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Analysis of Beta-band MEG Coherence in ASD during Direct Gaze Processing: Relationship to Social Cognition

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Analysis of Beta-band MEG Coherence in ASD during Direct Gaze Processing: Relationship to Social Cognition

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Abstract

Gaze-following is a rudimentary behavior that forms the foundation of social communication, where aberrant social orienting is a defining feature of Autism Spectrum Disorders (ASD; Hoehl et al., 2009; Nummenmaa & Calder, 2009). Recent neuroimaging research has demonstrated increasing precision at identifying aberrant brain response patterns in individuals with ASD, but no studies have employed a more holistic neural network approach analyzing coherence (i.e., synchrony of neural oscillations) during direct gaze processing. The current study examined coherence between each pair of 54 brain regions and the relationship between average coherence and psychometric measures of social cognition in eleven participants with ASD and eight typically developing (TD) controls, who passively viewed direct gaze while undergoing Magnetoencephalography (MEG). Results revealed significant intra- and inter-hemispheric between-group differences in average coherence (1-45 Hz), providing preliminary support for increased long-range left hemisphere coherence and increased interhemisphere occipital-occipital activity in individuals with ASD.

Keywords: autism, neural synchrony, coherence, social cognition, beta-band Magnetoencephalography (MEG)

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Autism Spectrum Disorder (ASD) has reached "epidemic" proportions, and the Centers for Disease Control National Center for Health Statistics recently estimated that ASD affects 1 in 50 children between the ages of 6 and 17, which is an increase from the 2008 estimated prevalence of 1 in 88 (Blumberg et al., 2013; Centers for Disease Control and Prevention, 2012). "Autistic Disorder" or ASD is a social communication disorder characterized by qualitative impairment in social interaction and communication, in addition to the presence of restricted, repetitive, and stereotyped patterns of behavior, interests, and activities (American Psychiatric Assocation, Diagnostic and statistical manual of mental disorders, 2000). Specifically, the *DSM–IV–TR* (2000) 4th ed., text rev. identifies "marked impairment in the use of multiple nonverbal behavior such as *eye-to-eye gaze*, facial expression, body postures, and gestures to regulate social interaction" as a criterion for the diagnosis (p. 75).

Individuals with ASD demonstrate a variety of difficulties related to the social sphere and interpersonal relationships (Uddin, 2011). It is purported that deficits in social cognition may partially underlie and contribute to these social and interpersonal difficulties, including deficits in theory of mind, empathy, and affect recognition, at minimum (Couture, Penn, & Roberts, 2006). Since eye gaze is considered to be one of the most basic yet essential components of human interaction (Hoehl et al., 2009), studies have increasingly examined the neural correlates of this phenomenon and have purported that it may be an important precursor to higher order social cognitive processes. Research has shown that direct and averted eye gaze mediates both verbal and nonverbal social communications, including

direction of attention, facial identity, and emotional processing (Itier & Batty, 2009). It has been suggested that individuals with ASD may exhibit a diminished capability to obtain critical information, such as gaze direction, from the eye region resulting in social impairments (e.g., social responsiveness; Itier & Batty, 2009; Pitskel et al., 2011; Senju, Tojo, Yaguchi, & Hasegawa, 2005).

This study aimed to examine intra- and inter-hemispheric synchronicity of neuronal activity in individuals with ASD and typically developing (TD) participants who passively viewed direct gaze while undergoing Magnetoencephalography (MEG). Synchronicity of neural response refers to the degree to which networks of neurons within different brain regions oscillate (e.g., fire) within the same frequency. Networks on similar frequencies are known to transmit or receive neuronal information. Neural synchrony can be quantified by a MEG imaged coherence technique, which calculates the correlation between active cortical sites during a task or at rest (Elisevich et al., 2011; Gross et al., 2001). Measures of social cognition were administered and correlated with beta-band coherence measures during the direct gaze condition. Examining neural synchrony of gaze processing may illuminate a pathophysiological mechanism that underlies social deficits exhibited by individuals with ASD that may eventually serve as an endophenotypic biomarker and enhance diagnostic assessment.

A comprehensive literature review is provided below to elucidate the relative importance of eye gaze and social cognition to ASD and the current research proposal regarding neural synchrony of social gaze.

Background

Importance of Eye Gaze

Eye gaze is an important mediator of social interactions, as it indicates another person's focus of attention in dyadic and triadic interaction (e.g., joint visual attention) (Hoehl et al., 2009). Eye gaze serves a significant adaptive function by providing information about interests or dangers in the environment. Additionally, eye gaze provides more sophisticated information, such as the possible mental states of others (e.g., we might infer what another is thinking from the focus of their gaze). The ability to detect and respond to another individual's gaze, therefore, has remarkable implications for social interaction and communication (Nummenmaa & Calder, 2009). From an evolutionary standpoint, infants are born with an initial set of biases and preferences for eye gaze, where salience of the eye region helps to shape subsequent development. The specialization of gaze cueing develops throughout childhood and continues into adulthood (Farroni, 2003).

Development of Eye Gaze

Research has shown that eye gaze conveys critical information long before vocal language is acquired, as it has been shown to facilitate learning during the first few months after birth (Hoehl et al., 2009). Research indicates that gaze cueing in infants involves two critical features: lateral motion and a brief, preceding period of eye contact with an upright face (Johnson & Farroni, 2007). An upright face with mutual or direct gaze has been shown to engage mechanisms of attention that enables young infants (4 and 5 months) to respond to subsequent shifts in gaze (e.g., averted gaze; Farroni, 2003). Direct gaze has also been demonstrated to hold salience for newborns, as "looking time" increased for familiar faces

(i.e., faces of individuals that previously interacted with the infant) than for a familiar face with averted gaze (Guellai & Streri, 2011). Infants following the typical developmental trajectory begin to engage in "true" gaze-following between 9 and 11 months, as they develop the ability to orient to gaze cues instead of merely body following (Meltzoff & Brooks, 2007).

Studies of gaze-following in TD individuals reveal that reflexive attentional processes account for spontaneous orienting to gaze cues. Reflexive orienting processes have been demonstrated in infants as young as 4 months. Measurement of saccade responses suggests that an underlying, reflexive mechanism is responsible for the orienting response (MacPherson & Moore, 2007; Nation & Penny, 2008).

Literature reveals that gaze-following can be affected by a number of variables, including gaze direction and physical proximity of stimulus in TD individuals. Although findings are generally mixed regarding the effect of stimulus gaze (i.e., direct or averted) on level of arousal, Helminen, Syrjälä, and Hietanen (2011) revealed that direct gaze resulted in higher skin conductance responses (SCR) and shorter duration of eye contact engagement by participants. Reduced physical proximity between individual and stimulus also resulted in increased level of arousal (Helminen et al., 2011). These results suggest that social interactions can elicit increased autonomic sympathetic arousal, where direct gaze may be more distressing than averted gaze in TD individuals. These results not only demonstrate implications for social interaction in TD individuals but also raise concern regarding the social communicative abilities of individuals who demonstrate aberrant response patterns to gaze cues.

Deficits in Gaze-following in ASD

The human face holds salience for social communication, where eye gaze has been identified as a critical component for social interaction (O'Reilly & Haan, 2009). Individuals with ASD, however, exhibit more universal deficits in the ability to process facial cues. Wallace, Coleman, and Bailey (2008) revealed substantial differences in facial processing abilities of TD adults compared to individuals with ASD. The study employed tasks of holistic processing, where individuals with ASD performed significantly more poorly than TD participants on tasks of facial feature discrimination. The results suggest that individuals with ASD have an impaired or absent ability to engage in holistic processing, which severely affects facial discrimination ability and social communication (Wallace et al., 2008).

Deficits in facial processing may be explained by an inability to holistically process stimuli. However, this justification does not elucidate reasons why individuals with ASD fail to follow the traditional developmental trajectory and orient to critical gaze information. Deficits in gaze-following behavior exhibited among individuals with ASD are commonly hypothesized as a manifestation of developmental inadequacies in theory of mind, learning processes, and inability to orient attention to stimuli (Nation & Penny, 2008), although the direction of the relationship has not been established. It is equally plausible that deficits in gaze-following subsequently affect theory of mind, learning, and the ability to orient to attention. Each theory alone is inadequate to explain the extent of deficits in gaze-following behavior exhibited by individuals with ASD; however, each theory identifies critical information for understanding the deficits that contribute to impaired social communication and "social cognition" in ASD.

One perspective evident in the literature is that the absence of theory of mind (ToM) accounts for gaze-following deficits exhibited by individuals with ASD. Theory of mind is the ability to infer another individual's mental and emotional state by one's capacity to detect and react to information relayed through gaze and eye contact. It has been argued that "Gaze direction is a behavior; attention is a state of mind," where ToM and gaze-following are distinct entities (Meltzoff & Brooks, 2007). Although demonstrating ToM is not necessary to elicit gaze-following behavior, ToM is believed to serve as the impetus for engaging in gaze-following behavior (Nation & Penny, 2008). Accordingly, research suggests that ToM is an innate process that is controlled by an eye direction detector (EDD) module and ToM mechanism (ToMM). Together, these components allow one to react and orient to the social significance of another's gaze. These components are believed to be impaired in individuals with ASD, leading to deficits in identifying the significance of another's gaze and absence of gaze-following behaviors throughout development (Hala & Carependale, 1997; Senju & Johnson, 2009). Nonetheless, discrepancies exist within ToM literature as some theorists suggest that ToM impairments underlie gaze following deficits in ASD, whereas others believe that gaze-following deficits account for impaired or absent ToM in individuals with ASD. With regard to the conceptualization of the current study, both viewpoints are mutually informative in understanding observed deficits in ToM and gaze-following in ASD.

An inadequate learning history has also been proposed to account for deficits in gaze-following. This hypothesis explains that individuals with ASD have insufficient experiences with eye gaze/reward pairings, where classical and operant conditioning can be used to overcome the lack of early conditioning experiences. Although individuals with ASD improve gaze-following behavior subsequent classical and operant conditioning procedures,

these gains are short-lived and lack generalization to naturalistic, social situations (Nation & Penny, 2008).

Aberrant neural functioning may explain short-lived gains in gaze-following behavior subsequent to behavior therapy, as conditioning procedures may not effect change in neural circuitry. The affective arousal model posits that eye contact initiates a mechanism of emotional arousal and autonomic sympathetic responses (e.g., visceral, endocrine), which affects the rewarding properties of eye contact in individuals with ASD. These emotional responses to eye contact have been found to elicit activation of the amygdala, which is a subcortical brain region that has been associated with emotional learning and memory modulation. The amygdala and fusiform gyrus are involved in detecting faces and directing attention to them and are implicated in the fear response. These areas have also been found to be affected during eye gaze responses in individuals with ASD (O'Reilly & Haan, 2009; Senju & Johnson, 2009).

The affective arousal model includes two distinct models, which explain that physiological arousal is associated with amygdala activity and the emotional salience of eye contact for individuals with ASD. The hyperarousal model contends that avoidance of gaze-following behavior in ASD serves an adaptive function, as eye contact elicits heightened physiological arousal (i.e., atypical fusiform and amygdala activation). This model further suggests that individuals with ASD actively avoid engaging in eye contact. In individuals with ASD, gaze is believed to lack the rewarding value it holds for individuals who have consistently experienced positive social interactions void of heightened physiological arousal. In a related vein, the hypoarousal model contends that individuals with ASD display reduced amygdala activity early in development. Hypoactivation of the amygdala is believed

to affect the ability of individuals with ASD to attach emotional salience and positive reward value to eye contact, thereby reducing motivation to participate in eye gaze (Corden, Chilvers, & Skuse, 2008; Dalton et al., 2005; Joseph, Ehrman, McNally, & Keehn, 2008; Kylliäinen, Braeutigam, Hietanen, Swithenby, & Bailey, 2006; Senju & Johnson, 2009).

Last, deficits in gaze-following behaviors among individuals with ASD are believed to emerge as a result of an impaired ability to orient to stimuli. Research indicates that gaze-following is a reflexive process, which is controlled by a network of neural structures. This network is hypothesized to include a mutual connection from the parietal cortex and amygdala to the superior temporal sulcus (STS) of the temporal cortex, which allows reflexive shifts in attention to occur in response to eye gaze (MacPherson & Moore, 2007; O'Reilly & Haan, 2009). It is suggested that individuals with ASD exhibit issues with shifting attention from a directional cue to the target of interest, which may explain subsequent deficits in spontaneous gaze-following behavior. Although this theory may appear to have the most credibility, it does not account for *why* individuals with ASD lack the ability to spontaneously shift attention between social stimuli. In fact, individuals with ASD have been shown to demonstrate reflexive attentional orienting to gaze cues, similar to individuals following the traditional developmental trajectory (Nation & Penny, 2008).

Studies, however, illustrate that individuals with ASD may process stimuli differently than TD individuals, regardless of their ability to reflexively orient to stimuli. This finding is evidenced by studies using a Posner-style cueing paradigm, which demonstrates that when individuals are presented with a picture of a face with an averted gaze (e.g., left or right gaze), they are "faster to detect, localize, or identify a target stimulus that subsequently appears at the location the face was looking (the valid location) rather than the nongazed-at

location (the non-valid location)" (Nation & Penny, 2008, p. 83). This effect is referred to as the validity effect, where studies have demonstrated that all individuals (TD and ASD) exhibit regardless of stimuli (i.e., photos of faces or arrows). These findings suggest that nonsocial mechanisms mediate gaze-following. Although individuals with ASD respond to gaze cues, social stimuli seemingly lack salience to elicit a preferential response (Nation & Penny, 2008). Deficits in social communication arise in individuals with ASD, as social and nonsocial stimuli are similarly processed. Therefore, individuals with ASD lack the capacity to view eye gaze as significant and meaningful for social interactions.

Studies of Direct and Averted Gaze-following

While a variety of hypotheses have been proposed to account for impairment in gaze-following in individuals with ASD, only recently have complex neuroimaging techniques been used to explore mechanisms of aberrant orienting to social cues (i.e., eye contact and gaze-following) in individuals with ASD. Studies examining direct and averted gaze provide insight about atypical patterns of gaze-following and its sequelae on social communication.

Early literature examining deviant patterns of gaze processing in ASD yields inconclusive results regarding the salience of gaze direction. Senju et al. (2005) used ERP to examine gaze-following responses to direct and averted gaze stimuli in children with high-functioning ASD and TD individuals. Typically developing children exhibited right hemisphere lateralization, a high degree of occipito-temporal activity during direct gaze as compared to averted gaze, and more accurately responded to faces with a direct gaze. Gaze direction, however, had no effect on children with ASD, and hemispheric lateralization was not observed (Senju et al., 2005). Pellicano and Macrae (2009) also found that gaze direction

did not affect the ability of children with ASD to perform a sex categorization task, but found gaze direction to positively influence performance among TD children. Specifically, direct gaze stimuli was found to enhance discriminative ability relative to averted or closed gaze stimuli (Pellicano & Macrae, 2009).

