An Eye-Tracking Measure of Joint Attention as an Autism Spectrum Disorder Endophenotype: Initial Validation in a Community Sample of Adults, Typically Developing Children, and Children with Autism Spectrum Disorder

By

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ABSTRACT

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Adviser: Michael Siller, Ph.D.

An important milestone in children's early social-communicative development is the ability to respond to others' bids for joint attention (RJA). It is well established that this ability to respond to another's gaze direction is a specific deficit in children with an autism spectrum disorder (ASD). We examined visual attention allocation during a set of social video vignettes that are intended elicit the coordination of attention with another person. This eye-tracking measure utilized modern technology to evaluate how individuals allocated their visual attention while watching social video vignettes. These videos display an adult model who gazes at a series of targets that appear and disappear in the four corners of the screen (congruent condition). Gaze allocation in the experimental condition is compared to a set of control stimuli where the model's gaze moves equally as often, but is not directed at the appearing/disappearing targets (incongruent condition). Feasibility of administering this experimental paradigm to typically developing adults (*n*= 44), children (*n* = 50), and children with ASD (*n*= 23) is evaluated. The performance of children with ASD and typically developing children is also compared on a battery of theory of mind tasks intended to evaluate children's ability to interpret the mental states of others. Results revealed several major findings. First, gaze allocation of adults and

typically developing children differed significantly between the congruent and incongruent conditions. Second, individual differences in gaze allocation were significantly predicted by features of the broad autism phenotype (BAP) in adults and typically developing children. Third, children with autism spectrum disorder scored significantly lower on theory of mind tasks when compared to typically developing children. Fourth, across both groups of children the Social Awareness Subscale form the Social Responsiveness Scale (SRS), a parent-report measure evaluating features of the broad autism phenotype, significantly predicted gaze allocation during our experimental eye-tracking stimuli and performance on theory of mind tasks. Fifth, also across both groups, theory of mind scores predicted gaze allocation during our eye-tracking measure of joint attention. These findings are consistent with the notion that our eye-tracking measure of gaze following captures a valid endophenotype associated with ASD.

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for teaching me that I don’t have to take no for an answer. Lastly, to my mother, Bonnie, thank you for being my confidant, shoulder to cry on, and constant supporter. Every day I look to the four of you and I see lives that are filled with love, integrity, and passion. I can’t imagine having better role models. To say that I am filled with gratitude for having you all in my life just doesn’t seem like enough.

DEDICATION

To my Mom and Dad, thank you for all your love and support.

You are my étoiles du Nord.

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GENERAL INTRODUCTION

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by a triad of behaviors, including impairments in reciprocal social interaction, impairments in communication, and the presence of restrictive, repetitive, or stereotyped patterns of behavior (American Psychological Association, 2000). This disorder presents more often in boys (Center for Disease Control and Prevention, 2009) and has been found to be highly heritable. Concordance rates for monozygotic twins range from 70-90%, which is in significantly higher than the respective values for dizygotic twins (0-30%) (Steffenburg et al., 1989; Bailey et al., 1995; Rosenberg, Law, Yenokyan, McGready, Kaufman, & Law, 2009; Hallmayer et al., 2011).

In the current *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV, American Psychological Association, 2000), diagnostic criteria for ASD are based on a collection of 12 behavioral items clustered into three subdomains that correspond to the triad of deficits. According to these criteria there are 2,027 ways to be diagnosed with autistic disorder (and many more to receive a diagnosis of autism spectrum disorder), so two children with the same diagnosis may display few of the same behaviors (Jabr, 2012). The upcoming Fifth Edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5, American Psychological Association, 2012) characterizes ASD as a single diagnostic category, while emphasizing that individuals' clinical presentation varies substantially in terms of clinical specifiers (e.g., severity and verbal abilities) and associated features (e.g., known genetic disorders, epilepsy and intellectual disability). One of the more noticeable proposed changes, reorganizing the subdomains by collapsing the communication and social interaction subdomain, highlights the lack of universality of language impairments across the disorder as well as the inability to separate communication from associated social behaviors (American Psychological Association, 2012).

The clinical diversity associated with ASD, as well as difficulties identifying susceptibility genes that are replicable across independent samples (Bonora, Lamb, Barnby, Bailey, & Monaco, 2006), has prompted researchers to suggest that the etiology of ASD likely involves multiple genes interacting with the environment (Abrahams & Geschwind, 2008; Geschwind & Alarcon, 2006). Research over the last 20 years has provided support for this notion. Researchers have found that defined mutations, structural variations to specific portions of DNA, and known genetic syndromes, account for approximately 10-20% of autism spectrum disorder cases (for a review see Abrahams & Geshwind, 2008). Although, each of these specific cases account for, at most, 1-2% of total ASD cases (Abrahams & Geshwind, 2008).

Given that the etiology of ASD likely involves multiple genes interacting with each other, it is predicted that individual genetic risk factors are more closely related to specific features or components of ASD (i.e., endophenotypes) rather than ASD itself. Endophenotypes are measureable traits that are heritable and behaviorally relevant to a specific disorder or condition (*endo* meaning "inside" and *pheno* meaning "show"; Gottesman, & Shields, 1973). By using endophenotypes to identify genes associated with ASD, researchers may be able to reduce some of the heterogeneity in the behavioral manifestation of the disorder. Thus, defining and measuring relevant endophenotypes is an important step in advancing our understanding of the etiology of ASD.

Ideally, such endophenotypes should (1) be closely related to neural mechanisms involved in social information processing, (2) be associated with known behavioral characteristics of ASD, (3) be more prevalent in family members of individuals with ASD than individuals without a family history of ASD, and (4) be on a continuum with such traits in the general population (Geschwind & Alarcon, 2006; Abrahams & Geschwind, 2008; Pelphrey, Shultz, Hudac & Vander Wyk, 2011). Finally, to enable family-wide genetic linkage studies, endophenotype measures should be valid across the age span, for both individuals with ASD and neurotypical individuals.

Researchers working on identification of genes related to ASD have begun investigating potential endophenotypes. One of the most well researched endophenotypes has been language. About 20% of children with ASD are largely nonverbal or use fewer than 5 words a day (Lord, Risi, & Pickles, 2004), while many more children are verbal, but obtain language with a delay.

There is a growing body of literature on language in first-order relatives of individuals with autism spectrum disorder. A recent study found that in simplex families (families of multiple children but for which a single individual has ASD) 20% of the unaffected siblings reported a history of language delay (compared to 7% in the general population) (Constantino, Zhang, Frazier, Abbacchi, & Law, 2010). Further, about half of these 20% reported speech abnormalities associated with ASD (Constantino et al., 2010). Yirimiya and colleagues reported that unaffected siblings of children with ASD (Sibs-ASD) had significantly lower language scores at 14 months of age when compared to siblings of typically developing children (Sibs-TD) (Yirmiya, Gamliel, Pilowsky, Feldman, Baron-Cohen, & Sigman, 2006). Toth and colleagues measured language in 18-27 month old unaffected Sibs-ASD and Sibs-TD, and results indicated that Sibs-ASD scored significantly lower on tests of receptive language skills (Toth, Dawson, Meltzoff, Greenson, & Fein, 2007).

Genetic linkage studies (where unaffected siblings are paired with their affected sibling) have begun researching endophenotypes as a way to reduce sample heterogeneity. Since endophenotypes should be measurable in unaffected family members, they could be used to increase power in the search of ASD-related loci. So far, studies stratifying data based on language delay have reported some success in terms of increasing signal, but replication across independent research groups has yet to be established (Spence, Cantor, Chung, Kim, Geshwind, & Alarcón, 2006; Bradford et al., 2001; Buxbaum et al., 2001). This lack of replication could be a result of many factors, for example, alleles may be more closely related to language delay than ASD itself.

Researchers have also attempted to indentify theory of mind as an endophenotype for ASD. Theory of mind is a developmental skill that is defined as the ability to attribute mental states to others. This metalizing ability has been shown to be a deficit in some children with ASD (Baron-Cohen, Leslie, Frith, 1985; Heerey, Keltner, Capps, 2003, Tager-Flushberg, 1999). However, the deficit does not seem to be universal as studies have shown a sub-set of children with ASD who are able to pass theory of mind tasks (Happé, 1994; Baron-Cohen et al., 1985). Lower theory of mind scores have also been reported in some parents of children with ASD (Baron-Cohen, & Hammer, 1997; Losh et al., 2009), siblings of children with ASD (Dorris, Espie, Knott, & Salt, 2004) and typically developing children who display subclinical traits associated with ASD (Ronald, Viding, Happé, & Plomin, 2006). Yet, another study did not report deficits in siblings of children with ASD (Shaked, Gamliel, & Yirmiya, 2006).

It is possible that theory of mind and language have had limited success as candidate endophenotypes because neither theory of mind or language are core deficits of autism spectrum disorder. One area of future research should focus on the identification of endophenotypes that are closely associated with core deficits in ASD.

The possible applications for endophenotype research in ASD extend beyond reducing heterogeneity in genetics studies. For example, endophenotypes have the potential to be useful in efficacy testing of randomized clinical trials. Currently, many researchers measure the success of an intervention based on changes in ASD symptomology, often measured by the Autism Diagnostic Observation Schedules (ADOS-G; Lord et al., 2000). Presently considered the "gold standard", this standardized observational assessment measures behaviors associated with ASD across a series of tasks and yields a total score that allows classification of "autism" and "autism spectrum". Given that the ADOS quantifies the presence or absence of behaviors, it may not be sensitive enough to measure change or to capture the heterogeneity of the disorder. Unsurprisingly, the largest randomized clinical trial of a parent-mediated intervention in ASD to date, failed to report intervention effects in regards to changes in ADOS scores (Green et al., 2010). This study did however, report intervention effects for improvement in parent-child communication. Future research needs to determine if utilizing continuous measures specific to one core deficit (i.e., endophenotype measures) would provide more powerful analyses for randomized clinical trials in autism spectrum disorder.

The following three studies aim to validate a candidate endophenotype measure of autism spectrum disorder. This measure uses eye-tracking technology to evaluate how individuals visually process social video vignettes that elicit the coordination of attention with another person (i.e., how individuals respond to others' bids for joint attention). Chapter One presents data on associations between the broad autism phenotype and performance on our eye-tracking measure in a community sample of adults (N=44). A version of Chapter One was submitted to the *International Journal for Psychophysiology* on January 3rd, 2012 and is currently under review (Swanson, Serlin, & Siller, 2012a). Chapter two also presents data on associations between the broad autism phenotype and performance on our eye-tracking measure, but this time with a community sample of typically developing children (N = 50). A version of Chapter Two was submitted to the *Journal of Autism and Developmental Disorders* on February 14th, 2012 and is currently under review (Swanson, Serlin, & Siller, 2012b). Chapter Three compares typically developing children ($n = 24$) to children with autism spectrum disorder ($n = 21$) on a behavioral performance of theory of mind as well as our eye-tracking measure of joint attention (Swanson & Siller, 2012). Successful steps toward the validation of our eye-tracking paradigm are reviewed in the General Discussion.

CHAPTER ONE

Broad Autism Phenotype in a Community Sample of Adults Predicts Performance on an Eye-Tracking Measure of Joint Attention

1.1. Abstract

The current study constitutes the first step in a program of research that aims to develop, refine and validate a candidate endophenotype measure that has the potential to enhance our understanding of the etiology of Autism Spectrum Disorder (ASD). The proposed measure takes advantage of modern eye-tracking technology and evaluates how individuals allocate their attention when viewing social video vignettes that display an adult model who is gazing at a series of targets that appear and disappear in the four corners of the screen (congruent condition). Gaze allocation in the experimental condition is compared to a set of control stimuli where the model's gaze is not directed at the appearing/disappearing targets (incongruent condition). Data from the current study demonstrate the feasibility of administrating this experimental paradigm to a community sample of adults (N = 44) and reveal two major findings. First, the gaze allocation of adults differed significantly between the experimental and control condition. Second, individual differences in gaze allocation were significantly predicted by a self-report measure evaluating features of the broad autism phenotype (BAP). These findings are consistent with the notion that eye-tracking measures of gaze following capture a valid endophenotype associated with ASD.

Chapter One is a version of "Broad autism phenotype in a community sample of adults predicts performance on an eye-tracking measure of joint attention", M. Swanson, G.Serlin, & M. Siller, International Journal for Psychophysiology, January 3rd, 2012, currently under review.

1.2. Introduction

The ability to respond to another person's bid for joint attention (RJA) is an important milestone in children's early social-communicative development. Behaviorally, children learn to follow the gaze direction or pointing gesture of others by turning their head and eyes in the designated direction. For most children, first signs of this ability emerge around 3 months of age (D'Entremont, 2000), and continue to be consolidated in children's behavioral repertoire throughout the first year (Deák, Flom, & Pick, 2000; Moll & Tomasello, 2004). The act of following gaze remains important throughout development and into adulthood as demonstrated by a large body of literature studying gaze cueing and gaze following in adults (for a review see Frischen, Bayliss, & Tipper, 2007). Many of these studies use variations of a spatial cueing paradigm developed by Posner (1980). In one such variation participants are shown a centrally located face that gazes either left or right; after a time lag a target stimulus appears on one side of the face and participants are tasks with pressing a key once they have located the target stimulus. Studies have found that reaction times are faster when the target appears in the gazed at location when compared to a non-gazed at location (Friesen & Kingstone, 1998; Driver, Davis, Ricciardelli, Kidd, Maxwell, & Baron-Cohen, 1999). Pelphrey and colleagues (Pelphrey, Singerman, Allison, & McCarthy, 2003) used a slightly different paradigm to study brain activation in response to gaze following. In their paradigm, a stimulus appeared in one of six lateral locations, after a delay a computer generated model switched gaze to view the target or an empty location. Results indicated that brain activation in the superior temporal sulcus, intraparietal sulcus, and fusiform gyrus was significantly different when the model viewed the target in comparison to when she gazed elsewhere (Pelphrey et al., 2003).

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder, characterized by a triad of behaviors, including impairments in reciprocal social interaction, impairments in communication, and the presence of restrictive, repetitive, or stereotyped patterns of behavior (American Psychological Association, 2000). Several decades of research have demonstrated that children with autism spectrum disorder present with a characteristic deficit in RJA (Sigman, Dijamco, Gratier, & Rozga, 2004; Mundy, Sigman, Ungerer, & Sherman, 1986; Loveland & Landry, 1986). Most of the research regarding this disorder has focused on children with ASD between 3 and 5 years of age and shown that these children are less likely to follow an adult's gaze or pointing gesture to an object than either typically developing or developmentally delayed children. Despite early deficits in RJA, longitudinal research that followed children with ASD into middle childhood, adolescence and adulthood has reported that many of these individuals eventually demonstrate at least some proficiency in the ability to interpret others' attentional cues. In a longitudinal study by Sigman and colleagues, children with ASD successfully responded to about 40% of point-following trials when evaluated during the preschool years (mean CA= 3:11, SD= 1:0 years, Sigman & Ruskin, 1999). When re-evaluated at 13 and 19 years, these same individuals successfully responded to 88% and 81% of the trials, respectively (Sigman & McGovern, 2005). Despite these partial accomplishments in the ability to respond under experimental conditions to an examiner's bids for joint attention, it remains unclear whether deficits in spontaneous gaze following are present in childhood and persist into adulthood.

A review of literature on gaze cueing in individuals with ASD yields conflicting results (Frischen et al., 2007). Several studies have found support for gaze cueing effects in children with ASD (Swettenham, Condie, Campbell, Milne, & Coleman, 2003; Senju, Tojo, Dairoku, & Hasegawa, 2004; Kylliäinen & Hietanen, 2004). However, these results are in contrast to a study by Ristic and colleagues (Ristic, Mottron, Friesen, Iaocci, Burack, & Kingstone, 2005) comparing reaction times of a sample of high functioning adults with typically developing adult controls. When viewing a spatial cueing paradigm, control participants performed with the expected cueing effect, but reaction times for participants with ASD were indistinguishable across conditions. In an interesting follow-up study where the gaze location of the central stimulus could be predicted (i.e. the central stimulus looked at the target stimulus on 80% of the trials), both individuals with ASD and typical controls showed the expected gaze cueing effects (Ristic et al., 2005). Bayliss and colleagues (Bayliss, Pellegrino, & Tipper, 2005) have extended this research to individuals displaying the broad autism phenotype (BAP), these individuals present subclinical or mild predispositions to ASD-associated traits and preferences. Results from the study by Bayliss and colleagues (2005) indicated that individuals who displayed more BAP traits showed weaker cueing effects when compared to individuals displaying fewer BAP traits.

Current theories suggest that the etiology of ASD likely involves multiple genes interacting with each other (Abrahams & Geschwind, 2008; Geschwind & Alarcon, 2006). According to this model, it is predicted that individual genetic risk factors are more closely related to specific features or components of ASD (i.e., endophenotypes) rather than ASD itself. Defining and measuring relevant endophenotypes is an important step in advancing our understanding of the etiology of ASD. Ideally, such endophenotypes should (1) be associated with known behavioral characteristics of ASD, (2) be closely related to neural mechanisms that underlie these behavioral characteristics, (3) be more prevalent in family members of individuals with ASD than individuals without a family history of ASD, and (4) be on a continuum with such traits in the general population (Geschwind & Alarcon, 2006; Abrahams & Geschwind, 2008; Pelphrey, Shultz, Hudac & Vander Wyk, 2011). Finally, to enable family-wide genetic linkage studies, endophenotype measures should be valid across the life span, for both individuals with and without a diagnosis of ASD.

