Functional Connectivity based Machine Learning Approach for Autism Detection in Young Children using MEG Signals

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Abstract

Objective: Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder, and identifying early autism biomarkers plays a vital role in improving detection and subsequent life outcomes. This study aims to reveal hidden biomarkers in the patterns of functional brain connectivity as recorded by the neuro-magnetic brain responses in children with ASD.

Approach: We recorded resting-state MEG signals from thirty children with ASD (4-7 years) and thirty age, gender-matched typically developing (TD) children. We used a complex coherency-based functional connectivity analysis to understand the interactions between different brain regions of the neural system. The work characterizes the large-scale neural activity at different brain oscillations using functional connectivity analysis and assesses the classification performance of coherence-based (COH) measures for autism detection in young children. A comparative study has also been carried out on COH-based connectivity networks both region-wise and sensor-wise to understand frequency-band-specific connectivity patterns and their connections with autism symptomatology. We used Artificial Neural Network (ANN) and Support Vector Machine (SVM) classifiers in the machine learning framework with a 5-fold cross-validation technique.

Main results: To classify ASD from TD children, the COH connectivity feature yields the highest classification accuracy of 91.66% in the high gamma (50-100 Hz) frequency band. In region-wise connectivity analysis, the second highest performance is in the delta band (1-4 Hz) after the gamma band. Combining the delta and gamma band features, we achieved a classification accuracy of 95.03% and 93.33% in the ANN and SVM classifiers, respectively. Using classification performance metrics and further statistical analysis, we show that ASD children demonstrate significant hyperconnectivity.

Significance: Our findings support the weak central coherency theory in autism detections. Further, despite its lower complexity, we show that region-wise coherence analysis outperforms the sensor-wise connectivity analysis. Altogether, these results demonstrate the functional brain connectivity patterns as an appropriate biomarker of autism in young children.

Keywords: Autism Spectrum Disorder; Children; Brain Oscillations; Coherence; MEG; Classification

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1. Background

Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder that disrupts the brain's ability to manage information. ASD is defined by social communication and interaction difficulties, attention deficits, and limited interests. Another core symptomatology of ASD is delayed and disordered language development. ASD influences individuals in numerous ways, varying from mild to severe symptoms [1], and causes significant debilitating effects on the quality of life, with a high cost to the overall economy [2]. Its' prevalence rate in children is reported to vary from 0.23% in India [3], 1.7% in the UK [4], to 2.5% in the USA [5]. There is no cure for autism, but early identification followed by suitable intervention can reduce symptom severity, supporting the development and subsequent learning of an autistic child [6–12]. Notably, dominant behavioral symptoms of ASD emerge later in the developmental phase, so there is a critical need to identify early signs of ASD [13].

Autism exhibits an extensive variability of developmental disabilities, which is assumed to be related to aberrant anatomical and functional neural connectivity [14]. Here, the authors want to identify early neural markers of ASD in young children. Recent electrophysiological studies pinpoint unusual functional brain circuitry as a basic feature of this disorder [15]. The temporal dependency of neurological activation patterns of physically isolated brain areas is characterized as Functional Connectivity (FC) [15–18]. Coherence, which determines the consistency of relative amplitude and phase between any pair of signals in each frequency band, is one of the most promising FC metrics of the frequency domain. The present study hypothesizes that ASD may be reliably differentiated from normal brain function in young children by analyzing their neural connectivity between regions during ongoing brain oscillations. The authors, in particular, employ coherence (COH), the magnitude component of complex coherency measures, to distinguish ASD from typically developing (TD) children using magnetoencephalogram (MEG) signals. Coherence quantifies the similarity measure of neural oscillatory activity between two brain regions [19]. COH is significant as coupling between a pair of sensors cannot be completely understood without the information on its frequency structure over a relatively long period [20]. This study aims to analyze how the underlying neurophysiological connectivity patterns of autistic children differ from TD children using resting-state neuroimaging signals based on a machine learning classification framework. The electroencephalogram (EEG) and MEG are two non-invasive neuroimaging techniques for measuring brain activity. Here, the MEG signal is preferred as it is reference-free and offers practical advantages (i.e. quicker preparation time) over EEG. In this experiment, brain responses were recorded from children between 4-7 years of age using a MEG device specially customized for children while watching cartoons of their choice. There were sixty children – thirty were diagnosed with ASD, and the other thirty were age and gender-matched TD children. This study performs artificial neural network (ANN) and support vector machine (SVM) based modelling for distinguishing ASD children from TD children by analyzing their ongoing large-scale brain responses using coherence connectivity measures. We compared these features through region-wise and whole-brain sensor-wise connectivity analyses.

1.1. Related Work

Autistic children's distinctive behaviors imply that their brains process the information differently than their TD peers of the same age. To clarify these disparities, a few hypothetical models have been presented. For example, according to the weak central coherence theory [21], autistic people tend to over-focus on fine points of interest and have trouble integrating relevant descriptions. This issue was later hypothesized to be caused by a loss in brain network integration [17, 22], which was later translated into decreased global and increased local synchronization [23]. In addition, the oscillatory changes in ASD are consistent with a disturbance in the balance of excitation and inhibition [24–26], as well as disruption in functional connectivity and altered thalamic function in multiple frequency bands of the neuronal oscillations [27].

Several neuroimaging studies have examined the association between the properties of neuronal oscillations and cognitive ability in ASD children. To understand atypical brain lateralization and neuronal circuitry of the autistic brain, a study [28] demonstrated altered brain connectivity in 3- to 7-year-old autistic children using a custom child-sized MEG system. This study found the rightward connectivity between the parietal and temporal regions in autistic children in gamma band oscillations [28, 29]. The study [28] suggests that rightward connectivity between the parietal and temporal regions was found in children with ASD in the gamma band, whereas no such rightward lateralization was found in the normal pattern of TD children of age 3-7 years. However, even in that study [28], the unpaired t-test demonstrated no significant correlation with the laterality index via gamma band in the TD children group. Hence, in brain connectivity, no such laterality bias had been found in normal children. According to the study [29], autistic children had significantly less leftward lateralization than TD children in terms of P50m intensity. Multiple regression analysis also revealed that a shorter P50m latency in both hemispheres was significantly connected with higher language-related performance in TD children, although this latency was not correlated with nonverbal cognitive ability or chronological age. The ASD children did not show any significant correlation between P50m latency and language-related ability; instead, increasing chronological age significantly predicted less P50m latency in the right hemisphere. This literature [29] also implies that auditory-related brain structure in ASD is shaped in a language-ability-independent manner while being impacted by chronological age in the right hemisphere. In the auditory association area, children with ASD show rightward asymmetry in brain volume (i.e., posterior superior temporal gyrus and planum temporale).

Another study [30] demonstrated the ability in the visual reasoning task and found that the higher reading/decoding ability was associated with rightward lateralization of the brain connectivity between the parietal and temporal regions in ASD children. This study [30] has examined the association between the properties of neuronal oscillations and cognitive ability in ASD children using MEG signals. Moreover, it focuses on FC and how FC relates to cognitive abilities in young children with ASD. Particularly, to assess “visual reasoning” cognitive ability, the study used the modified scores from the Kaufman Assessment Battery for Children (K-ABC) [31] Matrix Analogies subtest. These “Matrix Analogies” tasks are used to illustrate visual reasoning skills. The Matrix Analogies test allows participants to choose a picture or design that best completes a visual scene or pattern.

