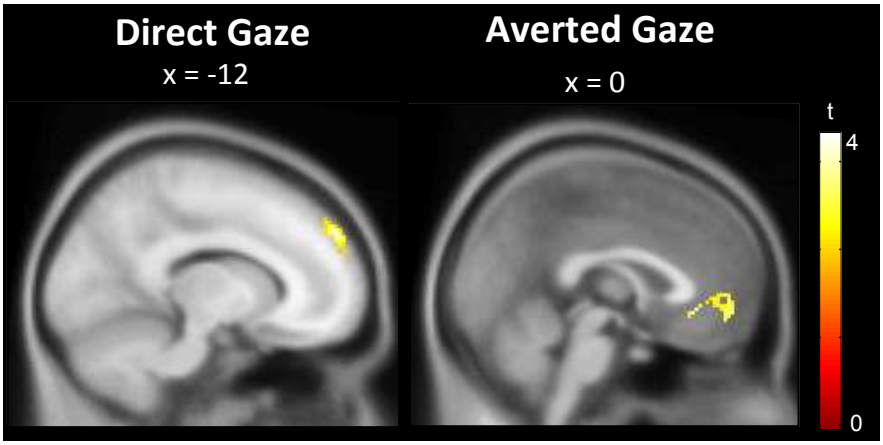

Figure 5. Between group changes in activity for CBT versus comparison groups from baseline to post-treatment. The CBT group showed greater changes in MPFC activity following treatment when processing faces with a direct gaze (left) and averted gaze (right) relative to the comparison group. There were no areas in which the comparison group showed more changes in activity relative to the CBT group. Images are thresholded at $t > 2.51$, volume = 568 mm^3, $p < 0.05$, corrected.

Table 6

Observed Peaks for CBT versus Comparison Groups (post > pre) for Faces With Averted and Direct Gaze

			Direct Gaze				Averted Gaze			
	BA	H	*x*	*y*	*z*	*t*	*x*	*y*	*z*	*t*
MPFC	9	L	-12	56	36	4.85				
	8	L	-8	46	46	3.11				
	11	L					-2	50	-14	3.39
	10						0	52	-4	3.56
Middle frontal gyrus	10	L	-22	56	22	3.24				
Anterior cingulate gyrus	32						0	32	-8	3.92
Insula	13	L					-32	-8	12	3.05
Claustrum		L					-26	8	18	4.28

Note: BA = probable Brodmann area; H = hemisphere; L and R = left and right hemispheres, respectively; *x*, *y*, and *z* = the Montreal Neurological Institute coordinates corresponding to the left-right, anterior-posterior, and inferior-superior axes, respectively; *t* = the highest t-score within a region. The threshold of significance was set at $p < 0.05$ corrected for multiple comparisons at the cluster level and $p < 0.01$ corrected for multiple comparisons at the voxel level.

When we examined changes in differential activation for the two gaze conditions within each group, the direct>averted gaze contrast showed no significant changes following treatment in either group. For the contrast averted>direct gaze, there was a significant increase in activation for the CBT group only in the precentral gyrus and insula (peak coordinates are shown in Table 5). No significant between-group differences were found for changes in activity following treatment for the contrasts direct>averted and averted>direct.

Three-Month Follow-Up

We examined changes in brain activity within each group at the 3-month follow-up (n = 7 for CBT and n = 6 for comparison). Analyses showed an increase in activation in subcortical regions (caudate) from baseline to follow-up for the CBT group for direct gaze, which may suggest that changes in neural activity were not maintained at the three-month follow-up timepoint for children in the CBT group (peak coordinates are shown in Table 7). However, null findings related to changes in social cognitive regions may also reflect a lack of power given the small sample size for follow-up. For the comparison group, analyses showed an increase in activation in regions implicated in emotion (cingulate gyrus, insula) as well as temporal (middle temporal gyrus) and occipital regions for direct gaze. No significant between-group differences were found for changes in activity from baseline to follow-up.

Moderators of Neural Treatment Outcomes

We assessed the relationship between participant characteristics and changes in neural activity following treatment. For the CBT group only (n = 13), regression analyses revealed that there was a significant correlation between older age and increased activity in the right MPFC pre- to post-treatment for the CBT group. Age was also significantly correlated with increased activity in the right VLPFC post-treatment for the CBT group (Figure 6). Older age was associated greater changes in activation pre- to post-intervention in regions implicated in emotion (anterior cingulate gyrus, anterior insula), and bilateral middle frontal gyrus. Peak coordinates for these regions are shown in Table 8. Overall, this indicates that older children demonstrated greater changes in neural activity.

Table 7

Peaks of Activation for the CBT and Play Groups for the Direct Gaze Condition at the Three-Month Maintenance Timepoint (follow-up > pre)

Region	BA	H	*x*	*y*	*z*	*t*
CBT						
Caudate		L	-4	22	-2	5.38
Play						
Middle temporal gyrus	39	R	38	-44	30	2.52
		L	-28	-54	24	6.79
Posterior cingulate gyrus	30	R	28	-48	20	5.76
	31	L	-28	-66	18	7.04
Insula		R	38	-36	18	8.50
Middle occipital gyrus	19	L	-32	-70	12	9.08

Note: BA = probable Brodmann area; H = hemisphere; L and R = left and right hemispheres, respectively; *x*, *y*, and *z* = the Montreal Neurological Institute coordinates corresponding to the left-right, anterior-posterior, and inferior-superior axes, respectively; *t* = the highest t-score within a region. The threshold of significance was set at $p < 0.05$ corrected for multiple comparisons at the cluster level and $p < 0.01$ corrected for multiple comparisons at the voxel level.

