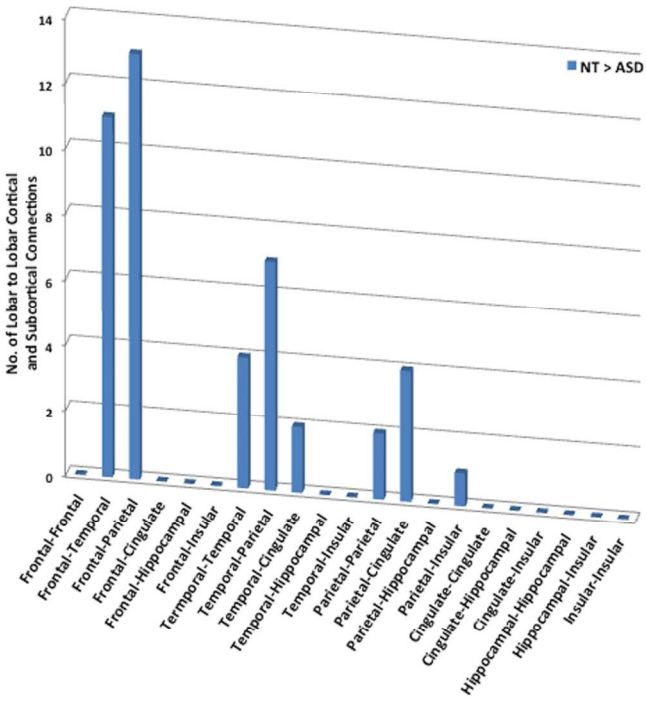
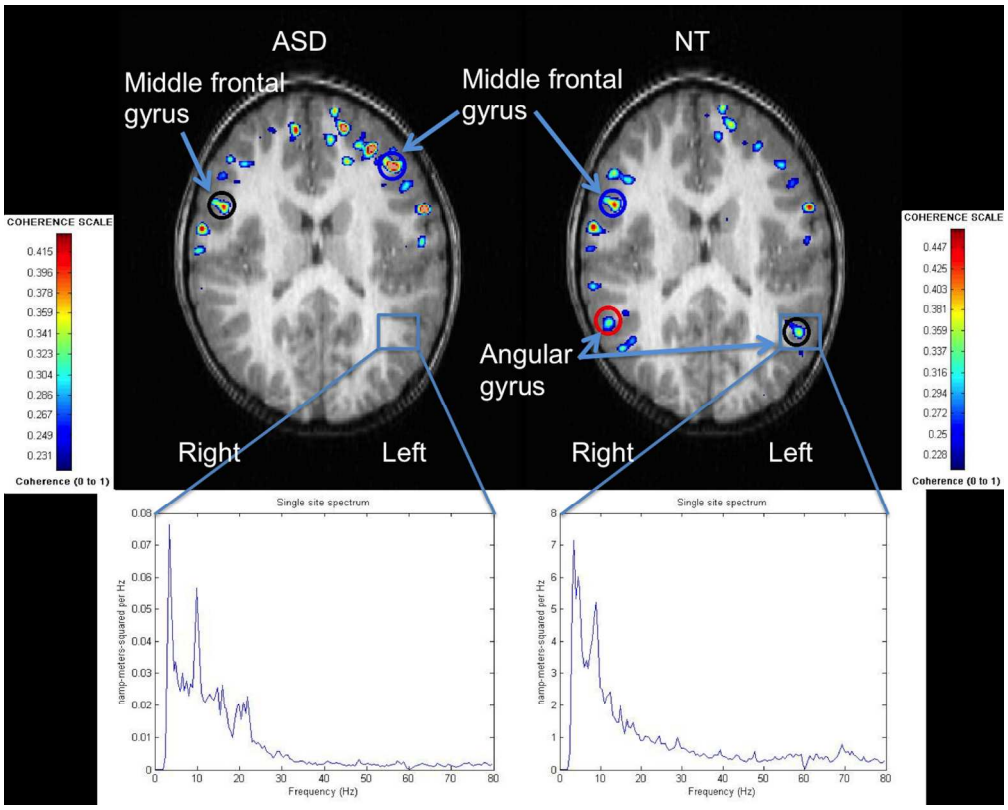


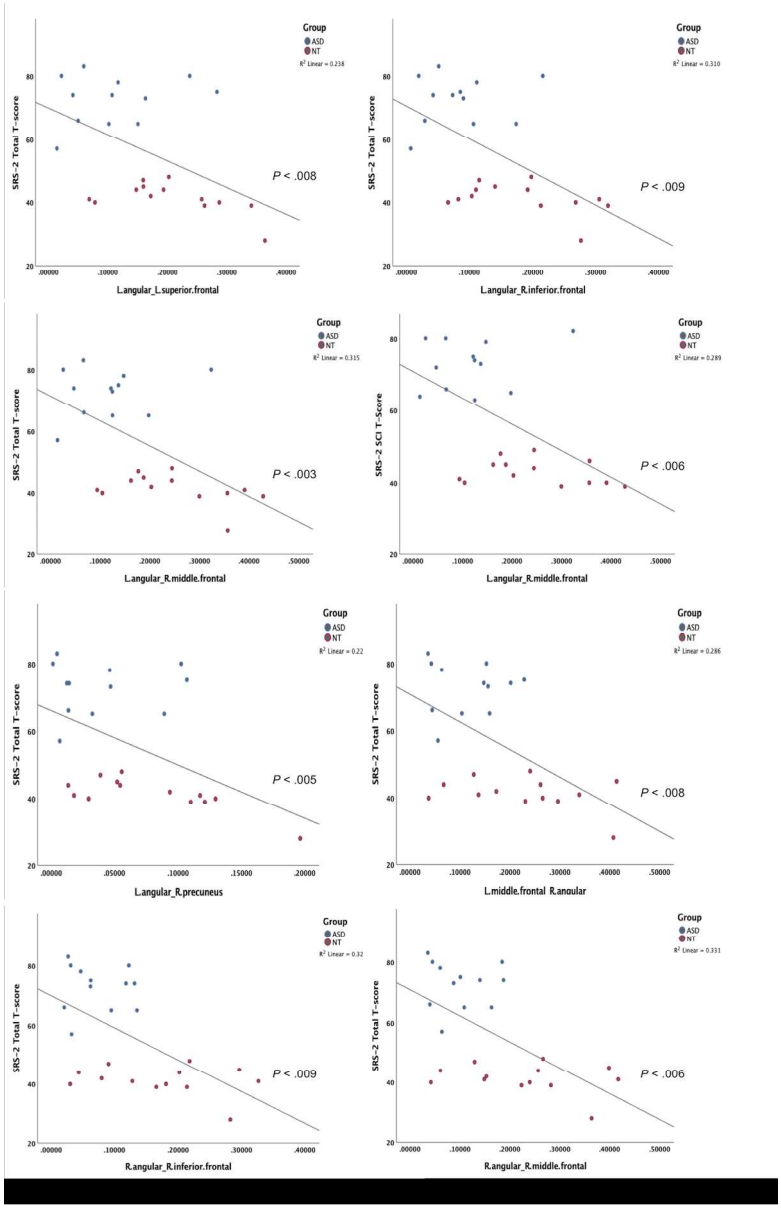
Regional cortical differences in gamma (30-80 Hz) band activity during resting state in NT compared to ASD. y-axis reflects the number of statistically different region-to-region connections (of the 231) collapsed by lobar pairs (x-axis).

130x97mm (300 x 300 DPI)



Axial brain slices revealing regions of the pathway with the most significant difference in gamma band coherence, right middle frontal to bilateral angular cortices, and power spectra in representative ASD and NT participants.

175x139mm (300 x 300 DPI)



Significant Kendall Tau correlation coefficients between the Social Responsiveness Scale-2 Total, Social Communication and Interaction Subscale (for NT and ASD) and brain region pairs with statistically significant between group differences in gamma band coherence.

178x277mm (300 x 300 DPI)

Patterns of Altered Neural Synchrony in the Default Mode Network in Autism Spectrum Disorder Revealed with Magnetoencephalography (MEG): Relationship to Clinical Symptomatology

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Number of text pages: 23
Number of tables: 4
Number of figures: 3

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Abstract

Disrupted neural synchrony may be a primary electrophysiological abnormality in Autism Spectrum Disorders (ASD), altering communication between discrete brain regions and contributing to abnormalities in patterns of connectivity within identified neural networks. Studies exploring brain dynamics to comprehensively characterize and link connectivity to large-scale cortical networks and clinical symptoms are lagging considerably. Patterns of neural coherence within the Default Mode Network (DMN) and Salience Network (SN) during resting state were investigated in twelve children with ASD (M_{Age}=9.2) and thirteen age and gender-matched neurotypicals (NT) (M_{Age}=9.3) with magnetoencephalography. Coherence between 231 brain region pairs within four frequency bands (theta (4-7 Hz), alpha, (8-12 Hz), beta (13-30 Hz), and gamma (30-80 Hz)) was calculated. Relationships between neural coherence and social functioning were examined. ASD was characterized by lower synchronization across all frequencies, reaching clinical significance in the gamma band. Lower gamma synchrony between fronto-temporo-parietal regions was observed, partially consistent with diminished default mode network (DMN) connectivity. Lower gamma coherence in ASD was evident in cross-hemispheric connections between: angular with inferior/middle frontal; middle temporal with middle/inferior frontal; and within right-hemispheric connections between angular, middle temporal, and inferior/middle frontal cortices. Lower gamma coherence between left angular and left superior frontal, right inferior/middle frontal, and right precuneus and between right angular and inferior/middle frontal cortices was related to lower social/social-communication functioning. Results suggest a pattern of lower gamma band coherence in a subset of regions within the DMN in ASD (angular and middle temporal cortical areas) related to lower social/social-communicative functioning.