Kylliäinen, Braeutigam, Hietanen, Swithenby, and Bailey (2006) found divergent results, demonstrating that direct gaze influenced performance on a task of discrimination for children with ASD. Motorbikes and photographs of faces with varying gaze directions (e.g., direct, averted, closed) were displayed sequentially during MEG imaging to individuals with and without ASD, and participants were instructed to indicate if sequential images were identical. Both groups recognized faces more accurately than non-face objects, but each group responded differently to direct and averted gaze stimuli. Individuals with ASD exhibited a strong, left lateralized response to photographs with direct gaze as compared to averted gaze at 240 ms. Typically developing individuals did not exhibit heightened response to direct gaze but demonstrated strong, right hemispheric lateralization to averted gaze stimuli (Kylliäinen et al., 2006). Senju, Kikuchi, Hasegawa, Tojo, and Osanai (2008) similarly demonstrated that direct gaze holds salience for individuals with ASD. Typically developing children and children with ASD detected direct gaze more quickly than averted gaze, whether the eyes were presented alone or within faces. Interestingly, children with ASD also distinguished direct gaze more efficiently during the presentation of inverted faces, which hindered performance in TD individuals (Senju et al., 2008).

Recent work by Kaartinen et al. (2012) illustrated that individuals with ASD exhibit elevated autonomic arousal to direct gaze relative to averted gaze stimuli. Skin conductance responses (SCR) of participants with ASD and TD individuals were recorded during the

presentation of live, direct, and averted gaze stimuli. Level of arousal was examined relative to gaze condition and social skill impairment, which was evaluated by a diagnostic interview. Results revealed that individuals with ASD exhibited elevated autonomic arousal during direct gaze relative to averted and closed eyes conditions, which was positively correlated with two measures of impaired social skills (e.g., language and other social communication skills, gestures and non-verbal play). No significant associations were observed between gaze condition and social impairment in TD individuals (Kaartinen et al., 2012). These results, in conjunction with the previous neuroimaging studies, suggest atypical functioning of neural substrates responsible for processing gaze cues in ASD. Heightened activation in response to direct gaze in individuals with ASD is hypothesized to be a function of amygdala activation, where the emotional salience of the stimuli provokes activation of amygdala circuitry (Kylliäinen et al., 2006).

Research examining response latency following the presentation of direct and averted gaze provides further support for aberrant neural functioning in individuals with ASD. Elsabbagh et al. (2009) found that infants of siblings with ASD, as compared to infants with no family history of ASD, exhibited prolonged latency of the occipital P400 event-related potentials (ERP) component in response to direct gaze stimuli. The P400 ERP component has been observed to be relevant for face processing, attention modulation, and top-down visual processing in infants. It is notable that responses at earlier latencies were similar among both groups of infants (Elsabbagh et al., 2009).

Previous studies have used complex gaze cueing procedures and have yielded inconclusive findings of the relative significance of gaze direction to social orienting and impairment in individuals with ASD. More recent studies have not only explored how

individuals with ASD orient to gaze direction but have also examined the neural substrates that correspond to orienting behaviors. Lajiness-O'Neill et al. (2010) are among the first to explore neural mechanisms of gaze orienting in ASD by utilizing a passive viewing task and MEG in high-functioning adolescents with ASD and TD age- and IQ-matched participants. Participants were asked to indicate whether a character's gaze was shifted congruently or incongruently to targets (asterisk), words, or faces. Results revealed that individuals with ASD exhibited higher mean amplitudes in left occipital and parietal brain regions during gaze shifts to targets and faces, and activation of inferior temporal regions at an earlier latency than frontal regions in response to words. Typically developing individuals, however, exhibited higher mean amplitudes in the right inferior temporal and medial orbitofrontal regions in response to targets and faces, and activation of frontal regions at an earlier latency than inferior temporal regions in response to faces.

Greene et al. (2011) found similar results in a study employing fMRI and a spatial cueing paradigm (e.g., directional gaze and arrow cues) to examine regional activation in high-functioning adolescents with ASD and TD age- and IQ- matched participants. Both groups demonstrated similar orienting patterns, and reaction times were faster for valid (congruent), gaze cues than to invalid (incongruent) and neutral representation arrow cues. However, striking variations in cortical activity were observed relative to group identity, as significant activity was observed for the directional gaze cue but not the directional arrow cue. Congruent with findings by Lajiness-O'Neill et al. (2010), TD participants demonstrated significant activity in frontoparietal regions, including the inferior frontal gyrus (IFG), premotor cortex, precentral gyrus, and supramarginal gyrus (SMG), where activity was largely lateralized to the right hemisphere. Significant activity was also observed in the

bilateral putamen and insula, in addition to lower-level visual regions in TD individuals. In contrast, adolescents with ASD exhibited significant activity only in the superior parietal lobule (SPL). Further exploratory analysis revealed that the STS activation varied as a function of group identity and gaze cue. Although differences were not significant, it is notable that TD individuals exhibited decreased activation of the STS in response to arrow cues, whereas decreased STS activity was observed in ASD individuals in response to gaze cues. Nonetheless, TD adolescents demonstrated distinct neural processing of nonsocial and social cues, but adolescents with ASD did not exhibit differentiated response patterns relative to stimuli (Greene et al., 2011).

Pitskel et al. (2011) also examined differential processing of direct and averted gaze in adolescents with high-functioning ASD and age- and IQ-matched TD participants. A dynamic, virtual-reality video that simulated a real world social encounter (e.g., male character passed through a doorway and approached viewer with a direct or averted gaze) was shown to participants while undergoing fMRI. Significant group by condition interactions were observed. Increased activation was observed in the right anterior insula (AI) during direct gaze in TD adolescents but was not modulated by gaze in adolescents with ASD. Individuals with ASD exhibited activation in the left lateral occipital cortex (LOC) in response to averted gaze, where TD individuals did not exhibit activation. Both groups demonstrated modulation of the right temporo-parietal junction (TPJ) and left dorsolateral prefrontal cortex (DLPFC), but hemispheric activation between the groups was not symmetrical. Adolescents with ASD activated the right TPJ in response to averted gaze and TD adolescents exhibited activation of the same structure during direct gaze. Similarly, the ASD group demonstrated activation of the DLPFC during direct gaze and the TD group

exhibited activation of this structure during averted gaze. Differential patterns of activation were exhibited relative to condition and group identity, as TD and ASD individuals exhibited contrasting responses.

Davies, Dapretto, Sigman, Sepeta, and Bookheimer (2011) adopted a similar approach to researching the neural bases of gaze processing in individuals with ASD, but they incorporated an emotion component. Children with ASD and age- and IQ- matched TD participants underwent fMRI while viewing emotionally expressive photographs (e.g., anger, fear, happiness, or neutral expression) of individuals displaying either direct or averted gaze. In response to direct gaze, TD individuals recruited frontal (bilateral ventrolateral prefrontal cortex or VLPFC, left ventral inferior frontal gyrus, and premotor cortex), subcortical (bilateral amygdala, left caudate head, and pulvinar nucleus of thalamus), and visual and face processing (occipital cortex and bilateral fusiform gyri) regions. Typically developing participants only recruited frontal areas in response to averted gaze. In contrast, individuals with ASD showed no significant difference in response pattern to direct and averted gaze conditions and exhibited activation of the left hippocampus, superior frontal gyrus (SFG), and medial parietal cortex during both cueing conditions. Individuals with ASD did not exhibit activation of the VLPFC, but TD individuals demonstrated heightened bilateral activation of this area during direct gaze. Notably, TD individuals exhibited stronger recruitment of the left VLPFC, medial temporal gyrus (MTG), and fusiform gyrus during direct gaze relative to averted gaze.

Previous literature demonstrates inconsistency regarding the relative differences in neural activation and behavioral orienting between direct and averted gaze processing. Nonetheless, research suggests that social gaze lacks salience for individuals with ASD as

compared with TD individuals, where reversed hemispheric processing of gaze cues in individuals with ASD as compared to TD participants has been observed. Early studies of ASD elucidated patterns of aberrant behavior and regional patterns of activation, whereas more recent studies have started to uncover gaze processing at a systems level. The literature reveals that individuals with ASD exhibit atypical patterns of neural functioning in response to gaze cues, and critical structures for face processing fail to activate in response to social stimuli. Greater exploration of the neural correlates of direct gaze is necessary to discern differences between individuals with ASD and TD individuals.

Direct gaze was specifically examined to address inconsistencies within the literature regarding patterns of activation associated with direct gaze. Individuals with ASD have been identified as exhibiting heightened autonomic responses (Kaartinen et al., 2012), prolonged activation of the P400 ERP (Elsabbagh et al., 2009), and stronger left lateralization in response to direct gaze stimuli (Kylliäinen et al., 2006). Additionally, direct gaze stimuli has been identified as enhancing performance on discrimination tasks for individuals with ASD (Senju et al., 2008), whereas other research has not observed enhanced performance (Pellicano & Macrae, 2009) or significant patterns of activation in relation to direct gaze as compared to averted gaze stimuli (Davies, Dapretto, Sigman, Sepeta, & Bookheimer, 2011; Senju et al., 2005). A holistic, whole-brain analysis of direct gaze processing would prove beneficial in clarifying patterns of activation and identifying a potential biological marker of aberrant functioning characteristic of ASD.

What is MEG? Utility of MEG in ASD Research

Magnetoencephalography (MEG) permits simultaneous analysis of whole-brain functioning during passive viewing of direct gaze. MEG is a non-invasive brain imaging

procedure that maps magnetic fields arising from cortical activity. MEG is an innovative imaging modality, in that it provides greater spatial and temporal resolution than other brain imaging methodologies such as EEG or fMRI. Previous studies have predominantly examined neural activation during gaze processing using fMRI (Davies et al., 2011; Greene et al., 2011; Pitskel et al., 2011), which does not provide information regarding latency and amplitude of activation in respective brain regions. To date, Electroencephalography (EEG) and MEG are the only functional imaging modalities that offer the capability to examine latency, amplitude, and coherence of neural response (Elisevich et al., 2011; Kaiser, Heidegger, Wibral, Altmann, & Lutzenberger, 2008; Roberts et al., 2009)

No known studies have analyzed the degree of synchronous neuronal firing during passive gaze tasks, which may provide meaningful information regarding neural connectivity necessary for social information processing. Social and behavioral abnormalities observed in individuals with ASD are hypothesized to arise as a result of weak central coherence or impaired integration of brain regions that permits higher level cognitive processing (Belmonte et al., 2004). Neural synchronicity, measured by coherence, is the degree to which neuronal circuits fire within the same frequency, where synchronized oscillations of low (delta, theta, and alpha) and high (beta and gamma) frequency bands are fundamental to coordinated activity of a normally functioning brain (Uhlhaas, Roux, Rodriguez, Rotarska-Jagiela, & Singer, 2010).

Gamma and beta-band frequencies have been associated with unique synchronization properties. Short- and long-range synchronicity have been observed to occur within gamma and beta-band frequencies, respectively (Kopell, Ermentrout, Whittington, & Traub, 2000; Schnitzler & Gross, 2005). The gamma and beta-bands have also been implicated in

coordinating neural synchronization, as they establish systematic phase lags between discharges of distributed neurons (Uhlhaas et al., 2010). Compared to the gamma-band frequency, beta-band rhythms have been observed to contribute to higher-level interactions among distant structures (Kopell et al., 2000; Schnitzler & Gross, 2005). Gross et al. (2004, 2006) utilized MEG and a visual-presentation protocol with pre-defined targets to demonstrate modulation of beta-band synchronization within the fronto-parietal-temporal attentional network, where the strongest synchronization was observed between the right posterior parietal and left frontal cortices in TD individuals. Notably, target processing was associated with increased power in the beta-band at 400 ms, where task-related attention demands and behavioral performance were directly related (Gross et al., 2004, 2006).

Synchronicity of neural activity in response to faces in particular has been observed to emerge and change over development. Specifically, TD adolescents have been found to exhibit increases in neural synchrony of the gamma and beta-band until late adolescence when reductions in phase-synchronization and amplitude of high frequency oscillations are observed to occur. Significant increases in high frequency oscillations are observed to reemerge in early adulthood, which is also associated with re-organization of the beta-band and an increase in theta synchronicity. Findings suggest that late adolescence is a time of critical change in neuronal synchrony, which results in increased temporal precision and overall synchronicity of neural response (Uhlhaas, Roux, et al., 2009).

It has been suggested that ASD may be explained by early impairments in brain development, which contributes to abnormal cortical circuitry. Belmonte et al. (2004) suggested that individuals with ASD exhibit impairments in short- and long-range neural connections and demonstrate reduced activity in integrative brain regions. An fMRI study of

functional connectivity revealed aberrant connectivity in the frontal and parietal regions of individuals with ASD, finding that individuals with ASD exhibited overall lower frontal-parietal connectivity than TD participants during an executive functioning task. Intra- and inter-hemispheric connectivity was not significantly different, but it is notable that intrahemispheric functional connectivity was marginally higher than interhemispheric connectivity in ASD and TD participants (Just, Cherkassky, Keller, Kana, & Minshew, 2007).

Uhlhaas et al. (2010) proposed that the expression of high-frequency oscillations might not be supported during infancy, which results in reduced temporal precision and ASD symptomatology. Milne et al. (2009; as cited in Uhlhaas, Pipa, et al., 2009) observed that oscillations of alpha and gamma band frequencies contribute to asynchronous activity in ASD, as visual evoked EEG recordings suggest abnormal modulation and recruitment during perceptual integration tasks. Similarly, Isler, Martien, Grieve, Stark, and Herbert (2010) also utilized visual evoked EEG recordings and found that individuals with ASD exhibited decreased interhemispheric synchrony in occipital areas and diminished functional connectivity compared to TD participants. Increased intrahemispheric activity was observed bilaterally in occipital regions at 4 Hz and in the upper alpha and lower beta-band frequencies (10-15 Hz), as well as in the upper beta-band frequency (16-23 Hz) in the right hemisphere. Interestingly, individuals with ASD have also been observed to exhibit increased upper beta (26 Hz) synchronization in interhemispheric parietal regions but decreased long-range interhemispheric connectivity as compared to TD participants during executive functioning tasks (Perez Velazquez et al., 2009).

Individuals with ASD are therefore believed to process information in "piecemeal" fashion, recruiting local brain networks and failing to globally communicate among brain region (e.g., poor connectivity among long-range connections; Brock, Brown, & Boucher, 2002; Uhlhaas & Singer, 2006; Uhlhaas et al., 2009; Uhlhaas, Roux, Rodriguez, Rotarska-Jagiela, & Singer, 2010; Wilson, Rojas, Reite, Teale, & Rogers, 2007). Few studies have examined the extent of asynchronous activity observed within the beta-band frequency in individuals with ASD, and no studies have examined beta power during passive viewing of direct gaze. Also, no studies have investigated the relationship between beta-band activity during passive viewing of gaze and indices of social cognition in individuals with ASD or control participants. This research would enhance our understanding of the association between neural substrates of gaze processing and social cognitive functioning in individuals with ASD, and potentially identify an endophenotypic, diagnostic biomarker of ASD.