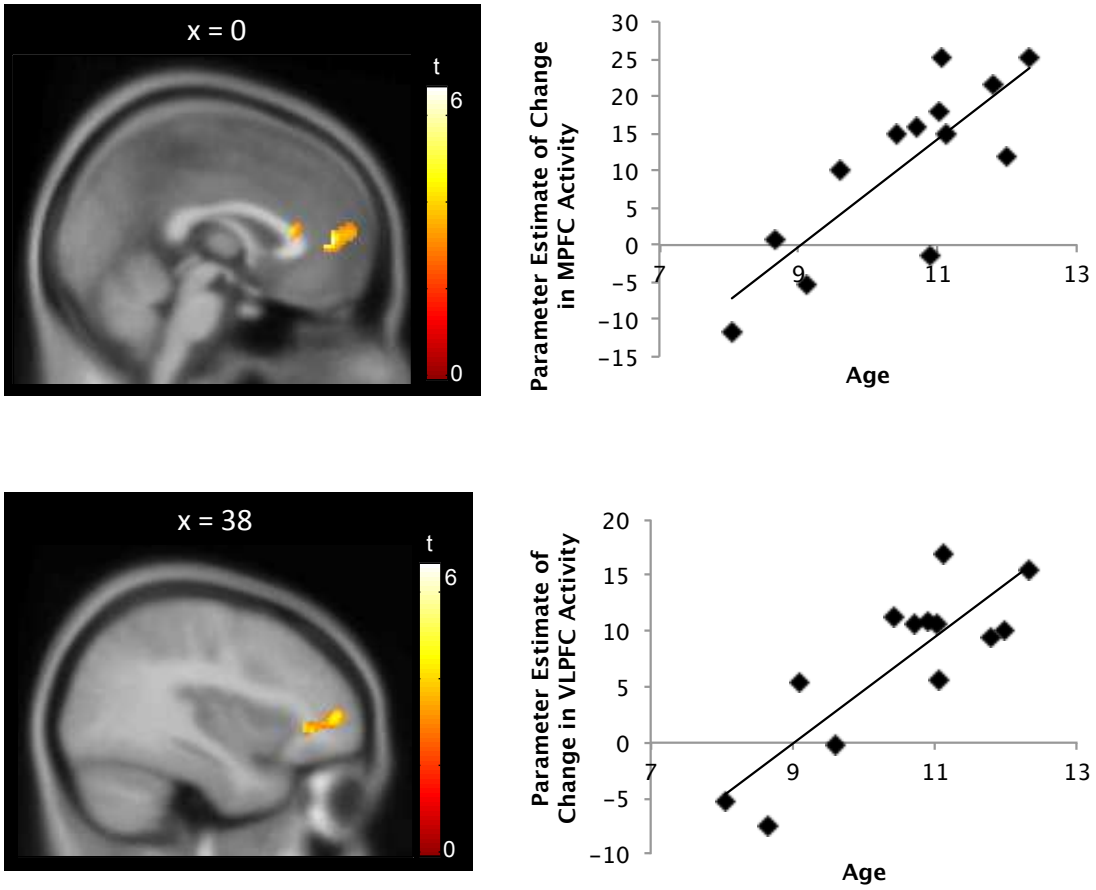

Figure 6. Age as a moderator of treatment outcomes for the CBT group. There was a significant correlation between age and increased activity in the MPFC (top) and right VLPFC (bottom) following treatment for the CBT group. Children were between the ages of 8 and 11, indicating that the children who were older demonstrated the greatest changes in activity in the regions shown. Parameter estimates of activity were averaged across each region (MPFC and VLPFC), extracted, and plotted for data visualization purposes. Images are thresholded at $t > 2.72$, volume = 568 mm^3, $p < 0.05$, corrected.

Table 8

Observed Peaks for Age as Moderator of Change in Activity for the CBT Group (post > pre) Across All Gaze Conditions

Region	BA	H	*x*	*y*	*z*	*t*
MPFC	10	R	8	58	10	6.00
VLFPC	47	R	36	34	-2	4.50
Anterior cingulate	32		0	48	8	6.28
Anterior insula		L	-24	24	16	4.85
Middle frontal gyrus	10	R	34	50	8	5.50
	10	L	-28	40	4	4.92

Note: BA = probable Brodmann area; H = hemisphere; L and R = left and right hemispheres, respectively; *x*, *y*, and *z* = the Montreal Neurological Institute coordinates corresponding to the left-right, anterior-posterior, and inferior-superior axes, respectively; *t* = the highest t-score within a region. The threshold of significance was set at $p < 0.05$ corrected for multiple comparisons at the cluster level and $p < 0.01$ corrected for multiple comparisons at the voxel level.

Neural Predictors of Treatment Outcomes

Regression analyses were conducted to evaluate the relationship between baseline brain activity and changes in social cognition and behavior. Across both groups ($N = 36$), baseline activity in the left FG was significantly correlated with improvement in social awareness (Figure 7A), as measured by the social awareness subscale of the Social Responsiveness Scale (Constantino, 2005). For the CBT group only ($n = 19$), activity in the right FG moderated changes in social awareness; specifically, children in the CBT group with greater baseline FG activity showed greater improvement in social awareness when viewing faces with a direct gaze (Figure 7B). Baseline activation in other areas associated with gains in social awareness included mentalizing and social brain networks (MPFC, IFG, temporal tip), frontal regions (SFG and MFG), areas involved in emotion processing (ACC and PCC), occipital cortex, and the cerebellum. Peak coordinates are shown in Table 9. There were no significant regions of activation associated with gains in social awareness for the comparison group.

Across both groups (N = 36), baseline activity in the right FG predicted improvement on a social cognition composite measure following treatment (Figure 7C). Baseline activation in other brain areas associated with gains on the social cognition composite included bilateral frontal regions (superior frontal gyrus). Peak coordinates are shown in Table 10.

