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Contrastive machine learning reveals in EEG resting-state network salient features specific to autism spectrum disorder

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ABSTRACT

We explore the potential of the contrastive variational autoencoder to detect latent disorder-specific patterns in the network, analyzing functional brain networks in autistic individuals as the case. Autism spectrum disorder has long troubled medical practitioners, neurologists, and researchers. It is due to its extremely variable nature, both neurologically and behaviorally. Though machine learning has been in use to automate autism diagnosis, little has been done to delve into its intricacies. Here, we attempt to understand the neural mechanisms of autism spectrum disorder using contrastive variational autoencoder in conjunction with feature engineering. Our proposed methodology results in a physiologically interpretable classifier with a remarkable F1-score (up to 95%) and reveals a weak frontal lobe functional connectivity in the alpha band for children with autism spectrum disorder. Our study suggests an increased focus on efficient frontal lobe EEG sampling. Additionally, it highlights the importance of the proposed pipeline for understanding the underlying neural abnormalities in autism over the traditional machine learning pipeline. Thus, the obtained results have proven a contrastive variational autoencoder to be a promising approach for discovering latent patterns and features in complex networks.

1. Introduction

Machine learning (ML) possesses the unique capability to identify hidden structures and non-obvious relationships within multidimensional complex data. This computational ability has initiated the widespread use of ML in complex systems analysis, including complex networks [1]. One of the significant fields of ML utilization is in the healthcare domain. Applications span finding biomarkers from medical images, accelerating drug candidate screening, automated disease diagnosis based on varying symptoms, assessing risk factors for neurological conditions, and determining phenotype subgroups to enable personalized treatment protocols [2]. The common premise across these use cases is that machine learning algorithms can find meaningful patterns hidden under a great deal of noise that proves impenetrable via manual examination. As healthcare continues generating exponentially greater volumes of patient data from expanding sources, the use of machine learning algorithms to uncover insights is accelerating a shift towards preventive, predictive, and precision medicine.

In biomedical research, we often come across multiple datasets with a prime focus on recognizing patterns that are more prominent in a particular dataset compared to a reference or background dataset, i.e., identifying patterns unique to data from the treatment group that are not present in the control group. In a broader sense, this problem is extremely relevant to the theory of complex networks [3,4]. Contrastive machine learning [5] offers a method to detect latent patterns. Contrastive learning algorithms employ the concept of comparing samples to reveal shared attributes among data classes and distinguishing characteristics that differentiate one data class from another. One such algorithm is contrastive principal component analysis (cPCA) [6]. cPCA helps to identify salient principal components by recognizing the linear combinations of features that are abundant in the treatment group compared to the control group. In contrast, the contrastive variational autoencoder (cVAE) algorithm [7] can learn nonlinear mappings between the input and latent space representations. This allows it to

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capture intricate patterns present in the data, making it suitable for tasks where linear techniques (such as PCA) may fall short [7]. Recent studies [8–10] demonstrate the potential of contrastive learning in understanding neurological disorders.

We explore the potential of the cVAE to detect latent disorder-specific patterns in the network, analyzing functional brain networks in autistic individuals as the case essential to the healthcare domain. Determining the underlying neural mechanisms of autism spectrum disorder (ASD) has long challenged health practitioners, neurologists, and researchers [11]. Machine learning can not only be used for early autism diagnosis but also to extract meaningful brain connectivity biomarkers from the abundance of connections using data from non-invasive neuroimaging. The concept is that machine learning can potentially distinguish atypical neural circuits indicating ASD condition. Several previous works [12–15] demonstrated such a machine learning capability, where functional features were found to better describe the neural mechanism of autism and automated the diagnosis of autism.

Functional networks refer to connected regions of the brain that interact to perform cognitive and behavioral functions [16,17]. These networks provide insights into principles of brain organization and evolution. Neuroimaging techniques have allowed researchers to map functional connections in the brain by analyzing correlations in activation patterns [18]. Disrupted functional connectivity has been associated with numerous neuropsychiatric disorders, e.g., ASD, attention deficit hyperactivity disorder, major depressive disorder, schizophrenia, etc. [19–21]. Functional network connectivity, therefore, holds promise for understanding brain disorders, detecting early disease stages, predicting outcomes, and monitoring treatment responses [22–25].