Using the same experimental paradigm [28], the ASD group revealed less connectivity between the left-anterior and right-posterior regions and a drop in theta band coherence compared to the TD group in another research [32]. The studies based on the connectivity-based analysis [18, 33] tried to uncover strong support for long-range underconnectivity in ASD, while the status of the local connectivity networks remains vague. Growing evidence is found in developing machine learning techniques to detect autism from behavioral and developmental data [34], genetic data and neuroimaging data [35, 36]. The advantage of machine learning in autism research is forming an objective and solid demonstrative algorithm based on human-coded behaviors.

1.2. Proposed Work

In this work, we address a few gaps in the literature. First, the application of MEG data-based machine learning methods in ASD research for the connectivity-based analysis is explored here; to date, autistic children were detected using a machine learning framework based on EEG and functional magnetic resonance imaging (fMRI) data in a large body of research [37–39]. It was observed that further investigation is necessary to decide the status of the short-range hypo/hyper-connectivity hypothesis in this research field. We discovered this gap in the state of short-range connection in the literature where contradicting claims were produced [18, 33]. We also identify what frequency-band-specific connectivity patterns are useful and how they relate to known autistic symptoms.

The objective here is to study and analyze how the underlying neural mechanisms of autistic children differ from TD children using MEG data based on a machine learning framework. For this, we aim to characterize the large-scale oscillations of brain activity using functional connectivity analysis and assess the classification performance of coherence-based measures for autism detection.

2. Materials and Methods

2.1. Participants

This study aims to find pivotal pathophysiological connectivity biomarkers of ASD in young children. Hence, we focused on the age range of 4-7 years (47-86 months) of young children (originally recruited from Kanazawa University's Hospital and the prefectural hospitals in Toyama). There were two groups of children: (i) ASD and (ii) TD. The ASD group had 30 children (4 girls) with a mean (± s.d.) age of 64.66 (± 10.12) months, and the TD group had 30 children (4 girls) with a mean (± s.d.) age of 64.83 (± 10.51) months; the two groups did not significantly differ in age (two-tailed t-test, $p > .95$). The ASD children were diagnosed by an experienced therapist and a clinical psychologist utilizing the Autism Diagnostic Observational Schedule, Generic (ADOS) [40] and the Diagnostic Interview for Social and Communication Disorders (DISCO) [41] criteria at the time of MEG. Specifically, ASD was confirmed with the ADOS cut-off and parent report on the social communication survey. All the typically developing children were native Japanese and had no reported language or behavioural problems. All the procedures were performed following the Declaration of Helsinki.

2.2. Experimental Procedure, Data Recording and Pre-processing

Resting-state MEG signals were recorded using a customized child-sized 151-channel Yokogawa MEG system [30] in a magnetically shielded room. During the MEG recording, the children were in a supine resting-state position and watching a cartoon video shown on a screen. The cartoon video was chosen before the experiment based on the preference of the individual participant. In addition, a staff member was present during the MEG recording to ensure that each participant was relaxed and steady while watching the video. The 3 minutes long resting-state MEG data were sampled at 1000 Hz and processed using a low-pass filter with a 200 Hz cut-off.

The MEG data are preprocessed and analyzed by Matlab-based toolboxes, FieldTrip [42], and custom-made Matlab scripts. Data were first visually inspected and notch-filtered at 50 Hz to eliminate power-line noise. Next, bad sensors were interpolated using cubic splines from the nearest neighbouring sensors determined through Delaunay triangulation [43]. Finally, large blink artifacts were removed by independent component analysis.

2.3. Data Analysis

We divided the broadband MEG signal into six standard frequency bands [44]: delta band (1-4 Hz), theta band (4-8 Hz), alpha band (8-13 Hz), beta band (13-30 Hz), low-gamma band (30-50 Hz) and high-gamma band (50-100 Hz). To classify ASD from TD children using resting-state MEG, we used a machine learning framework, consisting of the following main blocks - feature extraction, feature selection, and classification, as illustrated in the literature [45, 46].

2.3.1. Feature Extraction:

Figure 1 shows the feature extraction procedure. We used the magnitude part of the coherency to measure functional connectivity between two MEG sensors [23]. For any two sensors (x, y), first, we calculated individual power spectrum densities $S_{xx}(f)$, $S_{yy}(f)$ and their cross-spectral density $S_{xy}(f)$ using the Welch method [47]. The complex coherency was calculated as,

$$C_{xy}(f) = \frac{S_{xy}(f)}{\sqrt{S_{xx}(f).S_{yy}(f)}} \tag{1}$$

with f =1, 2, ... 100(Hz).

The coherence (COH) is the magnitude part of the complex coherency and is subsequently computed for each frequency band (fb) as follows,

$$\mathrm{COH_{xy}}(fb) = \left(\frac{1}{N_{fb}} \sum_{f=fb_{min}}^{fb_{max}} |C_{xy}(f)| \right) \tag{2}$$

where N_{fb} represents the number of frequency components in each band. For example, in the case of the alpha band, $fb_{min} = 8$ and $fb_{max} = 13$, so $N_{fb} = 6$. The COH values were averaged across frequencies within six frequency bands.

The COH values were averaged across frequencies within six frequency bands. Further, based on the sensor position, the COH values were grouped into ten distinct regions [48–50]: frontal (F_L & F_R), temporal (T_L & T_R), central (C_L & C_R), parietal (P_L & P_R) and occipital (O_L & O_R) regions, from both the left and right hemisphere, respectively. Here, all 151 MEG sensors were grouped into 10 regions of interest (ROIs), roughly corresponding to the five major cortical areas (frontal, central, temporal, parietal and occipital) of the left and right hemispheres of the brain. In this region-wise connectivity analysis, the feature dimension is 45 (10 region pairs combination or $^{10}C_2$) in each frequency band. In the sensor-wise analysis, the 151 sensors were treated individually irrespective of regions, leading to the feature dimension of 11325 ($^{151}C_2$).

