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Gamma oscillatory activity in autism spectrum disorder during a face cueing task

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Gamma Oscillatory Activity in Autism Spectrum Disorder during a Gaze Cueing Task

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ABSTRACT

Joint attention is a social interaction skill that normally develops in infancy and involves following another's gaze to a stimulus. This skill is absent or developmentally delayed in autism spectrum disorders (ASD), causing cascading effects on development. Neural synchrony in the gamma frequency band is thought to be involved in cognitive functions such as joint attention. The current study investigated differences in gamma power between neurotypicals and ASD as measured by magnetoencephalography (MEG) while performing a gaze cueing task simulating joint attention. Results support lower frontal gamma power in ASD, suggesting that impaired generation of gamma activity in the prefrontal cortex may be involved in impairments in social cognitive functions such as joint attention in ASD. In contrast to previous research, findings did not support higher posterior gamma power in ASD, indicating a need for further research to clarify the nature of gamma oscillatory activity in posterior brain regions in ASD.

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Introduction

Autism spectrum disorders (ASD) are characterized by impairments in social interaction as well as deficits in communication and stereotyped and repetitive behaviors, interests, and activities (American Psychiatric Association, 1994). Central to impairment in social functioning is the way in which people with ASD respond to joint attention bids. Joint attention refers to the ability to follow another's gaze towards a relevant object or event in the environment. Among neurotypical children, this skill develops early in infancy and is vital to the development of various other skills including receptive and expressive language. Joint attention skills have consistently been shown to be impaired in individuals with ASD, which is thought to in turn contribute to other deficiencies such as communication impairments. Recent findings suggest that impaired joint attention skills are not solely attributable to fundamental perceptual deficits but, rather, are due to a lack of the special preference for attending to eyes that is observed in neurotypicals. In order to investigate abnormalities in neurological function underlying joint attention deficits in ASD, the current study examined previously collected magnetoencephalography (MEG) recordings of participants with ASD and neurotypicals while performing a gaze cueing task designed to simulate a joint attention bid. In this task, participants viewed a character whose gaze shifted to the left or right, after which a target appeared either congruent or incongruent with the direction of the character's gaze.

Advances in neuroscience have allowed the development of new understandings of the neural mechanisms that may be impaired in ASD by providing high-resolution spatial and temporal information about neural activity; it has recently become apparent that both are necessary to a comprehensive understanding of these disorders. Two theories that integrate

current findings from spatially and temporally focused neuroimaging techniques are that (a) there is an abnormal balance of excitatory and inhibitory processes in ASD, and (b) functional connectivity, primarily increased connectivity within posterior regions and decreased connectivity between posterior regions and frontal regions, is abnormal in ASD. Following from these is a third theory, that (c) impairment in inhibitory processes creates over-connectivity within local neural networks, thus impairing differentiation of signal from noise and preventing development of long-range functional connectivity needed to communicate salient information between brain regions.

The current study seeks to provide supporting evidence for these three related theories by demonstrating (a) higher evoked gamma power (here defined as 42 Hz) in posterior regions during a gaze cueing task in ASD relative to neurotypicals, consistent with an increased ratio of excitatory to inhibitory activity and over-connectivity within local networks in posterior regions; (b) lower induced gamma power in the frontal region in ASD relative to neurotypicals, consistent with impaired long-range functional connectivity; and (c) a smaller difference in induced gamma power between incongruent and congruent conditions (i.e. congruency effect) in the frontal region in ASD relative to neurotypicals, consistent with impaired discrimination of signal from noise and impaired differentiation between stimulus conditions.

The following review of the current literature will describe normal joint attention, its impairments in ASD, and the neural mechanisms underlying normal and impaired joint attention; normal gamma-band neural synchrony and abnormalities in gamma-band activity in ASD; the utility of MEG in studying ASD; the relationship between gamma abnormalities and the theories of central coherence and imbalance of excitatory and inhibitory processes in

ASD; and the role of gamma-band activity in the processing of eye gaze in both neurotypicals and ASD.

Background

Gaze Following and its Impairments in ASD

Deficits in social interaction are one of the more striking and impairing symptoms of ASD, due to both the importance of social interaction itself and because of the cascading effects on language acquisition and other social learning. Eye gaze is one of the most fundamental components of social interaction, and the human brain is specialized to quickly derive information from others' eyes, as the design of the human eye has evolved to convey specific and often highly salient information by representing different emotions and other social signals with different shapes of the sclera, or eye white (Emery, 2000). One of the hallmarks of ASD is a failure to detect and/or respond in a typical manner to the information conveyed by others' eyes, as performance on tasks involving eye gaze has been consistently found to be impaired in ASD. Possible explanations for this phenomenon include a failure to attend to the eye region (Dalton et al., 2005), or an increase in amygdala activation in response to viewing eyes which increases autonomic arousal and thus makes eyes aversive (Dalton et al., 2005). Another possible explanation is that the abnormal perceptual processes that have been found in ASD (Brown, Gruber, Boucher, Rippon, & Brock, 2005; Orekhova et al., 2008) could interfere with correct detection of relevant information conveyed by the eyes.

Another possible explanation for impaired gaze following could be that ASD involves a deficit in orienting to directional cues that is not specific to eyes. One study has found that neurotypical adults showed a longer latency in visually orienting to directional eye gaze cues than to arrow cues and longer latency in orienting to a left-side target cued by right-directional eye gaze than a right-side target cued by right-directional gaze. However, high-

functioning ASD adults differed from neurotypicals in two ways: they did not respond differentially to eyes and arrows and did not show the right-side congruence effect for eyes. However, neurotypicals and high functioning ASD adults did not show significantly different reaction times (Vlamings, Stauder, Son, & Mottron, 2005). This suggests that while there is not a specialized response to eyes in ASD as there is in neurotypicals, there is not an overall deficit in orienting to directional cues. A study of children with ASD found that while ASD had overall longer latency in orienting to any directional cues, neurotypical children showed shorter latency in orienting to eye gaze directional cues than to arrow cues while children with ASD did not show different latencies in responding to eyes and arrows (Senju, Tojo, Dairoku, & Hasegawa, 2004). This again suggests a lack of preferential response to eyes in ASD that is not accounted for by deficits in orienting to directional cues.

Joint attention. Preferential responsiveness to eye gaze directional cues is necessary to the skill of joint attention, i.e. following eye gaze to a relevant object or event (Frischen, Bayliss, & Tipper, 2007). This skill includes both responding to a joint attention bid by following another's gaze to a stimulus and initiating a joint attention bid by moving one's gaze to a stimulus in order to direct another's attention to it. In neurotypicals this skill set develops early in infancy, but either fails to develop or shows marked delays in ASD (Dawson et al., 2004). Joint attention deficits are one of the earliest observable indicators of these disorders (Charman, 2003). In one study, preschool children with ASD showed difficulty following adult gaze to an object compared to developmentally delayed controls, though they did not show impairment in orienting to targets, suggesting a deficit specific to social cueing (Leekam, Lopez, & Moore, 2000). Furthermore, infants with ASD have been found to fail to initiate joint attention in comparison to both neurotypicals and

developmentally delayed controls (Charman et al., 1997), suggesting an important deficit in social communication from a very young age. Another study found that when predictiveness of gaze cues was varied, in this case correctly cueing the appearance of a target either 50% of the time or 80% of the time, neurotypicals consistently oriented to eye gaze direction regardless of its predictiveness while ASD oriented to eye gaze direction only when it was predictive (i.e., 80% group) of target location (Ristic et al., 2005). This suggests the possibility that gaze following in ASD is motivated by its correspondence to relevant environmental stimuli, whereas in controls gaze is preferentially attended to for its social importance.

