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Aberrant Oscillatory Synchrony Is Biased Toward Specific Frequencies and Processing Domains in the Autistic Brain

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ABSTRACT

BACKGROUND: Prevailing theories suggest that autism spectrum disorder (ASD) results from impaired brain communication, causing aberrant synchrony among neuronal populations. However, it remains debated whether synchrony abnormalities are among local or long-range circuits, are circuit specific or are generalized, reflect hypersynchrony or reflect hyposynchrony, and are frequency band–specific or are distributed across the frequency spectrum.

METHODS: To help clarify these unresolved questions, we recorded spontaneous magnetoencephalography data and used a data-driven, whole-brain analysis of frequency-specific interregional synchrony in higher-functioning adolescents and adults, with 17 ASD and 18 control subjects matched on age, IQ, and sex, and equal for motion.

RESULTS: Individuals with ASD showed local hypersynchrony in the theta band (4–7 Hz) in the lateral occipitotemporal cortex. Long-range hyposynchrony was seen in the alpha band (10–13 Hz), which was most prominent in neural circuitry underpinning social processing. The magnitude of this alpha band hyposynchrony was correlated with social symptom severity.

CONCLUSIONS: These results suggest that although ASD is associated with both decreased long-range synchrony and increased posterior local synchrony, with each effect limited to a specific frequency band, impairments in social functioning may be most related to decreased alpha band synchronization between critical nodes of the social processing network.

Keywords: Alpha band oscillations, Autism, Functional connectivity, Intrinsic synchrony, Magnetoencephalography, Social processing network

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Autism spectrum disorder (ASD) is a neurodevelopmental disorder defined by impairments in social functioning and communication abilities and the presence of restricted, repetitive behaviors. Although converging neuroscientific evidence suggests that ASD is associated with aberrant functional connectivity, much debate remains regarding its spatial scale and whether it consists of hypoconnectivity, hyperconnectivity, or both (1–3), and whether long-range connectivity, local connectivity, or both are abnormal in ASD (1,2,4). Magnetoencephalography (MEG) is particularly well suited to examine these issues because it provides not only measures of local synchronous activity, but also the coupling of synchronous activity between distal regions.

Synchrony in different frequency ranges is thought to reflect distinct biophysical mechanisms and play different roles in cognition. Abnormalities in synchrony seen in psychiatric and neurological disorders have been linked to aberrant neurotransmitter levels and receptor dynamics in animal and computational models (5,6). Additionally, different frequency dynamics are thought to arise from different cortical layers, perhaps reflecting top-down versus bottom-up interactions (7,8), though the frequency specificity of these layers and projections can vary across brain regions (9). Moreover, spontaneous frequency dynamics are similar to stimulus-related oscillations, supporting the idea that these oscillatory measures reflect intrinsic biophysical properties of a circuit (10). Thus, assessing abnormalities in synchrony can inform models of the biophysical underpinnings of aberrant functional connectivity in ASD.

Investigations of interregional synchrony in ASD using MEG and electroencephalography (EEG) have reported heterogeneous findings of both increased and decreased synchrony in a variety of frequency bands (11). These studies showed a mix of hyper- and hyposynchrony, often in the same study, across almost all frequency bands, including delta (1–4 Hz) (12,13), theta (13–15), alpha (14,15), and gamma (30+ Hz) (15). Two recent MEG studies that used source localization to identify the circuits involved in aberrant synchrony in ASD again

showed a mix of hypo- and hypersynchrony across many frequency bands and widely distributed across the brain using measures of frequency-specific envelope correlation (16,17) and synchrony (16,17). Notably, these studies used relatively large regions of interest, making it difficult to draw conclusions regarding abnormalities in particular networks.

Previous studies regarding the spatial pattern of connectivity differences in ASD using functional magnetic resonance imaging (fMRI) can broadly be put into two groups. One set of studies suggests that there is a complex pattern of hypoconnectivity or hyperconnectivity broadly distributed across many brain networks (3,18). Another set of studies suggests that domain-specific circuits related to the cognitive deficits seen in ASD are particularly hypoconnected, for example, circuits of the social brain, a set of brain regions that are selectively involved in social processing (19–21).