In the last decade, we have witnessed a notable shift from conventional machine learning models [26] to cutting-edge deep learning techniques [27] for autism diagnoses. Furthermore, researchers have explored a variety of data sources, transitioning from electroencephalography (EEG) to magnetoencephalography (MEG) [28], making substantial advancements in the diagnosis of autism. Considering only resting-state EEG, studies performed a comparative analysis of the well-known machine learning classifiers, including support vector machines (SVM), naive Bayes, decision trees, etc. [29,30] to report their performance. Convolutional neural networks (CNN) and long short-term memory (LSTM) networks were also been utilized as complex classifiers [31–33]. Incorporating dynamic traits of EEG in the machine learning pipeline also proved to be useful in autism diagnosis [34,35]. An interesting advancement is seen in the study [36], where Dong et al. proposed a novel multi-task learning model with reinforcement optimization for classification. A CNN is used to distinguish autistic from neurotypical individuals, whereas reinforcement optimization ensures that the model effectively extracts and combines features.

All aforementioned studies used custom or publicly available datasets. Different functional connectivity measures were computed in almost all major frequency bands. Although all studies reported a prediction accuracy of above 80%, data inadequacy and class imbalance, however, make it harder to generalize the results. Unfortunately, the above-mentioned studies, devoted much of their focus to increasing the computational performance of developed models and, therefore, are void of any explanation regarding the neural mechanisms of autism. Such models, when deployed in the real world, proved to be more problematic [37]. Furthermore, to deal with the social world, autistic individuals make use of a wide variety of techniques. This behavior is commonly known as camouflaging [38]. Li et al. in this regard, reported that intellectually able autistic adults show remarkably neurotypical resting-state EEG [39]. Therefore, it appears that autism-specific variations in connectivity patterns are entangled with or concealed within the broader spectrum of neurotypical patterns.

The current study aims, first, to disentangle autism-specific and neurotypical functional network patterns based on resting-state EEG of children, second, to explore the functional connectivity subnetwork specific for ASD by proposing contrastive machine learning coupled with feature engineering and, third, to demonstrate the potential of cVAE to detect latent patterns and features in complex networks. Contrastive learning, specifically cVAE, was used to disentangle and enhance functional connectivity with autism-specific characteristics, whereas feature engineering was used to figure out functional connections that are most informative in autism diagnosis. We also demonstrate that interpreting the functional connections via feature engineering helps in understanding the underlying neural mechanisms of ASD. Finally, we demonstrate the superiority of our proposed pipeline over the conventional machine learning approach.

2. Materials and methods

2.1. Participants and data acquisition

We considered resting-state EEG data of two groups of children: ASD group (149 children) and neurotypical group (149 children). All children were tested by a clinical psychologist (GP) using the Autism Diagnostic Observation Schedule (ADOS-2). The inclusion criteria for ASD children were as follows: age from 2 to 16 years old (μ = 6.4 years, σ = 3.3 years); an autism diagnosis based on the ICD-10 Criteria (F84.0); ASD rating by ADOS-2 more than 8; no history of neurological or mental disease other than autism. The inclusion criteria for the control group were: age from 2 to 16 years old (μ = 7.2 years, σ = 3.1 years); no history of neurological or mental disease; no drug application; ADOS-2 less than 2; no epileptic activity in EEG.

Also, we considered another resting-state EEG data for an independent testing. This independently acquired dataset consisted of 102 ASD children (age: 3–12 years, μ = 7.1 years, σ = 3.1 years) and 104 neurotypical children (age: 3–12 years, μ = 7.3 years, σ = 2.9 years).