Joint attention is a building block in the development of social cognition and is thought to be related to the development of theory of mind, or the ability to attribute beliefs, desires, and intentions to others (Baldwin, 1995). A central feature of ASD has long been thought to be a lack of or abnormal development of theory of mind. Children with ASD have been found to fail to predict the behavior of others based on their assumed beliefs, which both neurotypical children and Down syndrome controls were able to do (Baron-Cohen, Leslie, & Frith, 1985). Though high functioning adults with ASD have been found to be unimpaired in the ability to recognize gender from photographs of only the eye region of faces and basic emotion from photographs of whole faces, they were impaired relative to neurotypical adults and adults with Tourette Syndrome on a task requiring discrimination of mental state based on the eye region, which is thought to index theory of mind abilities in adults (Baron-Cohen, Jolliffe, Mortimore, & Robertson, 1997). The relationship between joint attention and theory of mind is supported by the finding that initiation of joint attention in 20-month-old infants was predictive of their performance on several tasks requiring theory

of mind at 44 months (Charman et al., 2000).

Joint attention has been consistently found to play a role in mediating the acquisition of language, implicating deficits in joint attention as a contributing causal factor in developmental communication deficits. This mechanism is thought to operate primarily on the acquisition of nouns by associating a spoken noun with the object of an adult's attention (Baldwin, 1995). Scores on a measure of joint attention at 20 months among infants with ASD have been found to be positively correlated with gains in language ability between 20 and 42 months and negatively correlated with severity of social and communication symptoms (Charman, 2003). Furthermore, initiation of joint attention in preschool-age children with ASD has been found to be predictive of the development of language comprehension and production over the subsequent four to five years (Bopp & Mirenda, 2010). Further emphasizing the importance of joint attention deficits in ASD, a study of three to four year old children with ASD found that out of several measures of social development, initiation of joint attention was most discriminative of ASD from neurotypical and developmentally delayed controls, as well as being most predictive of concurrent language ability (Dawson et al., 2004).

Studies of neural activity provide further evidence for the vital role of joint attention skills. A study of event-related potentials (ERPs) in neurotypical infants found evidence that learning new words in the context of joint attention enhances encoding, as words learned in the context of joint attention prompted a late negative component when presented in conjunction with a picture that was incongruent with the meaning of the word. This component was thought to be related to difficulty in relating the picture to the previously learned meaning of the word and was not present with the words learned in the non-joint

attention condition (Hirotani, Stets, Striano, & Friederici, 2009). The negative component of the infant ERP, which indicates attentional processes, was enhanced in amplitude when neurotypical infants viewed objects in the context of a joint attention interaction (Striano, Reid, & Hoehl, 2006), suggesting that joint attention interactions facilitate infants in focusing their attention to relevant aspects of their environment.

Neural mechanisms of joint attention in neurotypicals. In order to understand why joint attention skills are impaired in ASD, it must first be understood how these skills develop in healthy controls. While neuroscience is still far from a comprehensive understanding of typical brain development, there has been considerable progress toward understanding the mechanisms underlying joint attention in neurotypicals. Exactly which neural mechanisms are involved is still subject to some debate, but the superior temporal sulcus (STS) has consistently been implicated in tasks involving response to eye gaze. Adolphs (2003) makes the distinction between the function of the fusiform gyrus, which is particularly adapted to processing structural and unchanging facial features, while the STS is specifically activated in response to changeable features of faces, e.g. when viewing eye and mouth movements. This distinction has since been further clarified by a study that found increased activation in the STS in response to simultaneous movement of the head and eyes, signaling a shift in attention similar to a shift in eye gaze only in comparison to the response to nonmoving faces and to a scrambled video indicating directional movement, while the fusiform gyrus responded similarly to both nonmoving faces and turning heads (Lee et al., 2010). A functional magnetic resonance imaging (fMRI) study found evidence that subregions within the STS may be specialized based on the body part that is perceived to be moving, as the superior and posterior portions of the right posterior STS were found to be

more responsive to observed eye movements as opposed to mouth or hand movements (Pelphrey, Morris, Michelich, Allison, & McCarthy, 2005).

Other brain regions implicated in following shifts in gaze include the medial frontal lobe and the inferior parietal lobe (Adolphs, 2003). A study of neurotypical infants found that their ability to respond to joint attention bids was related to left parietal activation and right parietal deactivation in electroencephalogram (EEG) recordings (Mundy, Card, & Fox, 2000). Mundy and Jarrold (2010) propose a more holistic model in which the development of joint attention in healthy infants is both generated by and shapes the development of a distributed and integrated neural network involving the frontal and parietal cortices, and they hypothesize that activation of this distributed network during joint attention beginning in infancy facilitates information processing and encoding.

Neural mechanisms underlying abnormal development of joint attention in ASD. Disrupted functioning of some of the same mechanisms thought to be involved in joint attention in neurotypicals, including the STS and medial frontal cortex, seems to be related to impairments in the development of joint attention skills in ASD. Differences in STS activation were observed when neurotypical and ASD adults were presented with gaze shifts that either correctly or incorrectly cued a target: controls showed significantly increased STS activation in response to incorrect cues relative to correct cues, while the ASD group showed no difference in STS activation in response to correct and incorrect cues (Pelphrey, Morris, & McCarthy, 2005). A study of three- to four-year-old children with ASD found that while they were not impaired on tasks indexing ventromedial and dorsolateral prefrontal cortex function in comparison to mental age-matched neurotypicals and developmentally delayed controls, the children with ASD were significantly impaired on a joint attention task, and joint

attention ability was significantly correlated with performance on the joint attention task (Dawson et al., 2002).

Abnormal hemispheric specialization is also thought to play a role in social impairment in ASD. An MEG study of seven- to twelve-year-olds with ASD found abnormally lateralized responses to eye gaze (Kylliäinen, Braeutigam, Hietanen, Swithenby, & Bailey, 2006). The ASD group displayed a much weaker right hemisphere response to averted gaze than was seen in neurotypicals, as well as left hemisphere activation in response to direct gaze that was not observed in neurotypicals. Furthermore, another MEG study of ASD adults found weaker right inferior occipito-temporal cortex activation in response to faces than in controls, as well as a lack of the priming effect for faces that was seen in controls (Bailey, Braeutigam, Jousmäki, & Swithenby, 2005). The ASD group also showed more response from overlapping brain regions in response to faces and other objects, whereas controls showed activation in a specific area in response to faces that did not overlap with areas that responded to other objects.