We attempt to resolve the spatio-oscillatory ambiguity across studies by using data-driven methods to examine synchrony without predefining frequency bands or regions of interest. Specifically, we compared interregional phase locking (22) between each pair of more than 5000 cortical locations in the brain at each frequency from 1 to 50 Hz and spontaneous local synchrony (measured by assessing spectral power) at the same frequencies in high-functioning adolescents and young adults with ASD and age-, IQ-, and sex-matched typically developing (TD) individuals. This method uses empty room data to normalize phase locking and has been shown to address concerns of spurious interregional synchrony due to activity spread arising from the source localization algorithm by suppressing spatially proximate synchronization (22). Although this reduces sensitivity to synchrony between regions that are near one another (e.g., increases the local false negative rate), it preserves the sensitivity to long-distance synchrony and greatly reduces the long-range false positive rate.

METHODS AND MATERIALS

Subjects

A total of 19 individuals with ASD (age = 18.9 ± 3.7 years; IQ = 111.1 ± 14.6; all male) and 19 TD individuals (age = 19.8 ± 3.0 years; IQ = 113.4 ± 11.4; all male) participated in the experiment. Two ASD individuals and one TD individual were excluded due to excessive head motion (greater than 0.5 cm). See Table 1 for a description of the included participants. All subjects were naive to the goals of the study. The Institutional Review Board of the National Institutes of Health approved all procedures, and written informed consent was obtained for all subjects. See the Supplement for clinical and neuropsychological details.

Recording

Neuromagnetic responses were recorded at 600 Hz using a 275-channel whole-head MEG system in a shielded room (VSM MedTech, Ltd., Coquitlam, Canada). The magnetometer is equipped with 275 radial gradiometers (273 were functional) and synthetic third-order gradient noise cancellation was used. Head position coils were placed at the nasion and left and right preauricular points to coregister the anatomical MRI and the MEG sensors. Head position was determined at the beginning and end of each run to ensure that head movements did not exceed 0.5 cm for any included participant. The amount of head motion, based on the root mean squared of the maximal displacement of the three head position coils across the 5-minute MEG scan, was not significantly different between the ASD and TD groups (average ASD head motion = 0.31 ± 0.09 cm; average TD head motion = 0.33 ± 0.07 cm; $p > .25$). Eyeblinks and eye movements were recorded using a bipolar electrooculogram electrode placed above and next to each subject's left eye.

Table 1. Demographic Characteristics of Participants

	Autism Spectrum Disorder	Typically Developing
Age, Years	18.9 ± 3.7	19.8 ± 3.0
Full Scale IQ	111.1 ± 14.6	113.4 ± 11.4
ADI Social	19.9 ± 6.6	
ADI Communication	13.9 ± 5.8	
ADI Restricted/Repetitive Behaviors	5.2 ± 2.7	
ADOS Communication + Social Interaction	10.7 ± 4.6	
Social Responsiveness Scale Total Score	70.9 ± 11.7	

Values are mean ± SD.

ADI, Autism Diagnostic Interview; ADOS, Autism Diagnostic Observation Schedule.

MEG Analysis

Spontaneous Phase Locking. Spontaneous phase locking measures the variability over time of the phase difference between every pairwise cortical location (22). To calculate phase-locking values (PLVs), the MEG source data were filtered using a continuous Morlet wavelet transform at each frequency between 1 and 50 Hz described by the following equation:

$$G(t,f) = \frac{1}{\sqrt{2\pi f}} e^{\left(\frac{-t^2}{2\sigma^2}\right)} e^{i2\pi f t}$$

where σ is the SD of the Gaussian envelope of the wavelet in the time domain. To ensure stability of the wavelet transform here we set σ to be $\frac{7}{2\pi f}$. The phase was then extracted from the wavelet data.

The spontaneous PLV is then defined as

$$PLV_l = \frac{1}{N}\left|\sum_{n=1}^{N} e^{i(\theta_{seed}(n)-\theta_l(n))}\right|$$

where N is the number of time points in the sample and $\theta_1(n)$ and $\theta_2(n)$ are the phase of the wavelet convolved data dipole 1 and dipole 2, respectively. The PLV found in empty room noise was subtracted from spontaneous PLVs to reduce the effects of spatially proximal crosstalk, as described in Ghuman *et al.* (22). All PLV results reported are based off of these normalized values. Taken together, these analyses yielded a 50 (frequencies) × 5124 (number of cortical dipoles) × 5124 (number of cortical dipoles) matrix of pairwise phase-locking values between each cortical dipole relative to empty room for each participant.