Features of Aberrant Social Cognition

As previously explained, individuals with ASD exhibit marked impairment in spontaneously orienting eye gaze in social situations. Collectively, these observed deficits in gaze-following behavior are associated with severe impairments in "social cognition" and social communication (Derntl & Habel, 2011). The construct of "social cognition" has been inconsistently defined within the literature. Researchers, however, generally agree that social cognition is a multi-dimensional construct that is purported to include but is not limited to theory of mind (ToM), empathy, and affect recognition (Bird et al., 2010; Hala, 1997).

Theory of Mind (ToM)

The construct of theory of mind (ToM) captures the essence of social deficits exhibited by individuals with ASD. Theory of mind refers to the ability to infer the desires,

emotions, beliefs, intentions, and other inner experiences of others that result in human action (Wellman, Cross, & Watson, 2001). Successful social interactions are dependent on inferring the internal states of others and responding appropriately (Derntl & Habel, 2011).

The construct of ToM emerged from research with primates. Primates viewed a series of videotapes scenes of struggling humans and correctly selected photographs that conveyed understanding of the situation (Premack & Woodruff, 1978), yet Piagetian and metacognitive traditions more comprehensively defined the construct of ToM. Jean Piaget's notion of "egocentrism," or the tendency of young children to focus on their own perspective with a relative inability to internalize another's perspective, is a critical feature of ToM (Carpendale, 1997). Although Piaget explained that this ability is lacking in individuals early in development, he explained that a child's awareness of another's perspective or point of view evolves and matures throughout development (Flavell, 2000). John Flavell, a developmental psychologist, elaborated on Piaget's later stages of development, focusing on metacognition and ToM. Flavell posits that metacognition is composed of three inter-related abilities: metamemory (ability to understand one's own memory process), knowledge of false beliefs (ability to know what we know), and appearance-reality distinctions (ability to distinguish real-appearing objects from real objects). Studies of perceptual perspectives yield two levels of visual perspective taking: 1) understanding that another person may not see something exactly as they do, and 2) understanding that other people have different perspectives. Flavell's theory redefines Piaget's notion of egocentrism, explaining that individuals who do not demonstrate perspective taking ability are not egocentric but are merely limited by their representation abilities. Flavell's perspective forms the basis of ToM and explains deficits in social cognition exhibited by individuals with ASD (Bergen, 2008).

The development of ToM is explained by a variety of hypothesis, including the theory-theory, theory-of-mind as innate model, and the stimulation-theory. The theory-theory hypothesis posits that children's understanding of the mind is essentially theory-like, where children utilize hypothesis testing (i.e., theory building and refutation) to make sense of human behavior. In contrast to the theory-theory model, ToM has also been viewed as an innate model. The theory-of-mind as an innate model suggests that ToM does not develop through hypothesis testing, but that it is an innate processing mechanism. The theory-of-mind mechanism (ToMM), as previously mentioned, affords the opportunity to "metarepresent," or the cognitive ability to understand beliefs or representations. In contrast, the stimulation-theory, a third theory of ToM development, contends that understanding of another's mind is gained through referencing one's own conscious experience. According to the stimulation-theory, personal conscious experiences allow one to "stimulate" an idea of what we would do, think, or feel given a certain situation. Although each viewpoint provides differing explanations regarding the development of ToM, each theory posits that ToM becomes more refined with development (Flavell, 2000; Hala & Carependale, 1997).

Theory of mind is a relatively recent construct, which has been explained by a variety of contrasting hypotheses. Various terms have also been used to refer to the phenomena of ToM, including naïve theory-of-mind, folk psychology, commonsense psychology, intuitive psychology, mindreading, and belief-desire psychology. The "belief-desire" characterization of ToM most clearly describes the underlying concept of ToM. From this perspective, beliefs are viewed as cognitive or mental attitudes about the world (e.g., thoughts, expectations, reasons, and assumptions), whereas desires include motivational states (e.g., hopes, wishes, wants and needs; Hala & Carependale, 1997; Wellman et al., 2001).

Accordingly, ToM research most commonly examines the concept of false beliefs, which posits that "unless you understand that people can be mistaken in their beliefs you don't truly understand beliefs at all" (Hala & Carependale, 1997, p. 192). Standard assessments of false belief include the "unexpected transfer" and "unexpected contents" tasks. The unexpected transfer task involves a story of two individuals and an object, where the object's location is changed upon the departure of one individual from the room. The participant is then asked where the individual will look for the object upon returning to the room. The participant who demonstrates ToM will explain that the participant will look in the original location, whereas the individual lacking ToM will contend that the individual will look for the object in its new location. The unexpected contents task is similar and asks participants to determine what they think is contained in a clearly marked box (e.g., box of crayons). Although both tasks are used to determine if children have developed ToM, the latter task addresses possible issues with underdeveloped cognitive capacity (i.e., ability to keep track of and integrate complex narrative; Hala & Carependale, 1997).

Theory of mind is generally studied within the context of infants and young children, and individuals with ASD are a common demographic (Flavell, 2000). Development of ToM is believed to occur from 2 to 7 years of age, where significant development is believed to occur between 3 and 4 years of age (Hala & Carependale, 1997). Theory of mind is generally absent in individuals with ASD, as cascading deficits in gaze and affect recognition contribute to significant impairment (Demurie et al., 2011; Fernandez-Duque & Baird, 2005; Hein & Singer, 2008; Sugranyes, Kyriakopoulos, Corrigall, Taylor, & Frangou, 2011). Research reveals that following a 16-week training program, children with high functioning ASD made minimal gains in their conceptual understanding of ToM and did not demonstrate

improved performance on ToM tasks (Begeer et al., 2011). This finding may suggest that prerequisite abilities (e.g., gaze-following and affect recognition) form the foundation for understanding ToM.

Mechanisms underlying ToM are purported to be impaired in individuals with ASD, where the ToMM has been hypothesized as contributing to deficits observed in individuals with ASD (Hala & Carependale, 1997; Senju & Johnson, 2009). Literature reveals that the medial prefrontal cortex (mPFC), temporal pole, and the superior temporal sulcus (STS) are activated during ToM tasks in children and adults (Hein & Singer, 2008; Sugranyes et al., 2011; Zilbovicius et al., 2006). If given specific instruction to attend to social stimuli, individuals with ASD have been found to exhibit comparable or exceeding activation patterns of control participants in these areas (Sugranyes et al., 2011).

Empathy

Empathy is a second component of social cognition and is defined as the ability to infer and convey understanding of another individual's thoughts and feelings (O'Reilly & Haan, 2009). Empathy is a multidimensional construct, as it is composed of affective and cognitive abilities including "empathic concern" (i.e., sympathy), affect recognition, and ToM (Demurie et al., 2011; Eisenberg, Losoya, & Guthrie, 1997; Miklikowska, Duriez, & Soenens, 2011). As such, it is a higher-level cognitive process that requires one to identify emotional states and intentionally adopt the perspective of another individual, while maintaining a clear separation between self and other (Decety, 2005; Eisenberg et al., 1997).

Theory of mind and affect recognition are intimately related to the study of empathy. Theory of mind has been identified as fostering empathy and sympathy in an individual, which inextricably involves an affective component (Eisenberg et al., 1997). Empathy is a

complex skill that develops and matures with age. Infants have been observed to exhibit "empathic distress" in response to another infant's cries (e.g., contagious crying and facial expression) as early as 1 month, where vocal and facial distress increasingly manifest in response to another infant's cries throughout the 1 to 9 month developmental period (Eisenberg et al., 1997; Geangu, Benga, Stahl, & Striano, 2010, 2011). The infant's ability to differentiate between the self and other becomes apparent at 9 months, and this skill has been observed to improve drastically between 2 to 3 years of age. During this time, children begin exhibiting self-recognition skills (e.g., identify self in mirror) and begin demonstrating prosocial, helping behaviors toward adults (Eisenberg et al., 1997; Geangu et al., 2011; Roth-Hanania, Davidov, & Zahn-Waxler, 2011). Children have been observed to empathize in immediate, situation-specific contexts until approximately 6 years old or until they develop sophisticated ToM and expressive language ability. The most advanced form of empathic responding, "sympathetic distress" (also referred to as "empathic concern") develops between 6 and 9 years of age and more fully matures in adolescence (Eisenberg et al., 1997; Hein & Singer, 2008). During adolescence mental flexibility and self-regulation continue to mature and facilitate empathic concern (Eisenberg et al., 1997).

Theorists have suggested that the perception-action model accounts for the development of empathy, which suggests that perceiving another individual's emotional state activates one's own mental representation of the same emotional experience. As such, the model purports that the cortical responses exhibited by an individual experiencing the emotion first-hand will mirror that of the observer (Decety, 2005; O'Reilly & Haan, 2009). Although imaging studies have not been conducted in infants and children, studies in adults have demonstrated support for the model (Hein & Singer, 2008; O'Reilly & Haan, 2009).

This phenomenon has been demonstrated in pain studies, where one participant observes an individual experience a painful situation. Results indicate that both participants demonstrate identical activation patterns in the bilateral AI, rostral anterior cingulate cortex (ACC), and primary (SI) and secondary (SII) somatosensory regions (Hein & Singer, 2008).

Moreover, the premotor and posterior parietal cortex are implicated more generally in empathy and activate in response to imagining one's own action, another's action, and imitating actions performed by a model. Research indicates that the prominent patterns of activation are also present in the STS, AI, and amygdala during tasks of imitation. The right hemisphere has particularly demonstrated importance in empathic responding, where localized damage to the parietal cortex corresponds to deficits in empathy. Orbitofrontal and dorsolateral regions, in addition to the right prefrontal cortex, have also been identified as key regions responsible for perspective taking, emotional reasoning, and overall empathic responding (Decety, 2005; O'Reilly & Haan, 2009).

Empathy is a multi-faceted ability that facilitates social communication and affects responsiveness in social situations. It has been shown to be a good predictor of interpersonal functioning and has been strongly associated with prosocial behaviors (e.g., helping; Miklikowska et al., 2011). Children with ASD exhibit deficits in empathy that are hypothesized to contribute to impairments in social communication (Geangu, 2009). Geangu et al. (2010) found that infants demonstrating ASD symptomology at 20 months display reduced empathic concern in response to another's distress. Reduced empathic concern was also exhibited among adolescents with ASD, as they consistently performed more poorly than TD individuals on measures of ToM and empathy (Demurie et al., 2011). Interestingly, one study indicated that the degree of AI activation was modulated by degree of alexithymia

but not ASD (Derntl & Habel, 2011). However, to date, neuroimaging studies generally have not exclusively examined empathy in individuals with ASD.

Affect Recognition

One important element of both social cognition and effective communication is the ability to accurately interpret nonverbal cues, such as facial/affect recognition. Affect recognition (or facial emotional recognition) has been independently examined as a dimension of social cognition (Sugranyes et al., 2011), as it has been identified as a skill inherent within empathic ability and closely related to ToM (Bird et al., 2010). Affect recognition has been broadly defined as the ability to infer emotional information (i.e., what a person is feeling) from facial expressions (Couture et al., 2006)**.**

While facial recognition plays a critical role in distinguishing among individuals (e.g., friend, foe, stranger), facial affect recognition plays a larger role in the development and maintenance of social interaction. Haxby, Hoffman, and Gobbini (2002) reported that facial affect recognition yields an abundance of information necessary to facilitate social interactions, as the information gleaned from facial affect recognition can help to make inferences concerning one's mood and intentions. Faces convey social information that is crucial for the understanding of social communication, where successful social behavior often depends on the ability to correctly discriminate emotion in facial expression (Baird et al., 1999). Deficits in the judgment of facial affect can negatively impact the quality of social relationships, as impairment in affect recognition may inhibit the acquisition of appropriate social behavior (Simonian, Beidel, Turner, Berkes, & Long, 2001).

Six basic emotional expressions (e.g., anger, disgust, fear, happiness, sadness, and surprise) have been identified as universally recognized and invariant across cultures (Ekman

& Friesen, 1971; Ekman et al., 1987). While it has been proposed that there are some core components in the recognition of emotional expressions that are innate (Ekman & Friesen, 1971; Elfenbein & Ambady, 2002), it is generally accepted that the ability to recognize affect from facial expressions develops with age (Durand, Gallay, Seigneuric, Robichon, & Baudouin, 2007). Facial affect recognition has been observed relatively early in life, where infants at 3 and 4 months can distinguish happiness from anger, fear, and surprise (O'Reilly & Haan, 2009). However, it has been suggested that this ability does not fully mature until the age of 10 (i.e., when they are able to consistently recognize emotions such as of fear, anger, and neutrality; Walker-Andrews, 1997). Other researchers have indicated that basic recognition of happiness or sadness is acquired with perfect accuracy around 6 years of age (Bruce et al., 2000; Durand et al., 2007), where these emotions are more consistently identified relative to more complex emotions, such as fear or disgust (Boyatzis, Chazan, & Ting, 1993).

Abnormalities in affect recognition have been reportedly associated with psychiatric disorders in both adults and children, where individuals with ASD characteristically exhibit deficits in affect recognition that inhibit effective interpersonal communication (Blair, 2003; Kuusikko et al., 2009). Individuals functioning at the "high-end" of the Autism spectrum exhibit selective impairments in inferring mental states from faces, where research has revealed that higher order social states require the extraction of critical information from the eye region (Baron-Cohen & Wheelwright, 1997). Despite demonstrated deficits in higher-order social skills, research suggests that recognition of basic emotions is often spared (Adolphs, Sears, & Piven, 2001). Kuusikko et al. (2009) indicated that individuals with ASD demonstrate skill at affect recognition, but perform more poorly on these tasks and are more

likely to perceive ambiguous stimuli as negative emotion relative to control participants. Interestingly, the study also revealed that older individuals with ASD demonstrated better affect recognition skills than younger ASD participants, suggesting that affect recognition may improve with age (Kuusikko et al., 2009**).** These findings suggest that individuals with ASD may be able to perceive information regarding basic emotions but fail to link the perception of the face to social judgments.