An analysis of a subset of the data presented here by Lajiness-O'Neill et al. (2010) found a higher normalized mean amplitude of the MEG signal in left occipital and parietal regions in ASD compared to neurotypicals during gaze cueing to targets, while neurotypicals showed a higher mean amplitude in the right medial orbitofrontal region. This provides support for a model that will be described here in greater detail, in which failure to appropriately limit activation in posterior regions impairs effective signaling to frontal regions, thus leading to lower activation in frontal regions. Furthermore, this analysis found areas of activation in ASD during gaze cueing to targets to be widely distributed throughout the left hemisphere, while activation in neurotypicals was predominantly concentrated in

right frontotemporal regions, consistent with previous findings of abnormal hemispheric specialization.

In addition to the previously mentioned neural network model of typical joint attention, Mundy (2003) has developed a corresponding model to account for the disturbances in joint attention and related social cognitive skills that are observed in ASD. An earlier formulation of this model hypothesized that the dorsal medial-frontal cortex (DMFC) and the anterior cingulate cortex (ACC) are involved in impairments in social orienting as well as the ability to integrate proprioceptive information about one's own actions with perceptual information about the behavior of others, both of which may be involved in impaired development of joint attention, theory of mind, and other social cognitive functions in ASD. In a more recent formulation of this model, Mundy, Gwaltney, and Henderson (2010) propose that performance on joint attention tasks is a useful index of impairment early in the development of ASD because they elucidate the previously mentioned ability to integrate proprioceptive information about one's own actions with perceptual information about the actions of others. The model proposes that joint attention behaviors are both generated by and shape the development of a distributed neural network involving anterior networks that include the prefrontal and insula cortices as well as posterior neural networks that include the temporal and parietal cortices.

Neural Synchrony and its Impairments in ASD

A fundamental question concerning how the aforementioned neural networks arise is what mechanisms allow both localized and widely distributed brain regions to communicate. Neuroscience has relatively recently begun to move forward from an understanding of the brain as a collection of discrete neural substrates each specialized to perform certain functions, toward a model in which these regions must communicate and coordinate their activity in order to give rise to the huge variety of complex and nuanced functions carried out by the human brain. One recently established mechanism involved in both local network synchronization and long-range communication between brain regions is the synchronization of neuronal activity that gives rise to oscillations in the gamma frequency band, defined as roughly 30 to 80 Hz, which can be measured with either EEG or MEG. Though intuitively it may seem that high-frequency neural activity would arise from excitatory processes, these high-frequency oscillations have rather been found to be generated by inhibitory processes, specifically the activity of fast-spiking GABAergic inhibitory interneurons (Bartos, Vida, & Jonas, 2007). Furthermore, observations of close correlations between the power of gamma frequency oscillations and the hemodynamic response in the cat visual cortex provide evidence that the high level of activity in these inhibitory interneurons while generating gamma frequency oscillations gives rise to an increase in the hemodynamic response that is positively correlated with the frequency of the oscillations (Niessing et al., 2005).

What do gamma oscillations do? One of the original hypotheses concerning the function of gamma frequency oscillations, particularly at approximately 40 Hz, was that they were the answer to the perceptual binding problem. This problem refers to the perplexing ability of the human brain to integrate various aspects of a percept that are processed by

different brain regions, such as size, shape, and color, into a single entity. It has since been well established that gamma oscillations are indeed involved in perceptual binding (Tallon-Baudry & Bertrand, 1999), but it has also become apparent that they are involved in many cognitive processes as well. Intracranial recordings in the monkey visual cortex have found an increase in gamma synchronization in neurons that were activated by selective attention to relevant stimuli (Fries, Reynolds, Rorie, & Desimone, 2001), indicating that gamma oscillations play a role in attentional processes. In addition to sensory processing and attention, gamma oscillations have also been found to be associated with working and long-term memory and may support complex cognitive functions by facilitating the neuronal communication necessary for coordination of local and long-range neural networks (Jensen, Kaiser, & Lachaux, 2007). Uhlhaas et al. (2009) recently proposed that gamma oscillations may in fact be the mechanism by which conscious experience is achieved.

It stands to reason that if gamma oscillations are involved in such a wide range of cognitive functions, abnormalities in neural synchronization in this frequency range could have profound implications. In fact, there is substantial evidence that abnormalities in gamma activity are involved in a wide range of psychological and neurological disorders. Gamma power has been found to be lower in people with schizophrenia than in neurotypicals, especially in the 40 Hz range, which is thought to reflect specific deficits in the ability to generate and maintain neural synchrony in the gamma frequency band (Light et al., 2006). Other findings reviewed by Uhlhaas and Singer (2006) include an excess of high-frequency neural activity including the gamma range in epilepsy, a reduction in resting-state gamma in Alzheimer's disease, and increased gamma synchrony in motor regions during movement in Parkinson's disease. The evidence on gamma abnormalities in ASD is so far

somewhat limited and has produced mixed results, such as findings of increased gamma power in some studies (Orekhova et al., 2007; Rojas, Maharajh, Teale, & Rogers, 2008) and decreased gamma power in others (Rojas et al., 2008; Wilson et al., 2007).Though these findings may appear contradictory, they may in fact be consistent with a model of neural networks which will be described here in more detail, in which excess high-frequency activity in brain regions involved in sensory processing causes ineffective signaling to other regions involved in cognitive functions, thus leading to decreased high-frequency activity in areas that are not being properly activated.

The interrelationships of different frequency bands and how they may operate to convey different levels of information between various brain regions simultaneously are not fully known, though there is evidence that synchronous gamma oscillations are a possible mechanism by which distributed neural networks may communicate (Harris, Csicsvari, Hirase, Dragoi, & Buzsáki, 2003). Given the properties of neural oscillation as laid out in Buzsáki and Draguhn (2004), one would expect downregulation in neighboring frequency bands concurrent with increases of 40 Hz power, since neighboring frequencies compete with each other within the same neuronal network. Slower frequencies (e.g. alpha or theta-band frequencies), however, can operate at the same time as higher gamma-band frequencies, and thus an increase in 40 Hz power would not necessarily require a simultaneous downregulation of slower frequencies.

The utility of MEG in ASD research. The neurological abnormalities in ASD appear to be relatively complex and have not yet been elucidated by investigations within the spatial or the temporal domain alone. Therefore, MEG seems to be a particularly useful modality for investigating ASD due to its good temporal and spatial resolution, particularly

when coregistered with structural magnetic resonance imaging (MRI) data that enable mapping of the MEG signal onto cortical regions. In a MEG study of auditory processing, Kaiser and Lutzenberger (2003) describe the advantages of MEG over fMRI for answering research questions to which more than just spatial localization of neural activity is relevant: while gamma band activity is closely correlated with the hemodynamic signal measured in fMRI, MEG provides more detailed information on the temporal aspect of neural activity, as well as revealing patterns of neural connectivity within local networks and between distal cortical regions. Roberts et al. (2008) detail the utility of MEG specifically for detecting abnormalities in auditory processing related to language in ASD because of the presence of structural abnormalities coupled with highly specific temporal differences as well as abnormal hemispheric specialization. The utility of MEG in ASD research is not limited to investigations of auditory processing, as it is becoming apparent that the fundamental nature of abnormal neural functioning in ASD lies not in the spatial or the temporal domain alone, but a combination of the two.