The current study constitutes the first step in a program of research that aims to develop, refine and validate a candidate for such an endophenotype measure. Specifically, the candidate measure takes advantage of modern eye-tracking technology to evaluate how individuals allocate their attention when viewing social video vignettes that elicit the coordination of attention with another person. The excellent temporal resolution of modern eye-tracking technology lends itself to the detailed analysis of spontaneous gaze following. Across the last decade research has established eye-tracking as a valid technology to investigate characteristics associated with ASD (for a review see Boraston & Blakemore, 2007; see also Pelphrey, Sasson, Reznick, Paul, Goldman & Piven, 2002; Klin, Jones, Schultz, Volkmar, & Cohen, 2002). Findings from this research show that gaze allocation of adults with ASD reliably differs from controls, particularly when viewing dynamic, social stimuli. It has been theorized that differences in gaze allocation during childhood may be the basis for neurodevelopmental atypicalities across the lifespan (Pelphrey et al., 2002; Speer, Cook, McMahon, & Clark, 2007; Fletcher-Watson, Leekam, Benson, Frank, & Findlay, 2009)

The eye-tracking stimuli evaluated in the current research were based on a set of functional magnetic resonance imaging (fMRI) stimuli originally developed by Justin Williams and colleagues (Williams, Waiter, Perra, Perrett, & Whiten, 2005). In the original stimuli, participants viewed short video clips that displayed a moving red dot as well as the face of a model that either followed the moving red dot with his eyes (congruent condition) or where the model's gaze moved equally as often but was always directed elsewhere (incongruent condition). Results indicated that brain areas associated with joint attention (most prominently the right ventral medial frontal cortex and the left anterior frontal cortex), were activated during the congruent condition, but were not activated during the incongruent condition (Williams et al., 2005). The analysis focused on differences in brain activation between the congruent and incongruent gaze shift sequences. Due to the limitations in temporal resolution characteristic for fMRI, the researchers were not able to evaluate specific moments in the gaze shift sequence (e.g., moments of gaze following) and thus attributed differences between the conditions to differences in whether participants were or were not ‘experiencing’ joint attention with another person (Williams et al, 2005). Since eye-tracking data can be collected with excellent temporal resolution (60Hz), the current study focused on specific time intervals within the stimuli that were selected to allow for the analysis of contextual gaze direction on visual attention allocation.

By studying a community sample of adults, we will (1) test the feasibility of administering this measure in an adult population, (2) evaluate whether gaze allocation during the experimental condition differs reliably from the control condition, and (3) test whether this variability is associated with features of the broad autism phenotype (BAP). We aimed to test two hypotheses:

Hypothesis 1: Gaze time allocation to the Face and Target AOI will differ significantly between the congruent and incongruent conditions.

Hypothesis 2: Differences in gaze time allocation between the two experimental conditions are predicted (i.e., moderated) by features of the broad autism phenotype.

1.3 Methods

1.3.1 Participants

Forty-four adult college students were recruited through the Introduction to Psychology research pool of Hunter College-City University of New York in New York, NY, and through word of mouth. Participants ranged in age from 18 to 50 years (*M* = 23.58; *SD* = 7.33; 70% male) and the sample was diverse in terms of ethnicity and race (47.7% White, 18.2% Asian, 15.9% Hispanic, Latino, or Spanish, 6.8% African American, 2.3% Middle Eastern, 9.1 % Mixed/Other). The majority of participants (63.3%) were born in the United States and had completed an average 2.89 (*SD*= 2.12) years of college. Many of our participants were first generation college students, 41.9% of their mothers and 46.6% of their fathers had completed a Bachelors Degree.

1.3.2 Procedures

Participants were tested during a single laboratory visit at Hunter College, City University of New York. Assessment sessions lasted about 60 minutes and included the administration of our eye-tracking measure of joint attention. In addition, participants completed the Broad Autism Phenotype Questionnaire (BAPQ; Hurley, Losh, Parlier, Reznick, & Piven, 2007) as well as a brief demographic questionnaire. Informed consent was attained from all participants and the study was conducted in accordance of the Institutional Review Board at Hunter College, City University of New York.

1.3.3 Eye-tracking Measure of Joint Attention

1.3.3.1 Eye-tracking stimuli. Participants were presented a series of 8 randomly presented videos that were each 34 seconds long and included 4 gaze shifts trials (see Figure 1.1 for a still image). Before stimulus presentation participants viewed a short video clip that indicated they would be watching short video clips with a model looking through a port hole and cartoon characters appears in the corners of the screen. Finally, participants are told to “just have a look”. Each video displayed the head and face of a model in the center of the screen, while targets appeared and disappeared in each of the four corners. Half of the videos were congruent (i.e., the model’s gaze followed the target on the screen) and the other half of the videos were incongruent (i.e., the model’s gaze was directed elsewhere). Videos began with a model looking straight into the camera for 4 seconds (simulating the model making eye contact with the participant). Next, a target (i.e., a popular cartoon character, © 2011 Nintendo/Pokémon) appeared in one of the four corners of the screen and 500 milliseconds later the model shifted her gaze to a corner for an average of 3.85 seconds, either congruent or incongruent. In both conditions, the model's gaze returned to the center of the screen 500 ms after the target disappears, after which the next trial was presented.

In comparison to the original stimuli developed by Williams et al. (2005), our experimental paradigm differed in several important ways: (1) each trial started with the model looking at the center of the screen (stimulating eye contact with the participant) to enhance the salience of the model's bid for joint attention, (2) the targets appeared in the four corners of the screen (rather than the bottom of the screen) in order to enhance attention to the face and to increase the distance between the Areas of Interest, and (3) the target was a randomly chosen popular cartoon character (rather than a red dot) in order to increase ecological validity and make the stimuli more engaging across the lifespan.

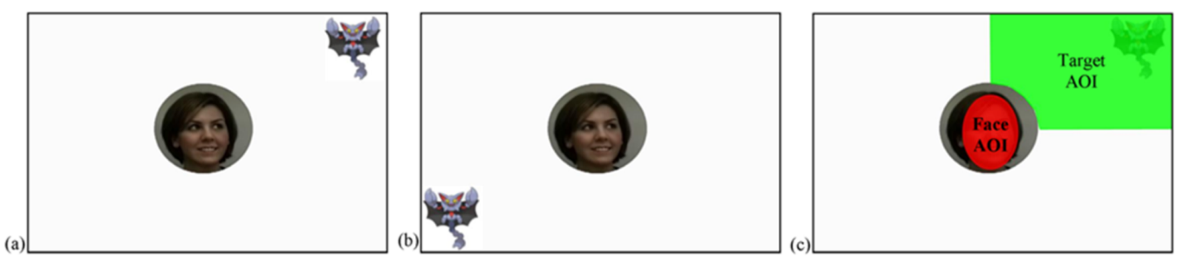

Figure 1.1. Sample stimuli and an illustration of the Areas of Interest (AOI) used in analysis. (a) sample congruent stimulus, (b) sample incongruent stimulus, (c) sample Face and Target AOIs.

1.3.3.2 Data acquisition and analysis. Stimuli presentation and participant eye gaze behavior was recorded using a Tobii T-60 eye tracker with infrared cameras integrated under a 43.18 cm LCD display monitor (TOBII Technology AB, Tobii T-60). Eye-movements from both eyes were collected at a rate of 60 recordings per second (60 Hz), from an average distance of 60 centimeters, with an accuracy of 0.5°. Videos covered a rectangular space on the screen of 21.5cm by 30.5 cm. Viewed at a distance of 60.0 cm, the videos correspond to a 20.3° and 28.5° visual angle. In terms of size, Faces were 8.4 cm and circular, while Targets were 5.0 cm squares. Viewed at a distance of 60.0 cm, Faces and Targets correspond to 8.0° and 4.8° visual angles. The eye-tracking system was completely non-invasive, allowing for free, unconstrained movement of the head and body. Data acquisition focused on specific time intervals (scenes) that were selected to allow for the analysis of gaze following. That is, the beginning of each scene was selected to coincide with the first frame when the target appeared on the screen; similarly, the end of each scene coincided with the moment the target disappeared from the screen. Thus, for each participant, we created 32 scenes (8 videos with 4 trials each), 16 of which were congruent and 16 incongruent.

To test our main hypotheses, eye gaze patterns during each scene were evaluated by specifying two Areas of Interest (AOI, Boraston & Blakemore, 2007): (1) Face AOI, or gaze to the model's face, and (2) Target AOI, or gaze to the target quadrant of the screen (see Figure 1.1). To quantify individuals' gaze allocation we employed the Tobii Studio metric "Total Visit Duration" which is defined as the duration of all visits within a given AOI (TOBII Technology AB, Tobii Studio version 2.2.5). A visit is defined as the interval of time between the first fixation on a given AOI and the next fixation outside the AOI. Fixations were defined using the Tobii Studio fixation filter which utilizes the method described by Olsson (2007) (see the Appendix for details). Since scenes varied in length (M=3.85, SD= .26, range= 3.33-4.44) we computed the percentage of gaze time spent in each AOI, relative to the duration of time participants spent looking on screen.

1.3.4. Broad Autism Phenotype Questionnaire

The Broad Autism Phenotype Questionnaire (BAPQ) is designed to be administered to adults, and aims to evaluate features of the broad autism phenotype (i.e., subclinical, mild predisposition to ASD-associated traits and preferences; Hurley et al., 2007). This self-report questionnaire asks participants to rate 36 items on a 6 point scale, with responses ranging from *very rarely,* to *very often*. Items are selected to make up three subscales that parallel deficits and behaviors common in ASD. The aloof subscale describes individuals who show little enjoyment in everyday social interactions; items from this scale include "I would rather talk to people to get information than to socialize". The pragmatic subscale highlights individuals who have difficulties communicating fluidly, in a reciprocal manner. Items in this subscale include "I have been told that I talk too much about certain topics." Finally, the rigid subscale describes individuals who have little interest, and difficulty coping with change. Items from the rigid subscale include "I like to closely follow a routine while working."Averages are computed for the total score and each subscale. Higher scores indicate a greater extent of subclinical symptoms of ASD. Table 1.1 outlines descriptive information for BAPQ scores in the current population.

Table 1.1. *Descriptive statistics for BAPQ total and subscale scores. Clinical cutoff scores determined by Hurley et al. (2007) and the percentage of our population that scored at or above Hurley's clinical cutoff is also reported.*

Variable	**Mean (SD)**	**Range**	**Clinical Cutoff**	**% above cutoff**
BAPQ Total Score	2.77 (.49)	1.97 - 4.30	3.15	13.63% (n=6)
Aloof Subscale	2.65 (.74)	1.33 - 4.72	3.25	20.45% (n=9)
Rigid Subscale	3.04 (.68)	2.00 – 5.00	3.50	20.45% (n=9)
Prag. Lang. Subscale	2.65 (.52)	1.75 - 4.17	2.75	43.18% (n=19)

Abbreviations: Prag. Lang. Subscale, Pragmatic Language Subscale.

Psychometric properties of the BAPQ were previously evaluated (Hurley et al., 2007), demonstrating excellent internal consistency; Cronbach's α scores were as follows: .94 for the aloof subscale, .91 for the rigid subscale, .85 for the pragmatic language subscale, and .95 across all item (Hurley et al, 2007). Further, a recent study comparing the BAPQ, Social Responsiveness Scale-A (SRA; Constantino, 2002), and Autism Spectrum Quotient (AQ; Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001) found that the BAPQ was the best of the three measures at quantifying the BAP in terms of internal consistency, criterion validity, and incremental validity in a large population of non-clinical adults (Ingersoll, Hopwood, Wainer, & Donnellan, 2011).

1.3.5. Statistical Analysis

Preliminary analyses were conducted to evaluate the quality of data collection for the eye-tracking paradigm. The On-task Percentage was computed for each trial, defined as the percentage of time during which the participant gazed at the screen. Results from fitting a mixed model using SAS Proc Mixed showed that the mean On-task Percentage did not differ significantly between the congruent and incongruent condition, $F(1, 1363) = 0.57$, $p = .45$. The mean On-task Percentage for each participant ranged between 80.1% and 99.8% ($M = 94.02$, $SD = 5.0$). No significant associations were found between the On-task Percentage and the subscales of the BAPQ, participant age or gender. For all subsequent analyses, trials with an On-task Percentage smaller than 50% were considered missing (0.7% and 1.6% for the congruent and incongruent condition, respectively). Further, no significant associations were found between looking time to the Target or Face AOI and participant age or gender.

To address the hypotheses, data were analyzed by fitting a series of mixed models using SAS Proc Mixed (SAS software, Version 9.2 Copyright © 2002-2008 SAS Institute Inc., Cary, NC, USA) with percent of viewing time for the Face and Target AOIs as outcome. All models were specified with a random intercept, which is equivalent to a Repeated Measure ANOVA.

Preliminary analyses showed that global characteristics such as age or gender were not related to gaze allocation during the joint attention paradigm or participants BAPQ scores, ($p > .20$).

1.4. Results

Hypothesis 1: Gaze time allocation to the Face and Target AOI will differ significantly between the congruent and incongruent conditions

We predicted that participants would allocate more gaze to the Face AOI in the incongruent than the congruent condition. Conversely, we predicted that participants would allocate more gaze to the Target AOI during the congruent than the incongruent condition. To test these hypotheses, we fit two mixed models with percent of viewing time to each AOI (Face, Target) as outcome. Experimental condition *(i.e., congruent vs. incongruent)* was entered as a fixed effect. Significance tests confirmed both of our hypotheses. As illustrated in Figure 1.2, participants allocated less attention to the Face AOI in the congruent (estimated marginal mean = 19.62%, SE = 2.48) than in the incongruent (estimated marginal mean = 23.66%, SE = 2.72) condition, $F(1, 1355) = 22.19$, $p < .0001$. Conversely, participants allocated more attention to the Target in the congruent (estimated marginal mean = 77.91%, SE = 2.68) than in the

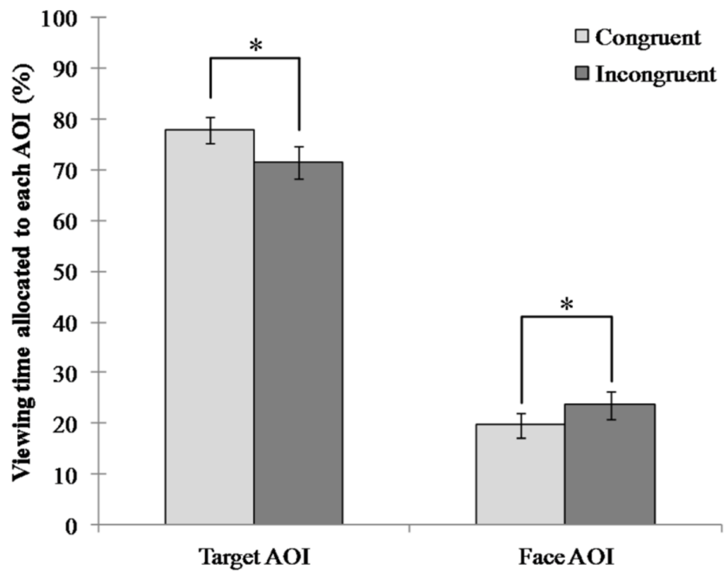

Figure 1.2. Sample stimuli and an illustration of the Areas of Interest (AOI) used in analysis. (a) sample congruent stimulus, (b) sample incongruent stimulus, (c) sample Face and Target AOIs.

incongruent (estimated marginal mean = 71.63%, SE = 3.20) condition, $F(1, 1355) = 45.92$, $p < .0001$.

Hypothesis 2: Differences in gaze time allocation between the two experimental conditions are predicted (i.e., moderated) by features of the broad autism phenotype

We predicted that differences in gaze time allocation between the congruent and incongruent condition would be more pronounced for participants with low BAPQ scores and less pronounced for individuals with high BAPQ scores. To evaluate this hypothesis, we fit a series of mixed models with Face AOI and Target AOI as outcome. All models included two main effects (i.e., BAPQ scores, experimental condition) and one interaction effect (i.e., BAPQ*condition). We first specified our models using the BAPQ total scores. Subsequently, we also specified models using the three BAPQ subscales (aloof, rigidity, pragmatic language). With regards to the Face AOI, results showed a significant condition*BAPQ total score interaction effect, $F(1,1354) = 4.82$, $p < .05$. Follow up analyses evaluating the three BAPQ subscales revealed that the BAPQ*condition interaction effect was significant for the aloof subscale, $F(1,1346) = 4.757$, $p < .05$ and marginally significant for the rigid subscale, $F(1,1346) = 3.69$, $p = .055$. With regards to the Target AOI, results showed a significant condition*BAPQ total score interaction effect, $F(1,1354) = 4.35$, $p < .05$. Follow up analyses showed that the BAPQ*condition interaction effect was significant for the aloof subscale, $F(1,1354) = 4.40$, $p <.05$ and the rigid subscale, $F(1,1354) = 4.80$, $p = .05$. The interaction between condition and the pragmatic language subscale was non-significant ($p > .50$) for both, the Face and Target AOIs.

To further probe the nature of these BAPQ*condition interaction effects, we used a ‘Regions of Significance’ approach to identify specific BAPQ values (i.e., upper limits) for which differences between the congruent and incongruent conditions were significant (Preacher, Curran, & Bauer, 2006). This method is statistically conservative and practically more meaningful than other methods used to analyze continuous moderators (i.e. splitting participants into quartiles). Separate RoS values were computed for the Face AOI and Target AOI. Table 1.2 reports the RoS values (upper limit) for the BAPQ total score as well as the two significant BAPQ subscales (i.e., aloof, rigid). In addition, Figures 1.3a and 1.3b display a graphic respectively. For example, participants with BAPQ aloof subscale scores below 3.21 reliably differed in their gaze allocation to the Face AOI between the congruent and incongruent condition. In contrast, participants scoring above this value (*n* = 9, 20.45%) did not reliably differ in their gaze allocation to the Face AOI between the congruent and incongruent condition (Figure 1.3b). Further, in the congruent condition individuals with higher aloof scores followed the model's gaze to the target less often when compared to individuals with lower aloof scores.

