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Altered development and multifaceted band-specific abnormalities of resting state networks in autism

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Abstract

Background—Extensive evidence indicates that cortical connectivity patterns are abnormal in autism spectrum disorders (ASD), showing both over- and under-connectivity. Since, however, studies to date focused on either spatial or spectral dimensions, but not both simultaneously, much remains unknown about the nature of these abnormalities. In particular, it remains unknown whether abnormal connectivity patterns in ASD are driven by specific frequency bands, by spatial network properties, or by some combination of these factors.

Methods—Magnetoencephalography (MEG) recordings (15 ASD, 15 controls) mapped back onto cortical space were used to study resting state networks in ASD with both spatial and spectral specificity. The data were quantified using graph theoretic metrics.

Results—The two major factors that drove the nature of connectivity abnormalities in ASD were the mediating frequency band and whether the network included frontal nodes. These factors determined whether clustering and integration were increased or decreased in cortical resting state networks in ASD. These measures also correlated with abnormalities in the developmental trajectory of resting state networks in ASD. Lastly, these measures correlated with ASD severity in some frequency bands and spatially specific sub-networks.

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Conclusions—Our findings suggest that network abnormalities in ASD are widespread, are more likely in subnetworks that include the frontal lobe, and can be opposite in nature depending on the frequency band. These findings thus elucidate seemingly contradictory prior findings of both over- and under- connectivity in ASD.

Keywords

development; autism; cortex; MEG activity; connectivity; resting state

Introduction

Multiple studies have documented abnormal functional connectivity in the brains of individuals diagnosed with autism spectrum disorders (ASD) (1–3). Many of these studies focused on functional connectivity in resting state networks (RSNs), which is particularly relevant for understanding autism because they are involved in self-reflection, social cognition [4, 5, 6], and theory of mind [7, 8], which are abnormal in ASD.

Most studies of RSNs functional connectivity in ASD find widespread functional under-connectivity [9, 10, 11], but some studies show a mixed picture, finding both under- and over-connectivity between different region pairs [12, 13]. Another study found no abnormalities at the whole-brain level, and predominantly reduced local connectivity in frontal and temporal regions [14].

The emergent picture of RSNs functional connectivity in ASD is thus not cohesive. It is further complicated by the fact that different studies used different age groups, as the developmental trajectory of these networks seems to be different in ASD individuals than in typical adolescents [15, 16]. Furthermore, motion artifacts can hinder accurate measurements of functional connectivity [14, 17], and the selected fMRI analysis method can also affect the results [18, 19]. Functional connectivity is mediated by various rhythms of cortical oscillations [20, 21, 22]. Building a neurophysiological model of ASD requires that we understand the specific functional abnormalities associated with different frequency bands, which cannot be accomplished with fMRI. However, to date, few studies have examined RSNs in ASD with high spectro-temporal resolution. One electroencephalography (EEG) based study found reduced functional connectivity in ASD during the resting state in the α band [23]. A series of studies of ASD using magnetoencephalography (MEG) found increased short-range and reduced long-range functional connectivity in the δ band [24], broadband abnormalities [25, 26, 27], decreased coherence in lower frequency bands [28], and abnormalities limited again just to the α band [26]. However, all of these studies lacked spatial specificity. Furthermore, none of the high spectro-temporal resolution studies looked at developmental trajectories of RSNs in ASD.

Since prior studies of RSNs in ASD focused on either the spatial domain (fMRI) or the spectral domain (EEG/MEG), the relationship between the two domains has also remained unknown. Such information is critical because brain networks are dynamic and complex in both space and time. As our recent studies of task-related functional connectivity have shown, studying brain networks simultaneously in space and time can greatly increase our understanding of the network abnormalities associated with ASD [29, 30].

Here, we further addressed these gaps by studying functional connectivity in RSNs in ASD with both spectro-temporal and spatial resolution, which was achieved using MEG with the signals mapped from the sensors onto cortical space. Specifically, we tested how functional connectivity in RSNs in ASD differs globally, locally, and across different frequency bands in the cortex. We also examined how these network properties changed with age and ASD severity.