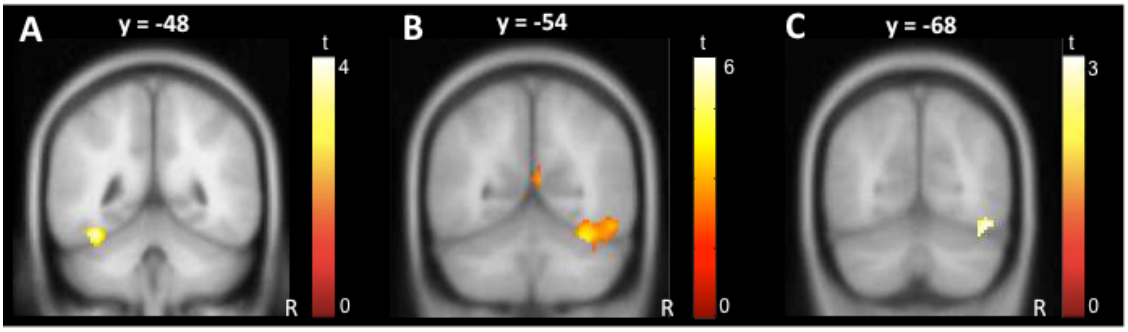

Figure 7. Fusiform gyrus activity is associated with response to social skills treatment groups for children with autism. Baseline activity in the fusiform gyrus (FG) was significantly correlated with improvement on the social awareness subscale of the Social Responsiveness Scale across both groups in the left FG (A) and for the CBT group only in the right FG (B). In addition, baseline activity in the right FG was correlated with improvements in social cognition following treatment across both groups (C). Images are thresholded at $t > 2.72$, volume = 568 mm^3, $p < 0.05$, corrected.

Table 9

Observed Peaks for Baseline Neural Activity as a Predictor and Moderator of Change in Social Awareness on the Social Responsiveness Scale (post > pre) Across All Gaze Conditions

Region	BA	H	*x*	*y*	*z*	*t*
Across Groups						
Fusiform gyrus	37	L	-38	-48	-20	4.55
CBT Group						
Fusiform gyrus	37	L	-36	-42	-18	5.18
	37	R	38	-54	-20	4.94
MPFC	8	R	12	42	50	5.16
Anterior cingulate gyrus	24	L	-14	38	4	5.44
	24	R	2	34	8	2.90
	32	R	4	46	6	4.38
Posterior cingulate gyrus	29	R	4	-54	12	4.07
	23	R	8	-48	24	3.54
Inferior frontal gyrus	44	L	-46	12	10	5.09
	45	L	-44	26	18	3.93
	47	L	-48	26	-2	3.81
Superior frontal gyrus	8	R	22	42	44	3.76
Middle frontal gyrus	46	L	-44	26	18	3.93
Temporal tip	38	R	32	10	-26	7.45
	38	L	-34	18	-34	5.33
Middle temporal gyrus	21	R	62	-4	-16	5.51
Middle occipital gyrus	19	R	48	-78	-4	5.83
Cuneus	18	R	16	-98	4	3.09
Lingual gyrus	18	R	20	-72	-14	3.61
Cerebellum		R	32	-58	-22	4.93
		L	-22	-50	-18	4.53

Note: BA = probable Brodmann area; H = hemisphere; L and R = left and right hemispheres, respectively; *x*, *y*, and *z* = the Montreal Neurological Institute coordinates corresponding to the left-right, anterior-posterior, and inferior-superior axes, respectively; *t* = the highest t-score within a region. The threshold of significance was set at $p < 0.05$ corrected for multiple comparisons at the cluster level and $p < 0.01$ corrected for multiple comparisons at the voxel level.

Table 10

Peak Coordinates for Baseline Activity as Predictor of Change in Social Cognition Composite Score When Viewing Faces with a Direct Gaze

Region	BA	H	*x*	*y*	*z*	*t*
Fusiform gyrus	37	R	42	-68	-18	3.25
Superior frontal gyrus	9	L	-22	58	30	3.12
	10	L	-34	52	24	2.98

Note: BA = probable Brodmann area; H = hemisphere; L and R = left and right hemispheres, respectively; *x*, *y*, and *z* = the Montreal Neurological Institute coordinates corresponding to the left-right, anterior-posterior, and inferior-superior axes, respectively; *t* = the highest t-score within a region. The threshold of significance was set at $p < 0.05$ corrected for multiple comparisons at the cluster level and $p < 0.01$ corrected for multiple comparisons at the voxel level.

CHAPTER IV

DISCUSSION

Summary of Findings

In the present study we investigated the neural effects of a cognitive-behavioral social skills treatment on gaze processing in school-aged children with ASD. As part of a larger clinical trial, the cognitive-behavioral intervention addressed three skill areas known to be impaired in children with ASD: nonverbal communication, emotion recognition, and theory of mind (Soorya et al., 2015). Both neural and behavioral outcome measures were administered at baseline, endpoint, and at a 3-month follow-up. Changes on the neural level were examined using an fMRI paradigm tapping into gaze and emotion processing.

Behavioral Outcomes

Behavioral analyses on the 24 children included in the final neuroimaging sample showed that participants in the CBT group made significant gains in social behavior following treatment relative to the comparison group. However, neither group showed significant improvements in social cognition following treatment. We also examined whether baseline participant characteristics (e.g., age, IQ) were moderators or predictors of treatment response. There were no moderating effects of baseline characteristics including age and IQ on changes in social behavior and social cognition composites for the present imaging sample. For the larger clinical cohort, verbal IQ moderated changes on the social behavior composite, whereby higher verbal IQ was associated with improvements in social behavior impairments for the CBT group (Soorya et al., 2015).

Age approached significance as a moderator of gains in social behavior for the CBT group in the larger cohort.

Neuroimaging Outcomes

When we examined changes in brain activity pre- to post-treatment within each group in response to direct and averted gaze, children in the CBT group showed increased activity in prefrontal networks implicated in social cognition, including the MPFC and VLPFC. Children in the CBT group also showed changes in activation in regions associated with visual processing (occipital cortex), emotion processing (cingulate cortex), fronto-temporal networks, and subcortical regions (caudate, putamen, thalamus). The comparison group did not show significant changes in activation pre- to post-intervention.

When we examined changes in activity between groups for direct and averted gaze conditions following treatment, children in the CBT group showed greater changes in activation in regions associated with mentalizing (MPFC), emotion processing (e.g., cingulate gyrus), and frontal networks (e.g., left middle frontal gyrus) relative to the comparison group. There were no significant areas of greater change in activity for the comparison group relative to CBT. When examining changes in differential activation for direct and averted gaze following treatment, no significant differences were found between groups.