Gamma abnormalities in ASD. While the exact nature of gamma abnormalities in ASD has yet to be determined, it is clear that abnormalities are present and may well be related to the profound developmental deficits that are characteristic of these disorders. One MEG study of children and adolescents with ASD found reduced 40 Hz power in the left hemisphere during an auditory click-train paradigm in comparison to neurotypicals, suggesting impaired ability to generate or sustain gamma oscillations (Wilson, Rojas, Reite, Teale, & Rogers, 2007). Another MEG study of adults with ASD and parents of children with ASD found that in comparison to neurotypicals, both had higher evoked, i.e. stimulus-locked, gamma power, but lower induced gamma power, which arises from self-paced

stimulus-induced cognitive processes. The difference between evoked and induced gamma power was hypothesized to be attributable to the lower phase-locking factor (PLF) in the ASD and parent groups, which is to say that the phase of the neuronal response was less consistent with external stimuli (Rojas et al., 2008).

Central coherence and gamma oscillations. One of the original theories concerning the underlying deficit in ASD was that it involved a lack of "central coherence" (Frith, 2003), or a tendency to experience the world in a piecemeal fashion rather than as unified percepts. This concept has since been borne out by neuroimaging studies that have found a lack of communication among distal cortical regions, thought to be facilitated by gamma oscillations, which may be the mechanism for this lack of integration of experience. According to Mundy's model of neural communication (2010), "Psychological development is most appropriately described in terms of continuous, incremental changes in the speed, efficiency and coordination of information processing networks that give rise to changes in knowledge and cognitive structures" (p. 412). Thus, impaired development of neural communication processes could cause the impaired development of psychological processes that is seen in ASD.

One theory of impaired neural communication in ASD proposes that in accordance with findings in genetics and in structural and functional imaging, cortical regions that in neurotypicals are functionally connected to the frontal lobe in order to produce higher-order cognitive functions fail to develop full functional connectivity in ASD (Geschwind & Levitt, 2007). This model does not propose a neural mechanism for this functional disconnectivity; however, it appears that it may be consistent with findings of abnormal gamma activity in ASD and the facilitation of long-range neural communication by gamma oscillations. In fact,

Brock, Brown, Boucher, and Rippon (2002) propose that the lack of central coherence in ASD can be explained by reduced functional connectivity between specialized cortical regions caused by a deficit in temporal binding as well as possible overconnectivity within localized regions, which are mediated by abnormal synchronization of gamma activity. The same authors have also issued an update of this model in which they incorporate the supporting evidence that had since accumulated, which was made possible by advances in EEG and MEG that provide high-resolution spatial and temporal information and allow better modeling of functional connectivity (Rippon, Brock, Brown, & Boucher, 2007).

Increased ratio of excitatory to inhibitory neural processes in ASD. A related theory about the nature of gamma abnormalities in ASD is that there is a disruption in the normal balance between excitatory and inhibitory processes in the brain, which has cascading effects on functional connectivity and thus has a profound effect on psychological processes. Orekhova et al. (2007) found higher induced midline gamma power in three- to eight-year-old boys with ASD than in neurotypicals during a sustained visual attention task. This study also found that gamma power was significantly correlated with developmental delay and that it decreased with increasing age of the participants. The authors suggest that the excess of high-frequency activity in ASD may be due to dysfunction in the GABAergic or glutamatergic receptors that are thought to be involved in generating high-frequency oscillations, and that the "noisiness" of neural networks with excessive gamma activity may impair the ability of those networks to be recruited to perform sensory and cognitive processes.

Another study by the same group found inhibited sensory gating in three- to eight-year-old children with ASD and mental retardation in comparison to neurotypicals as

indicated by a lack of suppression of the P50 response, a component of the auditory event-related potential, during an auditory click-train paradigm (Orekhova et al., 2008). When two clicks are presented in close succession, neurotypicals show reduced amplitude of the P50 component in response to the second click, an effect known as sensory gating. In this study, neurotypicals and the high-functioning ASD group showed normal P50 suppression, while children in the ASD group with mental retardation failed to suppress the response to the second click, though suppression improved with age among both groups. Furthermore, higher gamma power corresponded with impaired P50 suppression in the ASD group but not among neurotypicals. Again, this supports the hypothesis that a deficit in inhibitory processes, reflected in a lack of suppression of both unnecessary high-frequency activity and the P50 auditory response, is involved in ASD.

An EEG study of perception of illusory shapes in 11-17-year-old children with ASD and children with non-syndrome related mental retardation and no significant language disabilities (referred to as moderate learning difficulties, or MLD) found that while the groups did not differ in their ability to detect illusory figures, the ASD group showed significantly higher parietal induced gamma power while viewing the figures, while the pattern of gamma activity in MLD was similar to patterns found in non-impaired adults (Brown, Gruber, Boucher, Rippon, & Brock, 2005). The authors postulated that the increased gamma power observed in the ASD group reflected impaired inhibitory processes, such that high-frequency activity in neurons that were not involved in representing the salient stimulus were not inhibited, thus decreasing the signal-to-noise ratio. Also apparent in the ASD group was a lack of difference in gamma power between conditions in which an illusory figure was present or not present, indicating a failure to modulate gamma activity

appropriately in response to different stimulus conditions. This was consistent with earlier findings by Grice et al. (2001), in which ASD did not show different EEG gamma responses in an upright and an inverted face condition, in contrast to neurotypicals who showed higher frontal gamma power in response to upright versus inverted faces, thus showing a lack of discrimination between stimulus conditions in ASD.

Rubenstein and Merzenich (2003) propose a model in which at least some forms of ASD are caused by an increased ratio of excitatory to inhibitory neural activity in networks involved in memory and in sensory, social, and emotional processing, possibly due to increased excitatory glutamatergic activity or decreased inhibitory GABAergic activity that, in turn, appears to be caused by combinations of multiple genetic and environmental factors. There may also be dysfunction in neural networks involved in regulation of other networks, and the highly interrelated nature of the development of all of these functional networks means that dysfunction in one network can have cascading effects on many other networks. Therefore, the authors propose that a possible route for therapeutic intervention may be pharmacological treatments that reduce the ratio of excitatory to inhibitory activity, though such a treatment would likely be effective only if applied early in development before accumulation of the cascading effects on widespread neural networks.

In a similar vein, Belmonte et al. (2004) propose a computational neural network model as a unifying theory of ASD, which takes into account multiple proposed theories including lack of central coherence, impaired executive function, impaired functional connectivity between brain regions, an increased ratio of excitatory to inhibitory neural activity, and impaired neural synchrony in gamma band frequencies. This model synthesizes ASD research in the realms of behavior, genetics, neuroanatomy, and neurophysiology by

proposing that in neurotypicals, appropriately limited connectivity between small, localized neural units and selective long-range connectivity between local units allows differentiation of signal from noise and communication of salient information between local units, while in ASD, overconnectivity between local units impairs differentiation of signal from noise and prevents development of long-range functional connections to effectively communicate salient information.