Statistics. Nonparametric cluster-level statistics were used to compare groups and control for multiple comparisons (23). The overarching strategy used was to take the 50 × 5124 × 5124 matrix and collapse it across dimensions and then use what was found to inform analyses as the dimensions were expanded. First, the matrix was averaged across both spatial dimensions, yielding a 50-point frequency vector for each participant (Figure 1) through which differences in the frequency dimension were assessed. A *t* test between TD and ASD individuals was performed at each frequency. All the frequency points where *p* was less than .05 (not corrected for multiple comparisons, as this correction occurs at the cluster level, as described below) for TD versus ASD were determined and clustered on the basis of frequency adjacency. Cluster-level statistics were calculated by determining the sum of the *t* values within each cluster (cluster mass) and the maximum cluster mass across the data was determined. Permutations were then created after collecting the data across the 35 subjects in a single set. Eighteen participants were randomly placed into subset 1 and the remainder were placed into subset 2; a *t* test was performed between these random permutations and the maximum cluster mass was again determined as above. Ten thousand permutations were then performed to form the estimated null distribution of the PLV spectrum. The proportion of these permutations that had a smaller maximum cluster mass than the nonpermuted data was the *p* value calculated. Because of the global null hypothesis used for the cluster mass test, this method inherently controls for multiple comparisons (23). This yielded two clusters of significant differences, one in the theta band (4–7 Hz) and one in the alpha band (10–13 Hz).

See the Supplement for further statistical details for connectedness (Figures 2 and 3) and seed-based connectivity (Table 2 and Supplemental Figures S3–S8).

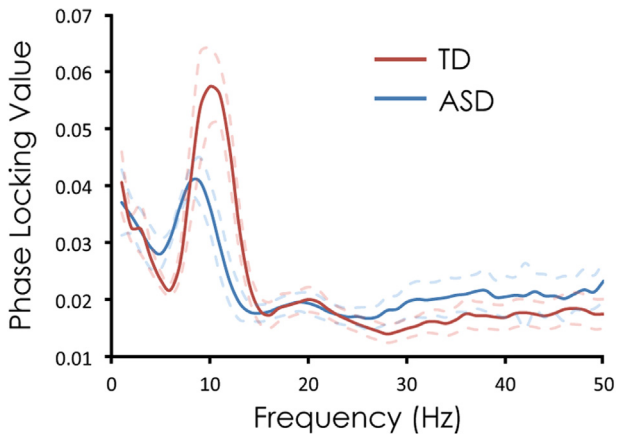

Figure 1. Spectral signature of global synchrony in autism spectrum disorder (ASD) and typically developing (TD) participants. Average phase locking between every pair of cortical points with respect to frequency (note empty-room phase locking is subtracted for each participant to reduce artifactual synchrony due to cross-talk between cortical locations). Significant theta band hypersynchrony (4–7 Hz) and alpha band hyposynchrony (10–13 Hz) is seen for individuals with ASD relative to TD individuals ($p < .05$; corrected for multiple frequency comparisons). Dashed lines indicate standard error bounds.