Analyses suggest that neural and behavioral changes may not be maintained at the 3-month follow-up. Within-group analyses showed that there were no significant changes in activation in social brain regions for the CBT group from baseline to follow-up. Likewise, between-group analyses showed no significant areas of greater change in

activation for the CBT group relative to the comparison group from baseline to follow-up. However, null findings could also be due to low power given the small sample size.

Regression analyses were conducted to investigate neural and behavioral moderators and predictors of treatment response. When we examined the relationship between baseline characteristics and changes in brain activity, older age was associated with greater change in activation pre- to post-treatment in brain regions implicated in emotion (ACC, anterior insula, VLPFC) and mentalizing (MPFC) for the CBT group only. We then examined the relationship between baseline neural activity and changes in behavior across both groups, and found that baseline activity in the FG predicted response to treatment. Specifically, children with greater baseline activation of the FG, particularly in the right hemisphere, demonstrated the greatest gains in measures of social competence including the social awareness subscale of the SRS-2 and the social cognition composite. However, caution is warranted when interpreting these results since no significant changes were found on measures of social awareness or the social cognition composite pre- to post-intervention in either group.

Implications

Behavioral Outcomes of Social Competence

In the present study we examined the neural mechanisms of response to CBT for social impairments in children with ASD relative to a child-directed play group. Clinically, for the 24 children in this neuroimaging study, the CBT group made significant improvements in social behavior following treatment relative to a comparison group. Significant gains in social cognition were not observed in either group. These findings are consistent with treatment outcomes from the larger clinical study (Soorya et

al., 2015). It is possible that changes in social cognition abilities, which includes a broad range of skills such as emotion recognition, imitation, and theory of mind, are more difficult to address. This interpretation is supported by results from other randomized-controlled trials of social skills groups for ASD that have not found improvements in social cognition on tasks of emotion recognition (Baghdadli et al., 2013; Lopata et al., 2010) and mentalizing stories (Solomon et al., 2004). In a recent meta-analysis of 22 intervention studies addressing theory of mind training in ASD, Fletcher-Watson and colleagues (2014) reported poor outcomes in the maintenance and generalization of social cognition abilities to other contexts, particularly emotion recognition and mentalizing. It is also possible that the cognitive aspect of social functioning was not effectively addressed by the Seaver-NETT program to a level that would yield a statistically significant benefit. A greater intensity or dosage of treatment beyond one hour per week or a greater duration of treatment beyond 12 weeks may be needed to significantly improve social cognition and associated skills.

Although developmental variables including age and verbal IQ were not found to moderate outcomes in this smaller imaging sample, in the larger clinical cohort, there was a moderating effect of verbal IQ on social behavior outcomes at endpoint. Higher verbal IQ scores were associated with greater change in the social behavior composite for the CBT group. Age also approached significance as a moderator of social behavior outcomes in the clinical cohort, with increased age associated with gains in social behavior for the CBT group. These findings have implications for identifying subgroups of children for whom a cognitive-behavioral approach may be most beneficial whereby

children with ASD who have greater verbal processing skills and are older may benefit from CBT to target core autism deficits.

Increased Activation of Social Brain Networks: MPFC and VLPFC

Medial prefrontal cortex. Consistent with our hypothesis, children in the CBT group showed increases in activity in social brain networks following treatment. In particular, greater activation was found in regions implicated in mentalizing and emotion processing including the MPFC and VLPFC, respectively, while viewing faces with direct and averted gaze. In contrast, children in the comparison group did not show significant changes in activity at endpoint. Between-group analyses confirmed that the effect of treatment on increased MPFC activity was greater in the CBT group relative to the comparison group when viewing expressive faces with a direct and averted gaze.

Hypoactivation of the MPFC has been found in people with ASD when viewing faces with varying gaze (Georgescu et al., 2013; von dem Hagen et al., 2014). Studies have shown that the MPFC is an integral part of the Theory of Mind network, which refers to regions of the brain implicated in mentalizing (see reviews by: Amodio & Frith, 2006; Frith & Frith, 1999; Frith & Frith, 2006; Frith, 2001; Gallagher & Frith, 2003; Saxe et al., 2004; Van Overwalle, 2011). In addition to its association with mentalizing, MPFC activation has been reported in typically developing individuals during gaze paradigms that include the processing of emotional expressions when participants are asked to make explicit judgements about emotions (Wicker et al., 2003), make appraisals about socially relevant expressions (Schilbach et al., 2006), and view gaze shifts (Hooker et al., 2003). Activation of the MPFC has also been found when viewing different gaze directions in the context of a neutral facial expression (Calder et al., 2002; Conty et al.,

2007; Kampe et al., 2003; Wicker et al., 1998) and shifts in gaze (Bristow et al., 2007; Mosconi et al., 2005; Williams et al., 2005). However, it is important to note that several studies did not find similar MPFC activation during passive tasks when viewing emotional expreessions with different gaze (Davies et al., 2011; Engell & Haxby, 2007; Hoffman & Haxby, 2000; Pitskel et al., 2011; Zurcher, Rogier, et al., 2013) and during active tasks when categorizing gender from faces (George et al., 2001). Similarly, several neuroimaging studies did not report activation of the MPFC during spatial cueing tasks of social (i.e., directional gaze) versus non-social (i.e., arrows) stimuli (Dichter & Belger, 2007; Greene et al., 2011; Hietanen et al., 2006; Kato et al., 2001; Vaidya et al., 2011) and during shifts in gaze (Pelphrey, Morris, & McCarthy, 2005; Pelphrey, Singerman, et al., 2003). Recruitment of the MPFC and other regions of the social brain during gaze tasks could be evoked to infer the goals and intentions behind another person's gaze, leading some to propose that gaze processing is linked to social cognition (see reviews by: Itier & Batty, 2009; Nummenmaa & Calder, 2009).