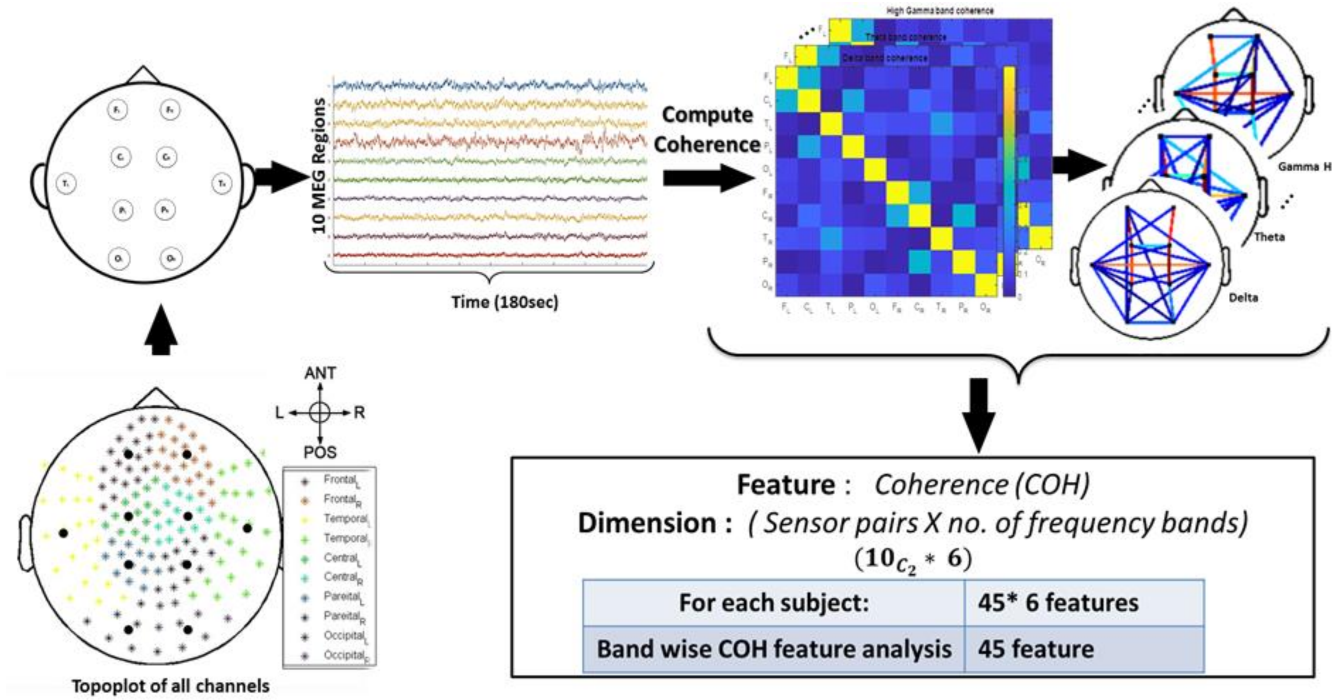


Figure 1: Representation of block diagram of feature extraction procedure: The whole-brain 151 MEG sensor-based topoplot is shown in the bottom left, where the 'black' dots represents the centroid of each (ten) region. Preprocessed MEG signals from these 10 regions are shown in the second part of the top row. After computing coherence from each region pair for the six frequency bands, the coherence connectivity matrices are shown in the third part of the top row. Finally, the connectivity networks of these six bands are represented in the last part of the top row using topoplots.

2.3.2. Feature Selection:

The objective of feature selection is to extract a subset of features by removing redundant features and keeping the most relevant features. As the student's *t*-test feature selection method performs better than the complex wrapper and embedded methods for a large number of features [51–53], we used this *t*-test based feature selection method. Here, in all sensor-based analyses, the feature dimension is huge, i.e., 11325 ($^{151}C_2$) dimensional features in each of the ASD and TD classes. Hence, the *t*-test feature selection method was deemed suitable for this study.

In short, the two-sample student's *t*-test traditionally tests the null hypothesis that the means of two populations are statistically the same against the alternative hypothesis that they are different.

$$\mathbf{H_0}: \ \overline{x_1} = \overline{x_2}$$

$$\mathbf{H_1}: \ \overline{x_1} \neq \overline{x_2} \tag{3}$$

where $\overline{x_1}$, $\overline{x_2}$: sample mean of class-1 and class-2 respectively. Let us consider class-1 is the ASD group and class-2 is the TD group. The t-statistics allows high values for features with a maximal difference of mean values between classes and minimal variability within each class. These features with high t-score values are selected based on the probability value or p-value, and the two groups are significantly different for these features. We selected those features associated with a p-value lower than a threshold [54, 55]; however, the whole analysis was repeated with different thresholds to investigate the impact of expanding the number of chosen features on classification performance [56].

2.3.3. Classification:

We executed a 5-fold nested cross-validation technique for the machine learning classification process following the same framework as [57]. We employed an ANN [58] and an SVM [59] as classifiers with 5-fold nested cross-validation (CV).

In the two-layered feedforward back-propagation ANN, an input layer, a hidden layer of ten neurons, and an output layer with two neurons represent the two classes (ASD and TD). The input layer's number of neurons varied depending on the feature type and the number of features selected. The scaled conjugate gradient algorithm was used for training [60]. We use five-fold cross-validation. To avoid overfitting, we use an early-stopping criterion on the validation loss with the verification of 6 epochs. Here, the maximum number of cycles was designated as 10000, and the mean squared error or the performance goal was set to 10e-5, empirically.

We also conducted experiments on another SVM-based classification framework for comparative assessment [59, 61, 62]. The SVM was trained using the RBF kernel [63, 64] with the grid-search-based tuning of the hyper-parameters gamma (γ) and C. We follow similar 5-fold cross-validation for this framework.

2.4. Performance Matrices

The problem of distinguishing between TD and ASD children is a two-class classification problem. Therefore, we calculated classification accuracy, sensitivity, and specificity as performance matrices [65]. Classification accuracy indicates the distinguishable ability of the connectivity features. Sensitivity refers to the proportion of ASD children appropriately classified as belonging to the ASD class, and specificity refers to the proportion of TD children correctly identified as part of the TD class.

3. Results

This section presents the detailed analysis and results of the experiments conducted to recognize autism in children. At first, we present the region-wise connectivity analysis followed by the sensor-wise analysis. Both the analyses are conducted in ANN and SVM frameworks and accompanied by frequency selective performance evaluations. A block diagram of the overall workflow is shown in Figure 2.

Along with the autism classification for both region-wise and sensor-wise calculations, we have provided additional discriminative, statistical, and topological analysis for better interpretability of the results.

3.1. Region-wise connectivity analysis

Table 1 shows the performance of frequency-band-specific coherence features in both ANN and SVM classifiers. Both classifiers performed well above the empirical chance level of 60% [66] for most frequency bands except for ANNs in the theta and beta band. In addition, both classifiers obtained the highest classification accuracy (above 90%) in the high gamma band. Further, specificity was higher than sensitivity for the ANN classifier across frequency bands.