Table 1.2. *The upper limit values for the 'Regions of Significance' (RoS) and the percentage of participants scoring outside the RoS for the BAPQ total and subscale scores.*

Variable	**RoS (upper limit)**	**Participants above RoS limit**
BAPQ Total Score Face AOI	3.20	11.36 % (n=5)
BAPQ Total Score Target AOI	3.49	11.36 % (n=5)
BAPQ Aloof Subscale Face AOI	3.21	20.45% (n = 9)
BAPQ Aloof Subscale Target AOI	3.65	6.81% (n = 3)
BAPQ Rigid Subscale Face AOI	3.39	20.45% (n = 9)
BAPQ Rigid Subscale Target AOI	4.07	9.09% (n=4)

Note. Regions of Significance (RoS) were not computed for the BAPQ pragmatic language subscale since the corresponding BAPQ*condition interaction effect was non-significant.
illustration of the condition*BAPQ aloof subscale interaction effect for the Target and Face AOI,

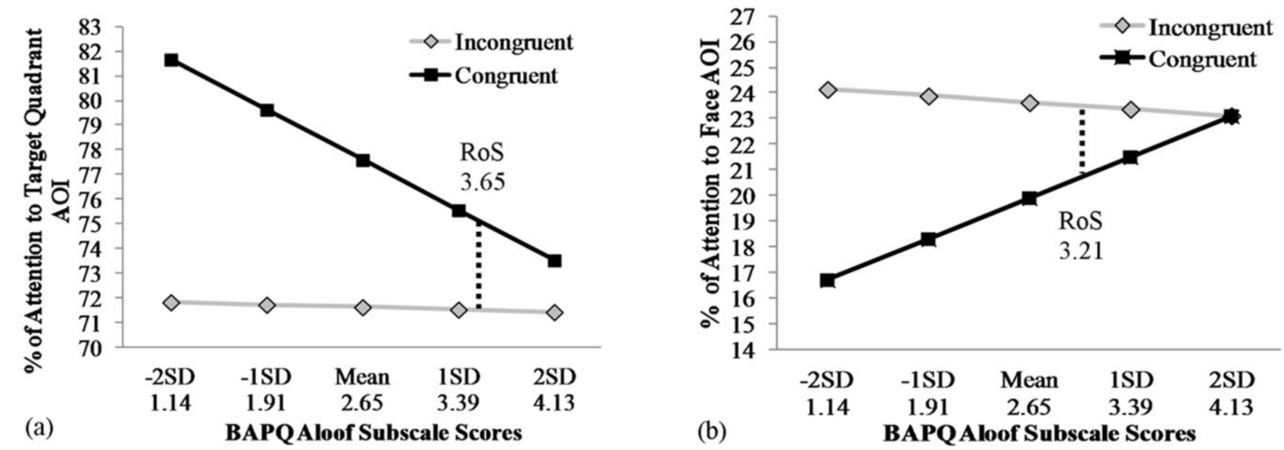

Figure 1.3. Graphs depicting of condition*BAPQ aloof subscale interaction effect for (a) Face AOI, and (b) Target AOI. Regions of Significance (RoS) are indicated with a dotted line.

1.5. Discussion

The current study constitutes the first step in a program of research that aims to develop, refine and validate a candidate endophenotype measure that has the potential to enhance our understanding of the etiology of Autism Spectrum Disorder (ASD). The proposed measure takes advantage of modern eye-tracking technology and evaluates how individuals allocate their attention when viewing social video vignettes that display an adult model who is gazing at a series of targets that appear and disappear in the four corners of the screen (congruent condition). Gaze allocation in the experimental condition is compared to a set of control stimuli where the model's gaze is not directed at the appearing/disappearing targets (incongruent condition). Data from the current study demonstrates the feasibility of administrating this experimental paradigm to a community sample of adults (N = 44) and reveals two major findings. First, the gaze allocation differed significantly between the experimental and control condition. Second, individual differences in gaze allocation were significantly predicted by a self-report measure evaluating features of the broad autism phenotype (BAP).

Preliminary analyses evaluating the quality of data collection for the eye-tracking paradigm revealed that the participants sustained a high level of attention throughout the repeated administration of 32 trials (less than 2% of trials had to be excluded due to a lack of eye-tracking data). As outlined in the introduction, in order to realize the true potential of an endophenotype measure, it is essential that the candidate measure is valid across the life span, for both individuals with and without a diagnosis of ASD. The current eye-tracking paradigm was specifically designed to be engaging across the life span and elicit maximum levels of attention from participants. For example, we chose dynamic over static images, each trial started with the model establishing eye contact with the participant, and we chose a variety of popular cartoon characters for targets. Even though it is likely that the attentional limitations of children, particularly children with ASD, will produce somewhat higher levels of missing data, the excellent quality of data collected in the current study are encouraging. Future studies should take into consideration potential improvements to our experimental paradigm. One improvement would be to add a condition where there is a target in the gaze quadrant, but also one in a comparison quadrant. Sustained fixations to an empty space are unlikely, so unsurprisingly we found very little looking time to gaze quadrants in our incongruent condition. By occupying comparison quadrants with a target, an analysis of looking time to non-gazed at quadrants would be more viable.

Results from this research revealed that adults showed several significant differences in gaze allocation between the congruent and incongruent condition. First, gaze allocation to the target was greater in the congruent than in the incongruent condition. This finding suggests that the target was inherently more interesting to the participant if the model's gaze was directed at the target as well, and less interesting if the adult model gazed elsewhere. A similar cuing effect has been reported in infants as young as four months of age (Reid & Striano, 2005). Second, gaze allocation to the model's face was greater in the incongruent than the congruent condition. One interpretation of this enhanced attention to the model's face in the incongruent condition is that participants may have followed the model's gaze to the empty corner, gazing back at the face after noticing that the corner was empty.

Results also showed that features of the broad autism phenotype reliably predicted individual differences in gaze allocation while viewing our experimental stimuli. Specifically, participants who reported few features of the BAP showed clear differences in gaze allocation between the congruent and incongruent condition. That is, they allocated more attention to the face during the incongruent than the congruent condition. Conversely, they allocated more attention to the target during the congruent than the incongruent condition. In contrast, for participants who reported more BAP features, differences in gaze allocation between the two conditions were less pronounced. To further investigate the nature of this significant condition-by-BAPQ interaction effect, we used a 'regions of significance approach' to identify specific BAPQ values for which differences between the congruent and incongruent condition were significant. Post-hoc analysis evaluating the BAPQ total score showed that a significant effect for experimental condition (i.e., congruent vs. incongruent) was evident for participants who scored lower that 3.20 and 3.44, when predicting the Face and Target AOI respectively.

Our results are in line with a recently published study by Chen and Yoon (2011) where adults viewed videos of a model speaking directly into the camera, or speaking but with averted eyes. Results indicated that participants with low BAP scores spent more time viewing the eyes during the direct condition than in the averted eyes condition, whereas the individuals with high BAP scores spent indistinguishable amounts of time viewing the eyes in the two conditions (Chen & Yoon, 2011).

The broad autism phenotype is a global construct that includes various associated features including aloof or rigid personality styles and pragmatic language (Piven, Palmer, Jacobi, Childress, & Arndt, 1997; Piven, Palmer, Landa, Santangelo, Jacobi, & Childress, 1997; Piven & Palmer, 1997; Landa, Piven, Wzorek, Gayle, Chase, & Folstein, 1992). Post-hoc analysis from the current study showed that pattern of gaze time allocation was specifically predicted by the aloof and rigid subscales of the BAPQ. Interestingly, these two subscales seem to map onto two competing current theories of gaze following deficits in ASD. A deficit in gaze following could result from a deficit in social understanding (Mundy & Sigman, 2006), which could present in adults as a lack of interest in social interactions (as measured by the aloof subscale). Alternatively, gaze following deficits could result from difficulties disengaging attention, which could present as a difficulty or resistance to change (as measured by the rigid subscale) (Couchesne, Townsend, Akshoomoff, Saitoh, Yeung-Courchesne, Lincoln et al., 1994; Zwaigenbaum, Bryson, Rogers, Roberts, Brian, & Szatmari, 2005; Elsabbagh, Volein, Holmboe, Tucker, Csibra, Baron-Cohen et al., 2009).

In the current sample of 44 adults, 18% of the participants scored above cut off on at least two subscales of the BAPQ, and thus meeting criteria for the BAP (Hurley et al., 2007). One limitation of the current study is that we measured the BAP with a single measure, and hence were unable to establish convergent validity of this constellation of behaviors. This is further an issue since information on the prevalence of features of BAP in the general population is limited, with estimates ranging between 2-23% (Baron-Cohen, Wheelwright, Skinner, et al., 2001; Losh, Childress, Lam, & Piven, 2008). Although, our prevalence rates may seem high, the averages found in our study are similar to that in a large study (N=626) recently published by Ingersoll and colleagues (2011). Specifically, for the BAPQ total score both our data and that of Ingersoll and colleagues averaged to 2.77. Averages for the subscales were also similar; we reported 2.65

for the aloof subscale, 3.04 for the rigid subscale, and 2.65 for the pragmatic language subscale, whereas Ingersoll and colleagues (2011) reported 2.53, 3.43, and 2.87 respectively. As emphasized by Rutter (2011), these finding are surprising in that it suggests that features of BAP in the general population are likely much more common than previously suspected.

During recent years, a growing number of studies involving typically developing populations have shown that BAP features reliably predict performance on behavioral tasks that are impaired in ASD. For example, features of BAP have been linked to individual's reaction time to gaze cues (Bayliss & Tipper, 2005) as well as performance on tasks evaluating theory of mind (reading the mind from the eyes test, Baron-Cohen, Wheelwright, Hill, Raste & Plumb, 2001) and executive function abilities (embedded figures task, Grinter, Maybery, Van Beek, Pellicano, Badcock, & Badcock, 2009). Finally, fMRI research involving a community sample of adults viewing the Stroop Task has also linked BAP features to greater deactivation of the posterior superior temporal sulcus, a brain region often implicated in social cognition (von dem Hagen, Nummenmaa, Yu, Engell, Ewbank, & Calder, 2011).

The current study was the first step in validating an endophenotype measure in a sample of adults. In order to fully validate this measure future research still needs to (1) relate this measure to neural mechanisms involved in social information processing, (2) determine what, if any, behavioral characteristics of children with ASD are associated with performance on this measure, and (3) determine if impaired performance on this measure is more prevalent in family members of individuals with ASD when compared to individuals without a family history of ASD.

CHAPTER TWO

Broad Autism Phenotype in Typically Developing Children Predicts Performance on an Eye-Tracking Measure of Joint Attention

2.1. Abstract

We examined visual attention allocation during a set of social video vignettes that are intended to elicit the coordination of attention with another person, compared to a control condition. Deficits in joint attention are a characteristic deficit of young children with autism spectrum disorder (ASD). Participants included 50 typically developing school-aged children between 3 and 9 years of age (*M* = 6:3, *SD* = 1:8). Results demonstrate that gaze allocation differed significantly between the experimental and control condition. Further, individual differences in gaze allocation were significantly predicted by a parent-report measure evaluating features of the broad autism phenotype. This study contributes to a research program that aims to develop and validate an endophenotype measure of ASD.

Chapter Two is a version of "Broad autism phenotype in typically developing children predicts performance on an eye-tracking measure of joint attention", M. Swanson, G. Serlin, & M. Siller, Journal of Autism and Developmental Disorders, submitted February 14th, 2012, currently under review.

2.2. Introduction

The etiology of the neurodevelopmental disorder, Autism Spectrum Disorder (ASD), likely involves multiple genes interacting with each other rather than a chromosomal abnormality of a single gene (Abrahams & Geschwind, 2008; Geschwind & Alarcon, 2006). According to this model, it is predicted that individual genetic risk factors are more closely related to specific features or components of ASD (i.e., endophenotypes) rather than ASD itself. Defining and measuring relevant endophenotypes is an important step in advancing our understanding of the etiology of ASD. Ideally, such endophenotypes should (1) be associated with known behavioral characteristics of ASD, (2) be closely related to neural mechanisms that underlie these behavioral characteristics, (3) be more prevalent in family members of individuals with ASD than individuals without a family history of ASD, and (4) be on a continuum with such traits in the general population (Geschwind & Alarcon, 2006; Abrahams & Geschwind, 2008; Pelphrey, Shultz, Hudac & Vander Wyk, 2011). Finally, to enable family-wide genetic linkage studies, endophenotype measures should be valid across the life span, for both individuals with and without a diagnosis of ASD.

Several endophenotypes have been proposed for ASD. Examples include: increased brain volume (Courchesne & Pierce, 2005; Palmen et al., 2005), language delay or impairment (Spence, Cantor, Chung, Kim, Geschwind, & Alacón, 2006), impaired facial expression identification (Spencer et al., 2011), deficits in executive function (Happé, Birskman, & Frith, 2001), and deficits in social cognitive skills like theory of mind. Theory of mind is the ability to attribute mental states to others, a developmental skill that has been found to be a deficit in children with ASD (Baron-Cohen, Leslie, Frith, 1985; Heerey, Keltner, Capps, 2003, Tager-Flushberg, 1999). Lower theory of mind scores have also been reported in some parents of children with ASD (Losh et al., 2009), siblings of children with ASD (Dorris, Espie, Knott, &

Salt, 2004) (although another study did not report deficits in siblings of children with ASD; Shaked, Gamliel, & Yirmiya, 2006), and typically developing children who display subclinical traits associated with ASD (Ronald, Viding, Happé, & Plomin, 2006). The current study expands on a line of research that utilizes a candidate endophenotype measure that takes advantage of modern eye-tracking technology to evaluate how individuals allocate their attention when viewing social video vignettes that elicit the coordination of attention with another person.

Responding to others' bids for joint attention

An important milestone in children's early social-communicative development is the ability to respond to others' bids for joint attention (RJA). At 3 months of age infants are able to follow the gaze direction of an adult 60% of the time when the adult is in close proximity and gazes at one of two objects directly in front of the infant (D'Entremont, 2000). Performance during this task only increases to over 80% when infants reach 5 months of age (D'Entremont, 2000). Research by Striano and Stahl (2005) found that 3 month old infants looked longer at an object while an adult was also looking at the object in comparison to periods of normal interactions, but it wasn't until 9 months when the infants were able to follow gaze of the adult during periods of coordinated joint attention (where the adult looked at the object, then regained eye contact with the infant before looking to the object again). Other research has found that around 9 months of age an infant will follow gaze direction of an adult when the target is outside the infant's immediate visual field (Moore, 2008).

Interestingly, it is not until 12 months of age when infants will follow an adult's gaze to objects that the infant cannot readily see, including objects behind the infant (Deák, Flom, & Pick, 2000) and objects behind a barrier (Moll & Tomasello, 2004). Tomasello proposes that it is right around this time when infants begin to realize that other people are intentional agents that have their own goals (1995). It is this new 'mind reading' ability that sets the stage for development of more complex social skills like language learning and theory of mind. Experimental studies have found that infants as young as 15-18 months (Houston-Price, Plunkett, & Duffy, 2006; Baldwin 1993a; Baldwin, 1993b) use gaze cues to learn novel object labels. Further, longitudinal studies have found that joint attention around 20 months of age predicts theory of mind abilities at 27-30 months (Nelson, Adamson, & Bakeman, 2008) and 44 months (Charman, Baron-Cohen, Sweetenham, Baird, Cox, & Drew, 2000).

Spontaneous gaze following in older children has received little attention in the typically developing literature. However, preschoolers with ASD show a characteristic deficit in their ability to respond to others' bids for joint attention (RJA, Sigman, Dijamco, Gratier, & Rozga, 2004; Mundy, Sigman, Ungerer, & Sherman, 1986; Loveland & Landry, 1986). Moreover, several prospective longitudinal studies of children with ASD have shown that individual differences in early RJA reliably predict children's subsequent language acquisition (Mundy, Sigman, & Kasari, 1990; Sigman & Ruskin, 1999; Sigman & McGovern, 2005; Anderson, Lord, Risi, DiLavore, Shulman, Thurm et al, 2007; Siller & Sigman, 2008; Sullivan, Finelli, Marvin, Garrett-Mayer, Bauman, & Landa, 2007).

Research from recent prospective longitudinal studies of baby-siblings of children with ASD (Sibs-ASD) has shown that deficits in RJA emerge very early in development. Sibs-ASD can be distinguished from baby siblings of typically developing children (Sibs-TD) as early as 12 months on a response to name measure (Nadig, Ozonoff, Young, Rozga, Sigman & Rogers, 2007), and 18 months on a point following measure (Cassel, Messinger, Ibanez, Haltigan, Acosta & Buchman, 2007). In a study comparing Sibs-ASD who later received a diagnosis of ASD to unaffected Sibs-ASD, RJA performance at 14 months predicted ASD outcome at 3 years, group differences in RJA were not significant at 14 months, but were significant at 24 months (Sullivan et al., 2007). Despite this growing body of research, it remains unclear whether alterations in spontaneous gaze following are found in older typically developing children who display traits of the broad autism phenotype.

By studying a sample of typically developing children, we will (1) test the feasibility of administering this novel eye-tracking measure to children across a broad age spectrum, (2) evaluate whether gaze allocation during the experimental condition differs reliably from the control condition, and (3) test whether this variability is associated with features of the broad autism phenotype (BAP).