During EEG recording, children sat comfortably in a chair after being asked to sit quietly with their eyes open. All children were under the supervision of their parents during the EEG recording procedure. Brain electrical activity was recorded using 19 electrodes for an averaged duration of 5 min and at a sampling rate of 250 Hz. Electrodes were placed in accordance with the 10–20 international system. Electrodes located on the left and right mastoids served as a joint referent for unipolar montage. Vertical electrooculogram (EOG) was measured using 2 AgCl cup electrodes located 1 cm above and below the corner of the left eye, and horizontal EOG was measured using 2 electrodes located 1 cm lateral to the outer corners of both eyes. Electrode impedances were maintained below 10 kΩ. The EEG signals were preliminary cleaned of artifacts using bandpass (1–100 Hz) and notch (50 Hz) filters and the ICA method. Artifact-free epochs were further analyzed; group-averaged duration of the epochs was 63.75 s.

2.2. Ethical statement

This study was conducted in accordance with the principles of the Declaration of Helsinki. The research methodology was approved by the ethics committee of the Institute of Higher Nervous Activity and Neurophysiology of the Russian Academy of Sciences (protocol No. 2 of April 30, 2020). The parents of all children signed informed consent to participate in this study. Children gave verbal consent to participate.

2.3. Functional connectivity

We focused our analysis on functional network constructed in alpha band (8–12 Hz) since our previous studies [15,25] demonstrated strong alterations in the specified band. Sensor-level functional connectivity was quantified using a measure known as “coherency”. Coherency essentially measures how the phases in two EEG signals are coupled with each other [40]. We utilized the concept of imaginary part of coherency to capture instantaneous signal interactions uninfluenced by volume conduction or field spread problem.

Imaginary part of coherency ($ICoh_{ij}(f)$) at each frequency f is extracted from the coherency ($C_{ij}(f)$) between two rhythms $x_i(t)$ and $x_j(t)$ as:

$$C_{ij}(f) = \frac{S_{ij}(f)}{(S_{ii}(f)S_{jj}(f))^{1/2}}$$

$$ICoh_{ij}(f) = imag(C_{ij}(f)),$$

where $S_{ij}(f)$ represents the cross-spectral density between rhythms $x_i(t)$ and $x_j(t)$. Additionally, $S_{ii}(f)$ and $S_{jj}(f)$ denote the respective auto-spectral densities. For the rest of paper, imaginary part of coherency will be addressed as Icoherency. Icoherency ranges from −1 to 1. When it is positive, it suggests interaction between x_i and x_j, with x_i preceding x_j, implying directional information flow from x_i to x_j. Conversely, a negative value suggests the reverse. Since the flow of information is a topic of another research, we considered only the absolute value of Icoherency ranging from 0 to 1.

For each studied participant, we constructed 19 × 19 connectivity matrices by calculating the Icoherency in frequency domain f = 8–12 Hz with the resolution Δf = 0.5 Hz. Subsequently, these Icoherency values were averaged across the alpha band to create a single Icoherency matrix per participant (Fig. 1B).

2.4. Disentangling functional connectivity

Our approach was grounded on the assumption that autism-specific variations in functional connectivity patterns may be concealed within the broader spectrum of neurotypical connectivity. In other words, the functional connectivity patterns observed in autistic individuals bear significant similarities to those in neurotypical individuals [8,9]. This similarity presents a challenge for straightforward discrimination using statistical methods or machine learning classifiers.

We employed contrastive variational autoencoders (cVAE) [7] to uncover the distinctive connectivity associated with ASD. In this framework, we treated functional connectivity from autistic participant as the target input "x_t", while connectivity from neurotypical participants was considered as the background input "x_b" (Fig. 1C). Given the network's symmetry along its diagonal, we inputted only $19 \times (19-1)/2 = 171$ unique connections. Two probabilistic encoders denoted as $q_{\phi_z}(z|x)$ and $q_{\phi_s}(s|x)$ were trained to estimate posterior probabilities for latent variables z and s, respectively (Fig. 1D). We used s to represent latent variables that are salient or relevant features and z to represent irrelevant features. Both encoders were structured with dense layers and the decoder $Q_\theta(\cdot)$ mirrored the architecture of encoders, reversing the order of units (Fig. 1E). Here, ϕ_s, ϕ_z and θ are the learning parameters.