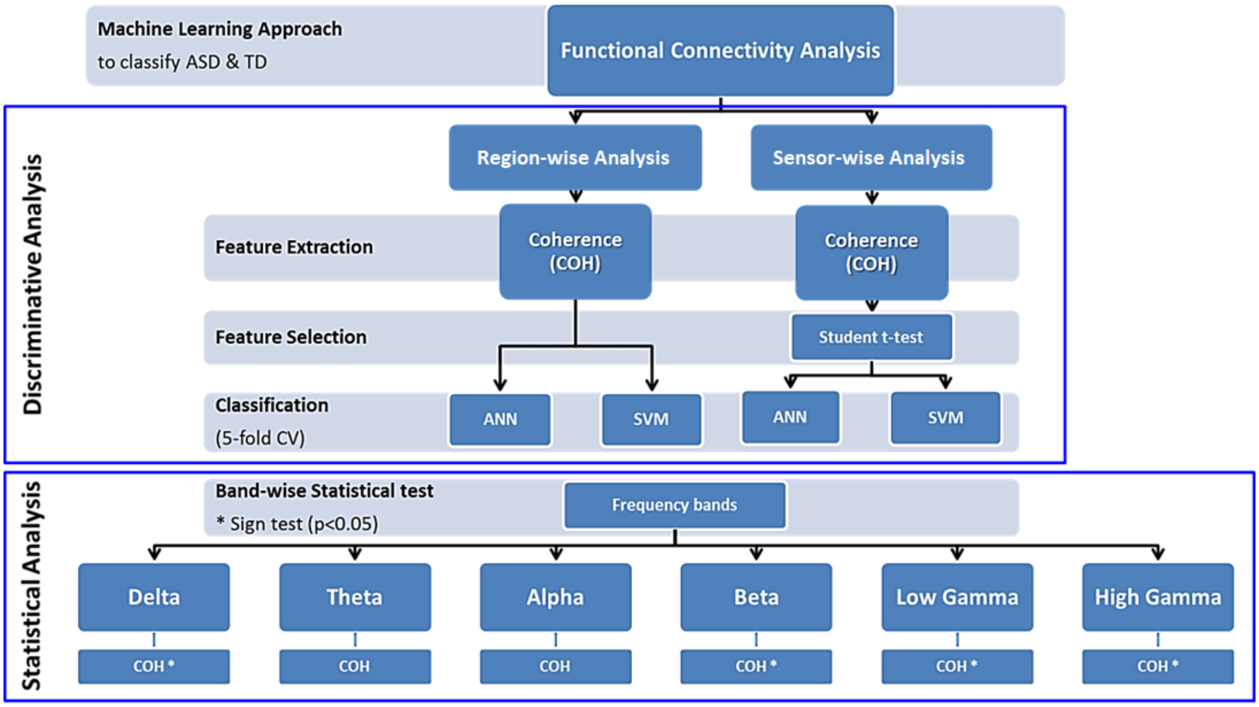


Figure 2: Representation of a block diagram of the overall workflow.

Table 1: Classification performance details of coherence features in region-wise analysis over each frequency band

Feature: COH	**Classification Performances matrices (%)**			
Frequency bands	**Classifier**	**Accuracy ± SEM**	**Sensitivity ± SEM**	**Specificity ± SEM**
Delta	ANN	79.20 ± 2.12	77.06 ± 3.69	81.33 ± 1.38
	SVM	76.66 ± 4.34	73.33 ± 7.60	80.00 ± 2.98
Theta	ANN	57.63 ± 1.13	54.93 ± 3.33	60.33 ± 1.89
	SVM	65.00 ± 4.94	70.00 ± 5.57	60.00 ± 5.96
Alpha	ANN	70.66 ± 2.43	70.00 ± 5.64	71.33 ± 5.95
	SVM	70.00 ± 3.80	73.33 ± 7.60	66.66 ± 4.71
Beta	ANN	58.50 ± 0.80	57.60 ± 3.05	59.40 ± 3.23
	SVM	66.66 ± 6.66	53.33 ± 8.69	80.00 ± 5.57
Low Gamma	ANN	85.43 ± 1.54	83.66 ± 2.53	87.20 ± 2.21
	SVM	88.33 ± 1.82	96.66 ± 2.98	80.00 ± 5.57
High Gamma	ANN	90.00 ± 2.24	89.66 ± 2.91	90.33 ± 2.12
	SVM	91.66 ± 4.71	96.66 ± 2.98	86.66 ± 7.30

3.1.1. Statistical analysis of Region-wise connectivity features:

We have performed additional statistical and quantitative analyses to enhance the proposed frameworks' reliability. To analyze what leads to classification performance, we have investigated how inter-hemispheric and intra-hemispheric connections are discriminated in terms of coherence values. Here, a higher coherence value indicates dominant connectivity between two sensors. We conducted a non-parametric sign-test [67, 68] comparing the coherence values of all six frequency bands averaged across all 30 TD subjects to those of age-gender-matched ASD subjects. We found that the ASD group has hyper-connectivity (higher coherence) than the TD group across all frequency bands. This trend is even more prominent in the inter-hemispheric connections ($p < 0.043$). For illustration purposes, in Figure 3, we plotted the connected networks with connection strengths from the coherence matrices of both classes.

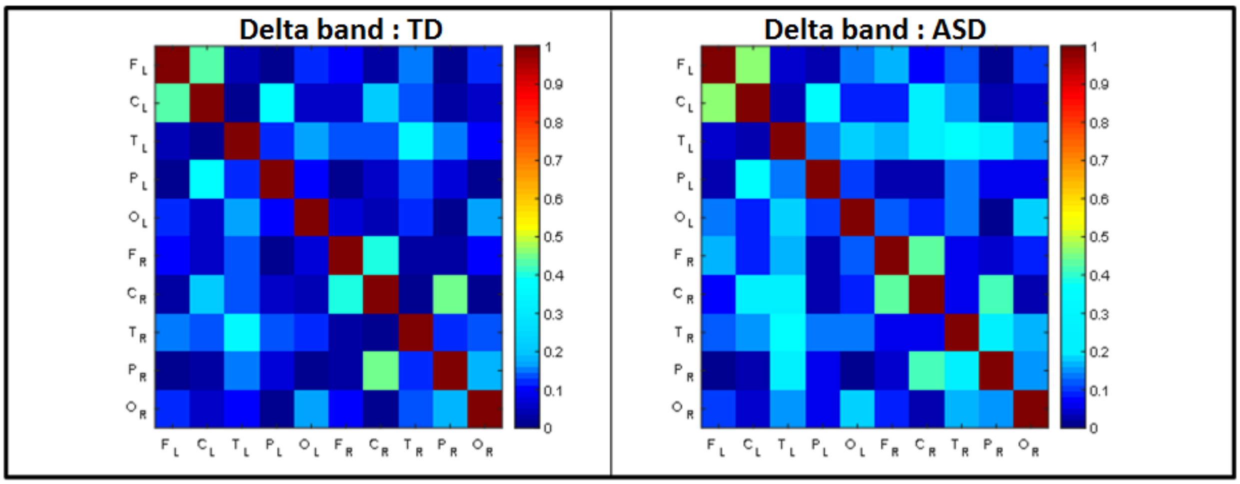


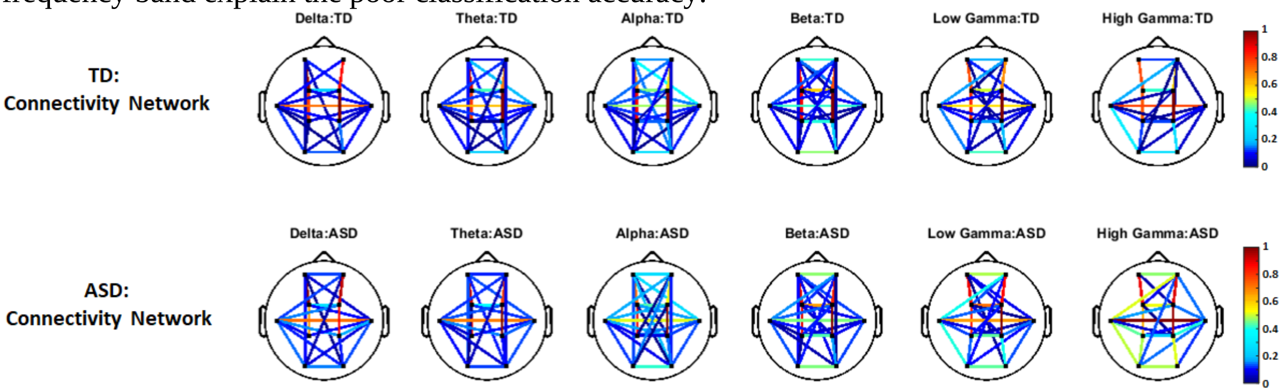
Figure 3: Representation of the coherence connectivity matrices: Region-wise coherence values in the delta band (randomly chosen) averaged over TD and ASD subjects.