To characterize the connectivity data within each frequency band, we used graph theory. Graph theory captures the essence of the multitude of interconnections between all areas on the cortex, which would otherwise be intractable. It reduces the dimensionality of the problem to a finite set of descriptive graph properties, and its mathematical underpinnings are well documented [31, 32]. The advantage of graph theory over analyses based on seeds or regions of interest is that it allows the study of multiple network properties simultaneously and on several spatial scales. Importantly, a previous task-based study has shown that global graph properties are qualitatively similar when calculated in either sensor or cortical space, demonstrating that the transformation from sensors to sources conserves the most fundamental properties of the network and is valid for this type of analysis [33].

In this study, our goal was to understand how network properties in ASD vary with spatial location and across different frequency bands. We hypothesized that resting state connectivity both between and within regions will be more impacted in frontal regions [12, 11]. We further hypothesized, based on current fMRI studies [15, 16], that while RSN connectivity in TD individuals evolves with age, such developmental changes will be attenuated in ASD individuals. Lastly, we hypothesized that ASD severity and network connectivity will be inversely correlated.

Materials and Methods

Participants, Experimental Paradigm, and Data Acquisition

The participants were 15 males aged 6–21 years and diagnosed with ASD and 15 matched TD males (Table S1 in Supplement 1). Participants with ASD had a prior clinical diagnosis of ASD and met a cutoff of > 15 on the Social Communication Questionnaire (SCQ), Lifetime Version, and ASD criteria on the ADOS. Individuals with autism-related medical conditions (e.g., fragile X syndrome, tuberous sclerosis) and other risk factors (e.g., premature birth) were excluded. All protocols were approved by the Massachusetts General Hospital Institutional Review Board, and informed consent was obtained from all participants.

MRI and MEG resting state data acquisition

T1-weighted, high-resolution, Magnetization-Prepared Rapid-Gradient Echo (MPRAGE) structural images were acquired on a 3.0T Siemens Trio whole-body MRI scanner (Siemens Medical Systems) using a 32-channel head coil. MEG data were acquired inside a magnetically shielded room (IMEDCO) using a whole-head Elekta Neuromag VectorView system composed of 306 sensors arranged in 102 triplets of two orthogonal planar

gradiometers and one magnetometer. The resting state paradigm consisted of a red fixation cross at the center of the screen, presented for 5 minutes continuously.

Data cleaning and motion correction

The data were spatially filtered using the signal space separation (SSS) method [34, 35] (Maxfilter software; Elekta Neuromag) to suppress noise generated by sources outside the brain. Head position was acquired at 200 ms time intervals using 4 HPI (head position indicator) coils, and the SSS procedure corrected for the participants' head motion. Artifacts from heartbeats and eye blinks were identified and removed using signal space projection (SSP; see SI and [36]).

Mapping MEG data to cortical space

For analysis in cortical space, the MEG data were mapped from the sensors onto a high-resolution cortical surface generated by FreeSurfer [37], using minimum-norm estimate [see section 3.1 in Supplement 1 and (38)]. For the analysis, the dipole timeseries were extracted for each vertex within a region.

Time series cleaning and analysis

The timeseries were band-pass filtered and downsampled for faster processing. The chosen frequency bands were δ (1–2 Hz), θ (3–7 Hz), α (8–12 Hz), β (13–30 Hz), and γ (30–70 Hz). For each individual frequency band the analytic signal $\hat{X}(t)$ was calculated. Signal spikes, dropouts, and epochs with excessive head movement were removed. The amount of data lost through cleaning was well below 10%, and did not differ between groups. We used orthogonal correlations [39] to compute the connectivity metric. This approach addresses the field spread issue [40] (but see also [41]). See section 4.2 in Supplement 1 for additional details.

Networks in anatomical space

Figure Figure 0 was generated by using a connectivity array of dimension $N \times N \times N_{time} \times N_{band}$ for each subject. For each band and each time point the corresponding $N \times N$ slice of this array represents a connectivity matrix. See section 4.3 in Supplement 1 for additional details.