2.3. Methods

2.3.1. Participants and Procedures

Between mid-2010 and mid-2011, 50 typically developing children (27 boys and 23 girls) between the ages of 3 and 9 years participated in this study. Families were recruited through local print and electronic advertisement. Participants were tested during a single laboratory visit at Hunter College, City University of New York. Parental informed consent and child assent was attained from all participants and the study was conducted in accordance of the Institutional Review Board at Hunter College, City University of New York. Mothers ranged in age between 24 and 49 years (*M*=33.39, *SD*= 5.97) and varied considerably in their educational attainment: 19.6% had an advanced degree (e.g. master's or doctoral degree), 17.6% had completed a standard college degree (e.g. bachelor's degree), 43.2% had a high school diploma, 7.8% had completed 11th grade. Educational information was unavailable for 11.8% of the mothers in our sample. The sample was predominantly Hispanic (33%) and African American (33%) but included groups of children with Asian (16%), European American (12%), and mixed (6%) ethnic and racial origin. Finally, 25% of the sample reported an annual household income of less than $20,000/year, 50% of the sample reported incomes of less than $40,000/year, and 75% of the sample reported incomes of less than $70,000/year. The diversity within this sample in terms of ethnic/racial origins and income is largely representative of the study site, New York City, NY, USA.

Assessment sessions lasted 120 minutes and included the administration of our eye-tracking measure of joint attention and a series of developmental and language assessments. In addition parents completed a questionnaire about sub-clinical behaviors associated with the broad autism phenotype (Social Responsiveness Scale, SRS; Constantino, 2002). Finally, parents completed a medical history questionnaire intended to screen for a broad range of neurodevelopmental disorders. All of the children in this sample were free of genetic conditions (i.e. Fragile X Syndrome, Down Syndrome, Tuberous Sclerosis, Angelman Syndrome) and developmental disorders (i.e. autism spectrum disorder, pervasive developmental disorder-not otherwise specified, Aperger's syndrome). One child had previously received a diagnosis of attention deficit disorder. Two children (4%) had a first degree relative, and 6 children (12%) had a second degree relative with an autism spectrum disorder. Likewise, 7 children (14%) had a first degree relative, and 6 children (12%) had a second degree relative with a learning disability or speech delay requiring therapy.

2.3.2. Assessment of Developmental and Language Skills

Children also participated in a series of standardized developmental assessments. Non-verbal cognitive skills were evaluated using four subscales from the Differential Abilities Scales II (DAS II; Elliott, 1990). Each of these subscales yields an age equivalent and standard score from which we calculated a composite non-verbal mental age score and a non-verbal mental standard score. Receptive language was measured using the Peabody Picture Vocabulary Test-4 (PPVT-4; Dunn & Dunn, 2007). In this untimed standardized test children are shown four color illustrations per page, the examiner then delivers a stimulus word, and the child indicates what picture corresponds to the stimulus word by pointing or verbally responding with the picture number. Expressive language was evaluated using the Expressive One-Word Picture Vocabulary Test, 4th Edition (EOWPVT-4; Brownell, 2000). The EOWPVT-4 is a standardized test of vocabulary where children are presented with a series of full color illustrations depicting objects, actions, or concepts and the examinee is asked to name each illustration (Brownell, 2000). Both the PPVT-4 and the EOWPVT-4 produce standard scores as well as age equivalents. For detailed participant characteristics, please see Table 2.1.

Table 2.1. *Participant characteristics, N=50*

Variable	**Mean**	**Standard Deviation**	**Range**
Chronological Age (years: months)	6:3	1:8	3:2-9:3
Receptive Language Age (years: months)	6:5	2:2	2:4-11:4
Receptive Language Standard Score	101.40	11.47	81-135
Expressive Language Age (years: months)	6:4	2:2	2:5-11:2
Expressive Language Standard Score	99.86	11.86	76-133
Non-verbal Mental Age (years: months)	6:10	2:2	3:11-11:7
Non-verbal Standard Scores*	106.12	13.08	82-132

Note. **n*=49.

2.3.3. Assessment of the Broad Autism Phenotype

The Social Responsiveness Scale (SRS; Constantino, 2002) is a 65-item parent report questionnaire designed to highlight behaviors that are characteristic of ASD. Parents report on a 4 point scale, with responses ranging from *not true*, to *almost always true*. The SRS has been standardized, and thus yields both raw scores and *T*-scores (Constantino, 2002). Items are selected to make up 5 subscales, examples include "Is aware of what others are thinking of feeling" from the social awareness subscale, "Is able to understand the meaning of other people's tone of voice and facial expressions" from the social cognition subscale, "Knows when he or she is too close to someone or is invading someone's space" from the social communication subscale, "Does not join group activities unless told to do so" from the social motivation subscale, and "Does extremely well at a few tasks, but does not do as well at most other tasks" from the autistic mannerisms subscale. Table 2.2 outlines descriptive information for SRS scores in the current population.

Table 2.2. *Descriptive statistics for Social Responsiveness Scale total and subscale scores, N*=50

Variable	**Raw Score**	***T*-Score**
	Mean (SD)	Mean (SD)
Total Score	35.02 (19.11)	51.92 (8.91)
Social Awareness Subscale	6.48 (3.09)	51.82 (9.90)
Social Cognition Subscale	6.66 (4.52)	52.26 (9.93)
Social Communication Subscale	10.84 (6.74)	50.74 (8.43)
Social Motivation Subscale	6.78 (4.27)	53.80 (10.15)
Autistic Mannerisms Subscale	4.26 (3.94)	50.52 (9.03)

Psychometric properties of the SRS were previously evaluated (Constantino, 2002), demonstrating excellent internal consistency; Cronbach's α scores were as follows: .94 for the male parent rating, .93 for female parent rating, .97 for clinical rating. The SRS has also been shown to have high discriminate validity when children with an ASD were compared to children with other psychiatric disorders, as well as high concurrent validity when a sample of children with autism were administered the SRS as well as the Autism Diagnostic Interview-Revised (ADI-R; Lord, Rutter, & Couteur, 1994) (Constantino et al, 2003; Bölte et al., 2008).

Total raw score cut-off points have been established for male and females in the general population as a way of screening for an ASD (a cut point of 70 and 65 is recommended for males and females, respectively). Use of these cut points results in sensitivity rating of .77, indicating an identification rate of 77% of children where a previous diagnosis has been established. Further, this measure has a specificity of.75, indicating that 75% of children who scores above the cut point qualified for a diagnosis in a follow up assessment (Constantino, 2002). Although none of our participants had received a diagnosis of an ASD, 10% of our male participants received scores above this cut-off (n= 5; M= 75.2, SD= 4.76, range= 71-82).

2.3.4 Eye-Tracking Measure of Joint Attention

2.3.4.1. Eye-tracking stimuli. Participants were presented a series of 8 videos that were each 34 seconds long and included 4 gaze shifts trials (see Figure 2.1 for a still image). At the center of the screen, each video displayed the head and face of a model, while targets appeared and disappeared in each of the four corners. Half of the videos were congruent (i.e., the model's gaze followed the target on the screen) and the other half of the videos were incongruent (i.e., the model's gaze was directed elsewhere). Videos began with a model looking straight into the camera (simulating the model making eye contact with the participant). Next, a target (i.e., a popular cartoon character, © 2011 Nintendo/Pokémon) appeared in one of the four corners of the screen and shortly thereafter the model shifted her gaze to a corner, either congruent or incongruent. In both conditions, the model's gaze returned to the center of the screen, after which the next trial was presented. Please see Swanson, Serlin, Siller, (2012a) for a detailed description of these stimuli.

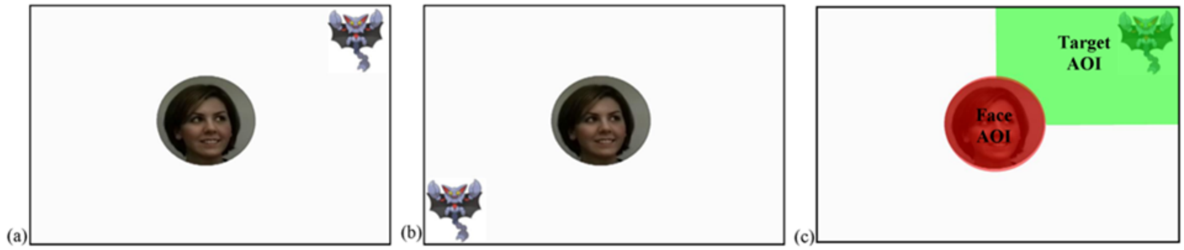

Figure 2.1. Sample stimuli and an illustration of the Areas of Interest (AOI) used in analysis. (a) sample congruent stimulus, (b) sample incongruent stimulus, (c) sample Face and Target AOIs.

2.3.4.2. Data acquisition and analysis. Stimuli presentation and participant eye gaze behavior was recorded using a Tobii T-60 eye tracker with infrared cameras integrated under a 17" LCD display monitor (TOBII Technology AB, Tobii T-60). Eye-movements from both eyes were collected at a rate of 60 recordings per second (60 Hz), from an average distance of 60 centimeters, with an accuracy of 0.5°. The eye-tracking system was completely non-invasive, allowing for free, unconstrained movement of the head and body. Data acquisition focused on specific time intervals (scenes) that were selected to allow for the analysis of gaze allocation. That is, the beginning of each scene was selected to coincide with the first frame when the target appeared on the screen; similarly, the end of each scene coincided with the moment the target disappeared from the screen. Thus, for each participant, we created 32 scenes (8 videos with 4 trials each), 16 of which were congruent and 16 incongruent.

To test our main hypotheses, eye gaze patterns during each scene were evaluated by specifying Areas of Interest (AOI, Boraston & Blakemore, 2007): (1) Target AOI, or gaze to the target quadrant of the screen and (2) Face AOI, or gaze to the model's face (see Figure 2.1). To quantify individuals' gaze allocation, we computed the percentage of gaze time spent in each AOI, relative to the duration of time participants spent looking on screen.

2.3.5. Statistical Analysis

Preliminary analyses were conducted to evaluate the quality of data collection for the eye-tracking paradigm. The On-task Percentage was computed for each trial, defined as the percentage of time during which the participant gazed at the screen. Results from fitting a mixed model using SAS Proc Mixed showed that the mean On-task Percentage did not differ significantly between the congruent and incongruent condition, $F(1, 1548) = 1.04$, $p = .31$. The mean On-task Percentage for each participant ranged between 32.31% and 99.48% ($M = 79.04$, $SD = 31.69$). For all subsequent analyses, participants were excluded if they had fewer than 50% of trials with valid On-task percentages (n=4). Further, for the remaining 46 children, trials with an On-task Percentage smaller than 50% were considered missing (11.82% and 15.76%, for the congruent and incongruent condition, respectively).

Next, we investigated whether child characteristics predicted individual differences in On-task Percentage. For this purpose we specified a series of mixed models using SAS Proc Mixed (SAS software, Version 9.2 Copyright © 2002-2008 SAS Institute Inc., Cary, NC, USA) with On-task Percentage as outcome. Throughout this analysis, we found no evidence of child characteristic-by-condition (congruent, incongruent) interaction effects ($p > .34$). Even though the main effect for children's chronological age did not reach conventional levels of significance, $F(1,1219)$, $p = .11$, results showed that On-task Percentage was significantly predicted by children's receptive, $F(1, 1219) = 8.39$, $p < .01$, and expressive language age, $F(1, 1219) = 7.92$, $p < .01$, as well as children's nonverbal mental age, $F(1, 1219) = 5.84$, $p < .05$. Individual differences in On-task Percentage were not related to the SRS total or subscale scores. These findings suggest that children with younger developmental ages found the demands of viewing our experimental stimuli somewhat more strenuous than children with older developmental age. Since we found no evidence to suggest that the association between On-task Percentage and child characteristics differed by condition (child characteristic-by-condition interaction effect), we ruled out the possibility that children's on-task behavior confounded our subsequent hypothesis testing.

2.4. Results

To address the two hypotheses, data were analyzed by fitting a series of mixed models using SAS Proc Mixed with percent of viewing time to Face and Target AOIs as outcome. All models were specified with a random intercept, which is equivalent to a Repeated Measure ANOVA.

2.4.1. Differences in Gaze Time Allocation between the Congruent and Incongruent Conditions

Based on our previous research on a community sample of adults we predicted that participants would allocate more gaze to the Face AOI in the incongruent than the congruent condition (Swanson et al., 2012a). Conversely, we predicted that participants would allocate more gaze to the Target AOI during the congruent than the incongruent condition. To test these hypotheses, we fit two mixed models with percent of viewing time to each AOI (Face, Target) as outcome. Experimental condition (i.e., congruent vs. incongruent) was entered as a fixed effect. Significance tests confirmed both of our hypotheses. As illustrated in Figure 2.2, typically developing children allocated less attention to the Face AOI in the congruent (estimated marginal mean (EMM) = 29.76%, SE = 1.91) than in the incongruent (EMM = 33.48%, SE = 2.50) condition, $F(1, 1222) = 6.82$, $p < .01$. Conversely, participants allocated more attention to the Target in the congruent (EMM = 66.72%, SE = 2.02) than in the incongruent (EMM = 62.54%, SE = 2.62) condition, $F(1, 1222) = 9.17$, $p < .01$.

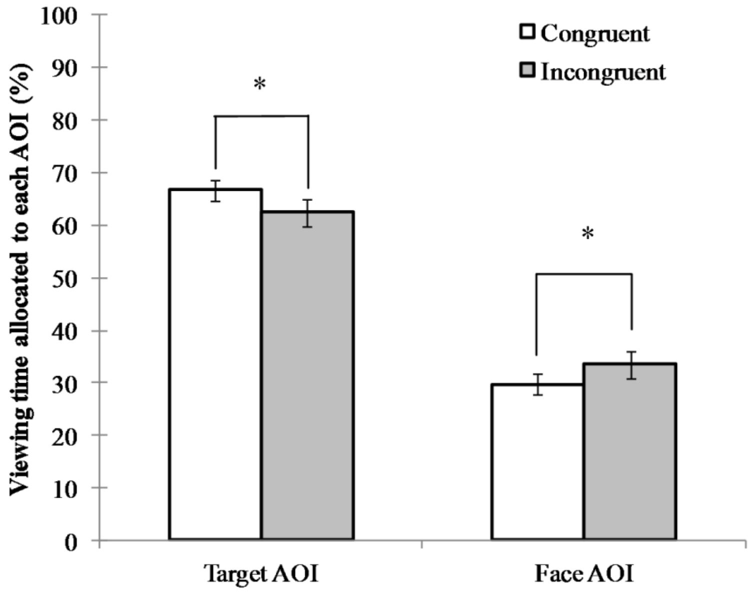

Figure 2.2. Percent gaze time allocation to the Face and Target AOIs during the congruent and incongruent conditions. * $p < .01$.

Next, to determine if global developmental measures were related to gaze allocation to the Target or Face AOI, we fit a series of mixed models with percent of viewing time to each AOI (i.e., Face, Target) as outcome. Tests revealed that the receptive language standard score-by-condition interaction was significant for viewing time to the Face AOI, $F(1, 1221) = 5.70$, $p < .05$. The corresponding receptive language standard score-by-condition interaction was not significant in regards to the Target AOI, $p = .07$. Other indicators of global development such as chronological age, language and mental age, or nonverbal cognitive standard scores were not associated with gaze time to the AOIs as either a main effect or an interactions effect ($p > .10$).

2.4.2. Association between Gaze Time Allocation and Features of the Broad Autism Phenotype

We predicted that differences in gaze time allocation between the congruent and incongruent condition would be more pronounced for participants with low SRS scores and less pronounced for individuals with high SRS scores. To evaluate this hypothesis, we fit a series of mixed models with Target AOI and Face AOI as outcome. All models included two main effects (i.e., SRS scores, experimental condition) and one interaction effect (i.e., SRS*condition). We first specified our models using the SRS Total *T*-scores. Subsequently, we also specified models using *T*-scores from the five SRS subscales (Social Awareness, Social Communication, Social Motivation, Social Cognition, and Autistic Mannerisms). Results are presented in Table 2.3.

Table 2.3. *Associations between gaze time allocation and features of the BAP, n = 46*

	Intercept	**Condition ME**	**SRS ME**	**SRS*Condition**	**RoS[1]**	
	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)	Upper limit	*n* above cutoff
			Dependent Variable: Target AOI			
SRS Total	32.91 (15.54)	21.44 (6.51)**	0.57 (0.29)	-0.33 (0.12)**	58.17	9
Social Awareness	35.26 (12.12)	21.19 (6.42)***	0.53 (0.22) *	-0.33 (0.11)**	56.95	16
Social Comm.	37.95 (15.94)	19.63 (6.88)**	0.48 (0.31)	-0.30 (0.13)*	56.27	11
Social Motivation	36.96 (15.02)	17.55 (6.15)**	0.47 (0.27)	-0.25 (0.11)*	59.86	11
Autistic Mann.	32.41 (12.86)	17.34 (6.53)**	0.60 (0.25)*	-0.26 (0.12)*	56.57	8
Social Cognition	49.49 (14.09)	14.62 (6.69)*	0.25 (0.26)	-0.20 (0.12)		
			Dependent Variable: Face AOI			
SRS Total	59.06 (14.55)	-14.75 (7.01)*	-0.49 (0.27)	0.21 (0.12) $^{+}$	57.74	10
Social Awareness	55.86 (11.72)	-14.34 (6.30)*	-0.43 (0.21)*	0.20 (0.11) $^{+}$	57.11	16
Social Comm.	55.78 (15.02)	-15.46 (7.63)*	-0.44 (0.29)	0.23 (0.14)		
Social Motivation	57.67 (14.50)	-12.77 (6.35)*	-0.45 (0.26)	0.17 (0.11)		
Autistic Mann.	59.37 (12.21)	-13.44 (6.71)*	-0.51 (0.24)*	0.19 (0.12)		
Social Cognition	42.00 (13.42)	-6.92 (7.66)	-0.16 (0.25)	0.06 (0.14)		

Abbreviations: ME, Main Effect; SE, Standard Error; RoS, Region of Significance; Social Comm., Social Communication; Autistic Mann., Autistic Mannerisms.
[1] Region of significance analysis only computed for significant SRS*Condition terms.
* $p < .05$; ** $p < .01$; *** $p < .001$; $^{+}p < .09$

Previous population studies have found that within the normal range of cognitive functioning, SRS scores are not associated with IQ (Constantino, Prybeck, Friesen, & Todd, 2000). In order rule out participant characteristics as a potential confound we computed correlations to examine possible associations between the broad autism phenotype and participant characteristics. Results showed non-significant trends suggesting that SRS *T*-scores may be associated with individual differences in receptive, $r = -.28$, $p = .06$, and expressive language standard scores, $r = -.27$, $p = .07$. Other indicators of global development such as chronological age, language age, nonverbal mental age, or nonverbal cognitive standard scores were not associated with SRS Total *T*-scores ($p > .20$). To test whether the SRS-by-condition interaction effects identified above can be attributed to individual differences in children's language abilities, expressive and receptive language standard scores were added to the mixed models testing our hypotheses. Variables were simultaneously added as a main effect and a language-by-condition interaction effect. In predicting the Target AOI, the SRS Total *T*-score-by-condition interaction effect remained significant even when individual differences in children's language abilities were statistically controlled.