Our results show that increased activity in the MPFC was observed only in the CBT group following treatment. It is noteworthy that Davies and colleagues (2011), using the same task, did not find activation of the MPFC in TD children as this was a passive viewing task that did not require the explicit appraisal of mental states. Moreover, it is important to emphasize that the participants in our study were not instructed to make any explicit judgments pertaining to the mental states of the actors. It is likely, therefore, that these observed differences in MPFC activity pre- to post-intervention for the CBT group may reflect a greater tendency to implicitly interpret emotion and gaze depicted in faces. Given that deficits in gaze processing may be linked

to mentalizing impairments in ASD (George & Conty, 2008), our data suggest that increased MPFC activity observed for the CBT group in response to emotional faces may reflect more automatic processing of the thoughts and feelings that are associated with an emotional face following a cognitive-behavioral approach for treating social skills deficits.

Our finding of greater MPFC activation during a passive gaze task following CBT relative to comparison is also consistent with results from a separate neuroimaging paradigm examining the neural correlates of mentalizing or irony comprehension that we empolyed as part of the larger study. During this irony task, children in the CBT group also showed increased MPFC activation following treatment relative to the comparison group (Wang et al., in preparation). The convergence of these findings from the gaze and irony comprehension tasks may highlight the potential of MPFC activity as a biomarker of treatment response. Given the heterogeneity of symptomatology associated with ASD, the identification of neural biomarkers may play an important role in informing treatment.

Ventrolateral prefrontal cortex. An increase in activation in the VLPFC was found in the CBT group following treatment. However, changes in VLPFC activation from baseline to endpoint were not significantly different for the CBT and comparison groups. The VLPFC is implicated in the labeling of negative affect and emotion regulation (Hariri et al., 2000; Hariri, Mattay, Tessitore, Fera, & Weinberger, 2003; Wang et al., 2004) as well as in making evaluative judgements (Cunningham, Johnson, Gatenby, Gore, & Banaji, 2003; Pinkham et al., 2008). Recent evidence suggests that the VLPFC is involved in mental state attribution (Dal Monte et al., 2014) and

hypoactivation of this region has been found in autism during social cognition tasks of biological motion (Kaiser et al., 2010), evaluation of trustworthiness (Pinkham et al., 2008), and gaze processing (Davies et al., 2011). We predicted that following treatment, children in the CBT group would show greater activity in the VLPFC for faces with a direct gaze relative to averted gaze compared to the play group. These predictions were based on prior findings from Davies and colleagues (2011) using the same paradigm of processing gaze in emotional faces, where TD children showed activation of the left VLPFC for emotional faces with direct versus averted gaze while children in the ASD group showed underactivity in this region. Our findings did not support this hypothesis. Alternatively, the lack of changes in differential VLPFC response for direct and averted gaze reflects increases in VLPFC activation for both gaze conditions, which could be due to CBT teaching that both direct and averted gaze give clues as to interpreting mental state.

ACC and Insula

Changes in activity in the ACC and insula were significantly greater for the CBT group relative to the comparison group following treatment when viewing faces with an averted gaze. The ACC and insula have been implicated in the processing of affect from faces (for a meta-analysis, see Fusar-Poli et al., 2009), and there is also evidence that the anterior portion of the insular cortex is involved in the awareness of internal emotional states (Craig, 2009). In a meta-analysis by Di Martino and colleagues (2009), activation of the ACC and insula was reported in studies using social tasks. Neuroimaging studies have shown that atypical activation of the ACC and insula is found in people with ASD when processing facial expressions and gaze direction (Georgescu et al., 2013; Pitskel et

al., 2011; Zurcher, Rogier, et al., 2013), gaze shifts (Dichter & Belger, 2007; Vaidya et al., 2011), and during mentalizing tasks (for a meta-analysis see Di Martino et al., 2009). Together, our findings of increased activation of the ACC and insula for the CBT group may reflect a greater subjective awareness of emotions or the integration of external stimuli (e.g., images of emotional faces) with participants' own internal states (e.g., the comparable subjective feeling elicited in the participant).

Three-Month Follow-up

At the three-month follow-up, changes in activity in 'social brain' networks were not maintained for the seven CBT participants with available fMRI data. This finding is also consistent with behavioral outcomes from the larger clinical sample where no significant changes in composite measures were found at follow-up (Soorya et al., 2015). This could suggest that 12 weeks may not allow adequate time for permanent changes on a behavioral level and a neural systems level. However, given that 11 participants were either excluded for follow-up analyses due to excessive motion or were lost to contact, the statistical power is limited for the maintenance timepoint fMRI analysis due to the small number of participants with available follow-up scans.

Behavioral Moderators of Change in Neural Activity

We examined baseline participant characteristics that are associated with changes in neural activity. There was a significant correlation between age and increased activity in the MPFC and VLPFC following treatment for the CBT group, such that children who were older showed the greatest increase in activity in these social brain regions. These results also complement findings from the larger clinical cohort of this randomized, comparative trial examining the behavioral effects of the CBT treatment, where older age

was marginally associated with greater improvement in social behavior (Soorya et al., 2015). Further, the moderating effect of age on increased MPFC and VLPFC activation may have implications for identifying subgroups of children with ASD for whom a particular treatment approach may be most benefical. Overall, our findings suggest that older chidren may benefit from a didactic, group CBT approach to treating social deficits at both the behavioral and neural levels.

Neural Moderators and Predictors of Treatment Response

We also examined the association between baseline neural activity and gains on measures of social behavior and cognition. Greater activity at baseline in mentalizing regions (MPFC and IFG) and areas implicated in emotion processing (ACC and PCC) was associated with improvements on parent-rated measures of social awareness on the SRS-2. Gains in social awareness for the CBT group was also correlated with greater baseline activity in the temporal tip, implicated in social cognition and mentalizing (Amodio & Frith, 2006; Frith, 2001; Gallagher & Frith, 2003; Schultz et al., 2003). Of particular note, we found that baseline activity in the FG was associated with improvement on measures of social awareness and social cognition following treatment. Specifically, greater baseline activation of the left FG predicted improvement in social awareness across groups. Activation of the right FG moderated gains on the social awareness subscale and social cognition composite for the CBT group only. Together, our findings suggest that children who exhibit a more typical neural response to faces at baseline may be more likely to show improvement following social skills groups, both for cognitive-behavioral and child-directed approaches.