Graph analysis of the full network

The graph analysis [42, 43] was based on the group networks in cortical (source) space (Figure 0). The graph density was kept constant at 10% by choosing a threshold such that the number of edges was 1/10 th of the possible number of edges (connections) between the N nodes defined by the Freesurfer template. The analysis was repeated for cost values of 5% and 20% [see (44) and section 5.4 in Supplement 1].

The graph theoretic metrics we used are defined in detail in section 5.2 in Supplement 1.

Graph analysis of sub-networks

We subdivided the network by anatomical regions: frontal (F), parietal (P), temporal (T), occipital (O), cingulate (C), and insula (I) (Table S2 in Supplement 1). A subset of the graph metrics described above were then applied to the individual sub-networks that can be formed from all possible pairs of anatomical regions, such as F:F, F:P, P:O, etc. Note that the results are independent of the ordering of the pairs.

Statistical analysis and correlations with age and ADOS

We used nested bootstrapping with 256 bootstrap realizations to assess statistical significance in Figures 2–5. The p-values were calculated using these bootstrap results, and further corrected for multiple comparisons across independent measurements. For Figures 1,2,4, which consist of group comparisons (Figures 1,2) or within group calculations (Figure 4), the p-values were multiplied by 5, to account for 5 independent measurements across different frequency bands. For Figure 3, the p-values were multiplied by 10, to further account for the independent measurements for the two group. The results were then further validated by repeating the analysis of Figure 1 on surrogate data, where subjects were given arbitrary group assignments. As expected, no group difference was observed (SI Figure S4).

For the within-group analysis of age and ADOS dependence on network connectivity, our metric of choice was weighted graph density ρ_w (also called weighted cost and sometimes interchangeably used with the phrase *connectivity strength*; see [45]), since it is the most general, robust, and direct connectivity measure which retains the maximum amount of information (after thresholding), providing increased sensitivity to our within-group analysis. However, it should be noted that ρ_w is a pure *connectivity* measure and thus less sensitive to graph *topology*.

For each of the 256 bootstrap realizations per group, we calculated the average ρ_w and age, and subsequently visualized the value pairs as a two-dimensional histogram. We fitted a linear-regression of $\log(\rho_w)$ versus age and calculated the ratio R of explained variance. The procedure was identical for the analysis of dependence on ADOS autism severity scores (see also section 5.5 in Supplement 1).

Results

Resting state connectivity matrix

We first examined connectivity within each of the five frequency bands, for each group, using the data as measured at the MEG sensors (sensor space).

Group differences were band specific and particularly clear in the higher frequency bands (Figure 0A). In γ , connectivity was stronger in the ASD group, whereas in β the TD group showed stronger connectivity overall, particularly in the frontal, temporal, and medial (cingulate) regions. The α band showed strong intra-posterior connectivity in both groups, but significantly more in the ASD group. In particular, the ASD group showed many more connections from the occipital areas to the parietal, temporal, and frontal regions.

We then mapped the data from the sensors onto the cortex, and repeated the same analysis in cortical space (Figure 0B). The network patterns were overall consistent but clearer in the source space analysis than in the sensor space analysis, thus further validating this already well-validated approach of mapping MEG data onto cortical space [46, 47, 48, 49, 50, 38, 33].

To quantify the group differences observed in Figure 0B, we focused on graph theoretic metrics, outlined and explained in Table 1. Several group differences emerged, indicating multiple abnormalities in the ASD group.

The mean shortest path length was significantly reduced in the ASD group in the γ band only (Figure 1A). The global efficiency measure showed more efficient network in the γ and α bands, and a less efficient network in the β band in the ASD group (Figure 1B). For clustering, significant group differences emerged only in the γ band, where the ASD group showed increased clustering (Figure 1C). Local efficiency was significantly higher in the ASD group in the α band, and significantly lower in the β band (Figure 1D).

For our anatomical measures, the mean anatomical distance between nodes was increased in ASD in the α and γ bands, and reduced in the β band (Figure 1E). Modularity (the percentage of within module edges) in the α band was significantly reduced in the ASD group (Figure 1F).

In summary, we found the strongest differences in network properties in the high frequency bands. In α and γ band the networks were more efficient, more integrated, and more distributed in the ASD group, while in the β band the network was less efficient, less clustered, less integrated, and less pervasive in ASD subjects.