We used below mentioned likelihood lowerbound for our target data x_t:

$$\mathcal{L}_{x_t}(x_{t_i}) \geq \mathbb{E}_{q_{\phi_z}(z)q_{\phi_s}(s)}[Q_\theta(x_{t_i}|s,z)] - KL(q_{\phi_s}(s|x_{t_i}) \parallel p(s)) - KL(q_{\phi_z}(z|x_{t_i}) \parallel p(z))$$

Similarly for background data x_b, the likelihood is:

$$\mathcal{L}_{x_b}(x_{b_i}) \geq \mathbb{E}_{q_{\phi_z}(z)}[Q_\theta(x_{b_i}|0,z)] - KL(q_{\phi_z}(z|x_{b_i}) \parallel p(z)),$$

where $i = 1, \ldots, 149$. $\mathbb{E}$ describes the reconstruction loss, *KL* describes the Kullback–Leibler divergence loss, *p(s)* and *p(z)* are the prior distributions of the relevant and irrelevant latent variables, respectively.

Likelihood lowerbounds or loss functions ($\mathcal{L}_{x_t}$ and $\mathcal{L}_{x_b}$) serve as a guiding principle during the training of cVAE. They ensure that the cVAE effectively learns to disentangle relevant and irrelevant features in the input.

Reconstruction loss: Reconstruction loss measures how well the decoder $Q_\theta(\cdot)$ can reconstruct the input x_*. It penalizes the overall model when the generated output deviates from the original input.

Kullback–Leibler (KL) divergence loss: KL divergence loss measures the discrepancy between the distributions of the latent variables (s and z) learned by the encoders ($q_{\phi_z}(z|x)$ and $q_{\phi_s}(s|x)$) and the predefined prior distributions, i.e., $p(s)$ and $p(z)$. By minimizing the KL divergence between the learned distributions and the prior distributions, the model is encouraged to distribute relevant features (s) and irrelevant features (z) appropriately in the latent space.

During training, the encoders and decoder were optimized simultaneously to minimize the overall loss function which comprises both the reconstruction loss and the KL divergence loss. This optimization process ensured that the encoders learnt to map the input (x_*) onto latent variables that effectively capture relevant (s) and irrelevant features (z). Similarly, the decoder $Q_\theta(\cdot)$ learnt to generate output from these latent variables, reconstructing the original input while separating out the relevant and irrelevant components.

Once the training was completed and parameters ϕ_s, ϕ_z and θ were learnt, we exclusively utilized the latent variable s_{x_t} obtained from the encoder q_{ϕ_s}. This variable was then concatenated with zeros, having the same size as z, and inputted into the decoder to generate the autism-specific functional connectivity x_T (Fig. 1D–F).

We employed t-test to assess the differences in reconstructed and original connectivity maps of the ASD group, Bonferroni correction was further applied to mitigate potential Type I errors.

2.5. Classification

We used a neural network to classify functional connectivity of autistic and neurotypical participants. After collecting connectivity vectors (x_T, x_t, and x_b), we utilized feature engineering to arrange connectivity features in descending order based on their significance in distinguishing between the two classes. We then systematically evaluated the classification performance by considering different subsets of features, denoted as n top features, with n ranging from 1 to N, where N represents the maximum available features, i.e., 171. This assessment enabled us to establish the relationship between classification performance and the number of top features examined. Subsequently, we pinpointed the optimal number of features that yielded satisfactory performance while also minimizing input dimensionality. This reduced feature set was regarded as the sought-after connectivity structure capturing the most informative connectivity changes for discrimination.

2.5.1. Feature engineering

Feature engineering holds significant importance in machine learning and it greatly influences model performance. In our case, the feature table encompassed 171 unique functional connections/features. However, using all features indiscriminately is generally unfavorable, as irrelevant or less relevant features can impair model effectiveness. To mitigate this challenge, we implemented a filter-type feature selection algorithm. Filter-type feature selection evaluates input features based on their intrinsic characteristics, such as feature variance and relevance to the target response. We opted for the minimum redundancy maximum relevance (mRMR) approach [41] for our specific feature selection. Through this process, we identified a compact feature set providing an optimal classification performance for our neural network classifier.