A variety of areas have been identified as important in the development of facial/affect recognition, including the the fusiform face area (FFA), lateral occipital cortex (LOC), fusiform gyrus (FG), and amygdala (Adolphs et al., 2001; Grelotti, Gauthier, & Schultz, 2002; Haxby et al., 1999). Primarily, the amygdala has been identified as important for signaling the salience of important faces, as it has been identified as an essential structure for the linkage between the perception of one's face to its conscious or unconscious social and emotional meaning (Adolphs, Baron-Cohen, & Tranel, 2002). The amygdala has been found to impact social judgments, and significant amygdala damage has been shown to impact one's judgments of trustworthiness and approachability from facial expressions (Adolphs, Tranel, & Damasio, 1998). Heightened amygdala activation may also reflect the extent to which a social encounter makes one feel guarded (Gobbini, Leibenluft, Santiago, & Haxby, 2000), while a reduction of activity in the amygdala may be associated with feeling more at ease and less guarded in a social situation. Research has indicated that the amygdala aids in emotional learning (Ono, Nishijo, & Uwano, 1995), signaling the emotional salience of events (Aggleton, 1993), social behavior (Brothers & Ring, 1993), social cognition (Castelli, Happé, Frith, & Frith, 2000), and the perception of facial expressions (Adolphs et al., 1998).

Neuroimaging studies are increasingly performed to gain an understanding regarding the neural structures implicated in impaired affect recognition in individuals with ASD. Although the FFA, LOC, and amygdala have been associated with facial recognition ability (Grelotti et al., 2002; Haxby et al., 1999), the amygdala and FG often receive greater attention with regard to affect recognition (Adolphs et al., 2002). Amygdala dysfunction may be the core dysfunction impacting the abnormal social interest in individuals with ASD (Adolphs et al., 2002, 2001; Sugranyes et al., 2011). Individuals with ASD who have bilateral amygdala damage demonstrate difficulty in making social judgments, as the amygdala is hypothesized to facilitate inferences between social stimuli and its meaning (Adolphs et al., 2002, 2001).

Impairments in facial affect recognition may be explained by abnormal functioning of the FG-amygdala system. Previous research has indicated that the FG is consistently hypoactive in individuals with ASD, where familiarity of face has been shown to be a modulator of FG activity (Bölte et al., 2006; Derntl & Habel, 2011). Individuals with ASD demonstrate less FG activity than controls in response to faces of adult strangers, but no differences in FG activity are observed between controls and individuals with ASD in response to their mother's face or faces of other children (Derntl & Habel, 2011). Interestingly, affect recognition training does not lead to increased activation of the FG upon later testing (Bölte et al., 2006), where observed hypoactivation of the FG may be explained by increased cortical thickness of the FG and decreased amygdala volume (Derntl & Habel, 2011).

Current Study

The current study aimed to analyze synchrony of beta-band activity using MEG during passive viewing of direct gaze and examine the relationship between neural synchrony and neuropsychological measures of social cognition in TD individuals and those with ASD. Synchronization of neuronal firing among brain regions was analyzed utilizing a MEG Coherence imaging technique (Elisevich et al., 2011). As previously discussed, to date, no studies have examined the contribution of the beta-band in gaze processing and its relationship to social cognition. Since a primary pathophysiological mechanism hypothesized to contribute to observed social deficits in individuals with ASD is aberrant neural synchrony, there were two primary goals of this study. The first was to identify patterns of neural synchrony within and between groups of participants during direct gaze, where long-range connectivity was analyzed intra- and inter-hemispherically within the beta frequency band. The second goal of the study was to examine the relationship between beta-band synchrony during direct gaze and performance on measures of social cognition in TD and ASD participants.

Findings of previous studies indicated that individuals with ASD exhibit patterns of hemispheric activation that differ from TD individuals. Individuals with ASD have demonstrated left hemispheric lateralization in response to direct gaze cues (Kylliäinen et al., 2006), including heightened activation of the DLPFC (Pitskel et al., 2011), whereas TD participants have exhibited right hemispheric lateralization and a high degree of occipito-temporal activity (Senju et al., 2005). Individuals with ASD have also been observed to demonstrate heightened activation of left occipital and parietal regions (Lajiness-O'Neill et al., 2010), in addition to the left hippocampus, superior frontal gyrus, and the medial parietal

cortex in response to gaze cues (Davies et al., 2011). Reduced activation of areas associated with eye gaze and facial processing have also been observed, including reduced activation of the superior temporal sulcus (Greene et al., 2011) and prolonged latency of the P400 potential (Elsabbagh et al., 2009).

Individuals with ASD have demonstrated decreased long-range connectivity compared to TD participants (Perez Velazquez et al., 2009). Reduced intra- and interhemispheric frontal-parietal connectivity (Just et al., 2007) and decreased interhemispheric synchrony in occipital regions (Isler et al., 2010) have been observed. Individuals with ASD have also been found to exhibit increased beta-band synchrony within intrahemispheric occipital and interhemispheric parietal regions (Perez Velazquez et al., 2009). Given that the results of previous studies suggest lateralization within the left hemispheric, reduced coherence of intra- and interhemispheric long-range connections, and increased coherence within parietal regions, the following hypotheses were proposed:

1. Individuals with ASD will exhibit decreased intrahemispheric coherence in the beta-band between long- range connections within the right hemisphere (e.g., frontal to occipital) and increased intrahemispheric coherence in the beta-band within the left hemisphere (e.g., frontal to occipital) compared to TD participants.
2. Individuals with ASD will exhibit decreased interhemispheric coherence within the beta-band between frontal-frontal, temporal-temporal, and occipital-occipital regions and increased interhemispheric beta-band coherence between parietal-parietal regions compared to TD participants.
3. Individuals with ASD will perform more poorly than TD participants on measures of social cognition.

4. Beta-band coherence will be positively correlated with measures of social cognition in individuals with ASD and TD participants.

Methods

Participants

Eleven participants with ASD (Mean age (SD/range) = 14 (3.3/9-19); mean IQ =109; Males = 10) and eight TD individuals (Mean age (SD/range) = 17.5 (2.9/12-20); mean IQ = 116; Males = 4) completed the study. Though the number of participants per group was relatively small, the robustness of the MEG technique provides considerable power to detect mean differences between groups. Previous imaging studies have recruited samples with comparable group membership and have yielded statistically and clinically meaningful results (Davies et al., 2011; Greene et al., 2011; Pitskel et al., 2011). The TD participants were slightly older than the ASD group ($t(17) = 2.42$, $p < .05$), and there were more males in the ASD group ($\chi^2 > .06$), consistent with the base rate of ASD in the general population. There were no significant between-group differences in intellectual functioning $t(17) = 1.08$, $p = 0.31$. Nine individuals with ASD and 2 TD participants also completed neuropsychological measures of social cognition.

Individuals were recruited over two years from the Autism Collaborative Center-Eastern Michigan University, Henry Ford Hospital (HFH), Washtenaw Intermediate School District, Ann Arbor Public Schools, the Interactive Autism Network, and through advertisement (see Appendix A) and peer nomination. Diagnoses were confirmed by the Principal Investigator, who is trained to administer the Autism Diagnostic Interview-Revised (Lord, Rutter, & Le Couteur, 1994) and Autism Diagnostic Observation Schedule (Lord, Rutter, DiLavore, & Risi, 1999). Participants were also diagnosed by clinical data using the

DSM-IV-TR (2000) 4th ed., text rev. diagnostic criteria. Informed consent was obtained from the participant's parent/guardian, as explained below.

The process of assent and consent. A telephone-screening interview was conducted with a parent of the participant prior to scheduling. The purpose of the project and verbal consent to serve as a participant in the project was obtained from a parent/guardian for individuals aged 9-16 prior to scheduling the first appointment and participation in the project. Information regarding the purpose and procedures of the cognitive testing, as well as the MEG procedure, was mailed to participants and parents/guardians. Also, the written consent and assent documents (see Appendix B and C) were sent for review prior to scheduling an appointment. These documents were explained further during the initial appointment, where participant and parent/guardian questions and concerns were addressed. Participants and their parents were also given thorough, yet simplified information regarding the procedures in terms that could be understood by the participants based on their age and intellectual ability. Cognitive testing (e.g., WASI Vocabulary and Matrix Reasoning) was then scheduled and completed prior to the imaging procedure. Understanding of the MEG procedures by the participant and parent/guardian were assessed by questions directed to participants and parents/guardian to assure their full understanding of the process and risks involved. Each participant or parent/guardian signed a consent form approved by the HFH internal review board and EMU Human Subjects Review Committee at the time of the MEG study.

Inclusion/exclusion criteria. Recruited individuals were functioning at least within the Borderline range of intellectual ability (>70 Full Scale IQ scores on the Wechsler Abbreviated Scale of Intelligence). Exclusionary criteria for ASD and TD participants

included Attention Deficit Hyperactivity Disorder (ADHD), any known history of head injury with loss of consciousness, epilepsy, or other neurological disorder. ASD participants taking medication must have been on a stable dose of their current medication regime for a minimum of one month, and preferably two months, prior to enrollment. TD participants were also excluded if a first-degree relative had a diagnosis of ASD. Exclusionary criteria for both groups included any known metal implants, pacemakers, braces, etc. that would interfere with the MEG procedure.

Design

This was a quasi-experimental within and between subjects design that examined beta-band synchronicity of intra- and inter-hemispheric brain activity during direct gaze and the relationship between beta-band synchronicity and neuropsychological indices of social cognition. Group membership was defined as participants diagnosed with ASD and TD individuals with no history of ASD in a first-degree relative.

Procedures

MEG procedure and protocol. Each participant underwent a MEG scan at Henry Ford Hospital (HFH). Following the completion of the MEG scan, the participant underwent neuropsychological assessment (e.g., NEPSY-II Theory of Mind and Affect Recognition subtest) with a graduate-level psychometrist, while the parent/guardian completed a questionnaire (e.g., Social Responsiveness Scale). Including the time to place a participant in the MEG imaging room, the MEG scans lasted approximately 90 minutes. After signing the consent form, each participant changed into a hospital gown and removed all metal articles from his or her body. Three small electrode coils, used to transmit subject location information to the neuromagnetometer probe, was affixed to the forehead with two-sided

tape. Disposable earpieces were placed in the ears with an additional localization coil attached to each earpiece. A commercial videotape eraser was used to demagnetize dental work. The participant laid comfortably on the bed, inside the magnetically shielded room. Standard automatic probe position routines were used to locate the head with respect to the neuromagnetometer detector coils and to digitize the shape of the head for co-registration to a standard MRI or the participant's MRI scan. The neuromagnetometer helmet containing the detector array was placed around the participant's head in close proximity to most of the cortical surface. The participant was asked to avoid both eye and body movements during data collection. Children and adolescents were given breaks as required throughout the examination between data collection runs (as explained below).

Passive gaze task. MEG field responses to gaze cues were recorded as participants responded to the gaze shift of a central character (human male face) and stimuli (symbol, word, or face) that appeared in his periphery. Continuous MEG field responses to gaze cues were collected for each of two 14-minute trials. In these two trials five task conditions were administered: direct gaze, averted gaze, and gaze cueing to a peripheral stimulus (symbol, word, or face). In the direct and averted gaze conditions, participants passively viewed a digital photograph of a character whose gaze was forward for 2 seconds. In the direct gaze condition 30 trials were administered; in the averted gaze condition, 30 left-gaze and 30 right-gaze trials were administered. In each of the three gaze conditions, the central character engaged in a random gaze shift toward the right or left for 1 second. A target (symbol, word, or face) then appeared at either the right or the left of the subject for 3 seconds. The next trial began with the character returning to a forward gaze for 2 seconds with no stimuli in the periphery. The location of the target stimulus was either congruent or incongruent with the

direction of the character's gaze. Sixty targets were presented in each gaze condition, including 30 congruent and 30 incongruent trials. A conditional button press during gaze cues to the peripheral stimuli conditions ensured engagement during the passive conditions. Trials were randomized between the five task conditions and were presented in two blocks, each lasting 14 minutes. For the purposes of this analysis, only the passive viewing of the direct gaze was considered.

MEG data acquisition and post-processing. 148 channel whole head MEG (4D Neuroimaging, Magnes WH2500) was used to collect cortical brain activity. During acquisition, the data was band-pass filtered at 0.1 to 100 Hz and digitally sampled at 508.63 Hz and continuously recorded for later analysis. The timing of stimuli were recorded as pulse codes (representing the type of stimulus) on a trigger channel simultaneously collected with the MEG data. In post-processing, noise artifacts due to heart and body movement were eliminated using an independent component analysis (ICA) of the data. Data were then forward and backward band-pass filtered from 1 to 40 Hz (low and high frequency bands), as well as 15 to 30 Hz (beta-band). Next, selective averaging was performed to identify the trials for only the direct gaze condition. The locations of these events on the trigger and response channels were used to select 2 second epochs of MEG data from this trial. The averaged epochs had a baseline of 500 ms before stimuli onset and 1500 ms of data after stimulus onset, although the analysis was performed only on MEG data from -200 to +650 ms after stimulus onset. The longer segment was included to ensure subjects did not have delayed responses.

MEG Data Analysis

MEG data was imaged using Multi Resolution-FOCUSS (MR-FOCUSS) (Moran,

Bowyer, & Tepley, 2005), a current distribution imaging technique, and Coherence imaging (Elisevich et al., 2011). The analysis was performed on MEG data from -200 to +650 ms after stimulus onset. As part of the processing, a source model of the brain was created for the MR-FOCUSS and Coherence imaging techniques using a standard MRI from a child, which was a T1-weighted high-resolution volumetric MR image. A MRI model for each subject was segmented and a cortical model with x, y, and z oriented dipoles at approximately 4000 cortical sites represented the brain surface. Sites were distributed such that each represented the same volume of cortical gray matter, and the model was morphed to fit the digitized head shape collected during the MEG acquisition.

MR FOCUSS. MR-FOCUSS is a current distribution imaging technique that can image simultaneously active brain regions involved in cognitive processing. MR-FOCUSS is able to image both focal and extended sources of simultaneous brain electric activity[1]. This technique will produce a time sequence of activated cortical regions in the brain from each subject while they are viewing the image of a human male gazing at them (Moran et al., 2005).

Coherence. Synchronization of neuronal activity can be quantified by calculating the coherence between cortical sites from MEG imaged brain activations. Coherence imaging analysis was performed to identify cortical sources that were active within the beta-band (15-30 Hz) during the direct gaze. These sources make up the underlying functional brain network, and coherence imaging provides the network map of this network. To calculate

[1] Control of focal imaging properties of the solution and noise suppression is accomplished by the use of an innovative multi-resolution model of source activity. MR-FOCUSS solutions are created by averaging a set of 20 solutions initialized with random amplitudes. Imaged activation common to all solutions is found in the average. This technique minimizes initialization bias and lower amplitude sources are more readily imaged.

coherence the data was first divided into 80 segments each containing 7.5-seconds of data[2]. Using the time sequence of imaged activity, coherence between active cortical model sites was calculated for each data segment then averaged for the completed study. The variance across this set of coherence calculations was a measure of the stability of the cortical network activity and allowed changes in coherence across time to be assessed for statistical significance. Coherence was performed to quantify the functional network connectivity that underlies passive viewing of direct gaze (Elisevich et al., 2011; Gross et al., 2001).