Lay Summary

Communication between different areas of the brain was observed in children with ASD and neurotypical children while awake, but not working on a task. Magnetoencephalography was used to measure tiny magnetic fields naturally generated via brain activity. The brains of children with ASD showed less communication between areas that are important for social information processing compared to the brains of neurotypical children. The amount of communication between these areas was associated with social and social communication difficulties.

Keywords: autism spectrum disorder; synchrony; coherence; gamma; magnetoencephalography (MEG); salience network; default mode network.

It is becoming increasingly apparent that ASD is a disorder of brain connectivity (Belmonte et al., 2004; Courchesne & Pierce, 2005; Kana, Libero, & Moore, 2011; Rippon, Brock, Brown, & Boucher, 2007a; Wilson, Rojas, Reite, Teale, & Rogers, 2007) characterized by a perplexing pattern of widespread functional hypo-connectivity (Just, Cherkassky, Keller, & Minshew, 2004; Kana et al., 2011; Ye, Leung, Schäfer, Taylor, & Doesburg, 2014) and hyper-connectivity (Anderson, Druzgal, et al., 2011; Barttfeld et al., 2011; Ye et al., 2014) between discrete brain regions. While investigations of brain morphology and genetics continue to mount (Anderson, Nielsen, et al., 2011; Davis et al., 2008; Kana et al., 2011; Raznahan et al., 2009; Schumann & Nordahl, 2011), studies exploring brain dynamics to understand aberrant connectivity are lagging considerably (Pérez Velázquez & Galán, 2013).

Investigations of functional connectivity in individuals with ASD have used a variety of techniques including functional connectivity MRI (fcMRI) (Anderson, Nielsen, et al., 2011), EEG (Murias, Webb, Greenson, & Dawson, 2008) and MEG (Tsiaras et al., 2011). In MEG and EEG studies, *connectivity is commonly inferred from measures of coherence across brain regions* (Elisevich et al., 2011; Geschwind, 2007; Murias et al., 2008). Coherence estimates the consistency of relative amplitude and phase between two signals in a given frequency band and thus provides information about the functional interaction between neural systems (Srinivasan, Winter, Ding, & Nunez, 2008). Recent reports suggest that impaired neural synchrony may be a primary pathophysiological mechanism in ASD contributing to abnormal functional connectivity in both local and long-range neural networks (Khan et al., 2013; Wass, 2011). Specifically, disruptions in neural synchrony are believed to contribute to hyperexcitability, vacillating cortical network development, and aberrant connectivity. Regional imbalances between

excitatory and inhibitory mechanisms are purported to reflect disruptions in glutamatergic and GABAergic neural transmission (Gaetz, Edgar, Wang, & Roberts, 2011).

The majority of resting state studies in ASD have used EEG (Billeci et al., 2013; Coben, Clarke, Hudspeth, & Barry, 2008; Coben, Mohammad-Rezazadeh, & Cannon, 2014; Murias et al., 2008) while resting-state investigations exploring neural coherence with MEG in ASD have been limited (Ghanbari et al., 2013; Kitzbichler et al., 2014; Tsiaras et al., 2011; Ye et al., 2014). While EEG represents changes in the extracellular dendritic propagation of the electrophysiological signal, the neuromagnetic fields of MEG result from intracellular ionic changes that are unattenuated by the skull; hence, offering an opportunity to more precisely probe potential electrophysiological signatures (Ray & Bowyer, 2010). Building a neurophysiological model of ASD also requires that we understand the specific functional abnormalities associated with different frequencies, and this cannot be accomplished with other functional methodologies such as fcMRI.

It has been suggested that impaired neural synchrony may represent an endophenotype that underlies the information processing impairments in ASD (Gandal et al., 2010; Rojas et al., 2011; Rojas, Maharajh, Teale, & Rogers, 2008). However, functional connectivity is mediated by neural synchrony within various frequency bands (Pletzer, Kerschbaum, & Klimesch, 2010), and it remains unclear how specific frequencies contribute to this complex pattern of over- and under-connectivity and their relationship to the behavioral phenotype. While aberrant patterns of synchronization of magnetoencephalographic signals have been reported in ASD (Cornew, Roberts, Blaskey, & Edgar, 2011; Murias et al., 2008; Perez Velazquez et al., 2009; Tsiaras et al., 2011), a clear characterization has not emerged and replication is warranted from independent laboratories.

Tsiaras et al., (2011) and colleagues examined resting state functional networks with MEG in a small sample of 8 adults with ASD. The authors reported attenuated short-range "connections" within bilateral temporal and frontal sectors as well as within the left parietal sector. All connections formed by the sets of temporal and frontal sensors with other sensors were diminished amongst ASD participants. In the first resting state MEG investigation of children and adolescents, Cornew and colleagues (2012) reported regionally specific elevations in delta (1-4 Hz), theta (4-8 Hz), alpha (8-12 Hz) and high frequency power (20-120 Hz; beta and gamma were collapsed) in children with ASD. Compared to controls, children with ASD demonstrated increased theta power in parietal and occipital regions and increased alpha power in posterior temporal, parietal and occipital regions. Increased alpha power was also observed bilaterally and both alpha and theta power were reported enhanced in midline regions in ASD. Moreover, only increased temporal and parietal alpha power was associated with greater symptom severity as measured by parent report on the Social Responsiveness Scale (SRS) (Constantino, 2005).

Ghanbari et al., (2013) examined functional connectivity using synchronization likelihood (SL) and multi-scale entropy (MSE) to quantify signal complexity in children with ASD (aged 6-15) and typically developing children. The authors noted that where functional connectivity was increased, complexity was decreased in ASD. An increase in short-range connectivity in the frontal lobes (delta band) and in long-range connectivity in the temporal, parietal, and occipital cortices (alpha band) was reported in ASD. In contrast, long-range connectivity was significantly reduced in the delta, theta, and beta frequencies. Edgar et al., (2015) recently examined the relationship between thalamic volumes and alpha activity using resting state MEG in children with ASD. Greater alpha activity was noted in regions bordering

the central sulcus as well as in parietal association cortices. Whereas greater left central sulcus relative alpha activity was associated with higher SRS scores, greater calcarine region relative alpha activity was associated with lower SRS scores. Taken together, these findings suggest that social deficits in ASD might be characterized by lower cortical and increased subcortical connectivity.

A limited number of MEG studies in ASD have also explored spontaneous high frequency gamma relative to low frequency activity (Rojas & Wilson, 2014). Gamma band oscillations (30-80+ Hz) are the most commonly studied cortical oscillation in psychiatric disorders (Maxwell et al., 2013), and findings thus far in task-activated (e.g. auditory, visual, somatosensory) paradigms in ASD have reported various alterations in gamma power and gamma coherence (Edgar, Khan, et al., 2015; Peiker et al., 2015; Port et al., 2016, 2017; Ross, Jamali, Miyazaki, & Fujioka, 2012; Sedley et al., 2012; Stroganova et al., 2011; Takesaki et al., 2016). Gamma frequency oscillations are thought to represent firing of inhibitory GABAergic interneurons (Uhlhaas et al., 2009; Uhlhaas & Singer, 2006), and a prevailing hypothesis states that loss or reduction of inhibitory interneurons may lead to impaired processing of social and emotional stimuli in ASD (Rippon, Brock, Brown, & Boucher, 2007b; Rubenstein & Merzenich, 2003). Alterations in gamma band activity have also been reported in parents, at-risk infants, and siblings of children with ASD (Rojas et al., 2008; Wilson et al., 2007). To date, a very limited number of studies have directly explored *spontaneous* neural synchrony in children with ASD using MEG and the results have been equivocal (Kitzbichler et al., 2015; Maxwell et al., 2013; Ye et al., 2014). Frequency-dependent hyper-connectivity in frontal, temporal, and subcortical regions in the beta and gamma frequency ranges and hypo-connectivity in parietal and occipital regions in theta and alpha bands has been reported in a small sample of adolescents with ASD

(Ye et al., 2014); network abnormalities have been reported to include subnetworks of the frontal lobes, with an overall increase in alpha activity and both regionally enhanced and diminished gamma activity noted in ASD participants spanning a broad age range (6 to 21 years) (Kitzbichler et al., 2015), yet those with the highest gamma band activity were reported to exhibit the greatest pathology in direct contrast to other reports (Maxwell et al., 2015).

In addition to the behavioral heterogeneity in ASD, progress has been hindered by studies that have included wide age ranges (e.g. 6-21) or only focused on adults (Tsiaras et al., 2011), varying methodologies, e.g. examining connectivity through sensor rather than source space (Ghanbari et al., 2013; Tsiaras et al., 2011), e.g. eyes-closed (Cornew et al., 2011; Edgar, Heiken, et al., 2015) compared to eyes open (Kitzbichler et al., 2014; Maxwell et al., 2013), and vastly different analytic techniques. A vital omission is that studies have minimally addressed the relationships between neural coherence, resting state networks, and the core symptoms of ASD, specifically social communication and restricted and repetitive behaviors (RRBs). In fact, no studies have explored the relationship between neural coherence and RRBs.