2.5.2. Shallow neural network

We employed a shallow neural network as a classifier. Fig. 2 shows a flow chart of entire simulation. Briefly, we constructed two feature tables after shuffling and concatenating $[x_t; x_b]$ and $[x_T; x_b]$ (Fig. 2B,C) and fed them one by one into a neural network. The neural network consisted of two hidden layers (ReLU activated) and one output layer (sigmoid activated) (Fig. 2C). The classes "Autistic" and "Neurotypical" were encoded as 1 and 0, respectively. We used k-fold cross-validation [42] strategy to encapsulate our entire classification pipeline. This validation scheme is particularly suited for scenarios where the dataset size is not exceedingly large. Within the k-fold cross-validation framework, we randomly partitioned the dataset into k folds, with k set to 10 in our case. Subsequently, for each k the kth group was

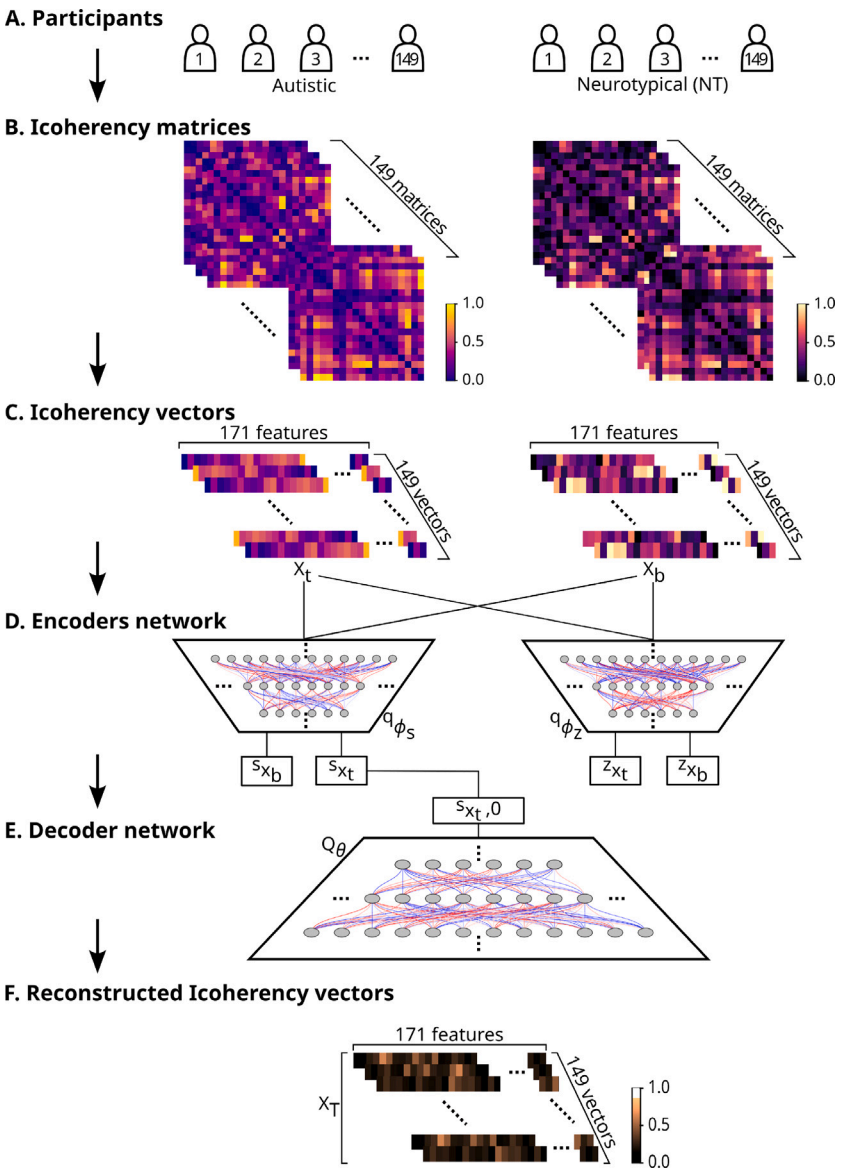

Fig. 1. Pipeline of reconstructing autism-specific functional connectivity. A. Balanced number of 149 participants in ASD and neurotypical groups, aged between 2–16 years. B. Subject-wise computation of Icoherencey matrices in alpha band. C. Reducing symmetrical 19 × 19 Icoherency matrices to Icoherency vectors containing 171 unique functional connections (19 × (19–1)/2 = 171) per vector. D. Structure of encoders q_{ϕ_*}, taking autism-specific connectivity as target input (x_t) and neurotypical connectivity as background input (x_b), producing latent variables containing salient (s_*) and irrelevant (z_*) feature information. E. Structure of decoder, taking input salient latent variables for the target input padded with zeros and producing output without irrelevant information. F. Reconstructed Icoherency vectors (x_T) for the ASD group losing the functional connectivity similarity with neurotypical.