3.1.2. Frequency band-wise feature analysis:

We compare the coherence connectivity network of six frequency bands averaged over 30 TD and that of age-gender-matched 30 ASD children. High (low) coherence values are represented by red (blue) color in the topoplot network connections, shown in Figure 4. The significance levels are also mentioned in the bottom part of Figure 4, followed by a statistical sign test. The ASD group has more network connections (with high COH values) than the TD group. In the delta, beta, low, and high gamma bands, we discovered that ASD children have significantly over-connection than TD children. Inter-hemispheric connections are found in delta, beta, and high gamma oscillations. Hyper-connectivity is observed along with the beta band over inter- and intra-hemispheric connections of the ASD group.

3.1.3. Discriminative connectivity features:

Discriminant coherence connections are demonstrated in this study using a t-test with a significance level of $p < 0.05$. In the delta and gamma bands, discriminant coherence features are more dominant in inter-hemispheric connection networks. In Figure 5, we have further shown the connectivity networks (by orange lines) that differentiate the ASD class from the TD class for each frequency band. Here the number of connections in each frequency band justifies the classification accuracy, i.e., in the high-gamma band, more discriminant coherence connections account for the highest classification accuracy. On the other hand, a few discriminant connections in the theta frequency band explain the poor classification accuracy.



Sign-test in Connectivity	*Delta*	*Theta*	*Alpha*	*Beta*	*Low gamma*	*High Gamma*
p-value						
Region wise connections	0.002**	0.232	0.371	1.4052e-07**	0.056*	0.002**
Inter-hemispheric conn.	0.014**	0.690	0.229	3.5882e-05**	0.229	0.014**
Intra-hemispheric conn.	0.115	0.263	1	0.002**	0.359	0.115

** p-value< 0.05
* p-value< 0.06
Significance level

Dominantly high coherence value of ASD

Figure 4: Representation of the comparison of the coherence connectivity network of six frequency bands averaged over 30 TD subjects and that of age-gender-matched 30 ASD subjects. The significance level is also mentioned in the Connectivity analysis, followed by the sign test. The color bar from blue to red represents the coherence value from 0 to 1.

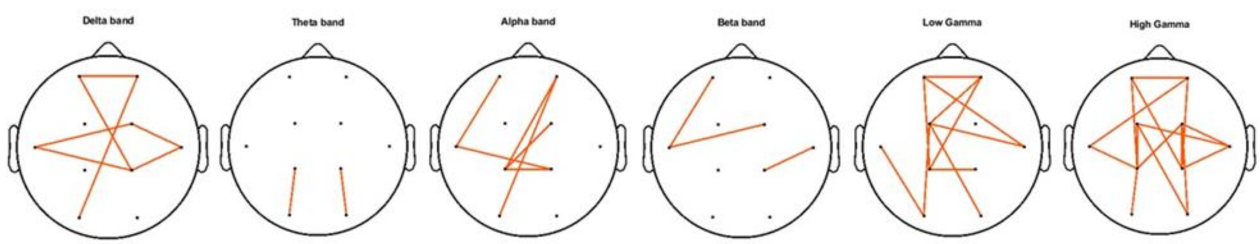


Figure 5: Representation of discriminant coherence connectivity network between ASD and TD subjects of six frequency bands in region-wise connectivity analysis.

3.2. Sensor-wise connectivity analysis

In order to develop a complete understanding of the coherence-based connectivity network, we have further extended the experiments by conducting the whole brain sensor-wise connectivity analysis. To find exact discriminative functional connectivity within 151 sensors, all combinations' coherence needs to be checked and analyzed. In this analysis, the COH connectivity features are computed within individual frequency bands for all 151 sensors. Hence, the feature dimension is ${}^{151}C_2$ = 11325. Concerning the computational complexity, we have further applied feature selection methods over these 11325 dimensional sensor-wise coherence features. We have varied the number of selected features by setting the p-value threshold between 0.005 to 0.05 with an interval of 0.005. We have trained the classifier frameworks for each case and compared them with the accuracy of the empirical change level of 60% [66]. The stricter p-value yields fewer selected features resulting in reduced classification accuracy. A suitable threshold is empirically ascertained for selecting the features. The classification outcome of COH features of each frequency band is illustrated in Figure 6 for ANN and SVM models. Both the classification model yields similar trends over all the frequency bands. The SVM model can classify better than the ANN model in terms of accuracy. In the case of specificity, the SVM model performs better than the ANN model; however, both models are comparable in sensitivity. Finally, from this experiment, we note that to classify autistic children from TD children, the low-gamma frequency band performs better than other frequency bands in both models. The highest classification performance of COH is found in the low-gamma band of 86.13 ± 3.04% in the ANN model and 90.00 ± 2.78% in the SVM model.

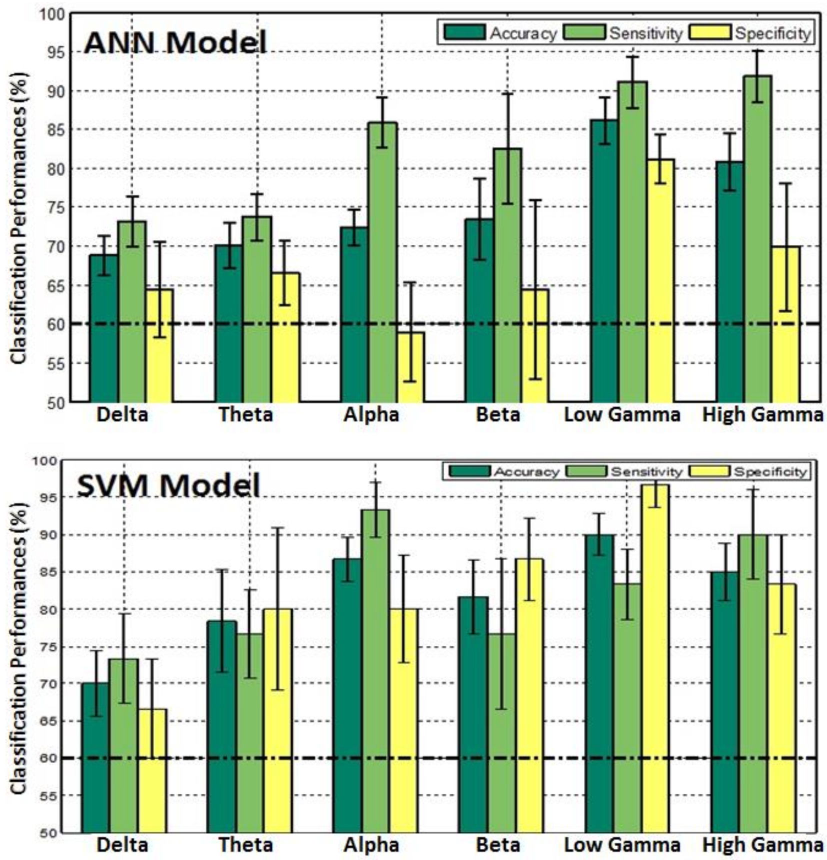


Figure 6: The classification performances (in %) of all six frequency bands (Delta, Theta, Alpha, Beta, Low Gamma, and High Gamma) in sensor-wise connectivity analysis.