The clarity of this aberrant connectivity pattern would be substantially enhanced if findings were articulated within a common framework such as the key resting state networks (RSNs). The Default Mode Network (DMN) and Salience Network (SN) are potentially the most relevant RSNs for understanding aberrant connectivity in ASD. The DMN constitutes a network purported to be essential for self-reflection, referential thinking, perspective taking, and memory (Gusnard, Akbudak, Shulman, & Raichle, 2001; Weng et al., 2010), core information processing deficits observed in ASD. Cortical regions associated with the brain's default network include the ventral medial prefrontal cortex, posterior cingulate/retrosplenial cortex, inferior parietal lobule, lateral temporal cortex, dorsomedial prefrontal cortex, and hippocampal formation (Amft

et al., 2014; Broyd et al., 2009; Buckner, Andrews-Hanna, & Schacter, 2008; Danielson, Guo, & Blumenfeld, 2011; Mars et al., 2012). The SN is purported to assist with the detection and orientation of attention to behaviorally relevant stimuli (Georgescu et al., 2013; Odriozola et al., 2015; Seeley et al., 2007). Key regions include the insular and cingulate cortices as well as subcortical limbic structures including the ventral striatum, amygdala, dorsomedial thalamus, hypothalamus, and substantia nigra/ventral tegmental area (Odriozola et al., 2015; Seeley et al., 2007).

In this investigation, we measured patterns of coherence between cortical regions implicated in the Default Mode and Salience Networks during rest in a well characterized population of children with ASD, ages 8-12, compared to age and gender-matched neurotypicals (NT). We hypothesized there would be decreased coherence between cortical regions of the DMN (e.g. medial prefrontal, posterior cingulate, ventral precuneus, medial/lateral/inferior parietal cortex) coupled with increased posterior synchronous activity and coherence within the SN (insular and cingulate cortex) in ASD consistent with their often-noted perceptual-cognitive style (Peiker et al., 2015; Takesaki et al., 2016). Based on prior work in our lab (Lajiness-O'Neill et al., 2014), we further predicted there would be a particular reduction in coherence in the gamma frequency band in ASD. Finally, we hypothesized that lower gamma coherence in the DMN and SN would be associated with more severe social/communication functioning in children with ASD. Additionally, given the limited literature from which to derive specific hypotheses about relationships between the DMN and SN with RRBs, an examination of these relationships was exploratory.

Methods

Participants

Twenty-five participants completed the study: twelve participants with ASD and thirteen neurotypical (NT) controls. The groups did not differ significantly in age, gender, or Full Scale IQ, with both groups generally performing in the Average to High Average ranges on the Wechsler Abbreviated Scale of Intelligence-2 (Wechsler, 2011). See Table 1 for participant characteristics. Four of the twelve ASD participants were taking psychotropic medications. Of the four, two were taking psychostimulants (Ritalin and Adderall), one was taking a sympatholytic medication to treat attention-deficit/hyperactivity disorder (Guanfacine), and one was taking an antipsychotic (Risperidone).

Individuals were recruited from two large metropolitan health care systems and underwent MEG procedures at Henry Ford Hospital (HFH). All potential participants were screened with the Social Communication Questionnaire (SCQ) (Rutter, Bailey, & Lord, 2008). ASD-likely participants required a Social Communication Questionnaire (SCQ) ≥ 11 (Corsello et al., 2007). Inclusion criteria for all subjects included at least Low Average intelligence ($\geq$80 Full Scale IQ) measured on the Wechsler Abbreviated Scale of Intelligence-2 (Wechsler, 2011). ASD-likely participants were subsequently diagnosed with Autism Spectrum Disorder based on the Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (American Psychiatric Association, 2013) diagnostic criteria and the Autism Diagnostic Observation Schedule-2 (Lord, Rutter, DiLavore, Risi, & Gotham, 2012). Exclusionary criteria for ASD and NT included a history of head injury, other neurological illnesses including active epilepsy/seizure disorder except febrile seizures, environmental deprivation, affective or anxiety disorders or other forms of psychopathology, and any known metal implants, pacemakers, braces, etc. that would

interfere with the magnetoencephalographic procedure. NT participants were excluded if there was a history of developmental delay or a first-degree relative with ASD. All APA Ethical Guidelines were followed and Institutional Review Board approval was obtained from all participating institutions.

Materials and Procedures

MEG Procedures

MEG Data Acquisition and Pre-processing. Cortical activity was recorded using a 148 channel whole head MEG system (4D Neuroimaging, Magnes WH2500) with magnetometer type sensors. Data acquisition included 10 minutes of eyes open passive recording. During acquisition, the data were digitally sampled at 508.63 Hz and band-pass filtered 0.1 to 100 Hz. Post-acquisition data processing was performed using MEG Tools, a Matlab-based software for cortical source imaging (CSI) that includes single current dipole and current distribution imaging (MR-FOCUSS) methods (Moran et al., 2005). In post-processing, a 3-85 Hz bandpass filter was used to remove noise artifacts due to breathing and body movement, and an additional independent component analysis (ICA) was used to remove cardiac artifact. In MEG, noise artifacts due to heart, respiration, and body movements are very large compared to brain activity. Our program inspects the entire 10 minutes of signal, identifies the first component (i.e., heart), and extracts that from the data automatically. Regarding large head movements, runs would have been repeated if the coils marking head position had moved more than 0.5 cm between the beginning and the end of the data collection run, although this did not occur in any subject. Regarding noise reduction, 4D Neuroimaging incorporates a set of reference sensors that are used to sample the environmental magnetic fields and create a file containing weights that are subtracted from the data during data collection since our system uses magnetometer type coils

and collects both patient and environmental magnetic fields. Our methods do not control for micro-saccades. If micro-saccades are observed in the data, they are typically seen only in the front 10 MEG channels and have not historically introduced significant error in the MEG data.

MEG Coherence Analysis. Synchronization of neuronal activity was quantified by calculating coherence between cortical sites identified as having higher amplitudes of activity during 10 minutes of resting state (Elisevich et al., 2011; Moran et al., 2006). Coherence is closely related to, but distinct from, the concepts of power, which describes the frequency composition of a single signal, and phase coherence, which takes into account phase relationship as well as synchrony between signals. Coherence is defined as a measure of synchrony between signals from different cortical regions within defined frequency bands. Our MEG-CSI is a computational analysis of the source localizations that have high cortical activity and are connected by the same frequency count. Imaged highly coherent brain sites are displayed directly into the specific regions of the brain (Source Space). In this study, the imaged activity within the DMN and the SN was used to calculate coherence. To calculate coherence (Elisevich et al., 2011; Lajiness-O'Neill et al., 2014), the MEG data was first divided into 80 segments each containing 7.5-second segments of data for computational efficiency. As noted above, all artifact removal has been conducted prior to the coherence calculation. Cross-spectra between ICA signals were calculated using a sequence of Fast Fourier Transform (FFT) spectra calculated using 0.5 sec windows with 25% overlap for frequency bins of 2 Hz width between 3 and 85 Hz. At the same time, a second ICA is performed to identify the areas in the brain where higher cortical amplitude activity is occurring and MR-FOCUSS is used to image these cortical locations. The imaging results and the signal cross-spectrum were then used to calculate the coherence between all pairings of identified cortical locations within each of the frequency bins.

For each of the active sources, the coherence with all other sources was calculated for each frequency and averaged across the bandwidth. Statistical analyses of cortical coherence levels (0=no coherence to 1=highly coherent) were used to quantify differences in network connectivity between groups (Elisevich et al., 2011).

Gray Matter Model. To localize cortical source activation in the DMN and SN, a model of gray matter was constructed from an age and gender appropriate standard T1-weighted high-resolution volumetric MR image. MEG Tools uses a probabilistic brain atlas composed of 54 structures (27 in each cerebral hemisphere) from manually delineated MRI data constructed by Shattuck et al. (2008) as a standard volumetric head model with each location specified in MNI305 coordinates. The realistic head model consists of x-, y- and z- oriented dipoles at approximately 4000 locations such that every location represents the same amount of gray matter identified in the MR image. MEG Tools uses a nonlinear volumetric transformation of the patient's brain to transform MEG coordinates to standard Talairach (Talairach & Tournoux, 1988) or MNI coordinates (Shattuck et al., 2008; 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). The MR images were co-registered with the individual's digitized head shape recorded at the time of MEG data collection. The MRI pixels 1mm x 1mm x1mm were rescaled (.98mm x .95mm x .97mm) to fit the digitized head shape. Since the pixels could be changed in all 3 dimensions, the top, sides, and back of digitized headshapes fit well. For this study, we only used 22 of the aforementioned 54 MNI defined regions in the brain (11 per hemisphere) that correspond to the identified DMN and SN regions. See Table 2 for a list of the 11 identified cortical regions. Of note, several subcortical regions implicated in the SN (e.g. thalamus and hypothalamus) cannot be reliably imaged with MEG due

to their depth. Thus, only cingulate and insular cortices were selected for further analysis within the SN.

Group Difference Testing. For each frequency band (theta, alpha, beta, and gamma), a Mann-Whitney *U*-test was conducted to assess group difference in average coherence values for each pair of brain regions within the DMN and SN (N=231). The False Discovery Rate (FDR) was used to adjust for multiple testing consistent with prior work (Lajiness-O'Neill et al., 2014). The Benjamini-Hochberg algorithm (Benjamini & Hochberg, 1995) was used to control the False Discovery Rate at 0.10; that is, no more than 10% of statistically significant differences within a group of Mann-Whitney U-tests were expected to be false positives. A q parameter of 0.10 was identified as the optimal threshold to minimize both Type I and Type II errors. Effect sizes (*r*) were also computed. We have also opted to rely on a Baysian approach (Wetzels et al., 2011) to identify a meaningful p-value cutoff for our analyses. Wetzels and colleagues (2011) used data from 855 t-tests to compare evidence from p-values, Bayes factors, and effect sizes. Studies that reported p-values of .05 provided only anecdotal evidence for findings according to Bayesian analysis. Only as p-values approached .01 did the evidence become substantial, according to the calculated Bayes factors.