designated as the validation set, while others $k-1$ groups constituted the training set. Feature engineering was then applied solely to the training portion of each fold to prevent data leakage. This process was iteratively performed, allowing each fold to serve as the validation set while the model was trained on the remaining folds. We conducted an in-depth evaluation of the classifier's performance by computing various classification scores which provide insights into the model's effectiveness in distinguishing between autism and neurotypical patterns. These performance scores encompassed accuracy, recall, precision and F1-score [43]. Additionally, we plotted the Receiver Operating Characteristic (ROC) curve [44] to assess how well our designed classifier distinguishes between classes.

2.6. Testing

We evaluated the performance of our proposed pipeline on an independently acquired dataset (see Section 2.1). This testing dataset went through the same preprocessing procedure as that of previous data. For comparison, we computed the same performance scores (i.e., accuracy, recall, precision and F1-score) and plotted ROC curve.

3. Results

Our initial assessment using original functional connectivity structures ($[x_t; x_b]$) revealed a limited capability in distinguishing autistic from neurotypical group. The designed neural network achieved an accuracy of 48.69% and F1-score of 48.25% using a 10-fold cross-validation approach (Table 1). This highlights the intertwining of functional connectivity patterns in autistic and neurotypical individuals.

To disentangle autism-specific functional connectivity, we used cVAE to reconstruct functional connectivity structures. An in-depth comparison between the original and reconstructed EEG functional connectivity structures in ASD revealed no statistically significant differences ($p > 0.05$, Bonferroni corrected, Fig. 3). This fact confirmed