3.2.1. Statistical analysis of sensor-wise connectivity features

We examined frequency-band-wise coherence connectivity in this sensor-wise connectivity analysis, followed by a statistical sign test. Applying this sign-test, we have found that the ASD group has significant ($p < 0.05$) over-connectivity (higher coherence values) as compared to the TD group in all six frequency bands. Discriminant coherence connectivity networks between ASD and TD subjects of six frequency bands are shown in Figure 7 using a statistical student t-test with a significance level of $p < 0.05$. The network representation rule in the topoplot is that the more significant (or lower the p-value) the connection, the higher value of the red component in Figure 7.

From this discriminative connectivity features analysis, we have found that ASD children have a hyper-coherence connectivity network compared to TD. The frontopolar (Fp) and frontal (F) regions demonstrate high coherence in lower oscillations (like delta and theta bands). In the alpha band, the functional connectivity network is more conspicuous ($p < 0.05$) in the left central and frontal regions. It is also found that with frontal and parietal regions, temporal anterior and temporal posterior regions have more discriminant coherence connectivity in low-gamma band oscillation. The coherence is higher in the high-gamma frequency band, mostly in the central, parietal and occipital regions. The discriminative coherence connectivity features are found over all frequency bands, particularly in the occipital region.

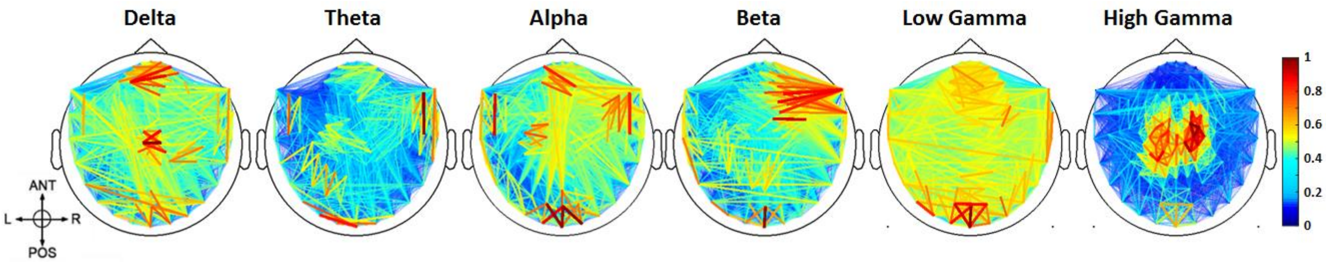


Figure 7: Representation of discriminant coherence connectivity network between ASD and TD subjects of six frequency bands in sensor-wise analysis. The color bar from blue to red represents the discriminant coherence value ranging from 0 to 1 between the classes.

3.3. Comparison between region-wise and sensor-wise connectivity

To find the discriminative frequency in this functional connectivity analysis, a comparison of the performances of region-wise and sensor-wise connectivity analysis is shown in Figure 8 for both the ANN and SVM model. These classification performances are represented through bar plots over whole 1-100Hz frequency oscillations along with six individual frequency bands. In both the ANN and SVM models, gamma bands perform better than other frequency bands. In addition, the delta band performs well with the high-gamma and low-gamma bands. From Figure 8, it is clear that the region-wise coherence performs better than cortical connectivity analysis by analyzing the classification accuracy over whole 1- 100 Hz frequency oscillations. Even in terms of complexity (number of features), the region-wise coherence connectivity analysis is preferable to the sensor-wise connectivity analysis as, in the first case, fewer features are used in the classification process.

The region-wise coherence analysis performs better than all-sensor connectivity analysis due to not only the terms of feature complexity but also may be the negligible effect of field spared. In our analysis protocol of region-wise analysis, the effect of field spread might be negligible as we have used region-wise MEG signals where all the 151 MEG channels were grouped into 10 regions of interest (ROIs), mainly corresponding to the five major cortical areas within each hemisphere. Thus, all region-wise field spread is diminished during inter-region and inter-hemispheric connectivity compared to sensor-wise field spread. Of note, magnetic field strength decreases approximately with the square of the distance from the source, and the sparse alignment of the MEG sensors (i.e., a large distance between the sensors) lowers the likelihood that a strong signal from a single source would reach many sensors. Hence for only 10 ROI in the region-wise analysis, the probability of this field-spred is reduced. Furthermore, the field-spread of sensors within a particular region is not counted during region-wise analysis.

3.3.1. Best performing bands of region-wise connectivity

Analysis of Frequency band-wise classification performances of both the ANN and SVM model over the region-wise connectivity shows that the performances of delta, low-gamma and high-gamma frequency bands are better than the remaining three frequency bands. Therefore, we select only these best-performing frequency bands to improve the classification performance further. These top-performing bands are collectively termed ‘Delta + Gamma’. Experiment with the ‘Delta + Gamma’ Frequency oscillations yields the highest classification accuracy of 95.03 ± 0.97 % with the ANN model. The performance details are tabulated in Table 2 for both the ANN and SVM classification models.

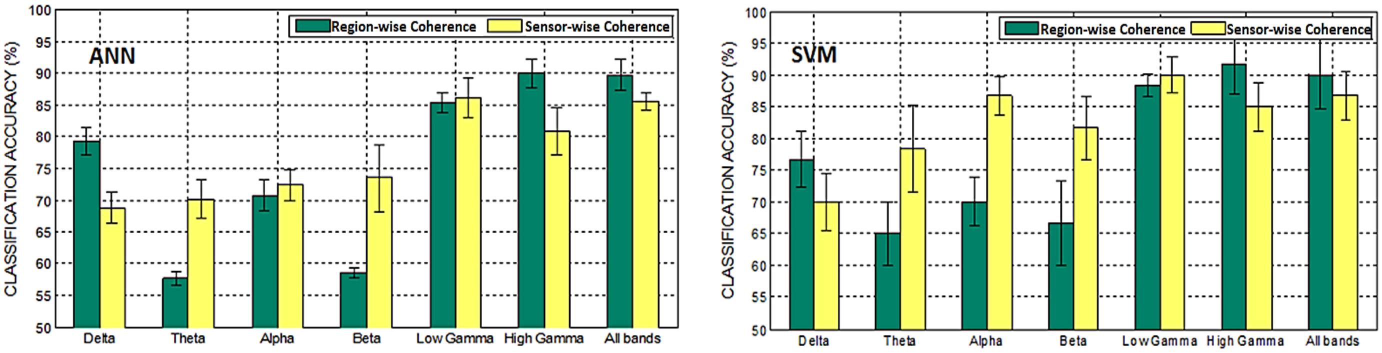


Figure 8: Representation of classification performances (in %) of ANN and SVM model over all frequency bands (Delta, Theta, Alpha, Beta, Low Gamma, High Gamma) along with whole 1-100Hz frequency oscillations.

Table 2: Classification Performance details of coherence features in region-wise analysis over best-performing bands

Feature: COH		**Classification Performances matrices (%)**		
Frequency bands	Classifier	**Accuracy ± SEM**	**Sensitivity ± SEM**	**Specificity ± SEM**
Delta + Gamma	ANN	95.03 ± 0.97	96.53 ± 2.04	93.53 ± 2.17
	SVM	93.33 ± 2.78	96.66 ± 2.98	90.00 ± 3.65

3.3.2. Statistical analysis of band-specific coherence

Based on the coherence-connectivity results, we confine our investigation, particularly on the ‘Delta + Gamma’ frequency range for the region-wise connectivity analysis. The differences in the coherence connectivity in ASD against TD groups for the best-performing bands are displayed in Figure 9. Here, the statistical t-test is performed to calculate the t-score of the coherence connectivity matrix between the ASD and TD groups. The colormap reports the value and the direction of the t-test under the null hypothesis that the region pairs have the same coherence values in both groups. The highlighted boxes (with ∗ marks) of Figure 9 indicate significantly different region pair-wise t-scores between ASD and TD children. It represents significant over-connectivity in ASD children. Even hyper-connectivity is observed along with inter-hemispheric connections in the ASD group.