Eye-gaze related gamma activity in neurotypicals. There is emerging evidence that neurotypicals demonstrate modulations in gamma power during tasks that require processing of eye gaze. An EEG study of neurotypical infants found higher evoked gamma power in occipital regions as well as higher induced gamma power in frontal regions in response to upright faces, which are highly salient sources of social information, as opposed to inverted faces, which are not generally sources of social information (Grossmann, Johnson, Farroni, & Gergely Csibra, 2007). Furthermore, Lee et al. (2010) found evidence for changes in gamma power associated with viewing shifts of social attention, in this case reduced gamma power in the STS in comparison to baseline. This is in contrast to previous studies demonstrating increases in gamma power during object perception; however, this study may be unique in localizing gamma oscillations within a specific brain region rather than over a general region, and the authors speculate that the localized decrease in gamma power could indicate neural desynchronization in which neurons are functioning independently in order to maximize the operational capacity of that brain region.

Eye-gaze related gamma activity in ASD. To this point, little research has directly addressed the characteristics of gamma activity in ASD during processing of eye gaze. One EEG study has found that infant siblings of children diagnosed with ASD who are thus part

of the broader ASD phenotype displayed higher gamma power in temporal regions during a baseline period and a differentiation of induced temporal gamma activity between direct and averted gaze that was delayed and of shorter duration than was found in neurotypicals (Elsabbagh et al., 2009). The first finding is consistent with an abnormal ratio of excitatory to inhibitory neural processes; the second is consistent with impairment in the ability to discriminate between distinct stimulus conditions that may be caused by impaired discrimination of signal from noise. Given the high level of importance attributed to impairments in gaze following and joint attention in ASD and emerging evidence for the important role that abnormalities in gamma band oscillations may have in ASD, more research is needed to determine the role that gamma abnormalities play in eye gaze processing and social cognition in ASD.

Aims of the Current Study

The current study seeks to provide support for a model of ASD in which an imbalance in the ratio of excitatory to inhibitory neural activity creates over-connectivity within localized neural networks and impairs the ability of these networks to distinguish signal from noise, and thus impairs the establishment of long-range functional connectivity. It was hypothesized that (a) consistent with an imbalanced ratio of excitatory to inhibitory activity and over-connectivity within local networks, ASD will show higher evoked gamma power in posterior brain regions in comparison to neurotypicals, and (b) consistent with impaired long-range functional connectivity, ASD will show lower induced gamma power in frontal regions relative to neurotypicals. Furthermore, it was hypothesized that (c) consistent with impaired discrimination of signal from noise and impaired differentiation between stimulus conditions, ASD will show a smaller difference in gamma power compared to neurotypicals in frontal regions between incongruent conditions in which eye gaze is directed away from a target and congruent conditions in which eye gaze is directed towards a target.

Methods

Participants

Eight participants with ASD (M_{Age} [*SD*/range] = 16.6 [4.9/13]; M_{IQ} = 120; Males = 4) and eight neurotypical controls (M_{Age} [*SD*/range] = 17.5 [2.9/8]; M_{IQ}= 115; Males = 4) completed the study. The groups did not differ significantly in age (t (16) = 1.79, p = .09) or gender (χ^2 = .11). There were no significant between-group differences in intellectual functioning, as both performed in the Above Average range on the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999), t(16) = 0.55, p = 0.60 (ASD M_{FSIQ} = 112; Control M_{FSIQ}= 116).

Individuals were recruited from Henry Ford Hospital, Washtenaw Intermediate School District (WISD), Ann Arbor Public Schools, and through advertisement and peer nomination. Subjects were diagnosed using the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition-Text Revision (DSM-IV-TR; American Psychiatric Association, 2000) diagnostic criteria. Diagnoses were confirmed with the Autism Diagnostic Interview-Revised (Lord, Rutter, & Couteur, 1994) or Autism Diagnostic Observation Schedule (Lord et al., 2000). Neurotypicals were age-, gender- and Performance IQ-matched to ASD. All APA Ethical Guidelines were followed and Institutional Review Board approval was obtained.

The WASI was individually administered by either a Masters'- or Doctoral-level student who was blind to the study's specific hypotheses at the Eastern Michigan University Psychology Clinic. Participation in the study was contingent on the individual functioning at least within the Low Average range of intellectual ability (>80 Full Scale IQ scores on the WASI). Exclusionary criteria for ASD and control participants included any known history

of head injury with loss of consciousness or other neurological disorders, and the presence of any metallic implant that would preclude the use of the MEG scanner, (*e.g*. braces on teeth, vagus nerve stimulator, deep brain stimulator, pace maker). Control participants had no history of ASD in a first-degree relative.

MEG Procedures and Protocol

Each participant underwent a MEG procedure at Henry Ford Hospital (HFH). After signing informed consent, each subject changed into a hospital gown and removed all metal from his or her body. Three small electrode coils, used to transmit subject location information to the neuromagnetometer probe, were affixed to the forehead with two-sided tape. Two more coils were taped on each cheek in front of the ear canal opening. A commercial videotape eraser was used to demagnetize dental work. The participants then lay on a bed in a magnetically shielded room. 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.

MEG Data Acquisition and Post-processing

148 channel whole head MEG (4D Neuroimaging, Magnes WH2500) was used to collect cortical activity. During acquisition, the data were band-pass filtered 0.1 to 100 Hz, 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 band-pass filtered from 1 to 50 Hz. Next, the locations of events on the trigger and response channels were used to select 2-second epochs of MEG data. All epochs had a baseline of 500ms before stimuli onset and 1500 ms of data after stimulus onset.

Gaze Cueing Paradigm

MEG field responses to gaze cues were obtained. Participants responded first to the gaze shift of the central character followed by stimuli that appeared in the periphery to examine the relationship between gaze direction and the object of interest. Participants viewed a digital photograph of a character whose gaze is forward for 2 seconds. The character engaged in a random gaze shift toward the right or left for 1 second. A target (asterisk) 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 stimuli was either congruent or incongruent with the direction of the character's gaze (see Figure 1). There were a total of 60 targets, with each set (congruent and incongruent) containing 30 responses to determine the averaged evoked response. The subject was asked to press the button when the subject was looking toward something. The test consisted of two segments each lasting 14 minutes.