Next, to be sure that the significant interaction effects were not the result of outliers in our sample we removed participants with first and second degree relatives with ASD. The SRS Total *T*-score-by-condition interaction effect was re-tested, and remained significant. Likewise, participants with SRS total raw scores above 70 were removed and the SRS Total *T*-score-by-condition interaction effect remained significant.

To further probe the nature of these SRS*condition interaction effects, we used a 'Regions of Significance' approach to identify specific SRS values (i.e., upper limits) for which differences between the congruent and incongruent conditions were significant (Preacher, Curran, & Bauer, 2006). This method is statistically conservative and practically more meaningful than other methods used to analyze continuous moderators (i.e. splitting participants into quartiles). Table 2.3 reports the RoS values (upper limit) for all significant SRS*condition interaction effects. In addition, Figures 2.3a display a graphic illustration of one of the stronger interaction effects, the condition* SRS Social Awareness Subscale *T*-score interaction effect for the Target AOI. For example, with regards to the Target AOI participants with SRS Social Awareness Subscale *T*-score below 56.95 reliably differed in their gaze allocation to the Target AOI between the congruent and incongruent condition. In contrast, participants scoring above this value (n = 16, 34.78%) did not reliably differ in their gaze allocation to the Target AOI between the congruent and incongruent condition. Further, although the condition* SRS Social Awareness Subscale *T*-score interaction effect did not reach convention criteria for significance, as a post hoc analysis we applied the RoS analysis. The analysis revealed that with regards to the Face AOI, participants with SRS Social Awareness Subscale *T*-score below 57.14 reliably differed in their gaze allocation between the congruent and incongruent condition, whereas participants scoring above this cutoff allocated gaze indistinguishably across the conditions.

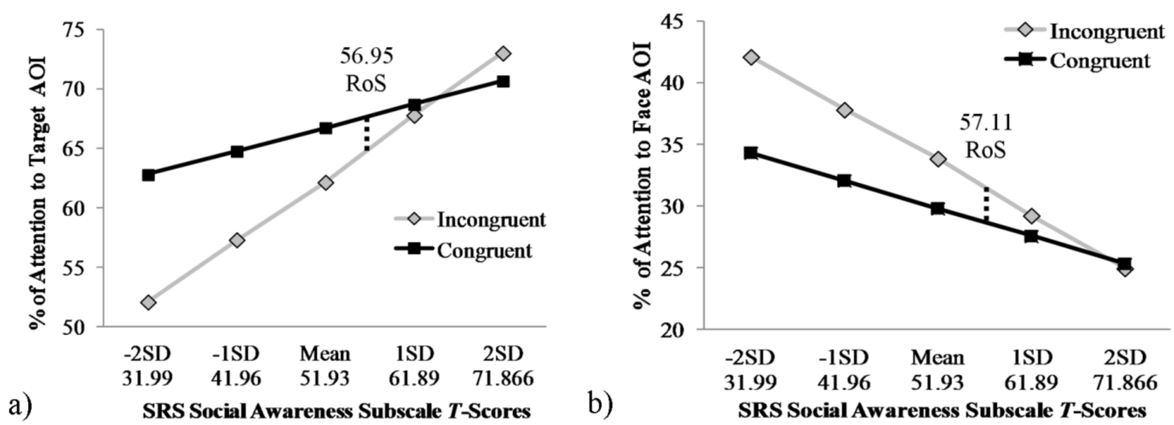

Figure 2.3. Graphs depicting of condition* SRS Total *T*-score interaction effect for (a) Target AOI, and (b) Face AOI. Regions of Significance (RoS) are indicated with a dotted line.

2.5. Discussion

The present study contributes to a research program that aims to develop and validate an endophenotype measure of autism spectrum disorder. This measure utilizes eye-tracking technology to evaluate how individuals allocate their visual attention while watching social video vignettes. These videos display an adult model who gazes at a series of targets that appear and disappear in the four corners of the screen (congruent condition). Gaze allocation in the experimental condition is compared to a set of control stimuli where the model's gaze moves equally as often, but is not directed at the appearing/disappearing targets (incongruent condition). The current project demonstrated the feasibility and validity of administering our paradigm to typically developing children across a broad age range. Results revealed two major findings. First, gaze allocation differed significantly between the experimental and control condition. Second, the Social Responsiveness Scale, a parent-report measure evaluating features of the broad autism phenotype significantly predicted gaze allocation during our experimental stimuli. Both of these findings replicate our earlier work in a community sample of adults that utilized a self-report measure of the broad autism phenotype (authors omitted, 2012).

In an effort to make our stimuli valid across the lifespan we chose color movies over static images. We also chose to use a variety of popular cartoon characters as targets. Despite the attentional limitations of children, we successfully collected data from 46 children (92%) aged 3 to 9 years. Two of the excluded children were boys, and 2 were girls, together they averaged 4 years and 9 months in age (ranging from 3 years, 2 months to 6 years, 8 months). Three of these four children were amongst the youngest third of our population, possibly indicating that the demands of our experimental paradigm may be too strenuous for some younger children. Of the children for which data collection was successful, we collected 88.18% of valid congruent trials, and 84.24% valid incongruent trials. Together with our previous research, these results demonstrate that our experimental paradigm is valid for young children as well as adults.

Results from this research revealed that typically developing children showed several significant differences in gaze allocation between the two conditions. First, gaze allocation to the target was greater in the congruent than in the incongruent condition. Second, gaze allocation to the model's face was greater in the incongruent than the congruent condition. Interestingly, these results replicate the same trends that we found in our adult data, although children in the current study spent much more time viewing the face (29.76% during the congruent condition and 33.48% during the incongruent condition) when compared to adults in our previous study (19.62% during the congruent condition and 23.66% during the incongruent condition). Likewise, children in the current study spent less time viewing the target (66.72% during the congruent condition and 62.54% during the incongruent condition) when compared to adults in our previous study (77.91% during the congruent condition and 71.63% during the incongruent condition). In the current study we did not find significant chronological age effects on children's gaze time allocation. Although seeing that adults and children differ in their gaze allocation an age effects could potentially be found if a larger age range were to be analyzed.

The results of the current study also demonstrated that aspects of the broad autism phenotype predicted individual differences in gaze allocation during our experimental paradigm. Children with fewer parent-reported features of the BAP showed clear differences in gaze allocation to the Target AOI between congruent and incongruent conditions. This finding is in contrast to children with more parent-reported features of the BAP, who spent indistinguishable amounts of time viewing the Target AOI across conditions. Post-hoc analyses utilized the 'regions of significance approach' to identify specific SRS Total *T*-scores for which differences between the congruent and incongruent condition were significant. Differences in gaze allocation to the Target AOI were only significant for children with SRS Total *T*-scores below 58.17, which corresponded to 80.44% of our population.

To our knowledge this is the first report of the BAP predicting eye gaze patterns in a community sample of typically developing children. However, there is a growing body of eye-tracking studies examining the broad autism phenotype in first order relatives of children with ASD. Merin and colleagues used eye-tracking during the Still Face paradigm and found that a subgroup of 6 month old sibs-ASD showed reduced gaze to the mother's eyes and an increased gaze to the mother's mouth, only one sibs-TD displayed this viewing pattern (Merin, Young, Ozonoff, & Rogers, 2007). However, in a follow up study reduced gaze to the eyes at 6 months was not related to symptom severity or symptom frequency at 24 months (Young, Merin, Rogers, & Ozonoff, 2009). Fewer studies have focused on school-aged typically developing siblings of children with ASD. In a study on 13 and 14 year old children, unaffected sib-ASD spent significantly less time fixating on the eye region of photographed faces when compared to sibs-TD (Dalton, Nacewicz, Alexander, & Davidson, 2007). Finally, parents of children with ASD have been shown to spend less time viewing the eyes of a face when asked to discriminate emotions when compared to parents of typically developing children (Adolphs, Spezio, Parlier, & Piven, 2008). All of these studies included groups of typically developing individuals, but none tested the broad autism phenotype in these control groups.

One limitation of the current study is that we did not administer an observational measure of the broad autism phenotype. Currently, the number of valid observational measures of traits associated with ASD is limited. The most well established observational measure in ASD research is the Autism Diagnostic Observation Schedule-General (ADOS; Lord et al., 2000), but the ADOS has not been widely tested in typically developing children so it remains unclear if the measure has enough sensitivity to be used in the typical population. Dawson and colleagues developed The Broad Phenotype Autism Symptom Scale (BPASS; Dawson, Este, Munson, Schellenberg, Bernier, & Abbott, 2007), a clinical interview that can be used with both adults and children. The BPASS has shown good internal consistency, but has yet to be standardized and tested for re-test validity.

In conclusion, the current study is a modest step in the validation of an endophenotype measure for autism spectrum disorder. Future research is still needed to fulfill the criteria of validation outlined above. One, research still needs to determine if impaired performance on this measure is more common in first order relatives of children with ASD. Second, the neural mechanisms involved in the social information processing of this paradigm still need to be evaluated, and third, behavioral characteristics associated with performance on this measure still need to be evaluated in a sample of children with autism spectrum disorder.

CHAPTER THREE

Relations Between an Eye-Tracking Measure of Joint Attention and a Behavioral Measure of Theory of Mind in Typically Developing Children and Children with Autism Spectrum Disorder

3.1. Abstract

In this final study differences in gaze allocation during an eye-tracking measure of joint attention are measured in typically developing children and children with autism spectrum disorder (ASD). This eye-tracking measure utilized modern technology to evaluate how individuals allocated their visual attention while watching social video vignettes. In the current study we also measured differences between children with ASD and typically developing children on a battery of theory of mind tasks intended to evaluate children's ability to interpret the mental states of others. Results revealed three major findings. First, children with autism spectrum disorder scored significantly lower on theory of mind tasks when compared to typically developing children. Second, across both groups of children the Social Awareness Subscale form the Social Responsiveness Scale (SRS), a parent-report measure evaluating features of the broad autism phenotype, significantly predicted gaze allocation during our experimental eye-tracking stimuli and performance on theory of mind tasks. Third, also across both groups, theory of mind scores predicted gaze allocation during our eye-tracking measure of joint attention.

3.1. Introduction

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by a triad of deficits, including impairments in social interactions, impairments in communication, and restrictive, repetitive, or stereotyped behavior (American Psychological Association, 2000). In young children with ASD, impairments in social functioning often involve abnormalities in joint attention; in older, verbal children with ASD, social deficits may manifest as deficits in theory of mind (ToM). Even though research on typically developing children suggests developmental continuity between joint attention and ToM (Charman, Baron-Cohen, Swettenham, Baird, Cox, & Drew, 2000; Nelson, Adamson, & Bakeman, 2008), this association has not been empirically demonstrated in children with ASD (Travis and Sigman, 2000).

Joint Attention in Typically Developing Children and Children with Autism Spectrum Disorder

In typically developing infants, responsiveness to others' bids for joint attention has been documented as early as 3 months of age using preferential looking paradigms (D'Entremont, 2000). Throughout the first year, this ability continues to be consolidated in children's behavioral repertoire, culminating in the use of gaze direction to aid language learning in 15 month old typically developing children (Baldwin 1993a; Baldwin, 1993b; Houston-Price, Plunkett, & Duffy, 2006). Children with ASD show a characteristic deficit in the ability to respond to others' bids for joint attention (RJA) (Sigman, Dijamco, Gratier, & Rozga, 2004, Mundy, Sigman, Ungerer, & Sherman, 1986; Loveland & Landry, 1986; Sigman & Ruskin, 1999). Moreover, recent research from prospective longitudinal studies of baby-siblings of children with ASD has shown that deficits in RJA can be reliably detected as early as 12 months (Nadig, Ozonoff, Young, Rozga, Sigman & Rogers, 2007). Despite these early and pervasive deficits in joint attention, longitudinal research that followed children with ASD into middle childhood, adolescence and adulthood has demonstrated that many children with ASD eventually acquire the ability to respond to others' bids for joint attention. In a longitudinal study by Sigman and Ruskin (1999), preschoolers with ASD (mean CA= 3:11, *SD*= 1:0 years) successfully responded to about 40% of RJA trials where an examiner pointed towards posters to the left, right, and behind the child, while calling the child's name (Sigman & Ruskin, 1999). When re-evaluated at 13 and 19 years, these same individuals successfully responded to 88% and 81% of the RJA trials, respectively (Sigman & McGovern, 2005).

Even though most children with ASD eventually acquire the ability to respond to others' pointing gestures, the developmental mechanisms that explain children's gains in RJA have not been investigated. Some children with ASD may develop RJA skills in the context of naturally occurring interactions, whereas others may acquire these abilities in the context of targeted interventions. Indeed, during the last decade a number of studies have shown that the ability to follow another person's pointing gesture can be effectively targeted as part of children's intervention programs (Whalen & Schreibman, 2003; Jones, Carr, & Feeley, 2006; Jones & Feeley, 2007; Rocha, Schreibman, & Stahmer, 2007). Despite these developmental gains in point following, it remains unclear whether deficits in spontaneous gaze following persist into later development.

Theory of Mind in Typically Developing Children and Children with Autism Spectrum Disorder

Theory of mind refers to the ability to explain and predict behavior in relation to mental states (e.g. intentions, beliefs, and desires; Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001). Most researchers agree that an explicit theory of mind, defined by a child's ability to interpret false beliefs, is first demonstrated around the ages of four to five in typically developing children (Wimmer & Perner, 1983; Wellman & Estes, 1986; Wellman, Cross, & Watson, 2001). In typically developing children the understanding of real and apparent emotions seems to develop slightly later. Studies have reported that only 19% of 4 ½ year olds (Peterson et al., 2005), and 68% of 5 ½ year olds (Wellman & Liu, 2004) were able to pass a test that requires children to understand that a person can feel one thing yet display a different emotion on their face.

Two studies have empirically tested the assumption that theory of mind skills become more sophisticated with development (Wellman & Liu, 2004; Peterson, Wellman, & Liu, 2005). In both of these studies a battery of theory of mind tests were administered to typically developing children. Guttman Scales and Rasch models were applied to the data, and results indicated that about 80% of the children fit the following pattern of theory of mind development: children are first able to understand the desires of another person, then they are able to understand false belief, and finally they are able to understand complex emotions (Wellman, & Liu, 2004; Peterson et al., 2005).

Numerous studies have demonstrated that, regardless of mental age, children with autism spectrum disorder have a deficit in theory of mind (Baron-Cohen, Leslie, Frith, 1985; Heerey, Keltner, Capps, 2003, Tager-Flushberg, 1999). Baron-Cohen and colleagues found that 85% of typically developing, and 86% of children with Down Syndrome, passed a false belief task. Strikingly, only 20% of mental-aged matched children with ASD passed the same task. Collectively, these studies have found that theory of mind is a common deficit in children with autism spectrum disorder, but it is not a universal deficit in ASD. In the aforementioned Peterson et al (2005) study, children with ASD did not follow the same pattern of theory of mind development as typically developing children. First, children with ASD pass tasks involving the desires of another person, they then begin to pass tasks of complex emotion, and lastly they begin to pass tests of explicit false belief (Peterson et al., 2005).

Using Eye-Tracking to Measure Social Cognitive Skills in ASD

Advances in neuropsychological techniques, specifically eye-tracking, have allowed researchers to begin asking questions about individuals' spontaneous processing of socially relevant information. Early studies have shown differences in social attention in adults sample (Pelphrey, Sasson, Reznick, Paul, Goldman & Piven, 2002; Klin, Jones, Schultz, Volkmar, & Cohen, 2002; Dalton et al., 2005). In one recent study, Fletcher and colleagues used a dynamic preferential looking task to compare social and non-social stimuli and results revealed that the first gaze fixation of adults with ASD were less likely to reveal a social preferences when compared to control adults (Fletcher-Watson, Leekam, Benson, Frank, & Finlay, 2009). Further, control adults, but not adults with ASD, fixated on the object in the line of the model's gaze more than would be expected at random (Fletcher-Watson, et al., 2009).

Similar research studies with children have shown mixed results. One study only found differences between typically developing children and children with ASD when stimuli were social and dynamic (Speer et al., 2007). Interestingly, when data from children with ASD and control individuals were combined, this research also revealed relations between SRS scores and gaze to eyes during the social, dynamic videos (Speer et al., 2007). In a recent study that utilized the language learning paradigm developed by Baldwin, results indicated that children with ASD were less likely to monitor the speakers gaze to assist in learning a new word when compared to typically developing children (Akechi, Senju, Kikuchi, Tojo, Osanai, & Hasegawa, 2011). However, several eye-tracking studies have not found group differences in looking time to faces when comparing typically developing children to children with ASD (McPartland, Webb, Keehn, & Dawson, 2011; Freeth, Ropar, Mitchell, Chapman, & Loher, 2011; Anderson, Colombo, & Shaddy, 2006).