Behavioral Assessment and Data Analyses

To examine group differences in behavioral indices, a series of Mann-Whitney *U*-tests were computed. Relationships between gamma coherence and clinical symptoms measured with the Social Responsiveness Scale-2 (SRS-2) (Constantino, 2005) and the ADOS-2 were examined with Kendall Tau correlation coefficients. For SRS-2, correlations were calculated for ASD and NT groups separately and then with groups combined. Given the small sample size and limited power, subsequently collapsing the groups allowed for an examination of overall relationships between coherence and social functioning irrespective of group membership. Correlations with SRS-2 scores were calculated only for gamma coherence values for which statistically significant

between-group differences were observed. The following index/domain scores were used as the primary dependent variables: 1) SRS-2 Total, 2) Social Communication and Interaction Index (SCI), 3) Restricted Interests and Repetitive Behavior Index (RRB), 4) ADOS-2 Total, 5) Social Affect Domain; 6) Restrictive and Repetitive Behaviors Domain.

Results

Coherence Imaging of Connectivity

Moderate to large effect size differences were noted across all frequencies; however, only those in the gamma band also met the established FDR and Bayes factor criteria. As such, only gamma band results will be discussed. **S**ignificantly higher coherence was noted in NT in 44 of the 231 pathways examined during resting state within the gamma frequency band; coherence was not significantly higher amongst ASD than NT for any of the examined pathways. See Table 2 for results of the Mann-Whitney *U*-test results and reported effect sizes (*r*) for which higher gamma coherence was noted in 44 pathways in NT children compared to children with ASD. Overall results revealed significant Mann-Whitney *U* values for the 44 region-to-region connections ranging from 120-132 (*Z* range = 2.28 to 2.94), corrected *p*-values ranging from .02 to .002, and with medium to large effect sizes (*r* range .46 to .59). According to Bayes factor criteria, only the top 27 of the 44 region-to-region differences in gamma band coherence identified by FDR constitutes substantial evidence for an alternate hypothesis. The remaining 17 region-to-region differences should be considered "anecdotal evidence" (Wetzels et al., 2011). Significant differences observed were primarily within the DMN, and no significant group differences were observed for pathways *within* the SN, although significant differences in coherence were noted between the identified regions of the SN and other cortical regions implicated in the DMN (6 cingulate and 1 insular region-to-region connections). Of the observed significant differences in

DMN regions, 29 (66%) were interhemispheric, 12 (27%) were right intrahemispheric, and 3 (7%) were left intrahemispheric. 29 (33%) involved parietal cortex, 28 (32%) involved temporal cortex, 24 (27%) involved frontal cortex, and 7 (8%) involved cingulate cortex. No pathways involving hippocampal cortices were significantly different between groups. Figure 1 displays the number of significant region-to-region differences in mean coherence within the gamma frequency band between ASD and NT groups summarized by lobar regions. Figure 2 illustrates the regions of the pathway with the most significant difference in gamma band coherence, right middle frontal to bilateral angular cortices, in representative ASD and NT participants. See Table 3 for frequencies of each DMN or SN region among pathways for which significant group differences in coherence were noted.

Group Differences in Psychometric Performance

The ASD group scored significantly higher (poorer performance) on the Social Responsiveness Scale and all subscales. See Table 4 for results of the Mann Whitney *U*-test. See Figure 3 for scatterplots of significant correlations between gamma band coherence and SRS-2 scores.

Relationship between Gamma Band Coherence and Clinical Symptomatology and Severity

Parent-Report: SRS-2 SCI. The SRS-2 Social Communication and Interaction (SCI) T-score, a subscale corresponding to one of the two main symptom domains of the DSM-5 criteria, was found to be significantly and negatively related to coherence between left angular and right middle frontal cortices, $\tau = -.40$, $p = .006$ in the total sample indicating that lower coherence (i.e. connectivity) was related to poorer social communication and interaction. No significant relationships were observed between SRS-2 SCI scores and gamma coherence among the ASD or NT subsamples.

SRS-2 RRB. The RRB subscale of the SRS-2 is the second subscale corresponding to DSM-5 criteria. No significant relationships were observed between SRS-2 RRB scores and gamma coherence among the ASD or NT subsamples. However, trends were noted when examining relationships between reported atypical/repetitive behaviors and gamma coherence in the total sample such that higher RRB behaviors were observed in children with lower coherence between: 1) left angular and right middle frontal gyri (p = .02), 2) left middle temporal and right inferior frontal gyri (p = .02), 3) left middle temporal and right middle frontal gyri (p = .01), 4) left superior temporal and right inferior frontal gyri (p = .01), 5), left superior temporal and right middle frontal gyri (p = .02), right middle frontal to right middle temporal gyri (p = .02), and right middle temporal to right superior frontal gyri (p = .02).

SRS-2 Total. No significant relationships were observed between SRS-2 Total and gamma coherence among the ASD or NT subsamples. However, within the total sample, overall lower social functioning (higher scores) as noted on the SRS-2 was significantly and negatively related to lower coherence between the left angular gyrus and: 1) left superior frontal, τ = -.38, p = .008, 2) right inferior frontal, τ = -.37, p = .009, 3) right middle frontal gyri, τ = -.42, p = .003 and 4) right precuneus, τ = -.41, p = .005; and between the right angular gyrus and: 5) left middle frontal, τ = -.38, p = .008, 6) right inferior frontal, τ = -.37, p = .009, and 7) right middle frontal gyri, τ = -.40, p = .006.

Performance-Based: ADOS Social Affect Domain. There were no significant relationships between the ADOS-2 Total score and gamma coherence in the ASD participants.

ADOS-2 RRB. There were no significant relationships between the Restricted and Repetitive Behavior (RRB) Domain score and gamma coherence in the ASD participants.

ADOS Total. There were no significant relationships between the ADOS Total score and gamma coherence in the ASD participants.

Discussion

Attempts to characterize large-scale neural network disruptions in neural synchrony in ASD have revealed a complex pattern of over- and underconnectivity (Anderson, Nielsen, et al., 2011; Courchesne & Pierce, 2005; Kana et al., 2011; Rippon et al., 2007a). Neural synchrony within the gamma frequency band, in particular, has surfaced as a potentially strong endophenotypic or biomarker candidate (Brown, Gruber, Boucher, Rippon, & Brock, 2005; Rojas et al., 2008; Sun et al., 2012; Wilson et al., 2007). However, to date, there have been few attempts to link findings on neural synchrony to known large-scale networks such as the Default Mode or Salience Networks in ASD. Moreover, the relationship between neural synchrony within these resting state networks and the core symptoms of ASD has not been examined. To shed light on the hypothesis that social and motor deficits in ASD are related to altered connectivity within the Default Mode and Salience Networks, we examined neural synchronization in the theta, alpha, beta, and gamma frequency bands using whole head MEG in 25 school-aged children with (n = 12) and without (n = 13) ASD, and examined the relationships between connectivity within and between these networks and ASD symptomatology.

Gamma Band Coherence

We hypothesized that there would be decreased coherence between cortical regions of the DMN (i.e., ventral medial prefrontal cortex, posterior cingulate/retrosplenial cortex, inferior parietal lobule, lateral temporal cortex, dorsomedial prefrontal cortex, and hippocampal formation) coupled with increased posterior coherence within the SN in ASD. Consistent with

emerging connectivity studies using functional magnetic resonance imaging (Odriozola et al., 2015), our investigation reveals support for hypoconnectivity and a pattern of reduced gamma band synchrony within some of the substrates of the DMN and between regions of the DMN and SN (specifically the cingulate), but not within the SN in ASD as compared to NT participants. ASD participants showed significantly lower gamma band coherence primarily between fronto-parietal, fronto-temporal, temporo-parietal, and parieto-cingulate cortices, and this reduction was most evident in interhemispheric connections between the angular gyrus with inferior and middle frontal (DLPFC) cortices, interhemispheric connections between middle temporal with middle and inferior frontal cortices, and within right-hemispheric connections between angular, middle temporal, and inferior and middle frontal cortices. Our findings are consistent with Tsiaras et al., (2011) and colleagues who also reported attenuated connections within bilateral temporal and frontal regions and within the left parietal sector in a small sample of adults with ASD. The current results are also consistent with a recent investigation by Pieker and colleagues (Peiker et al., 2015) who reported enhanced interhemispheric gamma band coherence in typically developing adults, whereas disrupted gamma band connectivity was noted between bilateral posterior temporal cortices in adults with ASD when completing a perceptual integration task. While lower gamma band coherence in our investigation was noted in connections between middle frontal cortices and other regions of the DMN, inspection of the data revealed that this was often consistent with involvement of the DLPFC rather than the medial PFC. Only a single pathway included the precuneus and no pathways included the hippocampal formation. Moreover, ASD did not show significantly higher gamma band coherence than NT within any of the examined DMN pathways nor was enhanced coherence observed in the SN or posterior cortical regions.

Consistent with prior EEG and more recent MEG investigations revealing differences in high frequency gamma band coherence (Peiker et al., 2015; Port et al., 2016, 2017; Takesaki et al., 2016), the current findings suggest a general decrease in inhibitory control via a loss or reduction in inhibitory interneurons. Individuals with ASD demonstrated an altered pattern of neural coherence consistent with hypoconnectivity within select components of the DMN (inferior/medial parietal and lateral temporal cortices), particularly within interhemispheric connections, which accounted for 66% of observed group differences. Gamma-band activity is purported to be critical for numerous cortical functions including basic sensory processing (Orekhova et al., 2008; Ross et al., 2012) (e.g. auditory, visual) as well as higher order cognitive functions (Jensen, Kaiser, & Lachaux, 2007; Stroganova et al., 2011). Converging independent investigations have revealed decreased cortical GABA in individuals with ASD (Gaetz et al., 2013; Rojas & Wilson, 2014), thus buoying the opinion that gamma band activity is dependent on a balance between excitatory and inhibitory neurophysiological functioning. Mixed results regarding the degree of involvement of the DMN is consistent with investigations using functional MRI in adults with ASD for which null findings have been reported between groups in regions of DMN during rest (Cherkassky, Kana, Keller, & Just, 2006) or for which reduced connectivity was localized to the medial PFC and left angular gyrus (Kennedy & Courchesne, 2008), the latter of which is very consistent with our results.