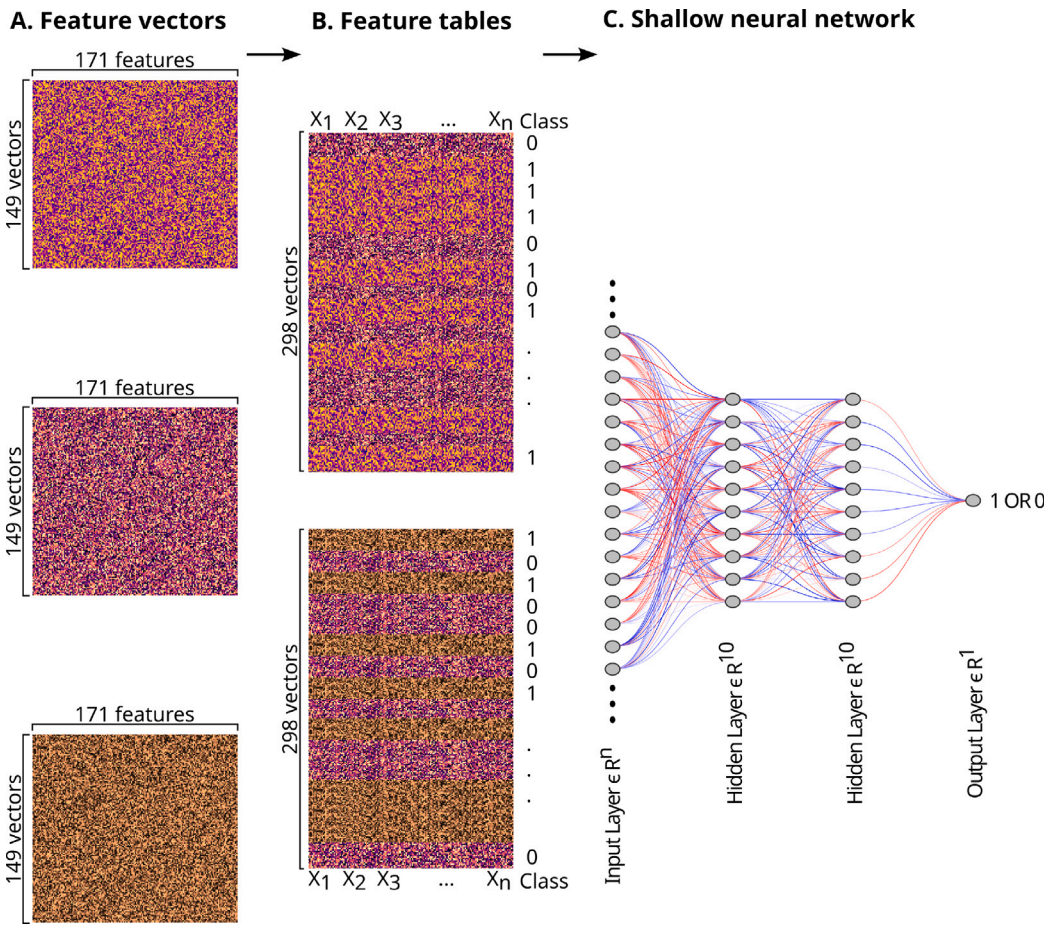

Fig. 2. Pipeline of classification. A. Icoherency feature vectors. Top represents original autism-specific functional connectivity (x_t, see Fig. 1C), middle represents neurotypical functional connectivity (x_b, see Fig. 1C), and bottom represents reconstructed autism-specific functional connectivity (x_T, see Fig. 1F). B. Feature table obtained after shuffling and concatenating feature vectors. Top incorporates original network ($[x_t; x_b]$) and bottom incorporates reconstructed network ($[x_T; x_b]$). Here, $n \in [1, 171]$, where 171 is the maximum number of features. C. Shallow neural network containing two hidden layers with ReLU activation and an output layer of one unit with sigmoid activation.

Table 1
Performance scores of the classifier. 10-fold cross-validation scores for each input. A substantial increase in performance is apparent with the reconstructed and Top-23 input.

Input network	Accuracy, %	Precision, %	Recall, %	F_1, %
Original ($[x_t; x_b]$)	48.69 ± 6.59	48.90 ± 6.84	47.62 ± 14.08	48.25
Reconstructed ($[x_T; x_b]$)	94.95 ± 3.63	92.23 ± 5.81	98.62 ± 1.15	95.32
Top − 23	94.97 ± 3.61	93.19 ± 4.89	97.33 ± 2.66	95.23

Table 2
Top-10 connections in the original and reconstructed networks.

Original network	Reconstructed network
F3 - P4	Pz - P4
Fz - T3	F8 - T3
Fz - F4	F7 - Fz
T3 - T4	F4 - F8
T3 - P3	F3 - P4
Fp2 - T4	F4 - C3
P4 - T6	Fp2 - O1
F4 - O1	F4 - P4
P3 - Pz	T4 - P4
T5 - T6	Fp1 - F8

the reliability of reconstruction of autism-specific functional connectivity. Fig. 3 is the visual representation of average original autism-specific, average reconstructed autism specific, average neurotypical connectivity and their difference.