Sub-network differences between groups

It is clear from Figure 0 that resting-state networks in different cortical regions are impacted differently in ASD. To take full advantage of the spatial resolution afforded us by mapping the MEG signal onto cortical space, we subdivided the network by anatomical regions: frontal, parietal, temporal, occipital, cingulate, and insula.

Our analysis of sub-network differences focused on two of our graph-theoretic measures: global efficiency and local efficiency. We chose these two measures for three reasons. First, these measures are more robust and stable with respect to the addition or removal of individual edges than shortest path length and clustering. Second, they are meaningful when referring to a smaller anatomical region where anatomical measures such as mean distance are artificially restricted. Lastly, these two measures showed the greatest group differences in the full network analysis, probably due to their relative robustness. Roughly speaking, for the smaller sub-networks too, global efficiency measures the degree to which these anatomically confined short- and medium-range networks are integrated, while local efficiency measures the extent to which they are segregated.

We computed global and local efficiency within each of our anatomically defined regions and pairwise between all region pairs (Figure 2). The majority of group differences for both

metrics were in the γ band, followed by the β and α bands. Fewest differences were observed in the δ band, and none at all in the θ band. In the δ band, the differences were anatomically confined to the occipital region (within occipital, and between occipital and other regions), with reduced efficiency (both local and global) in the ASD group. In the α band, both local and global efficiencies were increased in the ASD group, within and across several different anatomical regions. In the γ band, as in the α band, multiple within and across regions networks again showed increased efficiency, both local and global, in the ASD group, with the exception of local efficiency in networks involving the frontal regions, where no group differences were found. Lastly, while there were fewer group differences in the beta band, when such differences did emerge the results were complimentary to those of the alpha and gamma bands, showing reduced global and local efficiency in the ASD group. The only network in which no group differences were observed for either metric, in any frequency band, was confined to the parietal region.

Sub-network topology changes with age

The age range of the participants was from 6 to 21 years, which allowed us to study the impact of age on RSNs. We used weighted graph density (ρ_w ; [see also (45) and Equation S2 in Supplement 1] as our metric, since it reflects the connectivity of the network most generally and directly. We found a very consistent trend in the data. All networks that involved the frontal region, *i.e.* the within frontal networks as well networks from frontal to other regions, showed a clear trend of decreasing ρ_w with age in the β , θ and δ bands in the TD group. No such trend was observed in the ASD group, where ρ_w remained consistently lower and constant with age (Figure 3).

Sub-network topology correlates with ADOS score

Finally, we investigated whether ρ_w also correlated with the severity of ASD symptoms as measured behaviorally using the ADOS. We found such correlations in several of the subnetworks (Figure 4), all in the γ and β bands, where the greatest differences in ρ_w were observed. Consistent with the data shown in Figure 2, ρ_w in the γ band was positively correlated with ADOS scores, while ρ_w in the β band was negatively correlated with ADOS scores.

Discussion

Our findings suggest a highly complex picture of functional connectivity abnormalities in ASD. In the α and γ band the networks were more integrated, more efficient, and more distributed in the ASD group, while in the β band the networks were more globally integrated, more locally efficient, and more clustered in the TD group (see Table 2).

The overall increase of connectivity in α band seen in our study aligns well with the increase of α power during resting state in ASD previously reported by [51]. Also consistent, task-based studies of γ band abnormalities in ASD [52, 53] show a diverse picture of both increased [54] and decreased [55] γ power. At least one task based study [56] and one resting-state study [57] also found an increase of functional connectivity in the ASD group in some areas.

Recently, [27] analyzed band specific connectivity differences between TD and ASD in sensor space, using synchronization likelihood (SL) as a metric of functional connectivity. The focus of their study was on measures of complexity and the only graph metric they calculated was cumulative nodal strength. Despite these methodological differences, their finding of increased connectivity in the ASD group in δ and α bands is in striking agreement with our results.

The patterns we observed in the β band abnormalities were consistently in the opposite direction to those observed in other frequency bands. One possible interpretation of this finding is an imbalance in ASD between bottom-up and top-down processing. Studies of attention have shown that the β band is of particular importance for *top-down* feedback processing [58,59], while *bottom-up* feedforward processing is thought to be mainly mediated in γ band [60, 61], and subject to selective suppression controlled by α band oscillations [62]. This interplay between feedforward processing in γ band and feedback processing in β band dynamically controls the focus of attention [58].