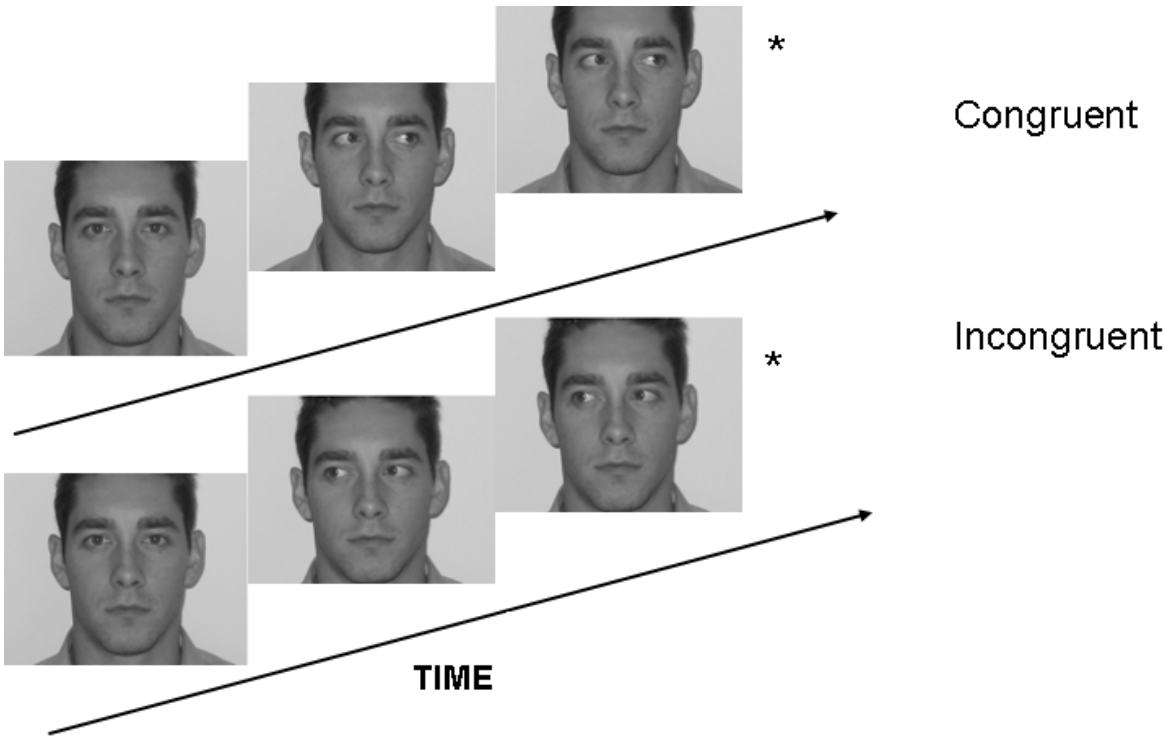

Figure 1. Schematic of the gaze cueing task.

MEG Data Analysis

MEG data was analyzed with the Matlab-based EEGLab toolbox (Delorme & Makeig, 2004). Methods for calculating evoked and induced gamma-band power (measured in dB) followed methods laid out in Tallon-Baudry and Bertrand (1999). Evoked gamma power (42 Hz) was calculated by averaging the raw MEG data over all trials, then performing a baseline-normalized spectral decomposition using a Morelet wavelet transformation. The Morelet wavelet transformation was used due to its better frequency resolution at higher frequencies as compared to a Fourier transform. Evoked power, i.e. activity that is time- and phase-locked to the external stimulus, is calculated in this way due to the fact that averaging retains only information about time- and phase-locked activity, which is then decomposed into spectral information (see Figure 3). Gamma power was averaged across a group of four occipital sensors chosen to correspond with the International 10-20 system (see Figure 2), and peak gamma power from 0 ms to 800 ms after stimulus onset was identified from among the power amplitudes exceeding a significance level of $p<.05$. Significance was calculated using a bootstrap method in which baseline spectral power is repeatedly sampled and averaged to create significance thresholds.

Induced gamma power was determined by performing a baseline-normalized spectral decomposition, then taking the average of the spectral power across all trials. Induced power, i.e. activity that is related to self-paced cognitive processes, is calculated in this way due to the fact that performing a spectral decomposition first retains all spectral information in the raw signal, much of which is lost by averaging the raw data, then taking the average of the spectral activity (see Figure 3). Gamma power was averaged across a group of four frontal sensors chosen to correspond with the International 10-20 system (see Figure 2), and

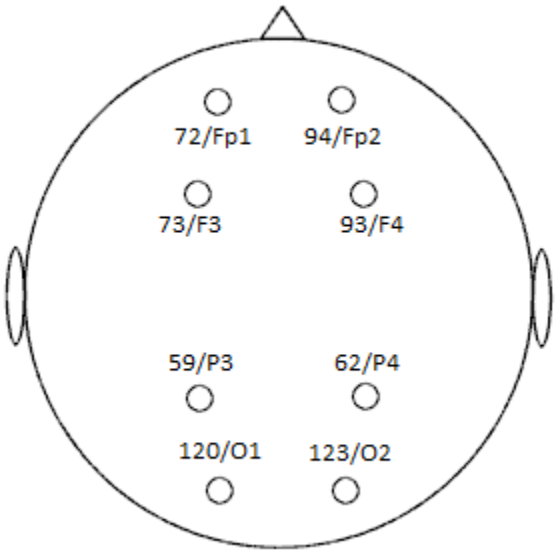

Figure 2. MEG sensor locations corresponding to the International 10-20 system.

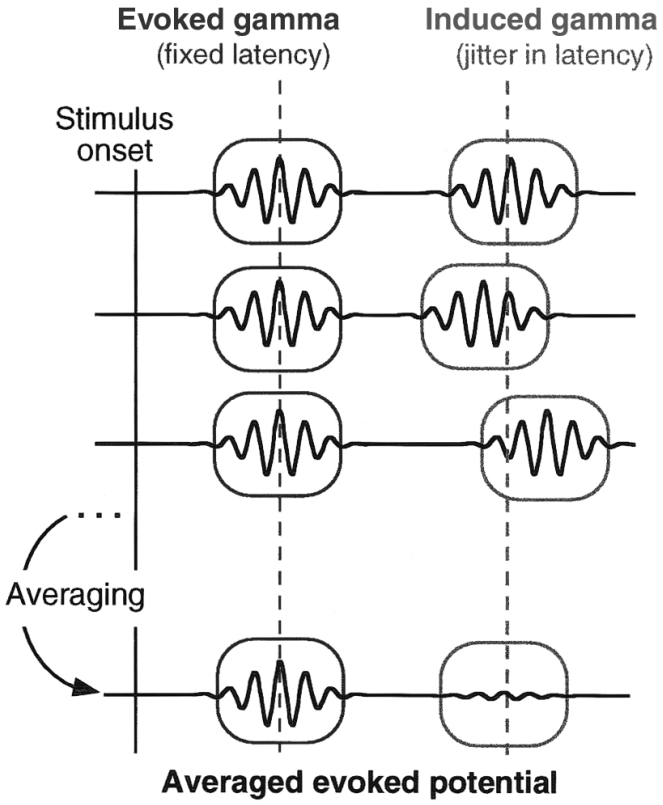

Figure 3. Illustration of calculation of evoked and induced gamma. Reproduced from Tallon-Baudry and Bertrand, 1999, p. 2

peak gamma power from 0 ms to 800 ms after stimulus onset was identified from among the power amplitudes exceeding a significance level of $p<.05$. Congruency effects were calculated for each subject by subtracting frontal induced gamma power in the congruent condition from frontal induced gamma power in the incongruent condition. Group differences for frontal gamma power, posterior gamma power, and congruency effects were examined with a *t*-statistic. Given the small sample size, *t*-tests were conducted using a Welch correction for unequal variances.