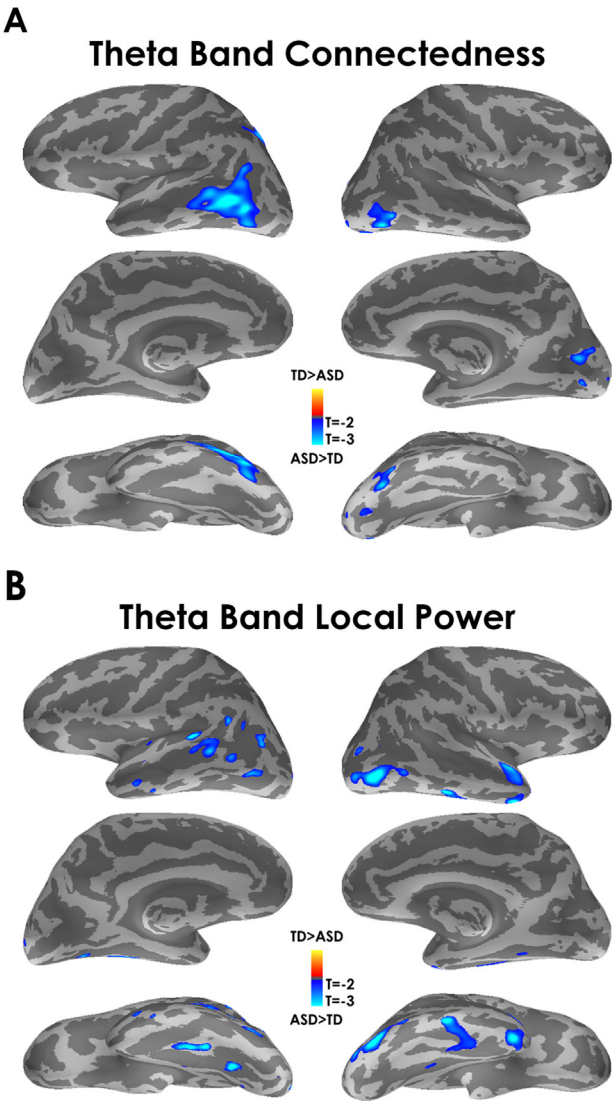

Figure 2. Map of theta band connectedness and local synchrony. **(A)** Map of theta band connectedness differences (*t* values) between autism spectrum disorder (ASD) and typically developing (TD) individuals. Connectedness at a cortical location is defined as the average phase locking between that location and every point on the cortex. All differences shown are significant ($p < .05$) after cluster correction for multiple spatial comparisons. **(B)** Map of theta band power differences (*t* values) between ASD and TD individuals. Theta band power (a measure of theta band local synchrony) is mapped onto each cortical location. Many similar regions that showed increased theta band connectedness in ASD also show increased theta band power. Indeed, when theta power is regressed out of theta band connectedness, i.e., the across-participant variability in panel **(B)** is regressed out of panel **(A)**, no significant clusters of theta band connectedness differences between ASD and TD individuals remain anywhere on the cortex (not shown).

RESULTS

Global Synchrony

We first assessed global differences in the interregional synchrony between the ASD and TD groups by averaging the PLVs between every pair of cortical dipoles in each subject at each frequency from 1 to 50 Hz (Figure 1). Greater theta band (4–7 Hz) synchrony

Table 2. Alpha Band Circuits That Show Hypoconnectivity in Autism Spectrum Disorder

Seed Region	Target Region of Significant PLV Difference	Peak Talairach Coordinate
RH pSTS	LH pSTS	–41 –57 16
	LH parietal	–54 –26 40
	LH insula	–33 –12 16
	LH extrastriate	–9 –73 28
RH Fusiform	LH fusiform	–41 –70 –11
	RH parietal	30 –44 32
	RH somatomotor	42 –23 54
RH Anterior Temporal	LH occipitotemporal	–37 –70 –11
	RH parietal	–29 –52 47
	RH medial occipital	23 –62 7
LH pSTS	RH STS	60 –38 14
	RH insula	42 –13 12
	RH fusiform	40 –31 –20
	RH orbitofrontal	19 34 –15
	LH dorsolateral prefrontal	–41 24 34
	LH ventrolateral prefrontal	–31 13 15
	LH fusiform	–41 –56 –14
	LH parietal	–48 –43 52
LH Fusiform	RH fusiform	48 –64 –20
	RH inferior temporal gyrus	59 –45 –2
	RH pSTS	47 –41 19
	RH parietal	57 –27 37
	RH insula	43 –9 7
	RH somatomotor	42 –10 51
LH mPFC	RH fusiform	34 –45 –12
	RH inferior temporal sulcus	60 –41 –16
	RH anterior STS	63 –14 –11
	RH frontoparietal operculum	60 –19 15

Seed regions are taken from the significant clusters in Figure 3. See also Supplemental Figures S3–S8.

LH, left hemisphere; mPFC, medial prefrontal cortex; PLV, phase-locking value; pSTS, posterior superior temporal sulcus; RH, right hemisphere; STS, superior temporal sulcus.

and reduced alpha band (10–13 Hz) synchrony were seen in the ASD group relative to the TD group ($p < .05$; cluster-level correction for multiple frequency comparisons).