In the *workspace model* [63], modular *feedforward* processors working in parallel independent networks are dynamically bound into one serial central network through higher level *feedback* processes. In this context, our results are consistent with ASD being associated with increased activity in modular feedforward processors, mediated via the γ band, concomitant with reduced binding of these modules into a central network [64, 65, 66], which is mediated by feedback processes in the β band [67, 68].

Results in the anatomically defined sub-networks were similar to those in the whole cortex with respect to frequency band analyses, but the increased spatial specificity allowed us to identify the regions and region pairs that made the greatest contributions to the differences in graph topology. In the γ band, we found increased global network efficiency in the ASD group across almost all regions and region pairs. We also found increased local efficiency (and thus clustering) in all sub-networks, except those networks that involve the frontal regions. Again, the picture was almost exactly reversed in the β band, where connectivity within and with frontal regions was associated with reduced global efficiency and reduced local efficiency in the ASD group. Unlike in the full network analysis, we found reduced global efficiency in the δ band in most subnetworks that included the occipital region, with reduced local efficiency in two of those local networks.

These findings are consistent with the interpretation proposed at the whole network level. Namely, we saw enhanced modular and feedforward processing mediated by the γ band in ASD, and reduced cognitive binding and feedback processing mediated by the β band. Furthermore, we saw far greater reliance on frontal processes in the TD group than the ASD group, again supporting the hypothesis that feedback processes are reduced in ASD while feedforward processes are enhanced in ASD.

In agreement with two recent fMRI studies [16, 15], we found reduced maturation of RSNs in ASD. Specifically, in the TD group we found decreasing connectivity strength with age in the β , θ , and δ bands in networks that involved the frontal region, i.e. both the within-frontal

network and networks between the frontal and other regions. No such trend was observed in the ASD group, where connectivity remained consistently lower and constant with age.

These findings might be interpreted as a “fine tuning” of the cognitive networks in healthy controls, such that with age smaller populations of neurons need to be recruited for long-range information integration [69]. Whereas in typical subjects the networks involving frontal regions start out strongly connected but evolve towards a less, and presumably more specifically, connected configuration, in the ASD group these same networks are only weakly connected to begin with and do not show any further development. This interpretation is consistent with the maturation track of the frontal lobe [70, 71], and associated abnormalities in ASD [72, 73, 74, 75].

The spectral components of our findings were perhaps less predictable. Group differences in developmental trajectory were observed only in the β , θ , and δ bands, and no age-related differences in the γ band. One possible interpretation may be that the γ -mediated feedforward processes are less adversely affected in ASD, while the β -mediated feedback processes are more adversely affected in ASD. We also documented age-related group differences in the δ and θ bands in sub-networks that included the frontal lobe. This was surprising because these same sub-networks showed no global group differences in either the θ or δ bands. This finding suggests that group differences in these bands and cortical regions are likely more subtle and likely become more pronounced with age. When a large age range is averaged, therefore, the signal is not strong enough to pick up on these group differences.

More generally, frequency band based developmental analysis is further complicated by developmental trajectories of the different frequency bands, that themselves mature with unique trajectories across bands and across different individuals. This issue becomes more prominent over wider age ranges, and of course with smaller group sizes. Thus, while the effects we observed as significant were robust, it is highly likely that we missed other, more subtle effects, that would require a more refined age based analysis, and much larger group sizes to detect. Another limitation of this work is that the group sizes are relatively small. However, in particular with respect to the developmental results, we believe that the fact that our results are in agreement with prior findings from fMRI studies [16, 15], both of which used similar age groups (6–17 and 10–18 respectively), and had larger group sizes, strongly support our conclusions.