Greater activation of the FG and other social brain regions at baseline could also be an indicator of "neural readiness" for social skills groups. While FG activity is primarily associated with face processing (Kanwisher et al., 1997), particularly in the right hemisphere (Dalton et al., 2005; George et al., 1999; Hooker et al., 2003; Lehmann et al., 2004; Morris, Pelphrey, & McCarthy, 2007; Schultz et al., 2000), some studies have suggested a role of the FG beyond the perception of faces. Activation of the right FG has been implicated in expertise for distinguishing objects (Gauthier & Tarr, 2002; McGugin, Newton, Gore, & Gauthier, 2014) and during mental state attribution tasks (Castelli, Happe, Frith, & Frith, 2000; Schultz et al., 2003). Greater right FG activity has also been shown to correlate with less severe social impairments or autism symptomatology (Scherf, Elbich, Minshew, & Behrmann, 2015). However, these findings should be taken with caution since neither group showed significant increases in social awareness or social cognition following treatment, and therefore the clinical significance is unclear. Although our sample is relatively small, our analysis offers a first step toward identifying potential neural predictors of treatment response for children with ASD—an essential goal of autism research given the heterogeneity of symptoms and the variability in treatment response among children with ASD (Kasari et al., 2014). Elucidating biomarkers of treatment response may also facilitate the characterization of children with ASD to receive a specific intervention approach to promote positive treatment outcomes.

There were no significant correlations with baseline neural activity and improvement on the social behavior composite for the CBT group. The lack of significant findings here may reflect that the domains assessed for the social behavior

composite (i.e., empathy, nonverbal communication, and social relations) are not directly associated with FG activation. Rather, the domains assessed for the social cognition composite overlap more closely with cognitive functions associated with FG activation including emotion and face processing (see reviews by: Kanwisher & Yovel, 2006; Vuilleumier & Pourtois, 2007).

Summary

To our knowledge, this is the first randomized, comparative trial demonstrating that a cognitive-behavioral approach for treating social deficits in children with ASD is associated with changes in neural activity. While few studies have examined the neural outcomes of behavioral interventions for ASD, preliminary findings suggest that social brain networks are sensitive to change following treatment (Ventola et al., 2013). To date, five studies have investigated the neural response to treatment for people with ASD, in which changes in social brain and executive functioning networks were reported following treatment. Four of these studies examined the effects of behavioral intervention and friendship training for young children and adolescents, including the Early Start Denver Model (ESDM; Dawson et al., 2012), Pivotal Response Treatment (Ventola et al., 2015; Voos et al., 2013), and the Program for the Education and Enrichment of Relational Skills (PEERS; Van Hecke et al., 2015). Another study examined computerized cognitive training for emotional processing in adults (Bolte et al., 2015). Together, findings from this study add to the growing body of literature demonstrating the plasticity of neural networks in response to treatment in ASD.

Methodological Considerations

One limitation in this study was the small sample size due to movement in the scanner and attrition. The neuroimaging sample of children with adequate scan data is small ($N = 24$) compared to the larger behavioral portion of the study ($N = 69$); the majority of participants were excluded from the final analysis due to inadequate scan data or excessive motion ($n = 35$), where a nearly equal number of participants were removed from analyses in the CBT group ($n = 18$) and the play group ($n = 17$). However, the neuroimaging sample ($N = 24$) remained equivalent to the larger clinical sample ($N = 69$) in terms of IQ and symptom severity.

The fMRI apparatus can be daunting for a child with ASD, especially given the prominent sensory sensitivities common to ASD and the plethora of sounds and vibrations that the participant is exposed to during a scan. As part of the study protocol, a mock scanner was available for children to acclimate to the fMRI setting. Mock scanners are similar in shape and size to an actual MRI and offer an opportunity for a simulated experience that includes typical sounds heard during an MRI, a rolling patient table, and a mock head coil. Motion may also be monitored during the mock scan using software such as MoTrak, allowing the researcher or clinician to provide feedback in real-time regarding movement. However, the MoTrak software was not available to our group during this study. In addition, analysis of the motion data following the fMRI scan would have provided an accurate estimate of motion artifacts above a previously set threshold (e.g., below 3 mm/degrees of motion or a ratio of 0.75 of functional runs retained after scrubbing). This would allow for a separate, second scanning session to be offered to the participant or used as exclusion criteria to reduce attrition due to inadequate scanner data.

In terms of attrition, three participants dropped out of the study and eight participants were unable to complete post scans. However, the overall majority of children were able to complete 12 weeks of treatment in addition to pre and post scans. Analyses of the 3-month follow-up data were also hindered by a small sample size, as many families were lost to contact, unable to complete the follow-up scans and/or behavioral report measures. This posed difficulties for ascertaining the maintenance of skills following the intervention.

In terms of generalizability, it is important to replicate these findings to fully understand treatment outcomes and transfer of skills to naturalistic settings such as the school environment and interactions with peers. In addition, the participants in this study were all verbally fluent, which also limits the generalizability of findings given the heterogeneity of symptoms, severity, and executive functioning among people with ASD. There is also a need for studies that examine the behavioral and neural effects of social skills treatments for adolescents and adults with ASD, as most published data on social skills treatments are based on young or school-aged children (Reichow & Volkmar, 2010).

Clinical Implications

Our findings suggest that a CBT approach to social skills groups may result in increased activity in social brain networks shown to be hypoactive in ASD. Deficits in making eye contact and following eye gaze are often a target for interventions that aim to increase the awareness and processing of social cues in the environment of individuals with ASD. While there is variability in treatment approaches, an overall goal is to teach individuals with autism how to interpret salient social stimuli such as facial expression

and eye gaze in order to develop social skills (e.g., understanding one's state of mind). The CBT intervention employed in this study capitalized on applying both "top-down" and "bottom-up" approaches to take advantage of the cognitive strengths and varied learning modalities of individuals with ASD. Top-down approaches provided children with explicit strategies for learning social skills. Bottom-up approaches promoted implicit awareness of social cues and increased motivation through behavioral strategies including breaking down a skill into concrete steps, modeling, rehearsal, and positive reinforcement.