No global difference was seen in local synchrony at any frequency corrected for multiple comparisons (Supplemental Figure S1).

Theta Band Synchrony

To determine the cortical underpinnings of increased theta band synchrony in the ASD group, we first averaged the theta band PLV between each cortical dipole and the rest of the brain in each subject, yielding a map of each dipole's average synchrony, or connectedness, to the rest of the cortex. We calculated *t* tests between the maps from the ASD and TD groups, producing a statistical comparison of the areas that contribute most strongly to the theta band hypersynchrony in ASD (Figure 2A). This analysis demonstrated that lateral occipitotemporal regions bilaterally showed significantly greater connectedness ($p < .05$, corrected for multiple comparisons) in the ASD group relative to the TD group.

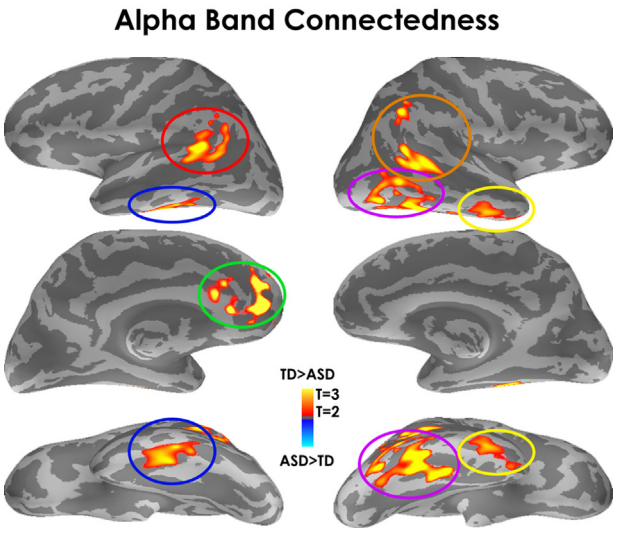

Figure 3. Map of alpha band connectedness. **(A)** Map of alpha band connectedness differences (*t* values) between autism spectrum disorder (ASD) and typically developing (TD) individuals. No significant clusters of local alpha band power were seen anywhere on the cortex when comparing between groups. All clusters of connectedness differences remain significant after regressing out local alpha band synchrony. Six clusters showed significant differences ($p < .05$) between ASD and TD individuals after cluster correction for multiple spatial comparisons. These clusters are bilateral posterior superior temporal sulcus (circled in red and orange), bilateral lateral fusiform gyrus/inferior temporal sulcus (purple and blue), right hemisphere anterior temporal cortex (yellow), and left hemisphere medial prefrontal cortex (green). Clustering was done using spectral clustering in Euclidean space (see Methods and Materials), which allows for nearby, noncontiguous patches to be part of the same clusters.

One question is whether theta band hypersynchrony is due to these regions' having locally increased theta band synchrony or is a result of increased interregional synchrony. To address this question we first calculated theta band power (an index of local synchrony) at each cortical dipole and calculated the between-group *t* test map for theta band power (Figure 2B). Increased theta band power results in an increase in the theta band signal-to-noise ratio, which can inflate synchrony values due to the complement of regression dilution (24). Most of the regions that displayed long-distance hypersynchrony also showed locally increased theta band power. To assess the contribution of this theta band power increase to the long-distance hypersynchrony, we calculated the map of each dipole's connectedness to the rest of the cortex after first regressing out the effect of theta band power from each dipole. After regressing out theta band power no areas of the cortex showed increased long-distance theta band synchrony in the ASD group relative to the TD group. This demonstrates that the greater theta band synchrony seen in ASD is due primarily to increased local theta band synchrony and not increased long-distance synchrony.