Lastly, we found that local network properties correlated with ASD severity, following the same trends as seen between TD and ASD subjects. In the γ band, the highest connectivity within the ASD group was found in those individuals with the highest severity as measured by the ADOS score. Conversely, in the β band the most strongly connected networks were found in individuals on the least severe end of the spectrum. These results provide additional evidence that the network differences we documented are indeed specific to ASD. The implication for cognitive processing is that ASD individuals who are more affected by the condition behaviorally have a greater increase of feedforward processing and decrease of feedback processing, which is consistent with the notion that reduced cognitive binding is a correlate of ASD severity.

Conclusions

In summary, we found that abnormalities associated with RSNs in ASD varied with cortical location, and that the nature of the abnormality (e.g., increased or decreased efficiency), if one existed, was consistent within each frequency band. Furthermore, sub-networks that included the frontal cortex were more likely to be abnormal and to develop abnormally in ASD.

Taken in combination, our findings suggest that network abnormalities in ASD are widespread, are more likely in sub-networks that include the frontal lobe, and can be opposite in nature depending on the frequency band. We found increased efficiency when we considered connectivity in the γ band, which likely mediates bottom-up processes and modular processing, and decreased efficiency in the β band, which likely mediates top-down processes and binding. These findings thus elucidate seemingly contradictory prior findings of both over- and under- connectivity in ASD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Sensor (top) and cortical space (bottom) networks in each of the five frequency bands.

Average networks for the TD group (TD). Average network for the ASD group (ASD).

Networks stronger in the TD group than the ASD group (TD > ASD). Networks stronger in the ASD group than in the TD group (ASD > TD). Only edges which were significant at an FDR corrected p-value of 0.1 are plotted.

Figure 2.

Network properties in the five frequency bands. The cost was fixed at 10% across groups.

Error bars denote standard error. Corrected p-values are denoted by symbols * $p < .05$, ** $p < .01$, *** $p < .001$

Figure 3.

Sub-network global and local efficiencies in each of the five different frequency bands.

Pairwise sub-networks are defined by the nodes in either of the paired regions and all of the edges between them. The regions are **F**rontal, **P**arietal, **T**emporal, **O**ccipital, and **C**ingulate.

Corrected p-values are denoted by symbols * $p < .05$, ** $p < .01$, *** $p < .001$

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Figure 4. Sub-network costs, measured in terms of weighted graph density, as function of mean age. Only frequency bands that showed significant group differences were plotted. X-axis denotes the mean age. Y-axis denotes weighted graph density. The data points are shown as a 2D histogram, where each point corresponds to one realization of the bootstrap procedure (256 realization total). The solid lines are linear-regression results of weighted graph density vs age; dotted lines show the 99% percentile. Star symbols denote corrected p-values (** $p < 0.01$) and R is the explained variance (only shown for $R > 0.35$).

Figure 5.

Sub-network costs, measured in terms of weighted graph density, as function of mean ADOS scores. Only frequency bands that showed significant group differences are plotted. X-axis denotes the mean total ADOS score. Y-axis denotes weighted graph density. The data points are shown as a 2D histogram, where each point corresponds to one realization of the bootstrap procedure (256 realization total). The solid lines are linear-regression results of weighted graph density vs age. Dotted lines show the 99% percentile. Star symbols denote corrected p-values (** $p < 0.01$) and R is the explained variance (only shown for $R > 0.35$).

Table 1

Summary of graph metrics

Measure	Definition	Informs about
Shortest path length	ℓ Equation S3	mean topological path length between all network nodes
Global efficiency	E_{glob} ; Equation S6	global integration across network
Clustering	C ; Equation S5	local clustering around nodes across network
Local efficiency	E_{loc} ; Equation S7	local segregation across network
Mean anatomical distance	SI 5.3	mean cartesian distance of all edges in anatomical space
% within- module edges	SI 5.3	modularity, fraction of “within module” versus “between module” edges

Table 2

Summary of changes in ASD group relative to TD group in all bands.

	Properties		Location	Age	ADOS
δ	integration	↓	occipital	✓(-)	X
	segregation	↑		frontal	
θ	X		X	✓(-)	X
				frontal	
α	integration	↑	widespread	X	X
	segregation	↑			
β	integration	↓	frontal & occipital	✓(-)	✓(↓)
	segregation	↑		frontal	
γ	integration	↑	widespread	X	✓(↑)
	segregation	↑	temporal & parietal		