Despite these inconclusive previous reports, eye-tracking studies may be uniquely poised to measure subtleties in RJA skills of children with ASD. Even though many individuals with

ASD eventually acquire the ability to respond to others' pointing gestures in an experimental context, eye-tracking paradigms allow researchers to evaluate spontaneous gaze following in the absence of gestural prompts. In the current study we aim to evaluate differences in gaze patterns during an experimental eye-tracking paradigm of joint attention in typically developing children and children with ASD. This eye-tracking paradigm assesses how individuals allocate their attention when viewing social video vignettes that elicit the coordination of attention with another person. We also aim to examine differences in performance on tests of theory of mind in children with ASD and typically developing. Further, we aim to determine in individual differences in traits associated with ASD are related to performance on our eye-tracking measure, or on tests of theory of mind. Finally, we aim to investigate if performance on tests of theory of mind is predictive of eye gaze patterns during our eye-tracking paradigm of joint attention.

3.3. Methods

3.3.1. Participants and Procedures

Between 2010 and 2011, 23 children with ASD and 24 typically developing children participated in this study. Families were recruited through local print and electronic advertisement. Participants were also recruited with the assistance of the Interactive Autism Network (IAN) Research Database at the Kennedy Krieger Institute and Johns Hopkins Medicine – Baltimore, sponsored by the Autism Speaks Foundation. Parental informed consent and child assent was attained prior to assessment commencement from all participants and the study was conducted in accordance of the Institutional Review Board at Hunter College, City University of New York.

Children in our typically developing group were predominantly African American (37%) and Hispanic (30%), but included groups of children with Asian (21%), European American

(8%), and mixed (4%) ethnic and racial origin. Children in our ASD group were predominantly of European American (40%) and of mixed racial origin (40%), but included samples of children with African American (10%) and Hispanic (10%) ethnic and racial origin. Mothers from both populations ranged in age between 24 and 49 years, with average ages of 33.60 years (*SD*= 6.15) for mothers of typically developing children and 39.90 years (*SD*= 6.24) for mothers of children with ASD. Of our families with typically developing children, 25% reported an annual household income of less than $20,000/year, 30% of the sample reported incomes of between $20,000/year and $50,000/year, 25% reported incomes between $50,000/year and $90,000/year, and 20% of the sample reported incomes in excess of $90,000/year. Finally, 20% of the sample of families of children with autism spectrum disorder reported an annual household income of less than $20,000/year, 15% of the sample reported incomes of between $20,000/year and $50,000/year, 15% reported incomes between $50,000/year and $90,000/year, and 50% of the sample reported incomes in excess of $90,000/year.

Assessment sessions lasted 120 minutes and included the administration of our eye-tracking measure of joint attention and a series of developmental and language assessments. In addition parents completed a questionnaire about sub-clinical behaviors associated with the broad autism phenotype (Social Responsiveness Scale, SRS; Constantino, 2002). Finally, parents completed a medical history questionnaire intended to screen for a broad range of neurodevelopmental disorders. Children with autism spectrum disorder also participated in the Autism Diagnostic Observation Schedules-General (ADOS-G; Lord et al., 2000). This standardized observational assessment measures behaviors associated with ASD across a series of tasks and yields a total score that allows classification of autism spectrum or non-spectrum.

3.3.2. Recruitment and Group Matching Procedures

All children in the ASD sample except one were referred to our project with a previous clinical diagnosis of ASD. The one child without a clinical diagnosis was referred due to parental concerns about ASD. On average, children were diagnosed at 3 years 8 months of age (*SD* = 1 year, 11 months). Of the 23 children with ASD that participated in this study, two children were excluded from subsequent data analyses. One child scored unusually high on our receptive language measure (receptive language age equivalent = 21 years, 11 months) and we were not able to find a matching typically developing child. The second child was excluded due to not meeting criteria for autism spectrum on the ADOS-G. Of the remaining 21 children, one child failed to complete the ADOS due to time constraints, and a second child missed the cutoff point for ASD on the ADOS-G by one point. Since both children received a community diagnosis of ASD and scored in the "severe range" on the Social Responsiveness Scale (SRS; Constantino, 2002), we decided to retain both children in the ASD sample.

Children with ASD were then group-wise matched on gender and PPVT-4 receptive language ages to a sample of typically developing children that were previously part of a larger study (Swanson, Serlin, Siller, 2012b). Typically developing children were excluded if they (1) received a SRS total raw score above the cut off points previously established for male and females in the general population (a cut point of 70 and 65 is recommended for males and females, respectively; Constantino, 2002), (2) received a diagnosis for a genetic condition (e.g. Fragile X Syndrome, Down Syndrome, Tuberous Sclerosis, Angelman Syndrome) or developmental disorders (e.g. autism spectrum disorder, pervasive developmental disorder-not otherwise specified, Aperger's syndrome), (3) had a first order relative with an ASD, (4) received standard scores below 70 on non-verbal mental abilities. The final sample included 24 typically developing control children. Across groups, all participants had normal, or corrected to normal vision.

3.3.3. Assessment of Developmental and Language Skills

Children participated in a series of standardized developmental assessments. Non-verbal cognitive skills were evaluated using four subscales from the Differential Abilities Scales II (DAS II; Elliott, 1990). Each of these subscales yields an age equivalent and standard score from which we calculated a composite non-verbal mental age score and a non-verbal mental standard score. Receptive language was measured using the Peabody Picture Vocabulary Test-4 (PPVT-4; Dunn & Dunn, 2007). In this untimed standardized test children are shown four color illustrations per page, the examiner then delivers a stimulus word, and the child indicates what picture corresponds to the stimulus word by pointing or verbally responding with the picture number. Expressive language was evaluated using the Expressive One-Word Picture Vocabulary Test, 4^{th} Edition (EOWPVT-4; Brownell, 2000). The EOWPVT-4 is a standardized test of vocabulary where children are presented with a series of full color illustrations depicting objects, actions, or concepts and the examinee is asked to name each illustration (Brownell, 2000). Both the PPVT-4 and the EOWPVT-4 produce standard scores as well as age equivalents. For detailed participant characteristics, and *t*-tests demonstrating that our samples are well matched on global characteristics, please see Table 3.1.

3.3.4. Assessment of the Broad Autism Phenotype

The Social Responsiveness Scale (SRS; Constantino, 2002) is a 65-item parent report questionnaire designed to highlight behaviors that are characteristic of ASD. Parents report on a 4 point scale, with responses ranging from *not true*, to *almost always true*. The SRS has been standardized, and thus yields both raw scores and *T*-scores (Constantino, 2002). Items are selected to make up 5 subscales, examples include “Is aware of what others are thinking of feeling” from the social awareness subscale, “Is able to understand the meaning of other people’s tone of voice and facial expressions” from the social cognition subscale, “Knows when he or she is too close to someone or is invading someone's space" from the social communication subscale, "Does not join group activities unless told to do so" from the social motivation subscale, and "Does extremely well at a few tasks, but does not do as well at most other tasks" from the autistic mannerisms subscale.

Table 3.1. *Participant characteristics*

Variable	**ASD group (*n* = 21)**	**TD group (*n* = 24)**	***t* value**	**Effect Size[1]**
Gender, M/F, No.	18/3	20/4	-.22	-0.08
	Mean (SD)	Mean (SD)		
Chronological Age, m	87.24 (18.39)	81.67 (19.21)	0.99	0.33
Receptive Language Age, m	85.10 (30.32)	86.83 (23.00)	-0.22	-0.06
Receptive Language SS	97.81 (21.58)	103.63 (9.15)	-1.15	-0.36
Expressive Language Age, m	83.29 (29.69)	82.13 (25.970)	-.14	0.04
Expressive Language SS	98.43 (18.76)	99.63 (10.72)	-.27	-0.08
Non-verbal Mental Age, m	84.90 (20.29)	87.50 (25.21)	-.38	-0.11
Non-verbal DQ	98.62 (19.13)	107.75 (22.18)	-1.47	-0.02
SRS Total Raw Scores	87.95 (24.30)	32.58 (14.75)	9.37*	2.88
SRS Total T-Scores	76.81 (11.55)	49.83 (6.80)	9.69*	2.89
SRS Social Awareness T-Scores	67.48 (9.93)	50.08 (9.50)	6.00*	1.79

Abbreviations: m, Months; SS, Standard Score; DQ, Developmental Quotient; SRS, Social Responsiveness Scale.[1]Hedges' *g* was used to calculate effect size. * $p < .001$.

Psychometric properties of the SRS were previously evaluated (Constantino, 2002), demonstrating excellent internal consistency; Cronbach's α scores were as follows: .94 for the male parent rating, .93 for female parent rating, .97 for clinical rating. The SRS has also been shown to have high discriminate validity when children with an ASD were compared to children with other psychiatric disorders, as well as high concurrent validity when a sample of children with autism were administered the SRS as well as the Autism Diagnostic Interview-Revised (ADI-R; Lord, Rutter, & Le Couteur, 1994; Constantino, Davis, Todd, Schindler, Gross, Brophy et al, 2003).

3.3.5. Theory of Mind Battery (Steele, Joseph, & Tager-Flushberg, 2003)

The Theory of Mind Battery is a set of tasks intended to investigate developmental change in ToM abilities in children with autism spectrum disorder (Steele et al., 2003). In the current study, we administered a Desire Task (Wellman and Wooley, 1990) as a gatekeeper task to determine whether children have the prerequisite skills to participate in our ToM battery. The Desire Task is designed to measure a participant's ability to predict a character's actions based on the character's desires. A two-dimensional character was used to tell a story where the character is looking for an object that could be in one of two locations. When the character fails to find the object in the first location, the child is asked where the character will look next (score = 0-4; passing criterion = 3). If the child indicated the character will look in the second location, they passed the task. Only those children who passed the desire task were administered the four tasks of our ToM battery (n = 17 for the ASD group, and n = 19 for the comparison group).

3.3.5.1. Unexpected-contents false belief task. Based on a task by Perner and colleagues (Perner, Leekam, & Wimmer, 1987), children were shown three familiar containers that have unexpected contents inside (for example, a crayon box with a toy car inside). During each of the three trials, children were asked if a previously identified friend from school will have knowledge of the unexpected contents. Two false belief questions were asked (Will X know what's inside?) and (What will X say is inside?) (score = 0-6; passing criterion = 4).

3.3.5.2. Location-change false belief task. In this classic first order false-belief task two pictures of a room are used in conjunction with two-dimensional characters to act out a scenario (based on Wimmer & Perner, 1983; Baron-Cohen, Leslie, & Frith, 1985). In each of these vignettes, the secondary character moves an object while the primary character is out of the room, and the child was asked a series of questions concerning the primary character's knowledge of the events (Does Maggie know where the apples are?) (Where will Maggie look first for the apples?) (score = 0-6; passing criterion = 4). If the child successfully passed the Location-Change False Belief task they then participated in the Second-order False Belief Task and the Moral Responsibility Task.

3.3.5.3. Second-order false belief task. Based on a task by Sullivan and colleagues (Sullivan, Zaitchik, & Tager-Flusberg, 1994), two stories are told in which a child character is to receive a surprise gift from a parent. Without the parent's knowledge, the child then finds the surprise gift. Second-order ignorance, belief and justification questions tapped participants' ability to conceptualize what the parent character thinks/knows about the child's state of knowledge concerning the gift (score = 0-6; passing criterion = 4).

3.3.5.4. *Moral responsibility task*.In this task children are shown a picture book used to tell four stories in which a primary child character makes plans with a friend. In both situations the child is unable to fulfill the commitment, but in one scenario it is due to an uncontrollable event (e.g., the car breaks down) and in the other scenario the commitment isn't fulfilled because the child cancels plans without telling their friend (based on Mant & Perner, 1988). At the end of each story child participants are asked to judge the child characters actions as "good", "bad", or "in between." (score = 0-6; passing criterion = 6).

3.3.6. Theory of Mind Scoring and Coding

Scores for Unexpected-Contents False Belief, Location-Change False Belief, Second-Order False Belief, and Moral responsibility were combined to create one composite Theory of Mind Score (ToM Scores) ranging between 0 and 24 points. For each child, Theory of Mind Tasks were scored from videotape by an independent research assistant. Inter-rater reliability was established with another research assistant based on video sequences of 32% of the study population. Inter-rater reliability was calculated at the level of summed scores for each of the 3 tasks and intraclass correlation coefficients were .94 for the Desire Task, .97 for the Unexpected-Contents False Belief Task, .96 for the Location-Change False Belief Task, 1.00 for the Second-Order False Belief Task, and .99 for the Moral Responsibility Task.

3.3.7. Eye-Tracking Measure of Joint Attention

3.3.7.1. Eye-tracking stimuli. Participants were randomly presented a series of 8 videos that were each 34 seconds long and included 4 gaze shifts trials (see Figure 3.1).

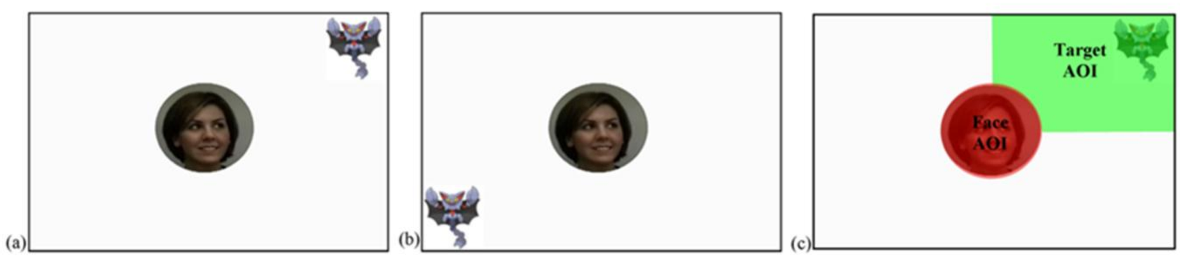

Figure 3.1. Sample stimuli and an illustration of the Areas of Interest (AOI) used in analysis. (a) sample congruent stimulus, (b) sample incongruent stimulus, (c) sample Face and Target AOIs.

At the center of the screen, each video displayed the head and face of a model, while targets appeared and disappeared in each of the four corners. Half of the videos were congruent (the model's gaze followed the target on the screen) and the other half of the videos were incongruent (the model's gaze was directed elsewhere). Videos began with a model looking straight into the camera (simulating the model making eye contact with the participant). Next, a target (i.e., a popular cartoon character, © 2011 Nintendo/Pokémon) appeared in one of the four corners of the screen and shortly thereafter the model shifted her gaze to a corner, either congruent or incongruent. In both conditions, the model's gaze returned to the center of the screen, after which the next trial was presented.

3.3.7.2. Data acquisition and analysis. Stimuli presentation and participant eye gaze behavior was recorded using a Tobii T-60 eye tracker with infrared cameras integrated under a 17" LCD display monitor (TOBII Technology AB, Tobii T-60). Eye-movements from both eyes were collected at a rate of 60 recordings per second (60 Hz), from an average distance of 60 centimeters, with an accuracy of 0.5°. The eye-tracking system was completely non-invasive, allowing for free, unconstrained movement of the head and body. Data acquisition focused on specific time intervals (scenes) that were selected to allow for the analysis of gaze allocation. That is, the beginning of each scene was selected to coincide with the first frame when the target appeared on the screen; similarly, the end of each scene coincided with the moment the target disappeared from the screen. Thus, for each participant, we created 32 scenes (8 videos with 4 trials each), 16 of which were congruent and 16 incongruent.

To test our main hypotheses, eye gaze patterns during each scene were evaluated by specifying Areas of Interest (AOI, Boraston & Blakemore, 2007): (1) Target AOI, or gaze to the target quadrant of the screen and (2) Face AOI, or gaze to the model's face (see Figure 3.1). To quantify individuals' gaze allocation, we computed the percentage of gaze time spent in each AOI, relative to the duration of time participants spent looking on screen.

3.4. Results: Between Group Analysis

A series of analysis were conducted to examine differences in performance between groups. For this purpose we compared typically developing children to children with autism spectrum disorder on our eye-tracking paradigm and theory of mind tasks.

3.4.1. Preliminary Statistical Analysis

Preliminary analyses were conducted to evaluate the quality of data collection for the eye-tracking paradigm. The On-task Percentage was computed for each trial, defined as the percentage of time during which the participant gazed at the screen. The mean On-task Percentage for participants with ASD (*n*=21) ranged between 48.50% and 99.35% (*M* = 80.52, *SD* = 16.42). The mean On-task Percentage for typically developing participants (*n*=24) ranged between 53.93% and 99.49% (*M* = 84.50, *SD* = 13.06). For all subsequent analyses, trials with an On-task Percentage smaller than 50% were considered missing. Across both groups, this criterion resulted in excluding 12.1% of the congruent, and 15.1% of the incongruent trials. Results from fitting a mixed model using SAS Proc Mixed showed that the On-task Percentage did not differ significantly across groups, or in the interaction of groups and condition.

Next, we investigated whether child characteristics (i.e., gender, chronological age, receptive language age and standard score, expressive language age and standard score, non-verbal mental age and standard score) predicted individual differences in On-task Percentage. For this purpose we specified a series of mixed models using SAS Proc Mixed (SAS software, Version 9.2 Copyright © 2002-2008 SAS Institute Inc., Cary, NC, USA) with On-task Percentage as outcome. Results indicated that On-task Percentage was significantly predicted by several child characteristics as main effects (receptive language age and standard scores, expressive language age and standard score, non-verbal mental age, and non-verbal developmental quotients), $p < .05$. Throughout this analysis, we found no evidence of characteristic-by-condition interaction effects, or child characteristic-by-condition-by-group interaction effects, $p > .05$. These findings suggest that children with younger developmental ages found the demands of viewing our experimental stimuli somewhat more strenuous than children with older developmental age. Since we found no evidence to suggest that the association between On-task Percentage and child characteristics differed by group (child characteristic-by-group interaction effect) or by the interaction between group and condition (child characteristic-by-condition-by-group interaction effect), we ruled out the possibility that children's on-task behavior confounded our subsequent hypothesis testing.