Results

It was hypothesized that (1) ASD would show higher evoked gamma power in posterior brain regions in comparison to neurotypicals, (2) ASD would show lower induced gamma power in frontal regions relative to neurotypicals, and (3) ASD would show a smaller congruency effect, i.e., the difference in gamma power in frontal regions between incongruent and congruent conditions, than neurotypicals. A priori hypothesis testing was conducted with three independent sample *t*-tests: (1) no significant differences were found between ASD and neurotypicals on posterior evoked gamma power; (2) group differences in frontal induced gamma power between ASD and neurotypicals approached significance ($p<.1$), with neurotypicals showing higher gamma power than ASD as predicted; and (3) no significant differences in congruency effects were found between neurotypicals and ASD. Cohen's *d* was calculated for between group differences in frontal induced gamma power, revealing a large effect size of .93. Group means and standard deviations for all conditions are shown in Table 1.

Post-hoc analyses revealed that the between group difference on frontal induced gamma power in the congruent condition as shown by an independent sample *t*-test approached significance ($p<.1$)[1], with neurotypicals showing higher gamma power than ASD. Cohen's *d* was calculated for between group differences in frontal induced gamma power in the congruent condition, revealing a large effect size of 1.10. No group difference in frontal induced gamma power was found in the incongruent condition. Paired sample *t*-tests comparing frontal induced gamma power in the congruent and incongruent conditions within each group found that the conditions were not significantly different from each other

[1] Mann-Whitney *U* tests confirmed that the mean differences on frontal induced gamma power and frontal induced gamma power in the congruent condition approached significance ($ps<.1$), indicating that assumptions of normality of the data were not violated.

Table 1

Gamma Power in 4 Frontal and 4 Posterior Sensors

	Neurotypicals	ASD
	M (*SD*)	*M* (*SD*)
Frontal Induced	1.36 (0.53)	0.97 (0.33)
Posterior Evoked	4.55 (1.35)	3.64 (1.53)
Frontal Induced (Congruent)	1.73 (0.75)	1.12 (0.37)
Frontal Induced (Incongruent)	1.56 (0.72)	1.44 (0.47)
Frontal Induced Congruency Effect	-0.17 (0.99)	0.32 (0.72)

in either the neurotypical or the ASD group.

To reduce the probability of a Type II error due to the small proportion of MEG sensors used in the original analysis (4 sensors in each of two regions, out of 148 total sensors), post-hoc analyses were conducted to determine group differences in gamma power in frontal and posterior regions based on all sensors in each region (17 frontal and 34 posterior; see Figure 4). Methods followed those used in the original analysis: gamma power was averaged across all sensors for each of the two regions, then peak gamma power from 0 ms to 800 ms after stimulus onset was identified from among the power amplitudes exceeding a significance level of $p<.05$. Consistent with the results of the original analysis, independent sample *t*-tests revealed that frontal induced gamma power was significantly higher in neurotypicals than in ASD ($p<.05$), while the two groups did not differ on posterior evoked gamma power. Cohen's *d* was calculated for between group differences in frontal induced gamma power, revealing a large effect size of 1.07. However, in contrast to the original analysis, no group differences were found in frontal induced gamma power in either the congruent or the incongruent condition alone, or in the congruency effect. Group means and standard deviations for frontal induced and posterior evoked gamma power calculated using all sensors in each region are shown in Table 2.

Another potential source of Type II error in the original analysis was the use of the averaged evoked signal rather than the non-averaged induced signal in examining gamma power in the posterior region. Though theoretical considerations indicated that group differences may have been present in stimulus-locked activity in posterior regions, particularly in the activity of the primary visual cortex, it was also possible that group differences in gamma activity would be present in non-stimulus-locked activity of the

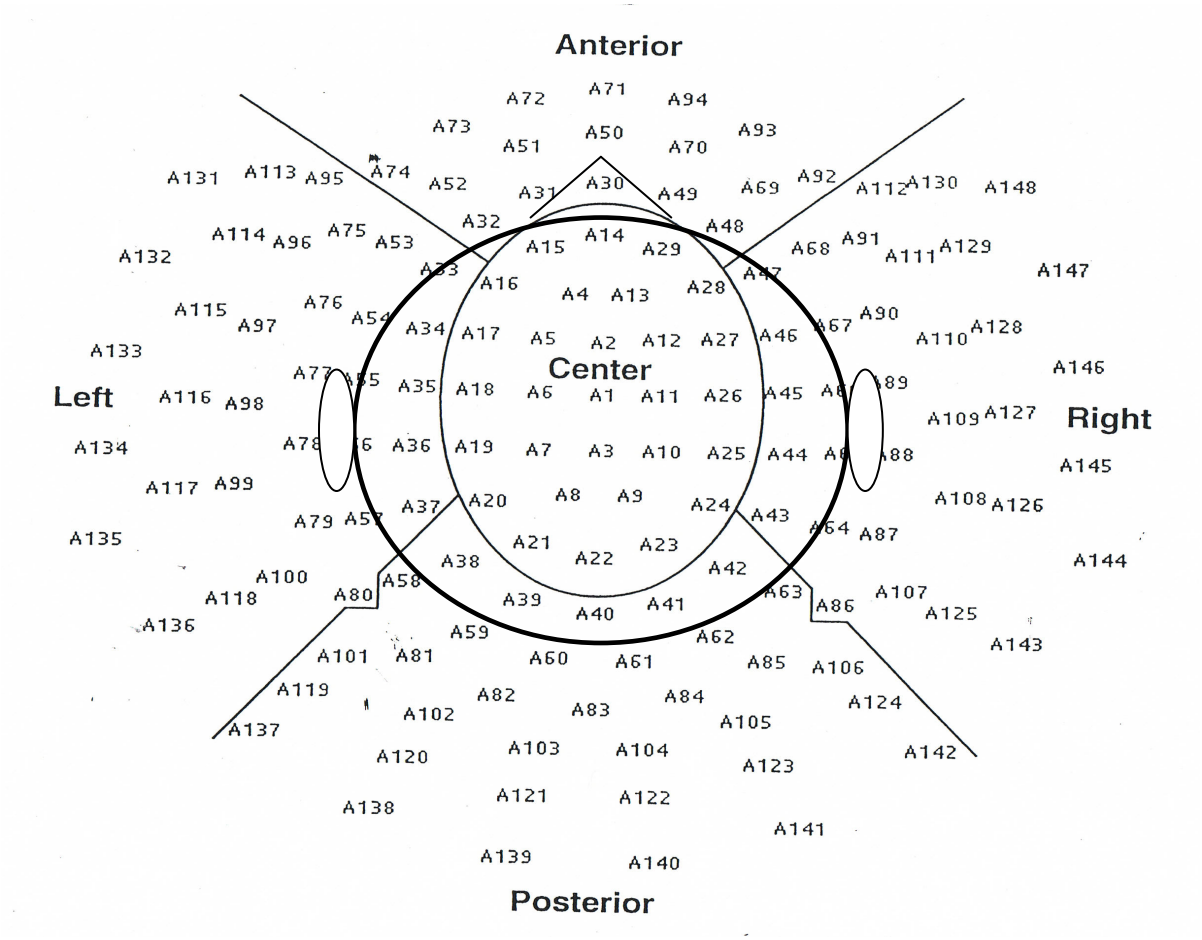

Figure 4. All 148 MEG sensor locations.