Alpha Band Synchrony

Figure 3 shows the *t* test between the ASD group and TD group connectedness maps in the alpha frequency band. This analysis yielded significant clusters ($p < .05$, cluster corrected for multiple comparisons) of hyposynchrony in the posterior

superior temporal sulcus (pSTS) bilaterally, lateral fusiform/inferior temporal sulcus bilaterally, and right hemisphere (RH) ventrolateral anterior temporal cortex. An additional significant cluster was seen in the left hemisphere (LH) medial prefrontal cortex, although this is with the caveat that this is a relatively deep structure and MEG has a relatively low signal-to-noise ratio for activity arising from it. Supplemental Figure S2 shows the *t* test for the full all-to-all connectivity matrix and a histogram of these *t* values. This full matrix shows that although there is structure to the alpha band hypoconnectivity in ASD preferring the clusters listed previously, there is also a degree of hypoconnectivity that extends beyond just these clusters. No regions of the cortex showed decreased local alpha band synchrony in the ASD group relative to the TD group and regressing out these local effects did not alter the significant clusters of long-distance hyposynchrony. This demonstrates that the decreased alpha band synchrony seen in ASD is primarily due to decreased long-distance synchrony. All of these significant clusters belong to regions involved in social processing.

We then used these clusters as seed regions of interest to create maps identifying the areas to which they were underconnected. These seeds show reduced connectivity with a number of other regions implicated in social processes, including other seed regions, as well as the insula, anterior temporal, and orbital frontal cortices. See Table 2 and Supplemental Figures S3–S8 for a list of all seed regions and peak coordinates for the resultant regions of hyposynchrony.

Correlations With Social Symptoms

We next asked whether the degree of connectedness of the areas that were hyposynchronous in ASD could predict the severity of these subjects' social impairments. We found that lower connectedness averaged across the six significant regions of hyposynchrony significantly correlated with greater social impairment as assessed by the Social Responsiveness Scale (total score) in the 17 participants with ASD (Figure 4; $r = -.48$, $p < .05$). The individual correlations for the six regions were the following: in the RH pSTS, $r = -.30$ ($p > .1$); in the RH fusiform, $r = -.53$ ($p < .05$); in the RH anterior temporal cortex, $r = -.3$ ($p > .1$); in the LH pSTS, $r = -.45$ ($p < .1$); in the LH fusiform, $r = -.33$ ($p > .1$); and in the LH medial prefrontal cortex, $r = -.39$ ($p > .1$). With 17 subjects, statistical power for these correlations is limited, though all had a medium effect size or greater (Cohen's criterion of $r > .3$) and one had a large effect size (RH fusiform; Cohen's criterion of $r > .5$). Also, although RH fusiform is the only one of these clusters that reached statistical significance at the p less than .05 level, all six are negative (e.g., greater hyposynchrony correlates with larger social impairment) and the probability of 6 areas all showing negative correlations by chance is low ($p < .05$). No positive correlations between symptom scales and alpha band synchrony were seen. Furthermore, the global hyposynchrony averaged across all pairs of cortical dipoles was not significantly correlated with the Social Responsiveness Scale ($r = .02$; $p > .1$).

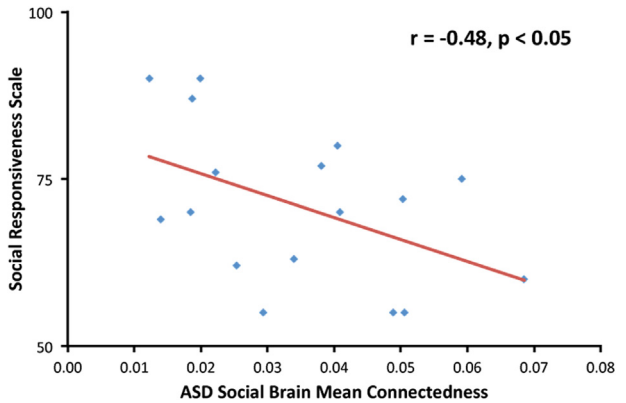

Figure 4. Correlation of alpha band connectedness with autism spectrum disorder (ASD) symptom severity. The mean alpha band connectedness across the six social brain regions that showed significant differences between ASD and typically developing individuals (see Figure 3) for each participant with an ASD is negatively correlated to the Social Responsiveness Scale total score.