3.4.2. Relations between Global Developmental Measures and Gaze Allocation to AOIs

Next, to determine if global developmental measures were related to gaze allocation to the Target or Face AOI, we fit a series of mixed models with percent of viewing time to each AOI (i.e., Face, Target) as outcome. In regards to the Target AOI, the expressive language standard scores-by-condition interaction approached significance, $F(43, 1197) = 3.37$, $p = .07$. Also, gender was significant as a main effect, $F(43) = 8.36$, $p < .01$, with boys spending more time looking at the target when compared to girls. In regards to the Face AOI, the expressive language standard scores-by-condition interaction also approached significance, $F(43, 1197) = 3.44$, $p = .06$. Moreover, gender was significant as a main effect, $F(43) = 8.60$, $p < .01$, with girls spending more time looking at the face when compared to boys. In order to account for a potential confounding variable, all subsequent models with Target and Face AOIs include expressive language standard scores both as a main effect and as an interaction effect with condition. Other indicators of global development such as chronological age, expressive and receptive language age, receptive standard scores, nonverbal mental age, or nonverbal cognitive standard scores were not associated with gaze time to the AOIs either as mains effect or interactions effects ($p < .05$).

3.4.3. Group Differences in Gaze Time Allocation to AOIs.

Based on our previous research we predicted that children would allocate more gaze to the Face AOI in the incongruent than the congruent condition (Swanson, Serlin, Siller, 2012a,b). Further, we predicted that differences in gaze allocation by condition would be more pronounced for typically developing children when compared to children with ASD. Conversely, we predicted that participants would allocate more gaze to the Target AOI during the congruent than the incongruent condition. Likewise, we predicted for the Target AOI that differences in gaze allocation by condition would be more pronounced for typically developing children when compared to children with ASD. Data were analyzed by fitting a series of mixed models using SAS Proc Mixed (SAS software, Version 9.2 Copyright © 2002-2008 SAS Institute Inc., Cary, NC, USA) with percent of viewing time for the Face AOI, Target AOI, and the Ratio of Target to Face as outcome. Experimental condition (i.e., congruent vs. incongruent), and Group (i.e., ASD group, control group) were entered as a fixed effects, and Experimental condition*Group was entered as an interaction effect.

In regards to the Target AOI results revealed significant main effects for condition. Across groups, children allocated more time to viewing the target during the congruent condition (estimated marginal mean = 65.69%, SE = 2.41), when compared to the incongruent condition (estimated marginal mean = 59.46%, SE = 2.83), $F(43, 1197) = 6.16$, $p < .05$. Main effects for group were not significant, $p > .05$. Further, no significant interactions emerged between the groups as a function of condition, $F(43, 1197) = 0.13$, $p = .72$.

In regards to the Face AOI results also revealed significant main effects for condition. Conversely, across groups, children allocated more time to viewing the target during the incongruent condition (estimated marginal mean = 36.05%, SE = 2.62), when compared to the congruent condition (estimated marginal mean = 29.81%, SE = 2.37), $F(43, 1197) = 6.57$, $p < .05$. Main effects for group were not significant, $p > .05$. Further, no significant interactions emerged between the groups as a function of condition, $F(43, 1197) = 0.01$, $p = .95$.

3.4.4. Group Differences in Theory of Mind Scores

Independent *t*-tests were computed to examine group differences in theory of mind composite scores (ToM Scores). Results indicated that the children with ASD scored an average of 12.59 points on the theory of mind tasks, whereas the comparison group scored on average 17.63 points (standard deviations were 8.44 and 4.98, respectively). Levene's Test for Equality of Variances tested significant, so a *t*-test with equal variances not assumed was used in the subsequent analysis. The *t*-test comparing the two groups was significant, t (34) = 2.15, $p < .05$. The 5.04 unit difference between groups translates to a Hedges' *g* of .74, indicating a medium to large effect size (Hedges, 1981). Since previous research has indicated that theory of mind is related to receptive language (for a review see Milligan, Astington, & Dack, 2007) we created a residual ToM score (R-ToM Score) that removes variance associated with children's receptive language abilities. An independent *t*-test comparing the two groups on this R-ToM score was also significant, t (34) = 2.63, $p < .05$.

We also computed the number of children from each group that passed each task. These data are presented in Table 3.2, and illustrate that more children in the typically developing group passed each test when compared to children with ASD. Chi-square analysis on each task did not reveal significant differences between the group in terms of percentage of participants passing each test. However, effect size using Cramer's V, revealed a small effect for the Unexpected Contents False Belief, and Location-Change False Belief Tasks.

Table 3.2. *Number and percentage of participants passing each task by group*

Theory of Mind Task	**ASD (*n*=17)**		**TD (*n*=19)**		**Chi-Square**	**Effect Size[1]**
	n	**%**	***n***	**%**		
Unexpected Contents False Belief	11	52%	17	71%	1.91	.23
Location-Change False Belief	10	47%	16	66%	1.76	.22
2nd Order False Belief	9	43%	13	54%	0.37	.10
Moral Responsibility	0	0%	2	8%	.42	.11

[1]Cramer's V was used to measure effect size.

3.5. Results: Across Group Analysis

In order to examine the relations between our experimental measures and symptom severity across a full range of functioning, we pooled both groups together. Scores on the SRS were used to determine level of traits associated with ASD. Results from our previous research indicated that SRS Social Awareness Subscale *T*-scores exhibited the strongest relationship in predicting gaze behaviors (Swanson et al., 2012b). For this reason, we focused our analyses on the SRS Social Awareness Subscale, which is intended to quantify an individual's ability to pick up on social cues, and represents the sensory aspect of triadic social situations (Constantino, 2002). As illustrated in Figure 3.2., although children with ASD and typically developing children differed significantly on SRS Social Awareness *T*-scores, when the groups were pooled the distribution of scores approximated a normal distribution.

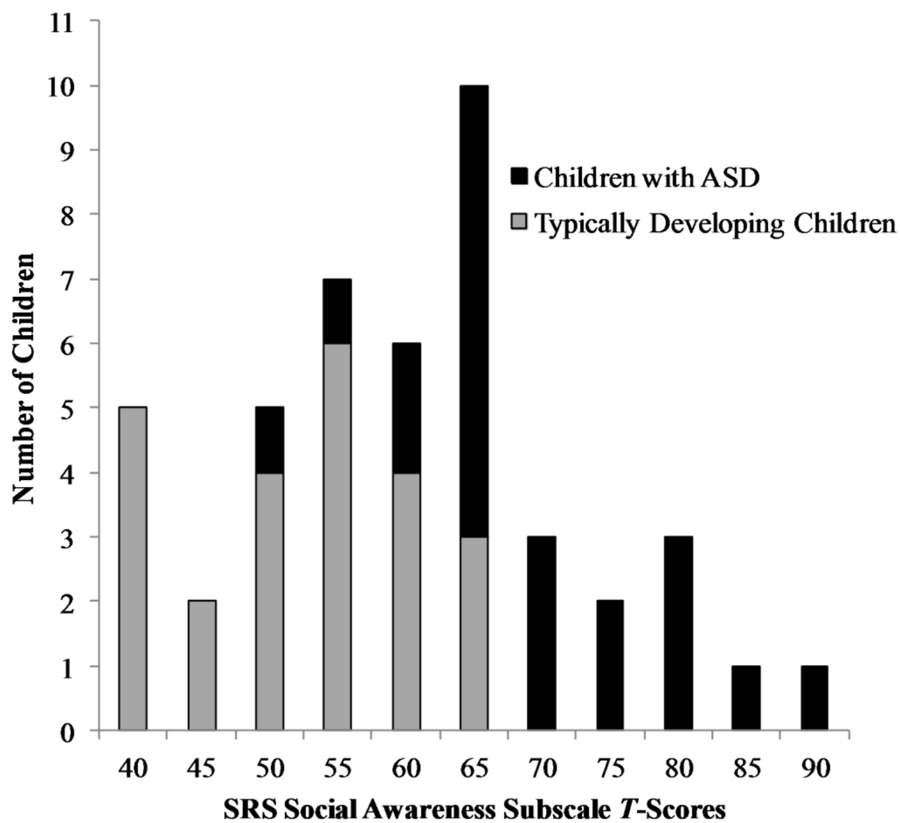

Figure 3.2. Distribution of SRS Social Awareness Subscale by group. *n*= 21 for children with ASD. *n*= 24 for typically developing children.

3.5.1. Preliminary Statistical Analysis

We computed correlations to examine possible associations between theory of mind, the broad autism phenotype, and other child characteristics. Previous population studies have found that within the normal range of cognitive functioning, SRS scores are not associated with IQ (Constantino, Prybeck, Friesen, & Todd, 2000). However, studies with populations of individuals with ASD have found a negative correlation between SRS scores and IQ (Constantino et al., 2000). In order rule out child characteristics as a potential confound we computed correlations to examine possible associations between the broad autism phenotype, theory of mind scores, and participant characteristics. Results are summarized in Table 3.3.

Table 3.3. *Correlations between descriptive variables and outcome variables*

Variable	**SRS Total *T*-Scores[1]**	**ToM Scores[2]**
	T-scores	
Gender	0.71	-0.65
	Pearson Correlation Coefficients	
Chronological Age, y	0.08	0.41*
Receptive Language Age, y	0.03	0.52**
Receptive Language SS	-0.12	0.20
Expressive Language Age, y	0.03	0.50**
Expressive Language SS	-0.04	0.25
Non-verbal Mental Age	-0.06	0.52**
Non-verbal DQ	-0.14	0.18

[1] n = 45; [2] n = 36; *p<.05, **p<.01.

No significant associations emerged between SRS Social Awareness *T*-scores and indicators of global development. Although results showed significant relations between ToM Scores and chronological age, expressive language age, receptive language age, and non-verbal mental age. A step-wise multiple regression was conducted to determine which of these child characteristics accounted for the most variability in ToM Scores. For this purpose theory of mind was entered as the outcome variable and the following were entered as predictor variables: chronological age, receptive language age, expressive language age, non-verbal mental age. The results indicated that receptive language age accounted for 27% of the variance, $F(1,34) = 12.60$, $p > .01$. The remaining child characteristics entered as predictor variables did not predict above and beyond receptive language age. To create a ToM measure that is independent of development, we created a residualized ToM score by removing variance associated with children's receptive language abilities. All subsequent analyses were based on this residualized ToM score (R-ToM Score).

3.5.2. Association between Gaze Time Allocation and Features of the Broad Autism Phenotype

We predicted that differences in gaze time allocation between the congruent and incongruent condition would be more pronounced for participants with low SRS Social Awareness scores and less pronounced for individuals with high SRS Social Awareness scores. To evaluate this hypothesis, we fit mixed models with Target AOI and Face AOI as outcome. All models included two main effects (i.e., SRS scores, experimental condition) and one interaction effect (i.e., SRS*condition). With regards to the Target AOI, results showed a significant condition*SRS interaction effect, $F(42,1196) = 4.30$, $p < .05$. In regards to the Face AOI, results showed a marginally significant condition*SRS interaction effect, $F(42,1196) = 3.52$, $p = .06$.[1]

[1] Statistical models with SRS Total *T*-Scores yielded non-significant interaction effects (SRS*Condition) for looking time to the Face and Target AOIs, $p > .05$.

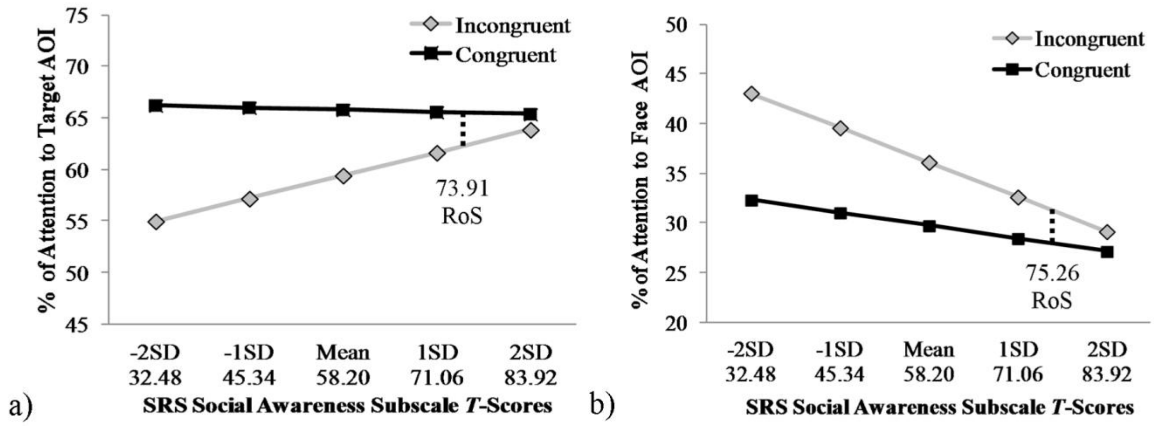

Figure 3.3. Graphs depicting of condition* SRS Social Awareness interaction effect for (a) Target AOI, and (b) Face AOI. Regions of Significance (RoS) are indicated with a dotted line.

To further probe the nature of these SRS*condition interaction effects, we used a ‘Regions of Significance’ approach to identify specific SRS values (i.e., upper limits) for which differences between the congruent and incongruent conditions were significant (Preacher, Curran, & Bauer, 2006). This method is statistically conservative and practically more meaningful than other methods used to analyze continuous moderators (i.e. splitting participants into quartiles). For example, with regards to the Target AOI participants with SRS Social Awareness Subscale *T*-score below 73.92 reliably differed in their gaze allocation to the Target AOI between the congruent and incongruent condition. In contrast, participants scoring above this value (n = 5, 11.11%) did not reliably differ in their gaze allocation to the Target AOI between the congruent and incongruent condition. All five of these children entered our study with a diagnosis of ASD. In regards to the Face AOI, participants with SRS Social Awareness Subscale *T*-score below 75.26 reliably differed in their gaze allocation to the Face AOI between the congruent and incongruent condition, whereas participants scoring above this cutoff (n = 5, 11.11%) allocated gaze indistinguishably across the conditions. Likewise, all six of these children entered our study with a diagnosis of ASD. Figure 3.3.a,b display a graphic illustration of the condition* SRS Social Awareness Subscale *T*-score interaction effect for both AOIs.

3.5.3. Association between Theory of Mind and Features of the Broad Autism Phenotype

A correlation between R-ToM Scores and SRS Social Awareness *T*-scores produced a significant correlation, r (36) = -.85, p <.001, indicating that individuals with higher SRS scores obtained lower ToM Scores when compared to individuals with lower SRS scores. These results indicate that theory of mind is related to symptom severity across the broader autism spectrum (i.e. from the sub-clinical broad autism phenotype to autistic spectrum disorder).

3.5.4. Association between Gaze Time Allocation and Theory of Mind

Finally, we examined relations between theory of mind (R-ToM Scores) and gaze allocation to Target and Face AOIs. Since receptive language ages were related to theory of mind scores, we used a residual score of theory of mind that removed variance from receptive language ages. We predicted that differences in gaze time allocation between the congruent and incongruent condition would be more pronounced for participants with high theory of mind scores and less pronounced for individuals with low theory of mind scores. To evaluate this hypothesis, we fit a series of mixed models with Target AOI and Face AOI as outcome. All models included two main effects (i.e., R-ToM scores, experimental condition) and one interaction effect (i.e., R-ToM*condition). With regards to the Target AOI, results showed a significant condition*R-ToM Score interaction effect, $F(33,969) = 8.662$, $p < .01$. In regards to the Face AOI, results showed a marginally significant condition*SRS interaction effect, $F(33,969) = 7.22$, $p < .01$.

Results indicated significant R-ToM*condition interaction terms for Target and Face AOIs. In regards to the Target AOI, children that had R-ToM scores greater than -5.67 allocated significantly different amounts of attention during congruent and congruent trials. Conversely, children scoring below this value (n = 6, 16.67%) did not reliably differ in their gaze allocation to the Target AOI between the congruent and incongruent condition. In regards to the Face AOI, children with R-ToM scores greater than -5.41 reliably differed in their gaze allocation between the congruent and incongruent condition. However, children scoring below this value (n = 6, 16.67%), did not significantly differ in their gaze allocation between conditions. For both the Target and Face AOI, all 6 children entered our study with a diagnosis of ASD.

3.6. Discussion

The current study aimed to measure differences in gaze allocation during an eye-tracking measure of joint attention in typically developing children and children with autism spectrum disorder (ASD). This eye-tracking measure was designed to evaluate how individuals allocated their visual attention while watching social video vignettes that display an adult model who gazes at a series of targets that appear and disappear in the four corners of the screen (congruent condition). Gaze allocation in the experimental condition is compared to a set of control stimuli where the model's gaze moves equally as often, but is not directed at the appearing/disappearing targets (incongruent condition). Results revealed several major findings. First, children with autism spectrum disorder scored significantly lower on theory of mind tasks when compared to typically developing children. Second, children with autism and typically developing children did not differ significantly in their gaze allocation to Face and Target AOIs. Third, across both groups of children, the Social Awareness Subscale form the Social Responsiveness Scale (SRS), a parent-report measure evaluating features of the broad autism phenotype, significantly predicted performance on theory of mind tasks. Likewise, the SRS Social Awareness Subscale significantly predicted gaze allocation during our experimental eye-tracking stimuli. Finally, across both groups, theory of mind scores predicted gaze allocation during our eye-tracking measure of joint attention.