Analysis of region-to-region coherence within the delta, theta and beta bands also revealed general reductions in power within the low frequency bands consistent with Ghanbari et al., (2015), but also regionally diminished and enhanced frequency specific neural synchrony and connectivity in ASD consistent with recent reports from other electrophysiological investigations (Edgar et al., 2014; Ghanbari et al., 2013; Maxwell et al., 2013; Ye et al., 2014). However, given

that our findings for low frequency neural coherence did not hold up following multiple comparison correction, the results should be considered preliminary.

Relationship Between Neural Coherence and Core Features of ASD

In this investigation, we also revealed lower gamma coherence between the left angular cortex and 1) right inferior frontal, 2) right middle frontal cortices, 3) left superior frontal, and 4) right precuneus as well as between the right angular cortex and 5) right inferior and 6) right middle, and left middle frontal cortices that was related to greater social difficulties for all children as reported on the Social Responsiveness Scale-2. Lower gamma coherence between the right angular and left middle frontal cortices was specifically related to lower perceived social-communication and interaction within total sample. These findings are strikingly similar to our prior investigation examining neural synchrony during eye gaze processing in school-aged children with ASD (Lajiness-O'Neill et al., 2014). Reduced connectivity in regions of the DMN, believed to be vital for such tasks as self-referential thought and theory of mind, likely contribute these social difficulties. Multiple regions and networks within the right hemisphere, particularly aspects of the superior and inferior parietal and superior, middle, and inferior temporal cortices and its connections to medial prefrontal regions have been consistently shown to be critical for complex social information processing (Bigler et al., 2007; Pelphrey, Morris, & McCarthy, 2004; Redcay, 2008; Zilbovicius et al., 2006). These are the very regions in which lowered gamma coherence and connectivity was the most pronounced in ASD.

Reductions in connections with the angular gyri, particularly the left angular gyrus, appeared to be a particularly vulnerable hub of the DMN in this investigation of children with ASD. The angular gyrus is implicated in semantic processing, word reading and comprehension, numerical processing, the DMN, memory retrieval, attention and spatial cognition, reasoning,

and social cognition (Seghier, 2013). The angular gyrus serves as a cross-modal hub in which converging multi-sensory (i.e. visual, spatial, auditory, somatosensory) information is integrated to allow us to understand and make sense of events, manipulate mental representations, and orient/reorient our attention to our environment. Lesions involving the left angular gyrus result in a host of neuropsychological phenomena including alexia, agraphia, anomia, aphasia, sentence comprehension impairment, acalculia, visual spatial and body schema disorders, and ideomotor apraxia (Binder, Desai, Graves, & Conant, 2009; Petreska, Adriani, Blanke, & Billard, 2007; Pugh et al., 2000). It has been purported to be the single best candidate for high-level, supramodal integration in the brain (Geshwind, 1965). With regard to semantic processing, the angular gyrus is known to play an essential role in behaviors requiring fluent conceptual combinations such as discourse, sentence comprehension, planning, and problem solving (Binder et al., 2009). As is evident, children with ASD often present with a number of these neuropsychological difficulties and a host of deficits in these cognitive and behavioral processes, clearly implicating abnormalities in connectivity with angular cortices.

We recognize that there are a number of limitations with this study. First, similar to other recent MEG investigations of children and adolescents (e.g. 10 TD, 16 ASD, Port et al., 2017), the sample size was small and our population was generally high functioning limiting generalization to children across the spectrum. Second, our ASD participants remained on their psychotropic medication regimens during the study given the perceived cost-benefit of motion artifact for participants taking ADHD medications as well as the practical challenges associated with withdrawing from medications with longer half-lives. We recognize that when one is evaluating a possible pathophysiological mechanism in any disorder, a critical issue is whether the observed neural abnormality is present at the outset of the disorder and precedes medication

exposure and the adverse effects of chronic illness. Recent studies examining alterations in neural synchrony in populations prescribed medications similar to our cohort (e.g. ADHD and schizophrenia) have reported variable results with respect to medication status on neural synchrony and the findings have been primarily reported in adult populations (Minzenberg et al., 2010; Ozerdem, Güntekin, Tunca, & Başar, 2008; Wilson, Heinrichs-Graham, White, Knott, & Wetzel, 2013). Nonetheless, these investigations indicate that psychostimulants and antipsychotics would have attenuated gamma frequency group differences, suggesting the robustness of our findings. Finally, the lack of statistically significant group differences within the SN may have been attributable to limitations of the methodology utilized in the current study. The MEG methodology utilized here was able to reliably image only two of the regions implicated in this network (cingulate and insular cortices), thus potentially limiting the ability of the current study to detect group differences in coherence within this network.

References

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders: DSM-5* (5th ed.). Arlington, VA: American Psychiatric Publishing.

Amft, M., Bzdok, D., Laird, A. R., Fox, P. T., Schilbach, L., & Eickhoff, S. B. (2014). Definition and characterization of an extended social-affective default network. *Brain Structure & Function*. http://doi.org/10.1007/s00429-013-0698-0

Anderson, J. S., Druzgal, T. J., Froehlich, A., DuBray, M. B., Lange, N., Alexander, A. L., … Lainhart, J. E. (2011). Decreased interhemispheric functional connectivity in autism. *Cerebral Cortex (New York, N.Y. : 1991)*, *21*(5), 1134–46. http://doi.org/10.1093/cercor/bhq190

Anderson, J. S., Nielsen, J. A., Froehlich, A. L., Dubray, M. B., Druzgal, T. J., Cariello, A. N., … Lainhart, J. E. (2011). Functional connectivity magnetic resonance imaging classification of autism. *Brain : A Journal of Neurology*, 3742–3754. http://doi.org/10.1093/brain/awr263

Barttfeld, P., Wicker, B., Cukier, S., Navarta, S., Lew, S., & Sigman, M. (2011). A big-world network in ASD: dynamical connectivity analysis reflects a deficit in long-range connections and an excess of short-range connections. *Neuropsychologia*, *49*(2), 254–63. http://doi.org/10.1016/j.neuropsychologia.2010.11.024

Belmonte, M. K., Allen, G., Beckel-Mitchener, A., Boulanger, L. M., Carper, R. A., & Webb, S. J. (2004). Autism and abnormal development of brain connectivity. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *24*(42), 9228–31. http://doi.org/10.1523/JNEUROSCI.3340-04.2004

Benjamini, Y., & Hochberg, Y. (1995). Controlling the false discovery rate: A practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society Ser. B*, *57*(1),

289–300.

Bigler, E. D., Mortensen, S., Neeley, E. S., Ozonoff, S., Kransy Johnson, M., L., Lu Provencal, S.L., J., … & Lainhart, J. E. (2007). Superior temporal gyrus, language function, and autism. *Journal of Autism and Developmental Disorders*, *33*(5), 539–543.

Billeci, L., Sicca, F., Maharatna, K., Apicella, F., Narzisi, A., Campatelli, G., … Muratori, F. (2013). On the application of quantitative EEG for characterizing autistic brain: a systematic review. *Frontiers in Human Neuroscience*, *7*(August), 442. http://doi.org/10.3389/fnhum.2013.00442

Binder, J. R., Desai, R. H., Graves, W. W., & Conant, L. L. (2009). Where is the semantic system? A critical review and meta-analysis of 120 functional neuroimaging studies. *Cerebral Cortex*, *19*(12), 2767–2796. http://doi.org/10.1093/cercor/bhp055

Brown, C., Gruber, T., Boucher, J., Rippon, G., & Brock, J. (2005). Gamma abnormalities during perception of illusory figures in autism. *Cortex*, (41), 364–376.

Broyd, S. J., Demanuele, C., Debener, S., Helps, S. K., James, C. J., & Sonuga-barke, E. J. S. (2009). Neuroscience and Biobehavioral Reviews Default-mode brain dysfunction in mental disorders : A systematic review, *33*, 279–296. http://doi.org/10.1016/j.neubiorev.2008.09.002

Buckner, R. L., Andrews-Hanna, J. R., & & Schacter, D. L. (2008). The brain's default network: anatomy, function, and relevance to disease. *Annals of New Yok Academy of Science*, *1124*, 1–38.

Cherkassky, V., Kana, R., Keller, T., & Just, M. (2006). Functional connectivity in a baseline resting-state network in autism. *Neuroreport*, *17*(16), 1687.

Coben, R., Clarke, A. R., Hudspeth, W., & Barry, R. J. (2008). EEG power and coherence in

autistic spectrum disorder. *Clinical Neurophysiology : Official Journal of the International Federation of Clinical Neurophysiology*, *119*(5), 1002–9. http://doi.org/10.1016/j.clinph.2008.01.013

Coben, R., Mohammad-Rezazadeh, I., & Cannon, R. L. (2014). Using quantitative and analytic EEG methods in the understanding of connectivity in autism spectrum disorders: a theory of mixed over- and under-connectivity. *Frontiers in Human Neuroscience*, *8*(February), 45. http://doi.org/10.3389/fnhum.2014.00045

Constantino, J. N. (2005). *Social Responsiveness Scale*. Western Psychological Services.