Our findings of significant improvements in social behavior for the CBT group indicate that a cognitive-behavioral approach to treating the core deficits in ASD may promote improvements in social competence. In addition, changes at the neural systems level were found in regions of the social brain for children in the CBT group. Treatments that emphasize the use of both explicit cognitive strategies (e.g., labeling emotions, guided practice, prompting, providing specific performance demands) and behavioral approaches (e.g., reinforcement) may promote the use of more implicit strategies during social situations, such as the ability to automatically derive meaning from gaze and emotional expressions in the absence of prompting. Though this work was limited by relatively small group sizes, it nevertheless contributes to our understanding of the social impairments in ASD and the plasticity of social brain networks in response to a CBI for social deficits.

Future Research

Efficacy of CBT for Treating Core ASD Impairments

We examined the neural and behavioral effects of a CBT-based social skills treatment on core ASD deficits, which addressed common areas of difficulty such as theory of mind. However, the range of symptoms, cognitive abilities, verbal processing skills, and severity among individuals with ASD can make the use of a single treatment modality, such as CBT, difficult. In combination with behavioral interventions, fMRI invites a greater understanding of treatment response without the potential bias and challenges of behavioral testing as well as parent- or self-report measures. Given the heterogeneity of ASD, neuroimaging biomarkers also offer new insights into the development of the next generation of treatments such as a personalized medicine approach. A greater understanding of neural biomarkers of treatment response may curtail many of the challenges in treatment planning for individuals with ASD. Specifically, the use of neuroimaging to inform the treatment approach could aid in identifying those for whom a particular treatment modality may be most optimal. However, more work is needed to identify neural biomarkers of treatment response that would help in determining the appropriate age, dose, and type of therapy to deliver in order to optimize the behavioral and neural development of children with ASD.

A comparative play group was used in this study to account for non-specific treatment effects such as time spent with a therapist and parental expectations of outcomes. Children in the play group did not show any significantly greater changes in activation pre- to post-intervention relative to the CBT group. While our sample size was small, it is possible that a child-directed approach may benefit the learning social skills

for subgroups of children; though, this is beyond the scope of this study. Future research that investigates the use of more play-based approaches for treating social deficits may provide valuable insight into understanding for whom a particular type of therapy approach is most beneficial.

Long-Term Neural and Behavioral Outcomes of Treatment

This study examined the maintenance of changes in behavior and brain activity at a 3-month follow-up, albeit future work is needed to examine long-term outcomes to fully assess the maintenance of skills and neural activity. While social skills interventions show promising outcomes in the treatment of youths with ASD to target core impairments, we have limited data on the long-term effects of children's social skills intervention experiences. In one study, Dekker and colleagues (2014) examined generalization and maintenance of social skills at a 6-month follow-up in a sample of Dutch children with ASD. The longest follow-up periods reported were five years for an early intervention program for children with ASD (Kasari, Gulsrud, Freeman, Paparella, & Hellemann, 2012) and one to five years for a parent-assisted social skills training program for children with ASD (Mandelberg, Frankel, Cunningham, Gorospe, & Laugeson, 2014). While many studies have reported benefits of social skills training for ASD, few have investigated long-term outcomes. Future work that investigates the long-term outcomes of social skills interventions is important for determining the maintenance and generalization of skills (Foxx, 2013), as well as if changes are maintained on a neural level.

Understanding the Active Ingredients of Treatment

A greater understanding is also needed of the active ingredients of behavioral interventions that may be effective in addressing core impairments of ASD. The CBT treatment used in this study employed three modules: nonverbal communication, emotion recognition, and theory of mind training. Because assessments were conducted pre- and post-treatment rather than after each module, it is difficult to determine which components are the most beneficial. In addition, assessments were conducted before and after 12 weeks of treatment, making it challenging to ascertain the neural and behavioral effects of each individual module or identify active ingredients. More work is needed towards teasing apart the active components of a treatment, which would provide a better understanding of who benefits most from which interventions, as well as the neural and behavioral mechanisms for why an intervention may work (Kasari et al., 2014).

Minimally Verbal People with ASD

Our study design focused on neural mechanisms of change in school-aged, verbally fluent children with ASD. However, neuroimaging and electrophysiology studies examining treatment outcomes are sparse for minimally verbal and young children with ASD (Tager-Flusberg & Kasari, 2013), especially given the impact of motion-related effects on decreased signal intensity. In addition, imaging methodology that accommodates the sensory sensitivities common to autism would aid progress towards making neuroimaging more amenable to people with ASD across a wider range of functional abilities. The use of electroencephalography (EEG) and functional near-infrared spectroscopy (fNIRS) are two techniques that offer temporal information of stimulus processing that are less sensitive to motion effects relative to fMRI. Techniques

such as EEG and fNRIS would also provide a greater understanding of the impact of early intervention on changes in brain activity. Additional research is needed to understand the neural correlates of social cognition and neural mechanisms underlying treatment response in minimally verbal and young children with ASD. Further, EEG and fNIRS may prove to be more beneficial for research with minimally verbal people with ASD where the rigorous procedures of MRI are not feasible due to attention and behavioral concerns.

Functional Connectivity: Understanding Interactions Between Networks

There is compelling evidence from neuroimaging studies that the deficits in social behavior and cognition in ASD may be associated with aberrant activity within as well as between social brain networks. While assessing connectivity or the relationship between social brain regions was beyond the scope of this study, the measurement of functional connectivity provides new insights for understanding the interactions between anatomically separate areas of the brain and how this integration is linked to behavior. It is possible that diminished connectivity between socio-emotional cortical regions may account for a lack of top-down modulation from downstream anterior regions such as the MPFC, which would attach salience to social information. Underconnectivity has been shown between fronto-temporal regions implicated in mentalizing and extrastriate cortex (Castelli et al., 2002; see review by Frith, 2001; Kana et al., 2015; Wicker et al., 2008) as well as between the amygdala and insular cortex (Ebisch et al., 2011). Underconnectivity has also been shown between voice-selective cortical regions in the posterior STS and structures involved in reward including the ventral tegmental areas and nucleus accumbens, and structures involved in emotion processing including the amygdala,

suggesting that weak connectivity may account for a diminished reward value and salience of speech in ASD (Abrams et al., 2013). In a recent study, Kana and colleagues (2015) reported decreased connectivity between the MPFC and the amygdala, temporal lobe, parietal lobe, and fusiform gyrus in adults with ASD during a mentalizing task of emotion judgments using real-life scenarios. Resting state findings from the Autism Brain Imaging Data Exchange (ABIDE) demonstrated a predominance of decreased corticocortical intrinsic functional connectivity, particularly for the temporal lobe, while hyperconnectivity was found primarily in subcortical regions including the thalamus and globus pallidus (Di Martino et al., 2014). There is also a growing body of evidence that hyperconnectivity within a number of different functional networks may be associated with social impairments in ASD (Di Martino et al., 2014; Uddin et al., 2013), as well as the variability of hypo- and hyperconnectivity within and between networks across the lifespan of children and adults with ASD (Nomi & Uddin, 2015a).