This finding suggests that the connectivity patterns of the delta, low-gamma and high-gamma bands play an important role in distinguishing ASD from TD children. The statistical difference shows increased ‘Delta + Gamma’ band coherence connectivity in lateral-frontal connections. In addition, we have found significant connections in central-left regions. Even lateral-temporal connections also have discriminative coherence connections. Overall, the ASD group shows increased short-range connections in lateral-frontal regions. This strongly supports the 'weak central coherence theory' [21, 69], which proposes that ASD individuals are only biased towards fine-grained local detail.

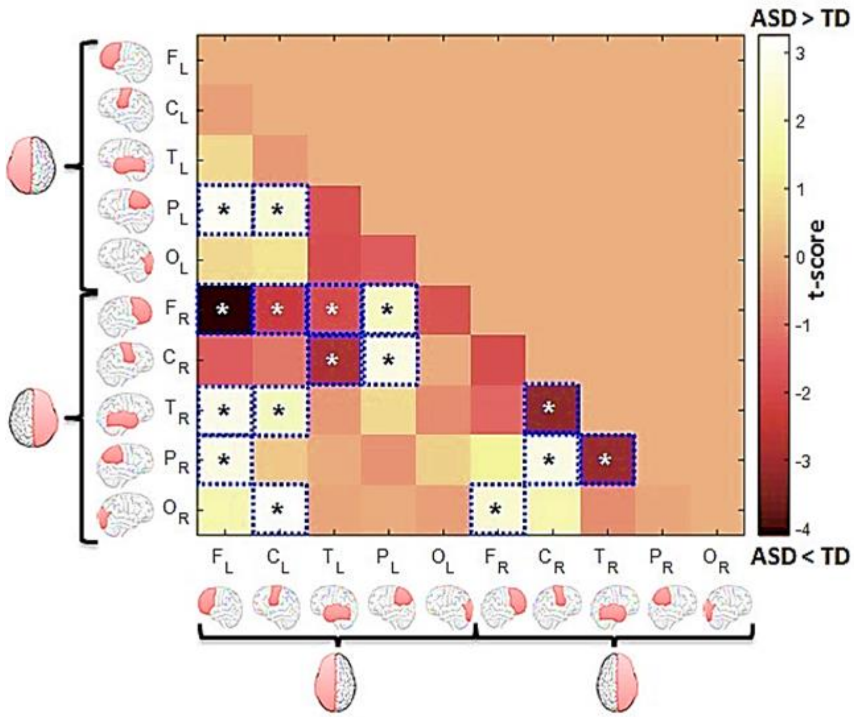


Figure 9: Coherence connectivity results in ASD vs TD, particularly shown for best-performing frequency oscillation, i.e., 'Delta + Gamma'. The connectivity adjacency matrix represents 10 region pair-wise t-scores of coherence values by calculating t-statistics in ASD against TD groups. The highlighted boxes (with $*$ marks) indicate significantly different region pair-wise t-scores between ASD and TD children.

4. Discussion

Several recent studies have looked into the possibility of detecting ASD using predictive machine learning models and determining group mean differences of resting-state neurophysiological characteristics. Various models and features have been used; for example, discriminant functional analysis using spectral power yielded 90% accuracy [70] and utilizing coherence 87% balanced accuracy [71]. Recently released research employing SVM on the spectral power and coherence in over 400 individuals also found that the accuracy was approximately 57% [72]. However, another recent study found just 56% test accuracy when employing big enough data sets, various features (power spectrum, connectivity measures), and multiple classifiers [73]. This autism detection literature is based on resting-state EEG data (fewer sensors). The heterogeneity and complexity of ASD [74] may be related to the disparities in classification performances; however, additional factors like unbalanced datasets, unbalanced age range and the absence of an unknown test dataset raise questions regarding the exact classification performance. In comparison, our study yielded a higher classification accuracy of 91.66% in the high gamma band when employing the coherence connectivity feature to distinguish age and gender-matched autistic children from TD children analyzing their MEG signals. We have implemented the 5-fold nested cross-validation technique in the machine learning framework for both the ANN and SVM models. This repeating 5-times nested cross-validation integrates parameter tuning and feature selection into machine learning model optimization to enhance model accuracy while avoiding overfitting. Our study reports the mean classification accuracy and the standard error of the mean (SEM) of the 5-times classification performances. Along with the classification performance measures, we presented further statistical analyses and discussed the potential interpretation of the identified biomarker.

4.1. Interpretation of our findings

In this study, we endeavor to address the literature gaps in autism research. It is found that further research is necessary to determine the status of the hypothesis of short-range over-connectivity. Even in the neuroimaging domain, the frequency-band-specific connectivity patterns and their relationships with known symptoms of autism also need to be further specified. Here, we compare the neuromagnetic brain responses of young children (4-7 years) with ASD to age and gender-matched TD children. Using features based on complex coherency in a machine learning classifier, we demonstrate that ASD from TD children can be classified with accuracy well above the chance level based on the MEG signal in sensor space. Further, we reveal that coherence showed higher classification accuracy in gamma frequency bands. Following that, we go over these findings in greater depth, along with some of the study's constraints.

Functional over-connectivity in autistic children: In this study, it is observed that brain oscillations and functional connectivity are consistently affected in ASD. Here, in a wide range of frequency oscillations, ASD children demonstrate significantly over-connectivity than TD children. The literature revealed high striatal functional connectivity found in autistic children, and a study of [16] measured widespread excessive patterns of FC in striatal-cortical circuitry relative to TD children. Using resting-state fMRI, another study reported increased FCs in nearly all striatal regions, limbic cortex, insula and pons in ASD children [75, 76]. However, few studies observed hyper-connectivity within several large-scale brain networks such as salience, default mode, frontotemporal, motor, and visual networks in children with ASD compared to TD children [77–79]. These results suggested that the functional connectivity in ASD brains differed from TD brains [80]. Our findings support the literature hypothesis that (i) functional connectivity in ASD brains differs from that in TD brains, and (ii) ASD children have hyper-connectivity.

Inter-hemispheric connectivity in autism: Selective attention is a major characteristic of persons with autism [81], and interhemispheric neural connections contribute to selective attention [82]. Interhemispheric communication facilitates the transfer of task-relevant information while suppressing the transfer of task-irrelevant data [83]. Here, relationships of hyper inter-hemispheric neural connections with autism symptomatology have been found in this experiment. This study found significantly more inter-hemispheric connections in ASD than TD in delta, beta and high-gamma oscillations. Relationships of high-gamma and delta frequencies are also found with each hemisphere as weak central coherence theory suggests that ASD individuals are merely 'biased' towards attention to fine-grained local detail and are less distracted by the whole external environment [21].