Cornew, L., Roberts, T. P. L., Blaskey, L., & Edgar, J. C. (2011). Resting-State Oscillatory Activity in Autism Spectrum Disorders. *Journal of Autism and Developmental Disorders*. http://doi.org/10.1007/s10803-011-1431-6

Corsello, C., Hus, V., Pickles, A., Risi, S., Cook, E. H., Leventhal, B. L., & & Lord, C. (2007). Between a ROC and a hard place: decision making and making decisions about using the SCQ. *Journal of Child Psychology and Psychiatry*, *48*(9), 932–940.

Courchesne, E., & Pierce, K. (2005). Why the frontal cortex in autism might be talking only to itself: local over-connectivity but long-distance disconnection. *Current Opinion in Neurobiology*, *15*(2), 225–30. http://doi.org/10.1016/j.conb.2005.03.001

Danielson, N. B., Guo, J. N., & Blumenfeld, H. (2011). The default mode network and altered consciousness in epilepsy, *24*, 55–65. http://doi.org/10.3233/BEN-2011-0310

Davis, L., Hazlett, H., Librant, A., Nopoulos, P., Sheffield, V., Piven, J., & Wassink, T. (2008). Cortical enlargement in autism is associated with a functional VNTR in the monoamine oxidase A gene. *American Journal of Medical genetics.Part B, Neuropsychiatric Genetics*, *147B*(7), 1145.

Edgar, J. C., Heiken, K., Chen, Y.-H., Herrington, J. D., Chow, V., Liu, S., … Roberts, T. P. L. (2014). Resting-State Alpha in Autism Spectrum Disorder and Alpha Associations with Thalamic Volume. *Journal of Autism and Developmental Disorders*, (1929). http://doi.org/10.1007/s10803-014-2236-1

Edgar, J. C., Heiken, K., Chen, Y. H., Herrington, J. D., Chow, V., Liu, S., … Roberts, T. P. L. (2015). Resting-State Alpha in Autism Spectrum Disorder and Alpha Associations with Thalamic Volume. *Journal of Autism and Developmental Disorders*, *45*(3), 795–804. http://doi.org/10.1007/s10803-014-2236-1

Edgar, J. C., Khan, S. Y., Blaskey, L., Chow, V. Y., Rey, M., Gaetz, W., … Roberts, T. P. L. (2015). Neuromagnetic oscillations predict evoked-response latency delays and core language deficits in autism spectrum disorders. *Journal of Autism and Developmental Disorders*, *45*(2), 395–405. http://doi.org/10.1007/s10803-013-1904-x

Elisevich, K., Shukla, N., Moran, J. E., Smith, B., Schultz, L., Mason, K., … Bowyer, S. M. (2011). An assessment of MEG coherence imaging in the study of temporal lobe epilepsy. *Epilepsia*, *52*(6), 1110–9. http://doi.org/10.1111/j.1528-1167.2011.02990.x

Gaetz, W., Bloy, L., Wang, D. J., Port, R. G., Blaskey, L., Levy, S. E., & Roberts, T. P. L. (2013). GABA estimation in the brains of children on the autism spectrum: Measurement precision and regional cortical variation. *NeuroImage*, 1–9. http://doi.org/10.1016/j.neuroimage.2013.05.068

Gaetz, W., Edgar, J. C., Wang, D. J., & Roberts, T. P. L. (2011). Relating MEG measured motor cortical oscillations to resting γ-aminobutyric acid (GABA) concentration. *NeuroImage*, *55*(2), 616–21. http://doi.org/10.1016/j.neuroimage.2010.12.077

Gandal, M. J., Edgar, J. C., Ehrlichman, R. S., Mehta, M., Roberts, T. P. L., & Siegel, S. J.

(2010). Validating γ oscillations and delayed auditory responses as translational biomarkers of autism. *Biological Psychiatry*, *68*(12), 1100–6. http://doi.org/10.1016/j.biopsych.2010.09.031

Georgescu, A. L., Kuzmanovic, B., Schilbach, L., Tepest, R., Kulbida, R., Bente, G., & Vogeley, K. (2013). Neural correlates of "social gaze" processing in high-functioning autism under systematic variation of gaze duration. *NeuroImage: Clinical*, *3*, 340–351. http://doi.org/10.1016/j.nicl.2013.08.014

Geschwind, D. (2007). Autism: searching for coherence. *Biological Psychiatry*, *62*(9), 949–50. http://doi.org/10.1016/j.biopsych.2007.09.001

Ghanbari, Y., Bloy, L., Christopher Edgar, J., Blaskey, L., Verma, R., & Roberts, T. P. L. (2013). Joint Analysis of Band-Specific Functional Connectivity and Signal Complexity in Autism. *Journal of Autism and Developmental Disorders*. http://doi.org/10.1007/s10803-013-1915-7

Gusnard, D. A., Akbudak, E., Shulman, G. L., & Raichle, M. E. (2001). Medial prefrontal cortex and self-referential mental activity: Relation to a default mode of brain function. *Proceedings of the National Academy of Sciences of the United States of America*, *98*(7), 4259–4264.

Jensen, O., Kaiser, J., & Lachaux, J.-P. (2007). Human gamma-frequency oscillations associated with attention and memory. *Trends in Neurosciences*, *30*(7), 317–24. http://doi.org/10.1016/j.tins.2007.05.001

Just, M., Cherkassky, V., Keller, T., & Minshew, N. (2004). Cortical activation and synchronization during sentence comprehension in high-functioning autism: evidence of underconnectivity. *Brain*, *127*(8), 1811.

Kana, R. K., Libero, L. E., & Moore, M. S. (2011). Disrupted cortical connectivity theory as an explanatory model for autism spectrum disorders. *Physics of Life Reviews*, *8*(4), 410–437. http://doi.org/10.1016/j.plrev.2011.10.001

Kennedy, D., & Courchesne, E. (2008). Functional abnormalities of the default network during self- and other-reflection in autism. *Social Cognitive and Affective Neuroscience*, *3*(2), 177.

Khan, S., Gramfort, A., Shetty, N. R., Kitzbichler, M. G., Ganesan, S., Moran, J. M., … Kenet, T. (2013). Local and long-range functional connectivity is reduced in concert in autism spectrum disorders. *Proceedings of the National Academy of Sciences of the United States of America*, *110*(8), 3107–12. http://doi.org/10.1073/pnas.1214533110

Kitzbichler, M. G., Khan, S., Ganesan, S., Vangel, M. G., Herbert, M. R., H??m??l??inen, M. S., & Kenet, T. (2015). Altered development and multifaceted band-specific abnormalities of resting state networks in autism. *Biological Psychiatry*, *77*(9), 794–804. http://doi.org/10.1016/j.biopsych.2014.05.012

Kitzbichler, M. G., Khan, S., Ganesana, S., Vangel, M., Herbert, M., Hämäläinen, M., & Kenet, T. (2014). Altered Development and Multifaceted Band-Specific Abnormalities of Resting State Networks in Autism. *Biological Psychiatry*, 1–10. http://doi.org/10.1016/j.biopsych.2014.05.012

Lajiness-O'Neill, R., Richard, A. E., Moran, J. E., Olszewski, A., Pawluk, L., Jacobson, D., … Bowyer, S. M. (2014). Neural synchrony examined with magnetoencephalography (MEG) during eye gaze processing in autism spectrum disorders: preliminary findings. *Journal of Neurodevelopmental Disorders*, *6*(1), 15. http://doi.org/10.1186/1866-1955-6-15

Lord, C., Rutter, M., DiLavore, P. C., Risi, S., & Gotham, K. (2012). Autism Diagnostic Observation Schedule-2. Los Angeles, CA: Western Psychological Services.

Mars, R. B., Neubert, F., Maryann, P., Sallet, J., Toni, I., & Rushworth, M. F. S. (2012). On the relationship between the " default mode network " and the " social brain ," *6*(June), 1–9. http://doi.org/10.3389/fnhum.2012.00189

Maxwell, C. R., Villalobos, M. E., Schultz, R. T., Herpertz-Dahlmann, B., Konrad, K., & Kohls, G. (2013). Atypical Laterality of Resting Gamma Oscillations in Autism Spectrum Disorders. *Journal of Autism and Developmental Disorders*. http://doi.org/10.1007/s10803-013-1842-7

Minzenberg, M. J., Firl, A. J., Yoon, J. H., Gomes, G. C., Reinking, C., & Carter, C. S. (2010). Gamma oscillatory power is impaired during cognitive control independent of medication status in first-episode schizophrenia. *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology*, *35*(13), 2590–9. http://doi.org/10.1038/npp.2010.150

Moran, J. E., Bowyer, S. M., Mason, K. M., Tepley, N., Morrell, M., Greene, D., … Barkley, G. L. (2006). MEG Coherence Imaging Compared to Electrocortical Recordings from NeuroPace Implants to Determine the Location of Ictal Onset in Epilepsy Patients. *International Congress Series: New Frontiers in Biomagnetism*, 673–676.

Murias, M., Webb, S. J., Greenson, J., & Dawson, G. (2008). Resting state cortical connectivity reflected in EEG coherence in individuals with autism. *Biol Psychiatry*, *62*(3), 270–273.

Odriozola, P., Uddin, L., Lynch, C. J., Kochalka, J., Chen, T., & Menon, V. (2015). Insula response and connectivity during social and non-social attention in children with autism. *Social Cognitive and Affective Neuroscience*, *Advance Ac*.