Changes in coherence and connectivity between brain regions implicated as having deviant electrophysiological activity in the ASD brain were quantified and subjected to further statistical analysis. Statistical analysis of cortical coherence level (0 to 1) was used to quantify differences in intra- and inter-hemispheric beta-band activity and connectivity between groups. These imaging techniques are completely integrated in the MEG Tools software package (Moran, 2008). A region-of-interest (ROI) tool implemented in MEG Tools was used to identify 54 regions in the brain. Brain locations can also be displayed in both Talairach (Talairach & Tournoux, 1988) and MNI (Shattuck et al., 2008) coordinates, as MEG Tools uses a nonlinear volumetric transformation of the standard child brain to

[2] For each of these data segments, signals from neuronal sources were isolated using an ICA spatiotemporal decomposition technique designed to extract signals from distinct compact sources that exhibit burst behavior and minimal temporal overlap with other active sources. These ICA signal components have MEG spatial magnetic field patterns corresponding to one or a few spatially distinct compact sources which are much easier to image accurately using the MR-FOCUSS source imaging technique (Moran et al. 2005). Separate from the imaging algorithm, the cross-spectrum between ICA signals was calculated. In these cross-spectrum calculations, a sequence of FFT spectra was calculated using 0.5 sec windows and 25% overlap with FFT amplitudes for 10 frequency bins of 1 Hz width between 15 and 30 Hz. The imaging results and the signal cross-spectrum were used to calculate the coherence between all pairings of active cortical locations within each of the 10 frequency bins. Finally, for each active source, the average coherence across frequencies and sources was calculated. In these coherence imaging results, the localization of imaged brain activity is strongly dependent on the frequency bands with greatest power.

transform MEG coordinates (Woods, Grafton, Watson, Sicotte, & Mazziotta, 1998). This enables the ROI tool to access an atlas of Brodmann's area identifiers and an atlas of cortical structures (Shattuck et al., 2008) which have been incorporated in ROI information display as part of the MEG tools program.

Neuropsychological Measures Performed Following the MEG Scan

Wechsler Abbreviated Scale of Intelligence (WASI) Vocabulary subtest. The WASI Vocabulary subtest is a 42-item assessment of word knowledge and verbal concept formation. The subtest includes 4 picture items and 38 word items, where the examinee is expected to name objects represented by pictures in items 1-4 and provide oral definitions to words for items 5-42. The WASI Vocabulary subtest can be administered to children, adolescents, and adults from the ages of 6-89 years. Items 1-4 are dichotomously scored (0 = *incorrect response or no response*, 1= *correct response*), but items 5-42 are scored on a continuum (0= *incorrect response*, 1= *partially correct response, 2 = correct response*). Scores can range from 0-80, where high scores indicate greater word knowledge and verbal concept formation. There are no reverse scored items (PsychCorp, 1999).

For children and adolescents age 9-16 years, the reliability coefficients range from .86 to .98. Test-retest stability for children aged 6-16 years was reasonably high (r = .85), where the interval was 2 to 12 weeks (mean 31 days). Inter-rater agreement also yielded a high degree of reliability (r =.98; PsychCorp, 1999). The WASI Vocabulary subtest was observed to have convergent validity, as it was highly correlated with the Wechsler Intelligence Scale for Children- Third edition (WISC-III) Vocabulary subtest (r =.72), WASI Similarities subtest (r =.82), and the Kaufman Brief Intelligence Test (K-BIT) Vocabulary subtest (r = .83; Strauss, Sherman, & Spreen, 2006, p. 291). The WASI Vocabulary subtest also

demonstrated discriminant validity, as it was moderately correlated with the WASI Block Design (r = .46) and Matrix Reasoning (r = .50) subtests. Factor analytic studies demonstrate further support for discriminant validity, as the WASI Vocabulary Varimax structure coefficient was modestly correlated (r = .37) with nonverbal components of the WASI (Canivez, Konold, Collins, & Wilson, 2009). Factor analysis also reveals that the WASI Vocabulary subtest loads onto the Verbal Comprehension factor (PsychCorp, 1999).

Wechsler Abbreviated Scale of Intelligence (WASI) Matrix Reasoning (MR) subtest. The WASI MR Subtest is a 35-item assessment of fluid intelligence, broad visual intelligence, classification and spatial ability, knowledge of part-whole relationships, simultaneous processing, and perceptual organization. The examinee views an incomplete matrix or series and selects the response option that completes the matrix or series. The WASI MR subtest can be administered to children, adolescents, and adults from the ages of 6-89 years. All items are dichotomously scored (0 = *incorrect response or no response*, 1= *correct response*) and there are no reverse scored items. Scores can range from 0-35, where higher scores indicate greater spatial ability and perceptual organization (PsychCorp, 1999).

For children and adolescents age 9-16 years, the reliability coefficients range from .86 to .93. Test-retest stability for children aged 6-16 years was reasonably high (r =.77), where the interval was 2 to 12 weeks (mean 31 days). Inter-rater agreement also yielded a high degree of reliability (r > .9). The WASI MR subtest was observed to have convergent validity with the Wechsler Adult Intelligence Scale- Third Edition (WAIS-III) Matrix Reasoning subtest (r = .66). The WASI MR subtest also demonstrated discriminant validity, as it was moderately correlated with the WASI Vocabulary (r = .50) and Similarities (r = .48) subtests for children and adolescents 9-16 years. Factor analytic studies demonstrate

further support for discriminant validity, as the WASI MR Varimax structure coefficient was modestly correlated (r = .38) with verbal components of the WASI (Canivez et al., 2009). Factor analysis also reveals that the WASI MR loads on the Perceptual Organization factor (PsychCorp, 1999).

NEPSY-II Theory of Mind (ToM) subtest. The NEPSY-II ToM subtest is a 21-item component of the Social Perception scale and assesses the participant's ability to understand mental functions and another's point of view through Verbal and Contextual tasks. The Verbal task assesses the participant's perceptions regarding belief, intention, emotion, deception, imagination/pretending, and imitation through stories, pictures, and questions asked by the examiner. The Contextual task assesses the participant's ability to relate emotion to social context, where they are asked to select a photograph that appropriately depicts the affect of a pictured individual. The NEPSY-II ToM subtest can be administered to children and adolescents aged 3-16 years. Scoring varies by item, where 15-items are dichotomously scored (0 = *incorrect response or no response*, 1= *correct response*), 5-items are scored 0-2 points (0= *incorrect response*, 1= *partially correct response*, 2= *correct response)*, and 1-item is scored 0-3 (as the item score is the sum of an A and B section). There are no reverse scored items and the NEPSY-II ToM subtest yields a ToM Total Score and ToM Verbal Score. The ToM Total Score is the sum of all item scores and can range from 0-28, where high scores indicate greater comprehension of other's perspectives, experiences, and beliefs. The ToM Verbal Score is computed by summing items 1-15 and aids in determining whether language ability confounds performance on nonverbal ToM tasks (Korkman, Kirk, & Kemp, 2007).

The NEPSY-II ToM subtest has demonstrated adequate internal consistency, as

reliability coefficients for ToM Total Score range from .76 to .84 in a normative sample of 3- to 6-year old children. Notably, the full range of scores is observed in children under 7-years of age and the distribution of scores is highly skewed thereafter due to the limited range in which this skill is developmentally acquired. Nonetheless, the ToM subtest has demonstrated clinical utility, as 70% of individuals with ASD obtain low scores on the ToM as compared to 10% of matched controls. Performance on the NEPSY-II ToM subtest was observed to be stable (r = .76) at 12-51 day retest (mean retest = 21 days). Inter-rater agreement was calculated as percent agreement rates between trained scorers and a high degree of reliability was observed (r= .99). The NEPSY-II ToM Total subtest score demonstrated convergent validity with Differential Abilities Scales-Second Edition (DAS-II), where a moderate correlation (r = .53) was observed between the ToM Total Score and the Special Nonverbal composite, a nonverbal task of cognitive functioning. Furthermore, the ToM Total Score was highly correlated (r =.74) with the Oral Expression subtest of the Wechsler Individual Achievement Test-Second Edition (WIAT-II), which requires the ability to create a narrative based on pictures of individuals engaged in various activities. The ToM Total Score was modestly correlated with the Pseudoword Decoding (r = .22), Math Reasoning (r = .26), and Spelling (r = .29) subtests of the WIAT-II, suggesting discriminant validity for social perception ability (Korkman et al., 2007). The factor structure of the NEPSY-II ToM subtest has not been evaluated.

Social Responsiveness Scale (SRS). The SRS is a 65-item questionnaire designed to assess interpersonal behaviors, communication, and repetitive/stereotypic behaviors characteristic of ASD. The SRS takes approximately 15-20 minutes to complete and provides a quantitative measure of social impairment. The SRS is a questionnaire pertaining

to children and adolescents aged 4-18 years, where teachers, parents, or caregivers may serve as respondents. Respondents are asked to "Circle the number that best describes the child's behavior over the past 6 months," and rate items based on a 4-point Likert scale (1=*not true*, 2=*sometimes true*, 3=*often true*, 4=*almost always true*). Items are scored from 0-4 and there are 17 reversed scored items. SRS Total raw scores can range from 1 to 195 with higher scores indicating severe impairment. SRS Total raw scores of 65 and 70, respectively, are recommended for the purpose of screening ASD conditions in females and males in nonreferred, general population groups. SRS Total *T*-Scores can also be used to interpret impairment of social functioning, where *T*-Scores of 59 or less are within the "normal" range, *T*-Scores of 60-75 are within the "mild to moderate range," and *T*-Scores of 76 or higher are within the "severe" range (Constantino & Gruber, 2005)

The SRS is composed of five treatment subscales of unequal item length: Social Awareness (8-items), Social Cognition (12-items), Social Communication (22-items), Social Motivation (11-items), and Autistic Mannerisms (12-items). The Social Awareness subscale assesses ability to discern social cues and items represent the sensory aspects of reciprocal social behavior. The Social Cognition subscale assesses ability to interpret social cues once they are discerned and items represent the cognitive-interpretive aspect of reciprocal social behavior. The Social Communication subscale assesses expressive social communication and items represent the "motoric" aspect of reciprocal social behavior. The Social Motivation subscale assesses the extent to which a respondent is generally motivated to engage in social-interpersonal behavior and items represent social anxiety, inhibition, and empathic orientation. The Autistic Mannerisms subscale assesses stereotypical behaviors or highly restricted interests characteristic of ASD (Constantino & Gruber, 2005).

Preliminary data indicate that the SRS has substantial internal reliability for Total raw score for males and females, respectively, across rating groups (parent rating: α = .94 for males; α = .93 for females; teacher rating: α = .97 for males, α = .96 for females; clinical rating α = .97 for males and females combined; Constantino & Gruber, 2005). Total scores were stable across a 3-month test-retest interval (r = .88) and a 27-month interval (r =.83; Constantino et al., 2003). Inter-rater agreement among mothers and fathers (r = .91), mothers and teachers (r = .82), and fathers and teachers (r = .71) were well within the acceptable range. The SRS was shown to have good discriminant validity, as social deficits were continuously distributed and reliably distinguished children with ASD conditions from those with other psychiatric disorders (Constantino & Gruber, 2005). The SRS was also observed to have concurrent validity with the Autism Diagnostic Interview- Revised (ADI-R), the "gold standard" for establishing a clinical diagnosis of ASD, as correlation coefficients ranged from .65 to .77 for maternal SRS ratings and ADI-R algorithm scores for each subdomain of ASD symptomology (Constantino et al., 2003). Each SRS subscale demonstrated internal consistency (Social Awareness α = .77; Social Cognition α = .87; Social Communication α = .92; Social Motivation α = .82; Autistic Mannerisms α = .90). Although the measure was designed to include five factors, only three domains emerged from factor analytic studies. Factor analysis failed to support the existence of independent subdomains, as phenotypic manifestations of ASD were disparately distributed across three criterion domains (social deficits, language deficits, and repetitive/stereotypical behavior). SRS subscales are not intended for independent use, as there is no indication that separate measures would provide additional predictive power or utility (Constantino & Gruber, 2005).

NEPSY-II Affect Recognition (AR) subtest. The NEPSY-II AR subtest is a 35-item component of the Social Perception scale and assesses the participant's ability to recognize affect (e.g., happiness, sadness, neutral, fear, anger, disgust). The NEPSY-II AR is comprised of tasks that ask participants to indicate whether two photograph depict the same affect, identify photographs depicting the same affect from a 3 to 5 item pool of photographs, and identify a photograph that depicts affect that is the same as a previously shown photograph. The NEPSY-II AR subtest can be administered to children and adolescents aged 3-16 years, and items are dichotomously scored (0 = *incorrect response or no response*, 1= *correct response*). There are no reverse scored items and the NEPSY-II AR subtest yields one primary score and six process scores, including: AR Total Score, Total Happy Errors, Total Sad Errors, Total Neutral Errors, Total Fear Errors, Total Angry Errors, and Total Disgust Errors. The AR Total Score is computed by summing all item scores, where process scores are calculated by summing incorrect responses provided per respective emotion. AR Total Scores can range from 0-35 for children and adolescents aged 7-16 years, where high scores indicate greater recognition and identification of emotion in facial expression. Percentile rankings for process scores are provided in the interpretive manual, in addition to cumulative percentages for Spontaneous Comments Total (i.e., total spontaneous comments observed during test administration), which provides insight regarding the participant's ability to inhibit responses (Korkman et al., 2007).

The NEPSY-II AR subtest has demonstrated adequate internal consistency, where reliability coefficients range from .84-.88 across children and adolescents aged 7-16 years. NEPSY-II AR Total Scores were observed to be moderately stable (r = .49-.66) at 12-51 day retest (mean retest = 21 days) for children and adolescents within the 9-16 age range, and

inter-rater agreement yielded a high degree of reliability (r = .98). The NEPSY-II AR subtest was minimally correlated with multiple WISC-IV, WNV, and WIAT-II subtests, suggesting that it measures a skill not strongly related to intellectual and academic ability, but provides evidence of discriminant validity for social perception. The NEPSY-II AR subtest demonstrated moderate correlation with the NEPSY-II ToM subtest in clinical populations (r = .53) as compared to non-clinical population (r = .21), providing evidence of convergent validity between subtests within the NEPSY-II Social Perception domain (Korkman et al., 2007). The factor structure of the NEPSY-II AR subtest has not been evaluated.

Data Analyses for Specific Goals and Hypotheses

Hypothesis 1 and 2 analysis. For each pair of brain regions (N = 1431), a *t*-test was used to assess for differences in average coherence values between ASD and TD participants. A *p* value was produced for each region. Because of the large number of tests (N = 1431) being performed simultaneously, using a significance level of alpha = 0.05 without adjusting for multiple testing would lead to a large number of false positive results. Bonferroni adjustments for multiple comparisons aim to control the Family Wise Error Rate. If a Bonferroni correction were applied to every test, there would be only a 5% chance of at least one false positive in the entire N = 1431 tests. Bonferroni corrections require the *p* value to be less than 0.05/N, where N is the number of tests. With N = 1431, this criterion becomes especially stringent, and many true differences may be missed (false negatives).