Table 2

Gamma Power in 17 Frontal and 34 Posterior Sensors

	Neurotypicals	ASD
	M (*SD*)	*M* (*SD*)
Frontal Induced	1.09 (0.61)	0.63 (0.15)
Posterior Evoked	3.67 (1.24)	2.85 (1.36)
Posterior Induced	0.77 (0.44)	0.93 (0.33)

posterior region, such as in the activity of the parietal cortex. Thus, additional analysis was performed to determine whether the neurotypical and ASD groups differed on posterior induced gamma power. However, independent sample *t*-tests revealed no group difference on posterior induced gamma power using all 34 posterior sensors, consistent with the original finding of no group difference on gamma power in the posterior region. Group means and standard deviations for posterior induced gamma power calculated using all posterior sensors are shown in Table 2.

Discussion

The results of this study support the hypothesis that ASD show lower induced gamma power in frontal regions than neurotypicals during a gaze-cueing task. Though the between-group difference in gamma power calculated using four sensors did not reach significance, post-hoc analysis using all sensors in the frontal region revealed significantly higher gamma power in neurotypicals than ASD. The fact that the neurotypical and ASD groups did not differ on full-scale IQ suggests that lower frontal induced gamma power is not attributable to lower IQ in the ASD group. Furthermore, the large effect sizes calculated using both four and 17 frontal sensors suggest that a clinically significant difference exists in induced frontal gamma power between ASD and neurotypicals.

In the four sensor analysis, the group difference in frontal induced gamma power appeared to be accounted for by a difference between the groups that approached significance in frontal induced gamma in the congruent condition (i.e., character's eyes directed towards the target), whereas there was no difference found in the incongruent condition (i.e., character's eyes directed away from the target). Again, the large effect size found for differences between ASD and neurotypicals in the congruent condition indicates a clinically significant difference. In the 17 sensor analysis, however, no between-group difference was found. It may be the case that a larger proportion of the signal from the four sensors used in the original analysis was generated by regions of the prefrontal cortex thought to underlie joint attention, such as the medial prefrontal cortex (Dawson et al., 2002; Mundy, 2003), whereas the signal from all 17 frontal sensors included proportionately more activity generated by areas not involved in joint attention. This interpretation is supported by

the finding of Lajiness-O'Neill et al. (2010), in an analysis of a subset of the data included here, of higher medial orbitofrontal activation in neurotypicals than in ASD.

To the author's knowledge, no studies in the current literature have investigated differences in gamma activity between neurotypicals and ASD during a gaze cueing task; therefore, proposed explanations for the observed between group difference in the congruent gaze condition in the four sensor analysis are speculative. Previous research has found that neurotypical infants show higher levels of prefrontal induced gamma activity in response to direct versus averted gaze (Grossmann, Johnson, Farroni, & Csibra, 2007). It may be the case that increased gamma power in the direct gaze condition facilitates the detection of important social information, since in most cases direct gaze or eye contact serves to convey more social information than averted gaze. This theory is supported by evidence of impaired differentiation of the temporal induced gamma response to direct versus averted gaze in ASD siblings in comparison to neurotypicals (Elsabbagh et al., 2009), as well as an impaired frontal induced gamma response to upright versus inverted faces in ASD adults in comparison to neurotypicals (Grice et al., 2001); both are consistent with impaired detection of socially relevant information. Theoretically, responding to a joint attention bid by following another's gaze to an object serves a similar function of detecting important social information. Thus, it may be the case that in the congruent condition of the eye gaze task in the current study, neurotypicals showed higher gamma power than ASD because neurotypicals were effectively detecting socially relevant information while ASD failed to do so.

The hypothesis that ASD would show higher posterior evoked gamma power was also not supported, as no significant differences were found in posterior evoked gamma power

between ASD and neurotypicals. In the current study, evoked gamma was examined on the theory that lower level sensory processes, as opposed to higher level cognitive processes, in which it was thought that ASD would show impaired inhibitory processes, would be produced primarily by stimulus-locked activity. However, based on the findings of previous studies which have indicated that ASD show higher induced gamma power over posterior regions (Brown et al., 2005; Orekhova et al., 2007), post-hoc analyses were also conducted to determine whether it could be the case that aspects of sensory processing produced by non-stimulus-locked activity were disrupted in the ASD group. In contrast to these previous studies, no significant between-group differences were found in posterior induced gamma power.

It could be the case that among high functioning ASD such as the participants in this study, generation of gamma activity in posterior regions is unimpaired or less impaired than in lower functioning ASD. Furthermore, the baseline condition in this task consisted of the character with eyes forward (i.e., direct gaze). Thus, this analysis detected whether the magnitude of the change between two different eye gaze conditions (i.e., direct versus averted) was different between the two groups. It may be the case that ASD do not show impaired differentiation of the posterior gamma response between different eye gaze conditions, but that differentiation is impaired in the frontal induced gamma response, as is indicated by this analysis.

The hypothesized difference in congruency effects (specifically, that neurotypicals would show a greater difference in frontal induced gamma between incongruent and congruent gaze cueing conditions) was not supported. Furthermore, post-hoc analyses indicated that frontal induced gamma was not significantly different in congruent and incongruent conditions

among either neurotypicals or ASD. As noted previously, the lack of literature addressing the characteristics of gamma activity in the context of gaze cueing in either neurotypicals or ASD makes it difficult to account for these particular findings. However, it may simply be the case that in neither group does the frontal induced gamma response reliably discriminate between eye gaze away from an object and eye gaze towards an object. It may also be the case that the gaze cueing paradigm used here was too artificial to adequately elicit differences between congruent and incongruent gaze conditions that may occur in a live interaction. Though it was originally hypothesized that ASD would show impaired discrimination between the two stimulus conditions, it appears to be the case that neither neurotypicals nor ASD showed reliable discrimination between these two conditions as indexed by induced gamma power.

These results are consistent with the theories of lack of central coherence and impaired executive function in ASD. Specifically, findings of lower gamma power over prefrontal cortex are consistent with Geschwind and Levitt's (2007) proposal that impaired central coherence in ASD is attributable to the failure of functional connectivity between PFC and other cortical areas to fully develop. To clarify whether the observed deficit in prefrontal gamma activity is in fact due to impaired functional connectivity between PFC and other cortical areas, future research will investigate phase coherence, an index of neural communication, between distal cortical regions in ASD. Furthermore, as gamma activity in the PFC is associated with executive function, findings of lower prefrontal gamma power in ASD are consistent with the theory of impaired executive function in ASD (Ozonoff, Pennington, & Rogers, 1991). To confirm that lower prefrontal gamma power in ASD is related to impaired executive function, future research should investigate the relationship

between gamma power and performance on executive function tasks in ASD as compared to neurotypicals.

Limitations of this study include the small sample size and the relatively high functioning status of all ASD participants, both of which could limit the generalizability of the findings presented here. However, given the fact that there is little to no information in the literature to date about gamma oscillatory activity in ASD in the context of eye gaze processing, the results presented here represent a preliminary step in understanding the role of neural synchrony in social cognitive impairment in ASD. Future research should further examine the characteristics of neural synchrony associated with social cognition in ASD, including examining lower functioning ASD, clarifying the nature of the gamma response to different types of eye gaze and utilizing various imaging techniques to investigate the nature of short- and long-range functional connectivity during social cognition in ASD.

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