Orekhova, E. V, Stroganova, T. A., Prokofyev, A. O., Nygren, G., Gillberg, C., & Elam, M. (2008). Sensory gating in young children with autism: relation to age, IQ, and EEG gamma

oscillations. *Neuroscience Letters*, *434*(2), 218–23. http://doi.org/10.1016/j.neulet.2008.01.066

Ozerdem, A., Güntekin, B., Tunca, Z., & Başar, E. (2008). Brain oscillatory responses in patients with bipolar disorder manic episode before and after valproate treatment. *Brain Research*, *1235*, 98–108. http://doi.org/10.1016/j.brainres.2008.06.101

Peiker, I., David, N., Schneider, X. T. R., Nolte, G., Scho, D., & Engel, X. A. K. (2015). Perceptual Integration Deficits in Autism Spectrum Disorders Are Associated with Reduced Interhemispheric Gamma-Band Coherence. *The Journal of Neuroscience*, *35*(50), 16352–16361. http://doi.org/10.1523/JNEUROSCI.1442-15.2015

Pelphrey, K. A., Morris, J. P., & McCarthy, G. (2004). Grasping the intentions of others: the perceived intentionality of an action influences activity in the superior temporal sulcus during social perception. *Journaol of Cognitive Neuroscience*, *16*(10), 1706–1716.

Perez Velazquez, J. L., Barcelo, F., Hung, Y., Leshchenko, Y., Nenadovic, V., Belkas, J., … Garcia Dominguez, L. (2009). Decreased brain coordinated activity in autism spectrum disorders during executive tasks: reduced long-range synchronization in the fronto-parietal networks. *International Journal of Psychophysiology : Official Journal of the International Organization of Psychophysiology*, *73*(3), 341–9. http://doi.org/10.1016/j.ijpsycho.2009.05.009

Perez Velázquez, J. L., & Galán, R. F. (2013). Information gain in the brain's resting state: A new perspective on autism. *Frontiers in Neuroinformatics*, *7*(December), 37. http://doi.org/10.3389/fninf.2013.00037

Petreska, B., Adriani, M., Blanke, O., & Billard, A. G. (2007). Apraxia: a review. *Progress in Brain Research*, *164*, 61–83. http://doi.org/10.1016/S0079-6123(07)64004-7

Pletzer, B., Kerschbaum, H., & Klimesch, W. (2010). When frequencies never synchronize: the golden mean and the resting EEG. *Brain Research*, *1335*, 91–102. http://doi.org/10.1016/j.brainres.2010.03.074

Port, R. G., Edgar, J. C., Ku, M., Bloy, L., Murray, R., Blaskey, L., … Roberts, T. P. L. (2016). Maturation of auditory neural processes in autism spectrum disorder — A longitudinal MEG study. *NeuroImage. Clinical*, *11*, 566–577. http://doi.org/10.1016/j.nicl.2016.03.021

Port, R. G., Gaetz, W., Bloy, L., Wang, D., Blaskey, L., Kuschner, E. S., … Roberts, T. P. L. (2017). Exploring the Relationship Between Cortical GABA Concentrations, Auditory Gamma-Band Responses and Development in ASD : Evidence for an Altered Maturational Trajectory in ASD. *Autism Research*, *10*, 593–607. http://doi.org/10.1002/aur.1686

Pugh, K. R., Mencl, W. E., Shaywitz, B. a, Shaywitz, S. E., Fulbright, R. K., Constable, R. T., … Gore, J. C. (2000). The angular gyrus in developmental dyslexia: task-specific differences in functional connectivity within posterior cortex. *Psychological Science*, *11*(1), 51–6. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11228843

Ray, A., & Bowyer, S. M. (2010). Clinical applications of magnetoencephalography in epilepsy. *Annals of Indian Academy of Neurology*, *13*(1), 14–22. http://doi.org/10.4103/0972-2327.61271

Raznahan, A., Pugliese, L., Barker, G., Daly, E., Powell, J., Bolton, P., & Murphy, D. G. M. (2009). Serotonin transporter genotype and neuroanatomy in autism spectrum disorders. *Psychiatric Genetics*, *19*(3), 147.

Redcay, E. (2008). The superior temporal sulcus performs a common function for social and speech perception: Implications for the emergence of autism. *Neuroscience and Biobehavioral Reviews*, *32*, 123–142.

Rippon, G., Brock, J., Brown, C., & Boucher, J. (2007a). Disordered connectivity in the autistic brain: challenges for the "new psychophysiology". *International Journal of Psychophysiology*, *63*(2), 164–72. http://doi.org/10.1016/j.ijpsycho.2006.03.012

Rippon, G., Brock, J., Brown, C., & Boucher, J. (2007b). Disordered connectivity in the autistic brain: challenges for the "new psychophysiology". *International Journal of Psychophysiology : Official Journal of the International Organization of Psychophysiology*, *63*(2), 164–72. http://doi.org/10.1016/j.ijpsycho.2006.03.012

Rojas, D. C., Maharajh, K., Teale, P., & Rogers, S. J. (2008). Reduced neural synchronization of gamma-band MEG oscillations in first-degree relatives of children with autism. *BMC Psychiatry*, *9*, 1–9. http://doi.org/10.1186/1471-244X-8-66

Rojas, D. C., Teale, P. D., Maharajh, K., Kronberg, E., Youngpeter, K., Wilson, L. B., … Hepburn, S. (2011). Transient and steady-state auditory gamma-band responses in first-degree relatives of people with autism spectrum disorder. *Molecular Autism*, *2*(1), 11. http://doi.org/10.1186/2040-2392-2-11

Rojas, D. C., & Wilson, L. B. (2014). Γ-Band Abnormalities As Markers of Autism Spectrum Disorders. *Biomarkers in Medicine*, *8*(3), 353–68. http://doi.org/10.2217/bmm.14.15

Ross, B., Jamali, S., Miyazaki, T., & Fujioka, T. (2012). Synchronization of beta and gamma oscillations in the somatosensory evoked neuromagnetic steady-state response. *Experimental Neurology*. http://doi.org/10.1016/j.expneurol.2012.08.019

Rubenstein, J. L. R., & Merzenich, M. M. (2003). Model of autism: increased ratio of excitation/inhibition in key neural systems. *Genes, Brain, and Behavior*, *2*(5), 255–267. http://doi.org/10.1046/j.1601-183X.2003.00037.x

Rutter, M., Bailey, A., & & Lord, C. (2008). Social Communication Questionnaire (SCQ).

Pearson, Inc.

Schumann, C. M., & Nordahl, C. W. (2011). Bridging the gap between MRI and postmortem research in autism. *Brain Research*, *1380*, 175–86. http://doi.org/10.1016/j.brainres.2010.09.061

Sedley, W., Teki, S., Kumar, S., Overath, T., Barnes, G. R., & Griffiths, T. D. (2012). Gamma band pitch responses in human auditory cortex measured with magnetoencephalography. *NeuroImage*, *59*(2), 1904–11. http://doi.org/10.1016/j.neuroimage.2011.08.098

Seeley, W. W., Menon, V., Schatzberg, A. F., Keller, J., Gary, H., Kenna, H., … Greicius, M. D. (2007). Dissociable Intrinsic Connectivity Networks for Salience Processing and Executive Control. *Journal of Neurosciences*, *27*(9), 2349–2356. http://doi.org/10.1523/JNEUROSCI.5587-06.2007.Dissociable

Seghier, M. L. (2013). The Angular Gyrus : Multiple Functions and Multiple Subdivisions. *The Neuroscientist*, *19*(1), 43–61. http://doi.org/10.1177/1073858412440596

Shattuck, D. W., Mirza, M., Adisetiyo, V., Hojatkashani, C., Salamon, G., Narr, K. L., … Toga, A. W. (2008). Construction of a 3D probabilistic atlas of human cortical structures. *NeuroImage*, *39*(3), 1064–80. http://doi.org/10.1016/j.neuroimage.2007.09.031

Srinivasan, R., Winter, W. R., Ding, J., & Nunez, P. L. (2008). EEG and MEG coherence: measures of functional connectivity at distinct spatial scales of neocortical dynamics. *J Neurosci Methods*, *166*(1), 41–52.

Stroganova, T. A., Orekhova, E. V, Prokofyev, A. O., Tsetlin, M. M., Gratchev, V. V, Morozov, A. a, & Obukhov, Y. V. (2011). High-frequency oscillatory response to illusory contour in typically developing boys and boys with autism spectrum disorders. *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior*, 1–17.

http://doi.org/10.1016/j.cortex.2011.02.016

Sun, L., Grützner, C., Bölte, S., Wibral, M., Tozman, T., Schlitt, S., … Uhlhaas, P. J. (2012). Impaired Gamma-Band Activity during Perceptual Organization in Adults with Autism Spectrum Disorders: Evidence for Dysfunctional Network Activity in Frontal-Posterior Cortices. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *32*(28), 9563–9573. http://doi.org/10.1523/JNEUROSCI.1073-12.2012

Takesaki, N., Kikuchi, M., Yoshimura, Y., Hiraishi, H., Hasegawa, C., Kaneda, R., … Minabe, Y. (2016). The Contribution of Increased Gamma Band Connectivity to Visual Non-Verbal Reasoning in Autistic Children : A MEG Study. *PLoS ONE*, 1–17. http://doi.org/10.1371/journal.pone.0163133

Talairach, P., & Tournoux, J. (1988). *A Stereotactic Coplanar Atlas of the Human Brain*. Stuttgart: Thieme.

Tsiaras, V., Simos, P. G., Rezaie, R., Sheth, B. R., Garyfallidis, E., Castillo, E. M., & Papanicolaou, A. C. (2011). Extracting biomarkers of autism from MEG resting-state functional connectivity networks. *Computers in Biology and Medicine*, *41*(12), 1166–77. http://doi.org/10.1016/j.compbiomed.2011.04.004

Uhlhaas, P. J., Pipa, G., Lima, B., Melloni, L., Neuenschwander, S., Nikolic, D., & Lin, S. (2009). Neural synchrony in cortical networks: history , concept and current status. *Neuroscience*, *3*(July), 1–19. http://doi.org/10.3389/neuro.07

Uhlhaas, P. J., & Singer, W. (2006). Neural synchrony in brain disorders: relevance for cognitive dysfunctions and pathophysiology. *Neuron*, *52*(1), 155–68. http://doi.org/10.1016/j.neuron.2006.09.020

Wass, S. (2011). Distortions and disconnections: disrupted brain connectivity in autism. *Brain*

and Cognition, *75*(1), 18–28. http://doi.org/10.1016/j.bandc.2010.10.005

Wechsler, D. (2011). Wechsler Abbreviated Scale of Intelligence-II. San Antonio, TX: Pearson, Inc.