The False Discovery Rate (FDR) is a widely-accepted, less-conservative approach to adjusting for multiple testing in large scale problems and was used for the analysis. The FDR is the proportion of tests declared significant that are actually different only due to chance (or the proportion of significant tests that are false positives). The Benjamini-Hochberg

algorithm was then used to control the FDR at 0.10 (Benjamini & Hochberg, 1995) It was expected that no more than 10% of the brain regions declared to have a significant difference in average coherence between ASD and TD will be false positives. From each *t*-test, a z-score was then computed according to the method of Efron (Efron, 2010) to summarize the difference in coherence values between ASD and TD participants. Positive z-scores indicated higher coherence in the ASD group.

Following the preliminary analysis, intra- and inter-hemispheric pathways were selected for further analysis as delineated by hypothesis 1 and 2. Hypothesis 1 identified intrahemisphere long-range connections as pathways that originated and terminated in different regions within the same hemisphere (e.g., left frontal to left temporal, left temporal to left occipital, right frontal to right occipital, and right temporal to right occipital). Hypothesis 2 identified interhemisphere connections as pathways that originated and terminated in the same region in each hemisphere (e.g., left frontal to right frontal, left temporal to right temporal, left parietal to left parietal, and left occipital to right occipital). Average group coherence values were obtained and independent samples *t*-tests were conducted.

Hypothesis 3 analysis. An independent samples *t*-test was used to examine group differences in performance on measures of social cognition (i.e., the NEPSY-II ToM Total Score, NEPSY-II AR Total Score, and SRS Total raw score).

Hypothesis 4 analysis. A Pearson product-moment correlation coefficient was used to examine the relationship between coherence and NEPSY-II ToM Total Score, NEPSY-II AR Total Score, and SRS Total raw score in ASD and TD groups.

Results

MEG Analysis: Coherence Imaging of Connectivity

No pathways within the beta-band (15-30 Hz) frequency were found to be significantly different between ASD and TD individuals during the direct gaze condition. Therefore, the coherence analysis was broadened to include all frequency bands between 1-45 Hz. Coherence values in 91 pathways were found to be significantly different between the ASD and TD participants during the direct gaze condition. Of the 91 pathways that were significantly different between the two groups, 40 pathways were excluded from the analyses because they did not meet criteria defined by hypothesis 1 and 2. Given these criteria, 51 pathways were examined in hypothesis 1 and 2 (i.e., 29 and 22, respectively).

Hypothesis 1. As a test of the hypothesis that individuals with ASD will exhibit increased left hemisphere coherence and decreased right hemisphere coherence in long-range connections (e.g., left or right frontal to occipital) compared to TD participants, average coherence values from one cortical region to the other were obtained and an independent samples *t*-test was conducted for left and right hemisphere long-range connections, respectively. Cortical coherence levels range from 0 to 1, where lower values signify decreased coherence and higher values indicate increased coherence. The average coherence value for the left hemisphere for ASD participants was $M = 0.32$, $SD = 0.10$ and were significantly different from that of the TD group ($M = 0.18$, $SD = 0.08$), $t(34) = 4.47$ $p < .01$. These results revealed that participants with ASD exhibited increased coherence in left hemisphere, long-range connections compared to TD individuals during response to direct gaze. The average coherence value for the right hemisphere for ASD participants was $M = 0.25$, $SD = 0.11$ and also found to be significantly different from TD participants ($M = 0.35$,

SD = 0.09), $t(20) = -2.47$, $p = .02$. These results indicate that participants with ASD exhibited decreased coherence in right hemisphere, long-range connections compared to TD individuals during response to direct gaze. Refer to Table 1 for between group differences in average coherence values of intrahemisphere brain pathways.

Hypothesis 2. To test the hypothesis that individuals with ASD will exhibit decreased interhemispheric coherence in frontal to frontal, temporal to temporal, and occipital to occipital regions and increased interhemispheric coherence in parietal to parietal regions compared to TD participants, average coherence values were obtained and an independent samples *t*-test was conducted. *t*-tests were conducted for frontal to frontal and occipital to occipital connections, but not for temporal to temporal connections, as no significant differences in coherence values between ASD and TD were identified in the preliminary analyses. Only one parietal-parietal connection was significant between groups. Average interhemispheric frontal to frontal coherence was found to be statistically different between the groups ($t(30) = -4.27$, $p < .01$) with ASD participants exhibiting decreased coherence in interhemispheric frontal to frontal pathways compared to TD individuals (M = 0.25, SD = 0.09; M = .40, SD = 0.11, respectively). Average interhemispheric occipital to occipital coherence was also found to be statistically different ($t(8) = 6.04$, $p < .01$) with ASD participants exhibiting increased coherence in interhemispheric occipital-occipital pathways compared to TD individuals (M = 0.49, SD = 0.06; M = 0.27, SD = 0.05, respectively). Only one pathway in the parietal region, the left angular gyrus to right angular gyrus, was identified as significantly different between groups. Participants with ASD demonstrated higher coherence in this parietal connection compared to TD individuals (M = 0.32 and 0.15,

respectively). Refer to Table 2 for between group differences in average coherence values of interhemisphere brain pathways.

Psychometric Data Analysis

Hypothesis 3. In order to compare scores between participants with ASD and TD individuals on measures of social cognition, an independent samples *t*-test was conducted. As expected, scores on the Social Responsiveness Scale were statistically significant between groups ($t(8) = 3.37$, $p = .01$). These results indicate that parents of participants with ASD ($M = 73.50$, $SD = 10.92$) endorsed greater impairment of social functioning than parents of TD individuals ($M = 44.50$, $SD = 10.60$). Refer to Table 3 for group differences in performance on each measure of social cognition.

Hypothesis 4. To assess the relationship between beta-band coherence and measures of social cognition, a Pearson product-moment correlation was calculated. The correlation between the Nepsy-II Theory of Mind Total Score and average beta-band coherence during direct gaze was found to approach statistical significance, $r(7) = .63$, $p = .07$, in participants with ASD. Due to the small number of participants that met age requirements to complete social cognition measures, correlations between measures of social cognition and coherence could not be completed for TD participants.

The analysis was broadened to examine the relationship between average coherence within a wider frequency range (1-45 Hz). Coherence values for intra- and inter-hemispheric pathways found to differentiate the groups were averaged across participants in the ASD group that had completed measures of social cognition and average coherence values during direct gaze were correlated with scores on measures of social cognition for each participant. The average coherence values during direct gaze in ASD were found to be positively

correlated with the Nepsy-II AR Total Score $r(7) = .34$, $p = .37$, $d = .73$, with a moderate effect size, suggesting higher coherence with higher affect recognition scores. The Nepsy-II ToM Total Score was negatively correlated with average coherence during direct gaze in ASD in regions that differentiated the groups, $r(7) = -.295$, $p = .44$, $d = -.62$ (moderate effect size), suggesting higher coherence with lower ToM scores. This suggests that higher coherence in left hemispheric regions and posterior occipital regions is associated with lower mentalizing abilities. Finally, average coherence values during direct gaze were negatively related to the SRS Total raw scores for the ASD group were, $r(6) = -.44$, $p = .28$, $d = -.97$, with a large effect size, suggesting higher coherence was related to lower social difficulties as reported by parents.

Table 1

Intrahemisphere Between Group Differences in Average Coherence for Direct Gaze (1-45 Hz)

		ASD (N=11)		TD (N=8)				
	Pathway	***M***	***SD***	***M***	***SD***	***t*-statistic**	***p* value**	
Long-range left hemisphere	L. AG & L. CUN	0.37	0.19	0.16	0.17	2.53	.02	*
	L. AG & L. IOG	0.46	0.17	0.21	0.13	3.42	.00	**
	L. AG & L. ITG	0.34	0.17	0.19	0.07	2.63	.02	*
	L. AG & L. LiG	0.23	0.13	0.12	0.11	2.00	.06	
	L. AG & L. MOG	0.50	0.14	0.20	0.13	4.71	.00	**
	L. AG & L. MTG	0.38	0.12	0.21	0.11	3.17	.01	**
	L. AG & L. SOG	0.38	0.16	0.14	0.16	3.28	.00	**
	L. AG & L. STG	0.32	0.10	0.19	0.07	3.33	.00	**
	L. CUN & L. PoG	0.21	0.13	0.10	0.09	2.09	.05	*
	L. CUN & L. SMG	0.21	0.14	0.10	0.10	1.99	.06	
	L. MFG & L. STG	0.24	0.11	0.35	0.13	-1.94	.07	
	L. MOG & L. MTG	0.49	0.12	0.31	0.19	2.51	.02	*
	L. MOG & L. SPG	0.27	0.16	0.13	0.10	2.08	.05	*
	L. MOG & L. STG	0.41	0.09	0.27	0.14	2.64	.02	*
	L. MOG & L. SMG	0.29	0.13	0.16	0.11	2.28	.04	*
	L. PoG & L. SOG	0.21	0.11	0.08	0.08	3.02	.01	**
	L. SFG & L. STG	0.18	0.09	0.27	0.07	-2.15	.05	*
	L. SOG & L. SMG	0.22	0.11	0.08	0.09	3.15	.01	**
Long-range right hemisphere	R. IFG & R. PoG	0.30	0.14	0.46	0.12	-2.54	.02	*
	R. IFG & R. STG	0.39	0.11	0.52	0.04	-3.75	.00	**
	R. LOFG & R. MOG	0.48	0.17	0.29	0.21	2.14	.05	*
	R. MFG & R. PoG	0.20	0.08	0.37	0.13	-3.56	.00	**
	R. MFG & R. STG	0.25	0.08	0.40	0.05	-4.55	.00	**
	R. MFG & R. SMG	0.18	0.09	0.29	0.10	-2.44	.03	*
	R. PoG & R. SFG	0.14	0.07	0.28	0.11	-3.32	.00	**
	R. PoG & R. STG	0.24	0.15	0.36	0.10	-1.84	.08	
	R. PrG & R. STG	0.23	0.14	0.35	0.10	-2.07	.05	*
	R. SFG & R. STG	0.17	0.08	0.30	0.07	-3.58	.00	**
	R. SFG & R. SMG	0.12	0.08	0.22	0.08	-2.57	.02	*

*p ≤ .05; **p ≤ .01

Note: AG= angular gyrus; CUN=cuneus; IFG= inferior frontal gyrus; IOG= inferior occipital gyrus; ITG= inferior temporal gyrus; LiG= lingual gyrus; LOFG= lateral orbitofrontal gyrus; MFG= middle frontal gyrus; MOG= middle occipital gyrus;

MTG= middle temporal gyrus; PoG= postcentral gyrus; PrG= precentral gyrus; SFG= superior frontal gyrus; SMG= supramarginal gyrus; SOG= superior occipital gyrus; SPG= superior parietal gyrus; STG= superior temporal gyrus

Table 2

Interhemisphere Between Group Differences in Average Coherence for Direct Gaze (1-45 Hz)

	ASD (N=11)		**TD (N=8)**				
Pathway	***M***	***SD***	***M***	***SD***	***t*-statistic**	***p* value**	
FRONTAL-FRONTAL							
L. IFG & R. IFG	0.36	0.14	0.52	0.09	-2.80	.01	**
L. IFG & R. MFG	0.29	0.16	0.42	0.07	-2.51	.02	*
L. IFG & R. PrG	0.20	0.08	0.35	0.09	-3.89	.00	**
L. LOG & R. IFG	0.46	0.16	0.64	0.07	-3.10	.01	**
L. LOG & R. MFG	0.35	0.16	0.53	0.05	-3.40	.01	**
L. LOG & R. PrG	0.24	0.10	0.44	0.11	-4.03	.00	**
L. LOG & R. SFG	0.28	0.16	0.42	0.10	-2.16	.05	*
L. MFG & R. IFG	0.31	0.15	0.48	0.11	-2.64	.02	*
L. MFG & R. MFG	0.25	0.15	0.40	0.13	-2.17	.05	*
L. MFG & R. PrG	0.17	0.09	0.33	0.12	-3.51	.00	**
L. MOFG & R. MFG	0.23	0.16	0.37	0.10	-2.19	.04	*
L. MOFG & R.PrG	0.14	0.10	0.28	0.08	-3.20	.01	**
L. PrG & R. SFG	0.14	0.09	0.25	0.13	-2.19	.04	*
L. SFG & R. IFG	0.24	0.12	0.38	0.08	-2.83	.01	**
L. SFG & R. MFG	0.20	0.14	0.31	0.09	-1.91	.07	
L. SFG & R. PrG	0.13	0.06	0.26	0.09	-3.72	.00	**
PARIETAL-PARIETAL							
L. AG & R. AG	0.32	0.16	0.15	0.07	2.93	.01	**
OCCIPITAL-OCCIPITAL							
L. CUN & R. IOG	0.46	0.22	0.24	0.25	2.03	.06	
L. MOG & R. CUN	0.49	0.14	0.26	0.26	2.33	.04	*
L. MOG & R. IOG	0.54	0.16	0.34	0.22	2.35	.03	*
L. MOG & R. MOG	0.56	0.15	0.30	0.20	3.22	.01	**
L. SOG & R. MOG	0.41	0.14	0.20	0.22	2.50	.02	*

*p ≤ .05; **p ≤ .01

Note. MOFG= middle orbitofrontal gyrus

Table 3

Group Differences in Performance on Measures of Social Cognition

	ASD (N= 9)		**TD (N=2)**			
Measure	***M***	***SD***	***M***	***SD***	***t*-statistic**	***df***
Nepsy-II Theory of Mind	22.44	3.17	27.00	1.41	-1.93	9
Social Responsiveness Scale*	73.50	10.92	44.50	10.61	3.37**	8
Nepsy-II Affect Recognition	13.56	8.81	13.00	2.83	0.09	9

Note. *ASD (N=8), **$p \leq .01$

Discussion

The main purpose of the study was to analyze neural synchrony using MEG during passive viewing of direct gaze and examine the relationship between neural synchrony and neuropsychological measures of social cognition in TD individuals and those with ASD. Neural synchrony or coherence refers to the degree to which networks of neurons fire or oscillate within the same frequency. Identifying patterns of asynchronous neural activity during eye gaze in individuals with ASD is important, since eye gaze is a critical component of social interaction and has been found to serve as an early predictor of later social cognitive processing. Eye gaze mediates social communication long before vocal language is acquired and facilitates learning during the first few months after birth (Hoehl et al., 2009). Research has revealed that individuals with ASD exhibit deficits in spontaneous gaze-following, process social and nonsocial stimuli similarly, and perform poorly on tasks of facial feature discrimination (Nation & Penny, 2008; Wallace et al., 2008). Since previous research suggests that individuals with ASD lack the capacity to view eye gaze as significant and meaningful for social interactions, research investigating connectivity underlying gaze

processing is critical, as it will permit greater understanding of the pathophysiology that underlies social communicative impairment in ASD and potentially identify a diagnostic biomarker of ASD.