The current project demonstrated the feasibility and validity of administering our eye-tracking paradigm to typically developing children and children with ASD across a broad age range. Valid trials were collected for 86% of total trails. Children with ASD and typically developing children did not differ significantly in their on-task percentages. Together with our previous research (Swanson et al., 2012a,b), these results demonstrate that our experimental paradigm is valid for adults as well as young children both with and without an ASD.

Children also participated in a battery of theory of mind tasks that included tests of first-order false belief, second-order false belief, and a moral responsibility. Children with ASD scored an average of 12.59 total points on theory of mind tasks, which is significantly lower than typically developing children's average scores, 17.63 points. This 5.04 unit difference between groups translates to a medium to large effect size for group differences in performance on theory of mind tasks. The current study adds to a body of literature reporting significant differences in theory of mind ability when children with ASD are compared to typically developing children (Baron-Cohen, Leslie, Frith, 1985; Heerey, Keltner, Capps, 2003, Tager-Flushberg, 1999). However, the current study also highlights that theory of mind is not a universal deficit in children with ASD. Forty-seven percent of children with ASD passed a test of first order false belief task (location change false belief task), and 43% passed a test of second order false belief. No children with ASD passed a task of moral responsibility, but only a small percentage of our typically developing children passed this task (8%, n = 2), possibly indicating a floor effect for this task.

Eye-tracking results from the current study indicate that typically developing children and children with an ASD displayed comparable amounts of visual attention the Face and Target AOIs. Both groups of children allocated more gaze time to the target in the congruent than in the incongruent condition. Further, both groups of children allocated more gaze to the model's face in the incongruent than the congruent condition. However, when collapsing data across both groups, results indicated that the number of present features associated with ASD predicted individual differences in gaze allocation during our experimental paradigm. Children with fewer parent-reported ASD symptoms showed reliable differences in their gaze allocation between the experimental and control condition. In contrast, children with higher parent reported symptoms failed to show differences in gaze allocation between the two experimental conditions. Follow up analyses using a “regions of significance” approach revealed that only six children (with the highest parent reported ASD symptoms) fell in the latter group. This suggests that gaze allocation is closer related to measures of symptom severity rather than diagnostic classification.

Results from this study also showed that theory of mind scores predicted gaze allocation during our joint attention eye-tracking task. Children with higher theory of mind scores demonstrated significantly different gaze allocation patterns to the Target AOI between congruent and incongruent conditions, which is in contrast to children with lower theory of mind scores who allocate indistinguishable amounts of gaze across conditions. To our knowledge this is the first experimental study in autism spectrum disorder that establishes a link between joint attention and theory of mind.

Current theories suggest that the etiology of ASD likely involves multiple genes interacting with each other (Abrahams & Geschwind, 2008; Geschwind & Alarcon, 2006). According to this model, it is predicted that individual genetic risk factors are more closely related to specific features or components of ASD (i.e., endophenotypes) rather than ASD itself. Results from the current study suggest that gaze allocation during our joint attention paradigm is more closely related to specific features of ASD (i.e., ToM, SRS Social Awareness Subscale) rather than ASD itself. This finding suggests that the process of developing and validating novel endophenotype measures is likely to be an iterative process. That is, neuropsychological endophenotype measures will also be more likely to be associated with behavioral endophenotypes than diagnostic classifications.

The eye-tracking measure utilized in the current study has received initial validation in a program of research that aims to identify an endophenotype measure that is (1) valid across the life span, (2) on a continuum with ASD traits in the general population (3) more prevalent in family members of individuals with ASD than individuals without a family history of ASD, and (4) associated with known behavioral characteristics of ASD (Geschwind & Alarcon, 2006; Abrahams & Geschwind, 2008; Pelphrey, Shultz, Hudac & Vander Wyk, 2011). Data from our previous research (Swanson et al., 2012a,b) has begun to address the first two of these points. We have demonstrated the feasibility of administrating this experimental paradigm to a community sample of adults (N = 44) and typically developing children (N = 50), and revealed two major findings. First, gaze allocation of adults and children differed significantly between the congruent and incongruent conditions. Second, individual differences in gaze allocation were significantly predicted by features of the broad autism phenotype (BAP). These findings are consistent with the notion that our eye-tracking measure of gaze following captures an endophenotype associated with ASD.

In conclusion, the current study is a modest step in the validation of an endophenotype measure for autism spectrum disorder. Future research is still needed to fulfill the criteria of validation outlined above. One, research needs to evaluate the neural mechanisms involved in the social information processing of this paradigm. Two, research needs to determine if impaired performance on this measure is more common in first order relatives of children with ASD, and third, genetic studies need to be conducted to determine if common genes mediate the relations between performance on our endophenotype measure and behavior.

GENERAL DISCUSSION

Current theories suggest that the etiology of ASD likely involves multiple genes interacting with each other (Abrahams & Geschwind, 2008; Geschwind & Alarcon, 2006). According to this model, it is predicted that individual genetic risk factors are more closely related to specific features or components of ASD (i.e., endophenotypes) rather than ASD itself. This dissertation reports on a program of research that aims to develop, refine and validate an endophenotype measure that has the potential to enhance our understanding of the etiology of Autism Spectrum Disorder (ASD). This measure takes advantage of modern eye-tracking technology and evaluates how individuals allocate their attention when viewing social video vignettes that display an adult model who is gazing at a series of targets that appear and disappear in the four corners of the screen (congruent condition). Gaze allocation in the experimental condition is compared to a set of control stimuli where the model's gaze is not directed at the appearing/disappearing targets (incongruent condition). The ability to respond to others' attentional cues (i.e., joint attention) is a characteristic deficit of young children with ASD.

The long-term goal of this research is to identify genetic risk factors that are associated with variation on the endophenotype measure. To develop a measure that has the potential to be fruitful in genetic research, endophenotype measures should (1) be valid across the lifespan, (2) be on a continuum with ASD traits in the general population, (3) be associated with known behavioral characteristics of ASD, (4) be closely related to neural mechanisms, and (5) be more prevalent in family members of individuals with ASD than individuals without a family history of ASD (Geschwind & Alarcon, 2006; Abrahams & Geschwind, 2008; Pelphrey, Shultz, Hudac & Vander Wyk, 2011).

Is our endophenotype measure valid across the lifespan? To evaluate if this experimental paradigm is valid across the lifespan we examined the quality of data collection and potential chronological age effects in all three populations. Results indicated that relatively few trials had to be excluded due to poor data quality (defined as less than 50% of looking time to the screen during a given trial). In the community sample of adults 2% of trials were excluded, in the sample of typically developing children 14% of trials were excluded, and in the sample of children with ASD, 16% of trials were excluded. Data was also evaluated to determine if age effects in gaze allocation to Face or Target AOIs were present in our data. Results revealed that for all three populations, chronological age was not significantly related to looking time to the screen, looking time to the Target AOI, or looking time to the Face AOI.

Further, results indicated similar trends in our data from community adults and typically developing children in terms of viewing time to Face and Target AOIs, although children spent much more time viewing the face (29.76% during the congruent condition and 33.48% during the incongruent condition) when compared to adults (19.62% during the congruent condition and 23.66% during the incongruent condition). Likewise, typically developing children spent less time viewing the target (66.72% during the congruent condition and 62.54% during the incongruent condition) when compared to adults (77.91% during the congruent condition and 71.63% during the incongruent condition). We conclude that our candidate endophenotype measure valid for presentation to adults and children aged 3 to 9 years, both with and without autism spectrum disorder.

Is our endophenotype measure on a continuum with ASD traits in the general population? Results from both our community sample of adults and typically developing children demonstrate that performance on our endophenotype measure is associated with ASD traits in the general population. Results showed that features of the broad autism phenotype reliably predicted individual differences in gaze allocation while viewing our experimental stimuli. To our knowledge this is the first report of the BAP predicting eye gaze patterns in a community sample of typically developing children. For both populations, participants with fewer reported features of the BAP showed clear differences in gaze allocation between the congruent and incongruent conditions. In contrast, for participants exhibiting more BAP features, differences in gaze allocation between the two conditions were less pronounced.

In our community sample of adults, the broad autism phenotype was measured by the self-report Broad Autism Phenotype Questionnaire (BAPQ; Hurley, Losh, Parlier, Reznick, & Piven, 2007). Of the three subscales in the BAPQ (Aloof, Rigidity, Pragmatic Language), of which the aloof subscale was the strongest predictor of gaze allocation during our eye-tracking stimuli. The aloof subscale aims to tap into an individual's level of enjoyment in social interactions. In our sample of typically developing children, the broad autism phenotype was measured by the parent-report Social Responsiveness Scales (SRS; Constantino, 2002). The SRS is composed of five subscales (Social Awareness, Social Cognition, Social Communication, Social Motivation, Autistic Mannerisms). Results from typically developing children indicated that the best predictor of gaze allocation during our stimuli was the Social Awareness subscale, which is meant to tap into an individual's ability to pick up on social cues. Together, results from adults and typically developing children may suggest that performance on our eye-tracking measure of joint attention has a stronger relationship to specific aspects of the BAP that involve social interactions than global measures of the BAP. In summary, we conclude that our endophenotype measure is associated with ASD traits in the general population.

Is our endophenotype measure associated with known behavioral characteristics of ASD? This program of research also indicated that performance on the candidate endophenotype measure is associated with known behavioral characteristics of ASD. Theory of mind, the ability to explain and predict behavior in relation to mental states, has been found to be a deficit in children with ASD (Baron-Cohen, Leslie, Frith, 1985; Heerey, Keltner, Capps, 2003, Tager-Flushberg, 1999). In Chapter Three, performance on a behavioral measure of theory of mind was found to predict gaze allocation on our endophenotype measure. Across groups (typically developing children, children with ASD), children with higher theory of mind scores demonstrated significantly different gaze allocation patterns to the Target AOI between congruent and incongruent conditions, which is in contrast to children with lower theory of mind scores who allocate indistinguishable amounts of gaze across conditions.

Although we provide initial support that our endophenotype measure is associated with behavioral ASD characteristics, future research is necessary to fully validate this criterion. Since our endophenotype measure is designed to engender the experience of responding to another's bid for joint attention, future studies should aim to determine if behaviors associated with response to joint attention (RJA; i.e., point following) are related to performance on the candidate measure in children with ASD. Since most children with ASD eventually acquire the ability to follow a point, it would be most powerful to conduct such a study during the time when RJA skills are developing (Sigman & McGovern, 2005).

Is our endophenotype measure closely related to neural mechanisms? The neural mechanisms involved in the social information processing of this paradigm have yet to be evaluated. Currently, the technology that allows for simultaneous collection of eye-tracking data during functional magnetic resonance imaging (fMRI) scans is not widespread and often results in reduced temporal and spatial sensitivity of eye-tracking data (Duchowski, 2007). For these reason it may be more appropriate to determine neural mechanisms during event related potential (ERP) which does not require the use of a scanner, mirrors or goggles to view stimuli.

Are abnormal gaze pattern on our endophenotype measure more prevalent in family members of individuals with ASD than individuals without a family history of ASD? This final criterion is also one not yet examined in this dissertation. Future research still needs to determine if impaired performance on this measure is more common in first order relatives of children with ASD. Future studies should include children with ASD, their parents, affected and unaffected siblings. These proposed analyses would allow for correlational testing of traits associated with the broad autism phenotype in children with ASD and their relatives. If BAP traits are influences by genes, we would expect relationships amongst family members to be stronger than relationships amongst participants that do not share genes. Genome wide association studies have the potential to take this line of research to the next level by attempting to implicate genetic variations associated with performance on our eye-tracking measure.

Other future directions. Future directions in this line of research could also involve modifications to the experimental paradigm. Many gaze following studies involve the simultaneous presentation of two or more targets (Friesen & Kingstone, 1998; Driver, Davis, Ricciardelli, Kidd, Maxwell, & Baron-Cohen, 1999), thereby allowing for an analysis of preferential looking time to gaze-at or not gazed-at targets. The addition of one condition to our paradigm would allow for a similar analysis. Four additional videos could be added that are identical to congruent and incongruent videos, but with the exception that there will be two targets appearing in each video. One target will be congruent with the model's gaze, and the other will be incongruent with the models gaze. Adding this condition will allow us to analyze participants' preference to look at a gaze-at target in comparison to a non-gazed at target.

Another possible improvement to this paradigm is to extend the metrics used to quantify the eye-tracking data. In the three previous studies the metric "Total Visit Duration" was utilized. This metric calculates all looking time to a given AOI after an initial fixation. A similar metric is

“Total Fixation Duration” which sums all fixations in a given AOI during a specified time period (Rice, Moriuchi, Jones, & Klin, 2012; McPartland et al., 2011). Recently however, researchers have begun to utilize metrics like “Mean Fixation Duration” to measure the tendency to linger on a stimuli, and “Number of Fixations” to measure the tendency to repeatedly orient to a stimulus (Chen & Yoon, 2011; Kaldy et al., 2011). Using these different metrics may allow for a more comprehensive and qualitative picture of the neuropsychological underpinnings of eye gaze patterns. Likewise, future research using this paradigm could redefine the areas of interest. Previous longitudinal studies have found that despite early deficits in RJA, some children with ASD demonstrate at least some proficiency in RJA later in development (Sigman & Ruskin, 1999). In spite of these partial accomplishments, it remains unclear if subtle differences in RJA exist (i.e., instead of responding to a name call by looking at the communicative partner in the eyes, they may look at the nose or forehead). By separating the Face AOI into mouth and eyes regions, eye-tracking data may begin to examine subtle differences is gaze patterns.

Future lines of research should begin to extend the ecological validity of this paradigm, both in terms of how well the paradigm engenders a social experience and how the paradigm contributes to joint attention as a general social cognition concept. Social interactions in everyday life involve a variety of responsive facial expressions and vocalizations. To increase the ecological validity of the social experience we could add vocalizations to the paradigm. For example, as the model shifted her gaze she could say “look at that” or “isn’t that cool”. Also, to make the paradigm feel more like a social exchange, we could increase the screen size so the face of the model is the same size as a human face during a face-to-face exchange. Alternatively, this paradigm could be modified to involve real time face-to-face interactions. Merin and colleagues (2007) successfully conducted a live eye-tracking experiment of the still face paradigm. In this study, mothers and infants (half of which had an older sibling with ASD) dyads were placed in adjacent rooms, each in front of a video camera and a monitor that allowed the dyads to live view each other. Infant eye gaze behavior was recorded using a eye-tracker and results indicated that there was a subgroup of 11 (20% of the entire sample) infants who demonstrated diminished eye gaze to their mother's eyes. Interestingly, 10 out of these 11 infants had an older sibling with ASD. Overall, the infants with an older sibling with ASD and control infants displayed similar levels of distress during the still face paradigm. These findings highlight the importance of ecological validity when conducting experiments involving social interactions. However, live interactions also add noise to an experimental design. For example, in the Merin study, mothers may have exhibited different levels of expressivity. On the whole, during face-to-face interactions it becomes much more difficult to ensure participants have similar experiences. Future studies will need to carefully weigh the pros of ecological validity with the cons of noisy data.

Finally, response to joint attention is just one facet of joint attention and social cognition. Initiating joint attention (IJA), or the attempt to share and direct the attention of another, is also a core deficit in children with ASD. Future research should determine if an eye-tracking paradigm can be developed that taps into all aspects of joint attention. Schilbach and colleagues (Schilbach, Wilms, Eickhoff, Romanzetti, Tepest, Bente et al., 2010) developed a paradigm for use during fMRI scanning where healthy adults "interacted" with a computer generated model. Objects appeared on either side of the model's face and above the model's head. In the "direct condition", the participants were told to pick an object to look at, and gaze contingency was used to direct the model's attention to the same object. Brain activation in the "direct condition" was then compared to the "respond condition" where the participant was told to follow the gaze of the model, and the "nonjoint condition" where the model looked in a corner opposite to the participant. Results indicated that the medial prefrontal cortex was activated during the "respond condition" and the ventral striatum was activated during the "direct condition" (Schilbach et al., 2010). Future research should extend this paradigm to determine if it is valid across the lifespan and in samples of individuals with autism spectrum disorder.

Appendix

During an eye gaze recording the Tobii T-60 eye-tracker collects raw eye movement by defining x/y coordinates 60 times a second. In the current studies the Tobii Fixation Filter was applied to raw data (Tobii Technology, Tobii Studio User Manual 2.1, 2010). This fixation filter is described in full detail in Olsson, 2007.

The process of defining fixations, (i.e., moments when the eyes fixation at one space), involves several steps. First, missing eye gaze data is identified. The filter will interpolate data if the duration is less than 100ms. Next, an algorithm is applied to the data to determine if two gaze points are within 35 pixels of one another. The following is an excerpt from the Tobii Studio Manual (2010) describing the process in detail:

> First, a feature, [*d*], is calculated as the vector difference between two data point windows located before and after the current gaze data point. Each window has a fixed number of [*r*] gaze data points, and the difference is calculated using the average x and y coordinates of these points. Once *d* has been calculated for all the data points in the recording, we then identify peak values, i.e. the d values which are greater than both of its two closest neighbors. Next, we go through the list of peaks once more and remove all the peaks that are smaller than the highest peak within a window of radius *r*. The peaks are then added to a list under the condition that they are at least as great as a user-defined threshold - [*h*] FixationRadius.
>
> The fact that the threshold is determined relative to the window size *r*, makes the algorithm behave like an I-VT filter. In fact, the window size is fixed to 5 data points, so this has the same effect as if *d* had been divided by 5, and the threshold had been h x 5 (for example, if the FixationRadius is set to 35pixels, it will be equivalent to setting a threshold to (35/(16.6×5)=0.42 pixels/ms, on a 60 Hz eye tracker). (p. 78)

The last step involved translating the list of peaks into fixations. The start and end of a fixation is defined by two consecutive peaks. Fixations are then assigned spatial locations by taking the median of the raw data points for the fixation interval. Last, after the location of all fixations is determined, nearby fixations (defined by the Euclidean distance) are merged into one single fixation.

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