Weng, S.-J., Wiggins, J. L., Peltier, S. J., Carrasco, M., Risi, S., Lord, C., & Monk, C. S. (2010). Alterations of resting state functional connectivity in the default network in adolescents with autism spectrum disorders. *International Meeting for Autism Research, May 2009, Chicago, IL, US; Data from This Study Were Presented at the Aforementioned Conference.*, *1313*, 202–214.

Wetzels, R., Matzke, D., Lee, M. D., Rouder, J. N., Iverson, G. J., & Wagenmakers, E. J. (2011). Statistical Evidence in Experimental Psychology: An Empirical Comparison Using 855 t Tests. *Perspectives on Psychological Science*, *6*(3), 291–298.

Wilson, T. W., Heinrichs-Graham, E., White, M. L., Knott, N. L., & Wetzel, M. W. (2013). Estimating the passage of minutes: deviant oscillatory frontal activity in medicated and unmedicated ADHD. *Neuropsychology*, *27*(6), 654–65. http://doi.org/10.1037/a0034032

Wilson, T. W., Rojas, D. C., Reite, M. L., Teale, P. D., & Rogers, S. J. (2007). Children and adolescents with autism exhibit reduced MEG steady-state gamma responses. *Biological Psychiatry*, *62*(3), 192–7. http://doi.org/10.1016/j.biopsych.2006.07.002

Woods, R. P., Grafton, S. T., Watson, J. D. G., Sicotte, N. L., & Mazziotta, J. C. (1998). Automated image registration: II. Intersubject validation of linear and nonlinear models. *Journal of Computer Assisted Tomography*, *22*(1), 153–165.

Ye, A. X., Leung, R. C., Schäfer, C. B., Taylor, M. J., & Doesburg, S. M. (2014). Atypical resting synchrony in autism spectrum disorder. *Human Brain Mapping*, *35*(12), 6049–66. http://doi.org/10.1002/hbm.22604

Zilbovicius, M., Meresse, I., Chabane, N., Brunelle, F., Samson, Y., & Boddaert, N. (2006). Autism, the superior temporal sulcus and social perception. *Trends in Neurosciences*, *29*(7), 359.

Table 1

	Autism Spectrum Disorder n = 12			Neurotypical n = 13				
	M	*SD*	*Range*	*M*	*SD*	*Range*	*U*	*p*
Age	9.17	1.03	8-11	9.31	1.25	8-12	80.50	.89
Gender males (χ^2)	11			12			.003	.95
WASI-2 FSIQ	101.60	13.93	76-127	112.08	9.05	95-126	95.00	.07
Vocabulary T-Score	47.5	15.03	25-75	56.46	8.93	37-68	94.00	.08
Matrix T-Score	53.00	7.56	38-66	52.00	11.12	26-65	71.00	.74
SCQ	18.08	8.12	11-30	1.69	2.02	0-7	1.00	< .001
ADOS-2 Total	15.71	4.99	7-21					
Social Affect	12.57	5.22	5-18					
RRB	3.00	2.65	1-8					

Note. WASI-2 FSIQ = Wechsler Abbreviated Scales of Intelligence-2 Full Scale Intelligence Quotient; Matrix = WASI-2 Matrix Reasoning; SCQ = Social Communication Questionnaire; ADOS-2 = Autism Diagnostic Observation Schedule, 2nd Edition; RRB = Restricted Repetitive Behaviors.

Table 2

Region-to-region connection	*U-statistic*	*Z-score*	*p-value*	*r (Effect Size)*
L. Angular to R. Middle Frontal	132	2.94	0.002	0.59
L. Angular to R. Inferior Frontal	127	2.77	0.005	0.55
L. Middle Temporal to R. Inferior Frontal	128	2.72	0.005	0.54
R. Angular to R. Middle Frontal	128	2.72	0.005	0.54
R. Inferior Frontal to R. Middle Temporal	128	2.72	0.005	0.54
R. Middle Frontal to R. Middle Temporal	128	2.72	0.005	0.54
L. Middle Temporal to R. Middle Frontal	127	2.67	0.007	0.53
L. Middle Temporal to R. Middle Temporal	127	2.67	0.007	0.53
R. Angular to R. Middle Temporal	127	2.67	0.007	0.53
R. Angular to R. Inferior Frontal	126	2.61	0.008	0.52
L. Angular to L. Cingulate	125	2.56	0.01	0.51
L. Angular to R. Cingulate	125	2.56	0.01	0.51
L. Middle Temporal to R. Angular	125	2.56	0.01	0.51
R. Angular to R. Superior Frontal	125	2.56	0.01	0.51
R. Angular to R. Superior Temporal	125	2.56	0.01	0.51
R. Middle Temporal to R. Superior Frontal	125	2.56	0.01	0.51
L. Angular to L. Superior Frontal	124	2.5	0.011	0.50
L. Cingulate to R. Middle Temporal	124	2.5	0.011	0.50
L. Middle Frontal to R. Angular	124	2.5	0.011	0.50
L. Superior Frontal to R. Middle Temporal	124	2.5	0.011	0.50
R. Cingulate to R. Middle Temporal	124	2.5	0.011	0.50
L. Angular to R. Middle Temporal	123	2.45	0.014	0.49
L. Middle Temporal to R. Superior Temporal	123	2.45	0.014	0.49
L. Superior Frontal to R. Angular	123	2.45	0.014	0.49
L. Supramarginal to R. Cingulate	123	2.45	0.014	0.49
L. Supramarginal to R. Inferior Frontal	123	2.45	0.014	0.49
R. Angular to R. Cingulate	123	2.45	0.014	0.49
L. Angular to R. Superior Temporal	122	2.39	0.016	0.48
L. Middle Frontal to R. Middle Temporal	122	2.39	0.016	0.48
L. Superior Temporal to R. Inferior Frontal	122	2.39	0.016	0.48
L. Superior Temporal to R Middle Temporal	122	2.39	0.016	0.48
R. Middle Temporal to R. Superior Temporal	122	2.39	0.016	0.48
L. Angular to R. Superior Frontal	121	2.34	0.019	0.47
L. Inferior Frontal to R. Angular	121	2.34	0.019	0.47
L. Middle Temporal to R Superior Frontal	121	2.34	0.019	0.47
L. Supramarginal to R. Middle Frontal	121	2.34	0.019	0.47
L. Angular to L. Middle Frontal	120	2.28	0.022	0.46
L. Angular to R. Angular	120	2.28	0.022	0.46
L. Angular to R. Precuneus	120	2.28	0.022	0.46
L. Insular to R. Angular	120	2.28	0.022	0.46

L. Superior Temporal to R Angular	120	2.28	0.022	0.46
L. Superior Temporal to R. Middle Frontal	120	2.28	0.022	0.46
L. Supramarginal to R. Middle Temporal	120	2.28	0.022	0.46
R. Inferior Frontal to R. Superior Temporal	120	2.28	0.022	0.46

Note. L. = Left, R. = Right.

Table 3.

Cortical Regions	Frequency in Region-to-Region Difference
Angular Gyrus	24
Middle Temporal Gyrus	19
Superior Temporal Gyrus	9
Middle Frontal Gyrus	9
Inferior Frontal Gyrus	8
Superior Frontal Gyrus	7
Cingulate Gyrus	6
Supramarginal Gyrus	4
Insular Cortex	1
Precuneus	1
Hippocampus	0

Table 4

	ASD Mean (SD) T-Score	NT Mean (SD) T-Score	*p*
SRS-2			
SRS-2 Total	72.50 (7.74)	41.38 (4.98)	< .001
Social Communication and Interaction Index	72.72 (6.83)	42.92 (3.45)	< .001
RRB Index	72.67 (7.17)	44.00 (3.24)	< .001
Social Awareness	67.00 (7.05)	44.46 (5.38)	< .001
Social Cognition	70.50 (8.31)	43.23 (3.40)	< .001
Social Communication	72.42 (9.01)	42.69 (2.87)	< .001
Social Motivation	66.17 (8.45)	45.46 (5.72)	< .001

Note. Mean T-Score = 50, SD = 10; RRB = Restricted and Repetitive Behaviors.

Figure Legends

Figure 1. Regional cortical differences in gamma (30-80 Hz) band activity during resting state in NT compared to ASD. y-axis reflects the number of statistically different region-to-region connections (of the 231) collapsed by lobar pairs (x-axis).

Figure 2. Axial brain slices revealing regions of the pathway with the most significant difference in gamma band coherence, right middle frontal to bilateral angular cortices, and power spectra in representative ASD and NT participants.

Figure 3. Significant Kendall Tau correlation coefficients between the Social Responsiveness Scale-2 Total, Social Communication and Interaction Subscale (for NT and ASD) and brain region pairs with statistically significant between group differences in gamma band coherence.

Table Legends

Table 1

Participant Characteristics

Table 2

Mann-Whitney U results and effect sizes for the significant region-to-region differences in gamma band coherence between ASD and NT children (NT > ASD).

Table 3

Frequency regions appeared in region-to-region connectivity differences between groups (NT > ASD) within the gamma frequency band for the 11 regions examined.

Table 4

Mann-Whitney *U* results of group differences between ASD and NT children on the Social Responsiveness Scale-2 (SRS-2).