Examination of the beta-band frequency is especially important given research that has identified its role in coordinating higher-level interactions among distant brain structures (Kopell et al., 2000; Schnitzler & Gross, 2005). The current study, however, did not observe significant group differences within the beta-band frequency during direct gaze. Uhlhaas et al. (2009) suggested that late adolescence is a critical period of neural restructuring, which impacts phase synchronization and amplitude of oscillations in the gamma and beta frequency bands until early adulthood. Given that the majority of the study's participants can be characterized as falling along the age continuum from late adolescence to early adulthood, the lack of significant between group differences in the beta-band may have been influenced by the age of participants. Therefore, a wider spectrum of frequency bands (1-45 Hz) was utilized for the analyses since significant group differences in synchronicity of neural response or coherence during direct gaze processing were not evident in the beta-band (15-30 Hz) independently. Inclusion of a wider spectrum of frequency bands was appropriate, since research has suggested that synchronized oscillations of all frequency bands (i.e., delta, theta, alpha, beta, and gamma) are fundamental to the coordinated activity of a normally functioning brain (Uhlhaas et al., 2010).

The current study revealed that participants with ASD exhibited increased average coherence within long-range, left hemisphere connections and decreased average coherence within long-range, right hemisphere connections as compared to TD individuals during processing of direct gaze. Altered or atypical asymmetry in brain function is expected in

individuals with ASD, as research has revealed that individuals with ASD exhibit reduced lateralization of language function within the left hemisphere compared to TD individuals. A variety of structural and functional imaging studies have not only demonstrated that individuals with ASD exhibit reduced, left hemisphere lateralization during tasks of verbal communication (i.e. language and auditory processing), but research has also revealed reversed hemispheric asymmetry and activation of the right hemisphere in individuals with ASD (Knaus et al., 2010; Lindell & Hudry, 2013; Wan, Marchina, Norton, & Schlaug, 2012).

The current study's finding of hemispheric asymmetry is consistent with the literature in relation to language, but functional differences within the nonverbal communication system (i.e. eye gaze processing) are not as well defined. Studies utilizing MEG to examine mechanisms of gaze orienting have revealed that participants with ASD exhibit strong left lateralization in response to direct gaze stimuli and TD individuals largely exhibit right hemisphere activation in response to gaze cues (Kylliäinen et al., 2006; Lajiness-O'Neill et al., 2010). More recently, a meta-analysis by Samson, Mottron, Soulières, and Zeffiro (2012) revealed that individuals with ASD generally exhibit enhanced activity of the temporal, occipital, and parietal regions and reduced activity of frontal regions during visual processing tasks involving faces, objects, and words. Specifically, Samson et al. (2012) suggested that individuals with ASD process facial stimuli (e.g. invariant features, eye gaze, and affect) by utilizing a large network of occipital and temporal areas that are specialized for processing other visual categories in TD individuals.

The current study found significantly increased average coherence in temporal to parietal, temporal to occipital, and parietal to occipital pathways within the left hemisphere, and significantly decreased coherence within frontal to temporal, frontal to parietal, and

temporal to parietal connections in the right hemisphere in ASD during gaze processing. These findings are consistent with a recent MEG investigation of averted gaze processing in individuals with ASD (Lajiness-O'Neill, Richard, Moran, & Bowyer, 2013). Although no other known studies have examined intrahemispheric coherence during a passive gaze cueing paradigm, these findings are congruent with results of an investigation of EEG resting state connectivity that found reduced coherence in frontal to parietal pathways and increased coherence in left temporal regions within the theta-band (i.e., 3-6 Hz as defined by the study) in adults with ASD (Murias, Webb, Greenson, & Dawson, 2007). A similar study by Léveillé et al. (2010) also found that coherence patterns differed between ASD and control participants and lateralized connectivity during REM sleep was reported. Specifically, Léveillé et al. (2010) revealed that adult participants with ASD exhibited greater EEG coherence than controls in communication between the left visual cortex and another region in close or distant proximity to the left visual cortex (i.e., left visual cortex to another region in the visual area or more anterior structure), as well as significantly lower coherence values in the right, frontal area compared to controls. A pattern of intrahemispheric asymmetry was further demonstrated by Lazarev, Pontes, Mitrofanov, and deAzevedo (2010), who utilized intermittent photic stimulation (IPS) to induce EEG oscillations. Male children and adolescents with ASD exhibited higher coherence within the left hemisphere during IPS at frequencies of 6-27 Hz compared to TD, which provides further support for altered intrahemispheric lateralization of coherence strength in individuals with ASD. These findings highlight the importance of investigating intrahemispheric coherence differences between TD individuals and those with ASD during gaze processing, as differences in neural synchrony of intrahemispheric short- and long-range connections revealed during resting

state support the possibility of altered coherence and connectivity that underlies gaze processing in individuals with ASD.

Significantly different interhemisphere coherence patterns were also found between TD and ASD participants when examining cross-hemispheric averages from frontal, parietal, and occipital regions. Structural imaging studies reveal that individuals with ASD exhibit significantly different volumetric properties of the corpus callosum and interhemispheric gray matter compared with TD controls, where structural differences likely impact functional communication between interhemispheric brain regions in individuals with ASD (Alexander et al., 2007; Anderson et al., 2011; van der Knaap & van der Ham, 2011). The current study revealed reduced interhemispheric average coherence between frontal regions in participants with ASD, which is congruent with findings by Coben, Clarke, Hudspeth, and Barry (2008), who found low delta and theta coherences across the frontal region in children with ASD during a closed eyes EEG recording. Decreased coherence in the bilateral frontal cortex was also revealed by Perez Velazquez et al. (2009), who utilized MEG imaging during an executive functioning task and indicated that the "normally observed enhanced synchrony" in control males did not occur in most of the ASD participants (p. 345). A finding of reduced connectivity in bilateral frontal regions is expected, given that gaze processing research has identified that individuals with ASD exhibit minimal or absent activation of frontal regions in response to gaze cues (Davies et al., 2011; Greene et al., 2011; Lajiness-O'Neill et al., 2010; Pitskel et al., 2011). In TD individuals, the medial prefrontal cortex (mPFC) has been consistently found to be active during direct gaze processing, even in infants, suggesting this region is organized for social communication at a very early age (Grossmann et al., 2008; Grossmann, Parise, & Friederici, 2010).

The current study specifically found increased interhemispheric average coherence in one parietal connection (i.e., left angular gyrus to right angular gyrus) among individuals with ASD during direct gaze processing. The angular gyrus is one structure within a network structures (i.e., "default network") that have been identified as active during resting state. Various imaging techniques have been used to examine connectivity and functional MRI studies have revealed conflicting results. Monk et al. (2009) found that individuals with ASD exhibit reduced connectivity within the left angular gyrus during resting state compared to TD controls and Weng et al. (2010) found that TD adolescents and those with ASD exhibit similar connectivity between the posterior cingulate cortex and bilateral angular gyri. More recently, Li, Xue, Ellmore, Frye, and Wong (2012) utilized diffusion tensor imaging (DTI), a structural/volumetric method, and found that individuals with ASD exhibit strong connectivity in the angular gyrus relative to control participants, but only within the left hemisphere. Interestingly, reduced activation of the bilateral angular gyrus was revealed in an ASD group during a theory of mind task (Kana, Libero, Hu, Deshpande, & Colburn, 2012), which comprises mentalizing ability purported to occur within a network that includes the mPFC and connections to the STS and intraparietal junction (IPJ; Grossmann et al., 2008, 2010). Individuals with ASD may have disrupted connections between anterior and posterior regions purported to underlie social communication, as they have been found to exhibit heightened parietal activity during tasks of gaze processing (Davies et al., 2011; Greene et al., 2011; Lajiness-O'Neill et al., 2010) but reduced coherence within and between frontal regions during face and gaze processing (Samson et al., 2012). Further examination of connectivity between association cortices (e.g. parietal to parietal) would prove beneficial, as parietal regions are hypothesized to be involved in a reflexive gaze processing network (i.e.,

parietal cortex, superior temporal sulcus, and amygdala; MacPherson & Moore, 2007; O'Reilly & Haan, 2009). An anterior-posterior network of structures is critical for social communication (i.e., mentalizing and gaze processing) and it is possible that individuals with ASD exhibit heightened connectivity of posterior regions (e.g., interhemispheric parietal connections) to compensate for decreased or atypical activity of anterior structures involved in gaze processing.

Significantly heightened interhemispheric occipital to occipital average coherence was revealed in individuals with ASD compared to TD participants in our study, which is contrary to the expected findings. Although studies examining gaze processing have found heightened activation of the occipital region, these findings have been predominantly lateralized to the left hemisphere (Lajiness-O'Neill et al., 2010; Pitskel et al., 2011). A recent meta-analysis of face processing revealed that individuals with ASD exhibit increased activation of the primary visual cortex, right lingual gyrus, and bilateral fusiform gyrus compared to controls (Samson et al., 2012), which is consistent with a recent study examining functional connectivity of face selective regions. Davies-Thompson and Andrews (2012) utilized fMRI during presentation of images (e.g., face, body, inanimate objects, places, and scrambled images of the former categories) to examine connectivity in TD individuals and revealed that they exhibit unique activation patterns of core face regions in the temporal and occipital lobe; evidence for significant functional connectivity between core face-selective regions, including the occipital face area (OFA) and fusiform face area (FFA) was provided, where the proportion of significant face selective voxels were in the right hemisphere. Interestingly, activity between face areas was found to be stronger for interhemispheric regions (e.g., right and left FFA) than for intrahemispheric regions (e.g.,

right OFA and left FFA). These results suggest that TD individuals exhibit heightened interhemispheric coherence, rather than intrahemispheric coherence, within occipital and temporal regions involved in face perception. Although our study did not reveal significant differences between groups within temporal-temporal connections, differences may have existed to a lesser degree. Research has suggested that individuals with ASD exhibit reduced interhemispheric coherence between temporal regions at resting state (Anderson et al., 2011). Since social communication (e.g., face processing) relies upon ventral processing, perhaps inclusion of stimuli more salient for this type of processing would have elicited greater connectivity between face selective regions (e.g., OFA and FFA) and those implicated in gaze processing (e.g., STS).

Moreover, the current study proposed that individuals with ASD would perform more poorly on measures of social cognition than TD participants. As expected, parents of participants with ASD endorsed greater levels of impaired social functioning on the SRS, which asks parents to rate level of impairment as it relates to social awareness, social cognition, social communication, social motivation, and autistic mannerisms. Increased SRS impairment ratings for individuals with ASD is commensurate with findings within the literature (Anderson et al., 2011; Kana et al., 2012; Weng et al., 2010; Zaki & Johnson, 2013). Significant differences were not found on other measures of social cognition, including the Nepsy-II Theory of Mind and Affect Recognition task, which may be explained by the small sample of TD participants eligible to complete measures due to age requirements. The clinical utility of these measures is a current area of debate, which may also contribute to the observed findings. Furthermore, increased SRS ratings may have

emerged due to the nature of self-report, which may have inflated parent ratings of the severity of social impairment.

The relationship between performance on measures of social cognition and average coherence was found to have moderate to large effect size in the ASD group, despite the small sample size. Given the limited number of TD participants that completed measures of social cognition, correlations were not computed. The magnitude of the relationship found between average coherence during direct gaze and affect recognition, theory of mind, and social responsiveness suggests that brain connectivity in individuals with ASD is moderately to strongly related to performance on social cognitive tasks. Specifically, affect recognition was found to be positively correlated with average coherence values during direct gaze in ASD participants, suggesting that connectivity is positively associated with affect recognition ability. Similarly, a study by Wright et al. (2012) suggests that reduced brain connectivity during an emotional face processing task negatively influences affect recognition abilities in individuals with ASD. Although connectivity within the lower frequency band (3-30 Hz) was similar between individuals with ASD and controls, gamma responses were largely absent in occipital areas for individuals with ASD when viewing emotional faces. Individuals with ASD were also found to exhibit a slower response rate for faces revealing disgust, happiness, and sadness, but they did not perform significantly poorer than controls. These results suggest that reduced connectivity at higher frequencies (i.e., gamma band) could have negative implications for affect recognition ability, which is a foundational skill that likely influences one's capability for ToM and degree of responsiveness in social situations. Thus, inclusion of the gamma band frequency would prove helpful for further investigations of brain connectivity during face and gaze processing tasks.

Moreover, ToM and social responsiveness were negatively correlated with average coherence (1-45 Hz) during direct gaze, which suggests that an inverse relationship exists between brain connectivity and proficiency at ToM and degree of socially responsive behavior. Studies have only recently begun to examine the relationship between patterns of brain connectivity and social cognitive skill. Herzig, Sullivan, and Evans (2012) examined the association between ToM performance and hemispheric activity, finding that enhanced performance on ToM tasks was associated with faster right hemisphere language processing and reduced right hemisphere dominance for face processing in control participants. Cortical connectivity during ToM tasks has also recently been examined, revealing that individuals with ASD exhibit significantly weaker connectivity in ToM-related regions (e.g., temporal and parietal regions) and ventral premotor areas, and also perform more poorly than controls on ToM tasks (Kana et al., 2012). Future studies utilizing coherence imaging techniques to investigate connectivity at higher frequency ranges (e.g., gamma band) during ToM tasks would prove helpful in elucidating the relationship between social cognitive skill and cortical connectivity.

The current study is the only known study to examine neural synchrony during passive viewing of gaze processing and its relationship to performance on measures of social cognition in TD individuals and those with ASD. Despite the contributions of this study to the ASD literature, there are a number of limitations of the current investigation. First, the study included a relatively small number of participants, who were matched on IQ and generally age, but not gender; there was one younger participant (i.e., 9-year old) in the ASD cohort, which largely contributed to the significantly lower average age of the ASD group. The small sample size of this study limits the external validity and conclusions that can be

drawn, yet it is comparable to a recent investigations (Catarino et al., 2013; Perez Velazquez et al., 2009; Pitskel et al., 2011). Inclusion of a greater number of participants within an age range for which tests of social cognition could be consistently administered would ensure that group differences could be examined. Secondly, the current study utilized photographs of individuals displaying direct gaze. Given that literature has revealed that live, social stimuli (i.e., live face) influences neural responses (Hietanen, Leppänen, Peltola, Linna-Aho, & Ruuhiala, 2008), future studies should consider utilizing stimuli that more closely mimics the characteristics one would encounter in a social interaction. Lastly, the data analysis was also restricted to examination of coherence during direct gaze. Although the current findings offer insight into the neural substrates underlying direct gaze, examination of findings related to both direct and averted gaze would likely provide a more comprehensive understanding of the complexity of gaze processing.