Relationship of frequency-band specific connections with autism symptomatology: We demonstrate functional connectivity-based autism detection over large-scale neural oscillations (from 1-100 Hz) to clarify the frequency-band specific connectivity patterns and their relationships with established autistic symptoms. In this study, low frequencies or delta oscillations are elicited in the autistic group, which is completely justified by the weak central coherence theory [21, 69]. It illustrates that autistic children are less distracted by the context of the whole external environment [21, 84]. Some studies detected delta frequency fluctuations which mean the manifestation of functional connectivity of the brain in the absence of external tasks [16]. Hyper-connectivity is observed along with the beta band over rightward lateralized connections of the ASD group. In literature, early responsivity in beta fluctuations is found in the autistic brain [85]. Rightward connectivity is found in children with ASD via high beta and low-gamma oscillations [28–30, 32]. Relationships of high gamma frequencies with the ASD group justify that autism characteristics are biased toward local vs global information processing. In autism, the feature of human information processing is disturbed, as the individuals with ASD are only focused on local detail elicited by high neural oscillation [84].

Association of Gamma band activity with ASD: The gamma band performs best to detect autism in this study. These findings are in line with the literature [23]. To classify autistic children from TD children, the coherence connectivity feature performs better (91.66%) in gamma frequency bands over all the frequency bands in region-wise analysis. In sensor-wise connectivity analysis, both the low and high-gamma frequency oscillations of coherence connectivity features perform better. Low gamma band activity is associated with perceptual and cognitive functions that are compromised in autism [23]. The whole gamma band anomalies have been verified as autism indicators [86]. Elevations in low-gamma and high-gamma are observed in anterior temporal, posterior temporal and occipital regions. Significantly elevated low-gamma (30-50 Hz) and high-gamma (50-90 Hz) were found in resting-state autism in a prior study [87].

Connection between brain regions and autistic behaviour: We have observed that the discriminative coherence connectivity features are found more in frontal and frontopolar regions. Using neuro-physiology and autism symptomatology, we attempted to explain this discovery. The prefrontal cortex (PFC), frontopolar (Fp) and frontal (F) lobes are involved in social interaction and responsible for human concentration [88], and these cognitive functions are different in ASD children than the TD children. Our findings reflect these cognitive aberrations in the F and Fp regions. Furthermore, in sensor-wise connectivity analysis, the discriminant features of all low to high frequencies are found in the occipital region. This observation supports the weak central coherence theory [21, 69], which proposes that ASD individuals are only biased towards fine-grained local detail. Though the typical human tendency to process incoming information in context for gist, this feature of information processing is disturbed in autism. Hence, in this experiment, the occipital site performs differently in TD children than in ASD children when MEG signals were collected during the eyes-open resting state.

4.2. Clinical potential

In this study, we can classify autistic children from normal children by recording their MEG signals using a data-driven approach. However, this is not the only finding of this study. We also explore the Frequency band-specific functional connectivity analysis based on a machine learning approach. Till now, particularly in connectivity analysis, a machine learning framework based on MEG data was not explored in autism children detection. Even we have analyzed the selected connectivity features and interpreted them in the context of the functioning of the brain. An advantage of this study is the use of MEG data to examine neuronal oscillations, and regional specificity in autism detection performed using feature engineering techniques. Previous studies on ASD detection have used various types of data, including behavioral [34], EEG [39] and resting-state functional magnetic resonance imaging [15, 35–38, 89]. Notably, our proposed approach yields better classification accuracy using MEG only.

4.3. Limitations and future directions

Our study has several limitations, as follows. First, our recording paradigm is not a classic resting-state one. During a resting state paradigm, participants are not provided with any external stimuli; instead, they fixate on a cross-hair (eyes open resting state) or keep their eyes closed (eyes closed resting state) and think of nothing in particular for a fixed duration. Unfortunately, the quality of resting-state neural data of young children is limited by head motion artifacts as it is extremely difficult for children who get bored easily and starts fidgeting. A behavioural intervention that effectively reduces head motion artifacts is to play a movie to keep the children sufficiently engaged and remain still and relaxed [90, 91]; therefore, we adopted this approach. Second, the motion-related artifacts are known to influence functional connectivity measures [92], and there could exist some differences between the ASD and TD groups in terms of movements during the MEG recording. We recorded the head positions of the participants using video monitors during the MEG recording, and MEG segments during which the head position of the participant had moved from its starting position were eliminated before conducting the analysis [30]. Unfortunately, the head movement data were not explicitly stored, and further, it is beyond the scope of this study to conduct a formal analysis of head movements. Further, head motions in young children during a brain recording session are considerably reduced if they watch a movie [90], as in our case. Of note, reduced head motion is mostly seen in children younger than 10 years, which is also the age range of our children [90]. Nevertheless, we suggest that future studies using specific head-movement correction techniques may provide more reliable evidence. Third, as mentioned earlier, watching a cartoon is not strictly a resting state, and there exist significant differences in functional connectivity patterns between these two states [90]. We did not measure to what degree our participants were engaged with their chosen videos, and these differences between the two groups might have influenced our findings regarding attention, emotion and overall engagement. However, it is interesting to note that this ecologically more appropriate condition (i.e. watching a movie or a cartoon), despite its inherent variability across participants, is a better indicator of brain-behaviour correlations than resting-state [93, 94]. Fourth, our analysis was entirely done in the sensor space; though coherence is widely used [28, 30, 32, 48, 95], it suffers from volume conduction effects [96, 97]. This could be mitigated in future studies by conducting connectivity analysis in the source space. However, an accurate source reconstruction requires individual structural MRI images, which can be troublesome to obtain for young children. Finally, statistical tests were conducted without any correction for multiple comparisons because our aim was not to claim any statistical significance; instead, we applied it as a statistical filter in the feature selection process. Further, the robustness of our approach was demonstrated by the reportedly high classification accuracy. Finally, the altered functional connectivity in young children with autism, as reported here, might not be solely associated with autism because the changes in the brain's connectivity are also found in attention-deficit/hyperactivity disorder (ADHD) [98], another developmental disorder comorbid with ASD [99]. Our study focused only on autism in this very young group of children (4-7 years). Future neuroimaging studies might include a larger age range, including adolescents with a broader developmental disorders (e.g. ADHD) assessment, to delineate the specific roles of such connectivity patterns.

5. Conclusions

The present study shows that autistic children can be differentiated from typically developing children based on their resting-state functional brain connectivity patterns obtained from the MEG signal recordings. We used coherence as a measure of functional connectivity. The functional brain network was found to be denser in autistic children when compared with normal children. Our findings conform with the hypothesis: (i) functional connectivity in the ASD brain is different from TD brain, and (ii) ASD children have hyper-connectivity. To classify autistic children from TD children, the coherence connectivity feature performs better in gamma frequency bands over all frequency bands. The overall statistical analysis of connectivity features yields further insights into autism among young children. We observed that ASD children demonstrate over-connectivity in delta, low and high-gamma bands. Even hyper-connectivity is observed along with inter-hemispheric connections in the ASD group. Overall, connectivity analysis, both region-wise and sensor-wise, reflects frequency-band-specific connectivity patterns and their relationships with the symptoms of autism.

6. Declarations

Availability of data and material: The codes would be made available at a reasonable request made to the corresponding author.

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Author Contributions: Conceived and designed the research: KB, JB, GS; Analyzed the data: KB; Contributed reagents/materials/analysis tools: GS; Wrote the paper: KB, JB with comments from KW, GS.

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