DISCUSSION

Our results suggest a theta and alpha band–specific pattern of increased local synchrony and long-distance hyposynchrony, respectively, in ASD. In the theta frequency band, greater local synchrony was seen in ASD in occipital, temporal, and parietal regions. In the alpha frequency band, hyposynchrony was seen in a circuit that included many regions strongly associated with social processes (25,26). Furthermore, the degree of hyposynchrony in the social brain significantly predicted the severity of social impairments in ASD. These results are in contrast with previous electrophysiological studies of ASD that either did not localize differences between groups, or found abnormalities that were neither well defined in frequency nor preferentially localized to a network of brain regions that underlie social processing.

A number of recent studies have used a variety of imaging methods to determine what areas, connections, and networks are abnormal in individuals with ASD. The results of these studies can largely be divided into two groups. One group of studies has reported a relatively widespread pattern of local and long-distance neural abnormalities in ASD, with large-scale brain properties associated with autistic symptom severity. Notably, this group of studies includes the majority of previous spontaneous MEG and EEG experiments. Another group of studies, including a series of studies from our laboratory, has suggested that neural abnormalities are primarily found in circuits related to specific cognitive domains related to autistic symptoms. For example, frontostriatal abnormalities have been linked to repetitive behavior in ASD (27). Studies from our lab (with partially overlapping participants as in the present study) and others have repeatedly shown abnormalities in the social brain in ASD linked to aberrant social processing. Specifically, a similar set of regions as those that show alpha band hyposynchrony in the current study have previously been shown to be preferentially hypoconnected in spontaneous fMRI (2,19–21,28,29) and have reduced cortical thickness in ASD (30). In the current report, as well as in many of previous reports, the abnormalities in ASD extended beyond the network of regions commonly associated with social processes. However, the result that

this network has the greatest degree of dysfunction in ASD is notable because it suggests that a general pattern across measurement modalities, with areas of the social brain (including the medial prefrontal cortex, pSTS, fusiform gyrus, and anterior temporal cortex) showing greater dysfunction relative to other brain regions. Additionally, a similar set of regions as those that show local theta band hypersynchrony in the current study were previously shown to be locally hyperconnected using spontaneous fMRI (31) and have increased cortical gyrification in ASD (32).

The results of this MEG study are generally supportive of the local overconnectivity (as inferred from local synchrony) with long-distance underconnectivity hypothesis in ASD (1) with three additions. First, the areas that had higher local theta band synchrony and lower long-distance alpha band synchrony were distinct. The spatial correlation between the theta and alpha band connectedness maps was very close to zero ($R = .03$; $p > .1$). This suggests that these local and long-distance effects are a result of distinct mechanisms or mediating compensatory processes, as opposed to prior hypotheses suggesting that nonselective local hyperconnectivity causes long-distance hypoconnectivity (1,33,34) or ones linking local and long-distance hypoconnectivity (35). Second, the alpha band long-distance hyposynchrony was seen preferentially in regions involved in social processing. Although the regions that show the greatest alpha band hypoconnectivity in ASD are consistent with regions of the social brain, future studies should functionally localize social brain regions to find regions of interest for connectivity analyses to reduce potential concerns of reverse inference. Third, the putative overconnectivity and underconnectivity were seen in the theta and alpha bands, respectively. Notably, Murias *et al.* (14) reported a similar general pattern of increased local theta band synchrony with long-distance alpha band hyposynchrony using high-density EEG in adults with ASD, though without localizing the cortical regions associated with these effects. This frequency-specific pattern of over- and underconnectivity is in contrast with a number of recent spontaneous functional connectivity studies using MEG and EEG that report a heterogeneous and complicated set of results in ASD. The analysis methods and subject populations in the current study and the Murias *et al.* (14) study shared critical similarities, although the studies with contrasting results did not. Both the current study and Murias *et al.* (14) excluded spurious synchrony using methods that suppress short distance connections in both studies. In contrast, other recent studies used a variety of synchrony measures, primarily ones that remove zero phase lag interactions (and may alter the results in the frequency domain) to address the spurious synchrony concern. Though it is notable that in the Murias *et al.* (14) study, due to the way that currents spread in EEG, spurious synchrony could not be fully excluded, in the current study the same caveat does not apply due to the use of MEG. In addition, the average age of the participants in the present study was 19 years old and was 23 years old in the Murias *et al.* (14) study, whereas the majority of studies that do not show the same theta and alpha band patterns involved substantially younger participants.