Future research in the area of gaze processing is essential. Prior research examining intrahemispheric and interhemispheric connectivity has primarily been conducted during resting state. Other studies examining structural and functional differences between TD individuals and those with ASD during gaze processing have lacked uniformity in experimental design (e.g., diversity of participant age, level of impairment, imaging techniques, and paradigm) that have hindered cohesive understanding of the neural substrates underlying gaze processing. Future research should utilize similar paradigms to investigate intra- and interhemispheric activity across spectral bands (i.e., low to high frequency), as such studies will better inform understanding of the neural substrates underlying social communication and advance our understanding of the pathophysiology of ASD.

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APPENDICES

Appendix A: Recruitment Flyer

EASTERN MICHIGAN UNIVERSITY
AND HENRY FORD HOSPITAL MEG LAB
ARE LOOKING FOR VOLUNTEERS
TO PARTICIPATE IN A STUDY OF BRAIN REGIONS IMPORTANT FOR
SOCIAL FUNCTIONING IN
AUTISM SPECTRUM DISORDERS

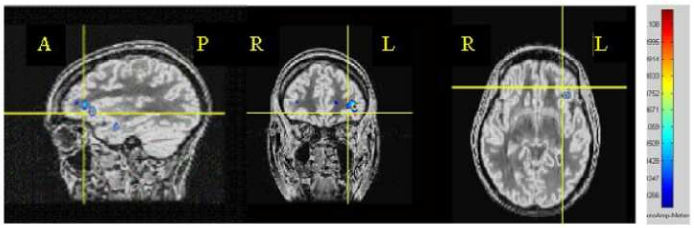
- We are looking for individuals with and without autism spectrum disorders.
- The research will examine changes that take place during social and thinking tasks so that we can eventually evaluate differences in the brain and behaviorally following social interventions.
- Only one examination that takes about one and a half hours is required.
- MEG is a completely non-invasive method of monitoring brain activity.
- The natural electrical activity of your brain can be measured in much the same way as a radio antenna picks up radio signals.
- This type of MEG exam has been performed on hundreds of individuals at Henry Ford Hospital.
- Participants will also complete thinking tasks and questionnaires about feelings and friendships.
- $50 stipend for participation

Magnetoencephalography (MEG)

Exclusion Criteria

- Weigh over 300 pounds
- Non removable metal implants
- Extensive dental work (Braces)
- English is not your first language

MEG Results



For more information or to find out if you are a candidate please contact:
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MEG: a non-invasive technique to localize functioning of the brain.

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Appendix B: Informed Consent

CONSENT TO PARTICIPATE IN A RESEARCH STUDY

1. WHY IS THIS RESEARCH BEING DONE?
The purpose of the research for which you have been asked to participate is to evaluate the changes taking place in the brain during visual and auditory stimulation during an attention task. To make reading this consent form easier, the word "you" refers to you or your child (if a minor) throughout the consent form. You have been asked to take part in a research study because you are an adolescent between 9-16 years of age with or without an autism spectrum disorder (ASD). There will be approximately 12 people in this research study at Henry Ford Health System (HFHS).
As part of this study, you will have a procedure called Magnetoencephalography. This procedure is not experimental. Magnetoencephalography (MEG), a noninvasive brain imaging tool, will measure magnetic fields and map brain regions important for joint attention. Joint attention refers to several behaviors that allow an individual to communicate through eye gaze and gesture. MEG is a completely non-invasive method of monitoring brain activity. The natural electrical activity of your brain produces very weak magnetic fields, which can be detected by a Neuromagnetometer in much the same way as a radio antenna picks up radio signals. This is a non-invasive safe form of studying the brain. This type of exam has been performed on hundreds of patients at Henry Ford Hospital without risk. This project is only being
conducted at Henry Ford Hospital.
This study is sponsored by Eastern Michigan University, Faculty Research Fellowship. This means that the sponsor is compensating HFHS for the costs of carrying out this research.

2. WHAT WILL HAPPEN IF I TAKE PART IN THIS RESEARCH STUDY?
a) You will be going to the Neuromagnetism Lab at Henry Ford Hospital in Detroit where the examination will be conducted. First, you will be asked to complete some thinking tasks and forms about feelings and friends that will take about 90 minutes.

For the MEG study, you will be asked to remove all metal objects, such as jewelry, watches, belts, and other metal items from your body. A videotape eraser will be used to demagnetize your dental work. A removable mark will be made on your face, two earplugs will be inserted into your ears and 3 small coils will be taped to your forehead, this will allow the computer to locate your head inside of the neuromagnetometer helmet. You will then be asked to lie on your back on a reclining bed with your head placed in the neuromagnetometer helmet. At the end of the examination, you will be able to leave and go about your usual business. During the study you will be observed by means of a video camera and an intercom system. You may ask to stop the study, if at any time you become uncomfortable.
During the study you will be asked to stay as still as you can and focus on the images filling your field of vision. Participants will view a photograph of a character whose gaze will be shifted toward targets (asterisk) projected onto a screen. This task will last 20-30 minutes. The total time required to complete the questionnaires and MEG study will take about 1 1/2 hours. You will be part of a study involving twelve participants who will undergo the procedure one time.

3. WHAT ARE THE RISKS OF THE STUDY?
There are no known risks for participating in the thinking tasks. The potential risks from the MEG study are negligible since the technology involves non-invasive recording of spontaneous brain activity while a subject lies quietly on a padded table inside a magnetically shielded room. Most subjects fall asleep during extended testing. The potential for the probe striking the subject's head exists, but is unlikely since the probe can be easily maneuvered via a CO2 driven air brake system. The shielded room is supplied with a constant flow of temperature-controlled air. There are no known

instances of injury to a subject by a commercial neuromagnetometer. Participants may experience some discomfort during the MEG procedures as they will be asked to remain as still as possible for the scans. However, as noted, breaks will be given during the MEG procedure as needed. You will be told about any information that is discovered that might affect your willingness to continue participation in the study.
You should tell the person obtaining your consent about any other medical research studies you are involved in right now. It is not expected that you will have any complications or discomforts from being in this study. There may be risks or discomforts that are not known at this time.

4. WHAT ARE THE BENEFITS TO TAKING PART IN THE STUDY?
You will not be helped by participating in this study. However, if you participate in this project, others may be helped by what is learned from this research as the study will help us to learn more about what thinking skills and parts of the brain are important for social skills. With this knowledge, we may be able to develop better treatments for social problems.

5. WHAT OTHER OPTIONS ARE THERE?
There are no alternatives treatments and/or procedures as this project is research about social functioning and is completely voluntary.

6. WHAT ABOUT CONFIDENTIALITY?
By signing this consent form, you agree that we may collect, use and release your personal and health information for the purpose of this research study.
We may collect and use:
• Your existing medical records.
• New health information created during this study.
• Health insurance and other billing information.
We may release this information to the following people:
• The Principal Investigator and his/her associates who work on, or oversee the research activities.
• Government officials who oversee research.
• The research sponsor, Eastern Michigan University.
• Your insurance company or others responsible for paying your medical bills.
• Other researchers at other institutions participating in the research.
Once your information has been released according to this consent form, it could be released again and may no longer be protected by federal privacy regulations.
This consent form, test results, medical reports and other information about you from this study may be placed into your medical record. Generally, you are allowed to look at your medical record. During the research study, you will not be allowed to look at your research study information that is not in your medical record.
HFHS or others may publish the results of this study. No names, identifying pictures or other direct identifiers will be used in any public presentation or publication about this study unless you sign a separate consent allowing that use.
This consent to use and release your personal and health information will expire at the end of this research study.
You do not have to sign this consent to release your medical information and may cancel it at any time. If you decide not to sign this consent or cancel your consent, you cannot participate in this study. If you notify us that you wish to stop participating in this study, we may continue to use and release the information that has already been collected. To cancel your consent, send a written and dated notice to the principal investigator at the address listed on the first page of this form.

7. WHAT IF I AM INJURED?
There are no procedures that are expected to result in injury. However, if a participant becomes ill during the study, he or she can notify the researchers conducting the study via intercom and video monitors.
Participants can be quickly transported to either clinic or the even closer emergency department, which is approximately 300 meters from the MEG lab.
There is no federal, state, or other program that will compensate you or pay for your medical care if you are injured as a result of participating in this study. You and/or your medical insurance may have to pay for your medical care if you are injured as a result of participating in this study. You are not giving up any of your legal rights by signing this consent form.

8. WHO DO I CALL WITH QUESTIONS ABOUT THE STUDY OR TO REPORT AN INJURY?
Renee Lajiness-O'Neill, Ph.D., or her staff member has explained this research study and has offered to answer any questions. If you have questions about the study procedures, or to report an injury you may contact Renee Lajiness-O'Neill, Ph.D., Assistant Professor of Psychology, at 734-487-11155.
If you have questions about your rights as a research subject you may contact the Henry Ford Health System IRB Coordinator at (313) 916-2024. The IRB is a group of people who review the research to protect your rights.

9. DO I HAVE TO PARTICIPATE IN THIS STUDY?
No, your participation in this research study is voluntary. If you decide to participate, you can stop at any time. If this happens, you may be asked to return for a visit for safety reasons. You will get the same medical care from HFHS whether or not you participate in this study. There will be no penalties or loss of benefits to which you would otherwise be entitled if you choose not to participate or if you choose to stop your participation once you have started. You will be told about any significant information that is discovered that could reasonably affect your willingness to continue being in the study.

10. WHO ELSE CAN STOP MY PARTICIPATION?
The Principal Investigator, sponsor or your doctor can end your participation in the research study at any time. If this happens, you may be asked to return for a visit for safety reasons.

11. WILL IT COST ANYTHING TO PARTICIPATE?
We do not expect there to be any additional costs to you if you participate in this study. Items related to the routine medical care that you would receive even if you did not participate in this study will be billed to you or your insurance company. You have the right to ask what it will cost you to take part in this study.

12. CONSENT
You have read this consent form or it has been read to you. You understand what you are being asked to do. Your questions have been answered. Any technical terms you did not understand have been explained to you. You agree to be in this study. You will be given a copy of this consent form.

_____ _____ _____
Signature of Subject's Parent or Guardian Date Time

_____
Print Name of Parent or Guardian and Relationship to Subject*

_____ _____ _____
Signature of Minor Subject Date Time

_____
Print Name of Minor Subject

_____ _____ _____
Witness to Signature Date Time

_____ _____ _____
Signature of Person Obtaining Consent Date Time

Appendix C: Informed Assent

CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Child's Assent

You are being asked to be in this research study because you are an adolescent with or without an autism spectrum disorder (ASD). This form explains the study. After reading this form, you can decide to be in the study or you can decide not to be in the study. Either choice is OK. If you decide to start the study and then change your mind, you can stop being in the study at any time. Please ask the study doctor or study staff to explain anything you do not understand. They will answer all the questions you have. You can ask questions about the study at any time.

WHY IS THIS RESEARCH BEING DONE?

The study doctor is studying changes that take place in your brain when you are asked to pay attention to something that you see. The study doctor wants to learn whether paying attention with your eyes is important for social skills and what parts of the brain are important for paying attention with your eyes.

The study has already been done with adults. It has helped us learn some things about what parts of the brain are important for paying attention with yours eye in adults without ASD.

If you want to be in the study, here is a list of things that will happen:

1. You will be going to the Neuromagnetism Lab at Henry Ford Hospital in Detroit where the project will be conducted.
2. You will be asked to complete some thinking tasks and forms about feelings and friends that will take about an hour and a half.
3. You will have a procedure called Magnetoencephalography (MEG). MEG is a tool that will help us see what parts of your brain are working when you are looking at pictures of someone else looking at faces, words, or a symbol that you will see on a screen. The natural electrical activity of your brain produces very weak magnetic fields, which can be picked up by a neuromagnetometer (a helmet with little detectors inside) in much the same way as a radio antenna picks up radio signals. This means that the tool just takes a picture of the normal activity that happens in your brain when you look at something. This is a safe form of studying the brain.

The MEG will take about 20 minutes.

• For the MEG study, you will be asked to remove all metal objects, such as jewelry, watches, belts, and other metal items from your body.
• A videotape eraser will be used to make sure there you don't have any dental work in your mouth that accidentally gets picked up by machine.
• A removable mark will be made on your face, two earplugs will be inserted into your ears, and 3 small coils will be taped to your forehead. This will allow the computer to locate your head inside of the neuromagnetometer helmet.
• You will then be asked to lie on your back on a bed with your head placed in the neuromagnetometer helmet.
• You will be asked to look at pictures of a person who is looking at faces, words, or a symbol and to press a button whenever the person is looking at something.
• During the study you will be observed with a video camera and there is an intercom system so that you can talk to the study doctor and staff. You may ask to stop the study at any time if you become uncomfortable.
• At the end of the study, you will be able to leave and go about your usual business.

WHAT COULD HAPPEN IF I DO THIS RESEARCH STUDY?
There are no known risks for completing the thinking tasks. Risks are unwanted things that could happen.
There are no real risks for completing the MEG study. There is a chance that you could get poked by one of the probes in the helmet, but this can be easily fixed. No one has been hurt by a commercial neuromagnetometer or one of its probes.
You might get uncomfortable during the MEG procedure because you will be asked to try to stay as still as you can. You will be given breaks during the MEG procedure whenever you need one.

WHAT IF I DON'T WANT TO BE IN THE RESEARCH STUDY?
If you do not want to be in this study, you do not have to. No one will be upset with you if you don't want to be in the study. You do not have to be in the study to get help for the difficulties you might experience because of autism. Talk to the study doctor about other choices.

WILL WHAT I SAY BE KEPT PRIVATE?
What you tell the study doctor or anything else may be written down. What is written down about you will be seen by the study doctor and other people who run and manage the study. People who make sure that the study is being done the right way may also see it. If the information about the study is sent anywhere else, it will not have your name on it.

Statement of Assent
I have talked to my parent(s) or guardian(s) about this study, and I would like to be in this study. I will be given a copy of this form to keep.

_____ _____
Printed Name of Subject Age
_____ _____/_____/_____
Signature of Subject (if capable of signing) Date
_____ _____/_____/_____
Signature of Parent/Legal Guardian Date

STATEMENT OF PERSON EXPLAINING ASSENT
To be completed by the person explaining assent (please check one):
□ Child read assent from independently.
□ Child was read the information contained in the assent form.
I have carefully explained to the subject and the subject's parent/legal guardian the nature and purpose of the above study. There has been an opportunity for the subject and the subject's parent/legal guardian to ask questions about this research. I have been available to answer any questions that the subject and the subject's parent/legal guardian has about this study.

_____ _____/_____/_____
Signature of Person Explaining Assent Date

_____
Printed Name of Person Explaining Assent