Imaging Genetics: Understanding Changes in Epigenetics in Response to Treatment

While integrating genetics was beyond the scope of this study, future clinical trials examining external or environmental factors that affect gene regulation, referred to as epigenetics, may prove useful in predicting treatment response and understanding changes in brain activity. Oxytocin, a neuropeptide that is dependent upon the expression of its receptor gene (OXTR), is involved in social behavior and has received much attention as a potential treatment for autism (Young & Barrett, 2015). Methylation of genes (addition of methyl or CH3 groups) serves to turn on or off gene expression, which can also be influenced by experience and environmental factors. Neuroimaging studies have reported associations between OXTR methylation as well as plasma oxytocin levels

and activation of regions implicated in social cognition and emotion regulation during social perception paradigms of biological motion (Jack, Connelly, & Morris, 2012; Lancaster et al., 2015) and emotional expressions (Puglia, Lillard, Morris, & Connelly, 2015). Given that the effectiveness of behavioral interventions targeting social information processing may also be modulated by OXTR methylation, future work investigating the association between plasma oxytocin levels or OXTR methylation patterns with changes in brain activity would provide a better understanding of the etiology of ASD, identification of biomarkers of treatment response, and changes in neural activation following intervention.

Concluding Remarks

Neuroimaging provides a noninvasive method of understanding the developmental pathology of ASD and neural correlates of social cognition. Deficits in social perception in ASD, such as mentalizing and the processing of eye gaze, may be due to aberrant activity in 'social brain' regions. The current study demonstrates the neural effects of a cognitive-behavioral treatment for social skills deficits on the plasticity of networks involved in social cognition in verbally fluent children with ASD. This study contributes to our understanding of the neural correlates of social deficits associated with ASD, biomarkers of treatment response, and the neural processes underlying response to treatment in networks crucial for social cognition.

In terms of clinical implications, social skills interventions combining cognitive and behavioral techniques may improve social competence for children with ASD. Given the paucity of data identifying biomarkers of treatment response in ASD, this study provides evidence for the MPFC as a potential neural biomarker of treatment response for

social skills training. With the heterogeneity of ASD symptomatology, however, a greater understanding of neural biomarkers could set the stage for the development of a personalized medicine approach. Future studies integrating an interdisciplinary approach of neuroscience and behavioral interventions could provide insights for next generation therapies. Particularly, treatments that are specific to the individual and target change at the behavioral and neural levels in a noninvasive and non-pharmacological manner.

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APPENDIX A

IRB APPROVAL LETTER FROM MOUNT SINAI SCHOOL OF MEDICINE

Date: 07/03/2015

To: **Ting Wang, PhD (Ting.Wang@mssm.edu)**

An Institutional Review Board (IRB) of the Mount Sinai School of Medicine approved the following human subject research to be conducted through 08/31/2015:

Project Title:	**Neural and Behavioral Outcomes of Social Skills Groups in Children with ASD**
Investigator:	**Ting Wang, PhD (Dept: PS - Psychiatry)**
Project Information:	**HS#: 11-01412** **GCO#: 09-0859(0002) Icahn School of Medicine at Mount Sinai**
Sites:	**Mount Sinai**

Between 07/15/2015 and 07/20/2015 please submit a completed FORM HRP-212: Continuing/Final Review Progress Report and required attachments, in order to request continuing IRB approval or study closure. No further reminders will be sent.

If you do not submit a completed FORM HRP-212: Continuing/Final Review Progress Report and required attachments to request continuing approval or study closure by **07/20/2015** you will not be able to submit new research to the IRB until this information has been submitted.

If continuing review approval is not granted before the expiration date of 08/31/2015, approval of this research expires on that date. If the IRB approval expires, all research activities must stop. This includes recruitment, advertisement, screening, enrollment, consent, interventions, interactions, and collection of private identifiable information. Advertisements currently running in the media must be pulled.

If you have any questions about how to submit this request, need help with the process, or have general questions about the IRB, please feel free to call us at 212-824-8200 or email us at IRB@mssm.edu.

Sincerely,
The Program for the Protection of Human Subjects Staff

cc: Study Contact(s): cc: Study Contact(s): Jesslyn Jamison (jesslyn.jamison@mssm.edu);

APPENDIX B

HSC APPROVAL LETTER FROM UNIVERITY OF HARTFORD

UNIVERSITY OF HARTFORD

Human Subjects Committee

January 14, 2014

Karim Ibrahim
76 Everit Street
New Haven, CT 06511

Dear Mr. Ibrahim:

Upon review by the Human Subjects Committee, your proposal, *Neural correlates of social cognition processing in autism following a cognitive behavioral social skills treatment,* has been approved according to conditions set forth in federal regulation 45 CFR 46.101(b), and is exempt from further review by this Committee.

Please keep in mind that it is your responsibility to notify and seek approval from this Committee of any modifications to your project, and that it is your responsibility to report to this Committee, any adverse events that occur related to this research project. Reporting forms are available online at the HSC website, http://uhaweb.hartford.edu/hsc.

This institution has an Assurance of Compliance on file with the Office of Human Research Protections (Federalwide Assurance FWA00003578).

Congratulations and good luck.

Sincerely,

Stephen J. Misovich, Ph.D.
Chair, Human Subjects Committee
Cc: J. Mehm

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