Previous studies have shown that theta band synchrony is increased in individuals with attention-deficit/hyperactivity disorder (ADHD) (36) and epilepsy (17,37), two conditions that have substantial comorbidity with ASD. In ADHD there is an ongoing debate regarding whether increased local theta band synchrony is due to a developmental delay (38) or maturational deviation (39). Specifically, local theta band synchrony has been shown to decrease with age in typical development (38,40). Further studies will be required to determine whether theta band synchrony in adolescents and young adults with ASD in the current study and the Murias *et al.* (14) study results from a developmental delay, which would be expected to be resolved later in adulthood, or a maturational deviation, which would be expected to persist into later life. In addition, localization of the theta band abnormalities to the temporal lobe is potentially relevant considering this is the most common generator of epileptic activity, increased local theta band synchrony is common in epilepsy, increased theta band synchrony is localized to the seizure onset zone (37), widespread increased theta band synchrony precedes ictal events in epilepsy (17), and there is significant ASD–epilepsy comorbidity (41). One caveat of the local theta band hypersynchrony result is that we cannot exclude the possibility that the cortical theta band increase is due to pathological activity in subcortical regions to which MEG is not as sensitive, such as limbic structures that are sometimes thought to provide input that drives cortical theta band oscillations (42). Given that these limbic structures are the most common generators of seizure activity in epilepsy, this could still provide a link between ASD and epileptiform activity. Taken together, increased local theta band synchrony may be related to a putative excitatory-inhibitory imbalance that has been hypothesized in ASD, as well as ADHD and epilepsy (43–45).

One putative role for alpha band frequency synchrony is top-down control over the timing of cortical processes used to coordinate the activity of large-scale neural circuits (46). A reduction in this top-down control process is generally consistent with the view of ASD resulting from excitatory-inhibitory imbalance (47,48). Recent modeling and ex vivo studies suggest that glutamatergic mechanisms are a primary contributor to cortical and thalamocortical alpha band frequency activity (49–51). Furthermore, a number of recent studies have emphasized the role of glutamate-associated abnormalities in genetic, postmortem, plasma, and animal studies of ASD (52–57). Indeed, there are a number of clinical trials examining the potential of drugs targeting glutamatergic processes for both ASD and fragile X syndrome (58). Thus, the reduced alpha band synchrony seen in the spontaneous MEG results here may be related to the previously described glutamatergic dysfunction in ASD.

Less coordinated neural activity preferentially in regions associated with social processing might also help explain a number of phenomena that have been reported in ASD. Specifically, studies have shown that the width of the temporal window required to bind audiovisual for social stimuli (e.g., how tightly in time mouth movements and voice must be aligned), but not for nonsocial stimuli (e.g., visual flash-beep), is larger in ASD than in healthy control subjects (59). Furthermore, recent studies suggest that individuals with ASD show greater perceptual impairments for dynamic social stimuli (60), which rely on integration of information over time and extended coordination of neural activity, compared with static social stimuli. Finally, it has also been shown that

individuals with ASD have aberrant speech–gesture integration, particularly during face-to-face social interactions (61). The spontaneous alpha band hyposynchrony reported here suggests that there is an intrinsic reduction in the temporal coordination of neural activity in the social brain in ASD.

Our findings suggest that ASD is characterized by increased local theta band synchrony in temporal, occipital, and parietal regions concurrent with decreased long-distance alpha band synchrony that is most prominent in the neural circuitry that underlies social processing. This later finding is strengthened by the fact that the degree of alpha band hyposynchrony was significantly correlated with social symptom severity. These are the first electrophysiological results to show a spatio-oscillatory pattern in the phase locking between regions of abnormalities relatively restricted to specific frequencies and circuits in ASD and support the hypothesis that ASD involves hypoconnectivity of the social brain. The cortical maps of these theta and alpha frequency band results are similar to previous studies showing abnormalities in these regions using structural MRI and fMRI measures in ASD. Thus, the present MEG study supports previous structural and hemodynamic findings in ASD and extends them by demonstrating a correspondence with specific abnormalities in the cortical oscillatory dynamics. Future studies will be required to assess the relationship between structural and functional abnormalities at the individual level and generally how these disparate measures can be integrated to gain a richer picture of the pathophysiology of ASD.

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