Upon feeding the reconstructed network ($[x_T; x_b]$) into the neural network, we achieved a substantial accuracy improvement to 94.95% (F1-score up to 95.32%). Table 1 details the performance scores of the classifier with the original ($[x_t; x_b]$) and with the reconstructed networks ($[x_T; x_b]$). Fig. 4 presents the ROC curve of the classifier trained using the 10-fold cross-validation scheme on the first dataset and the ROC curve for the test dataset.

Additionally, using mRMR approach, we found out the optimal subset of 23 features that resulted in accuracy of 94.97% (F1-score of 95.23%). Fig. 5 shows the performance of the neural network (Mean ± SD) on the number of top features. It describes how number of top features impacted the performance of classifier. One can see that classifier performance is gradually increasing with increase in number of top features (n) until it experiences saturation at $n \geq 23$. Thus, we deduce that $n = 23$ is an optimal feature set size providing sufficient information on functional network. It is worth noting that cVAE played an important role in disentangling autism-specific patterns from the broader context of neurotypical functional connectivity. This disentanglement is illustrated in Fig. 6. In original network, we can see that original autism-specific connectivity is intertwined and entangled with the neurotypical connectivity. However, an opposite trend can be observed in the reconstructed network, where the autism-specific connectivity appears more distinct and separated from the neurotypical.

The mRMR algorithm allowed us to delve further into the functional structure's intricacies. Our analysis revealed that the most informative

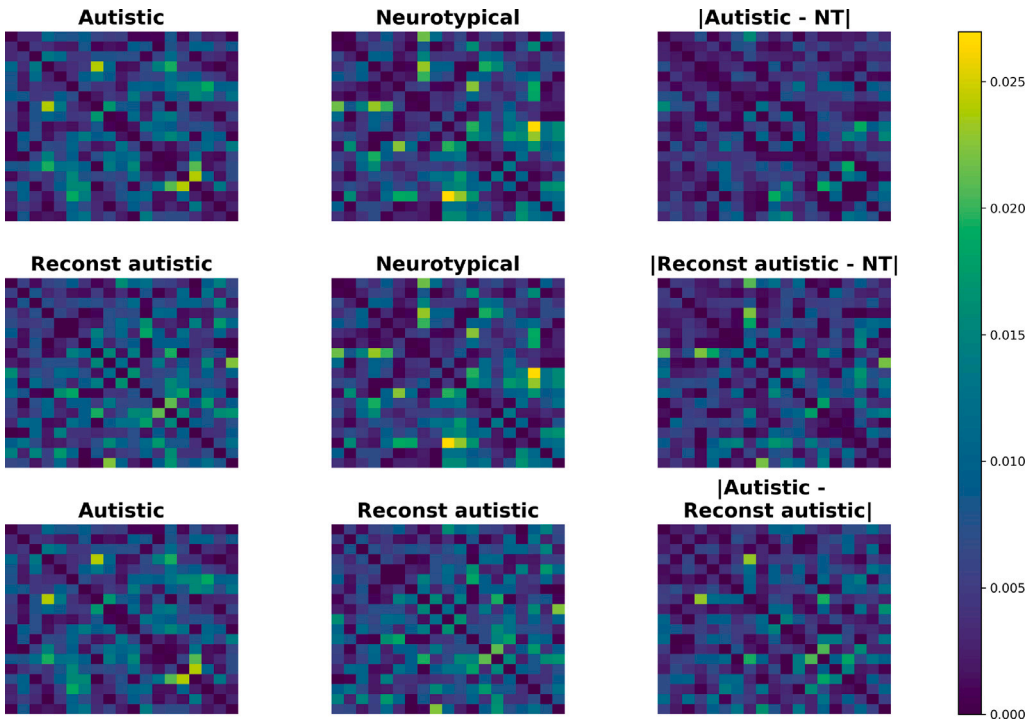

Fig. 3. Differences between the original autism-specific, reconstructed autism-specific, and neurotypical EEG Icoherency connectivity. T-test revealed no significance difference between the original and reconstructed connectivity of ASD group.

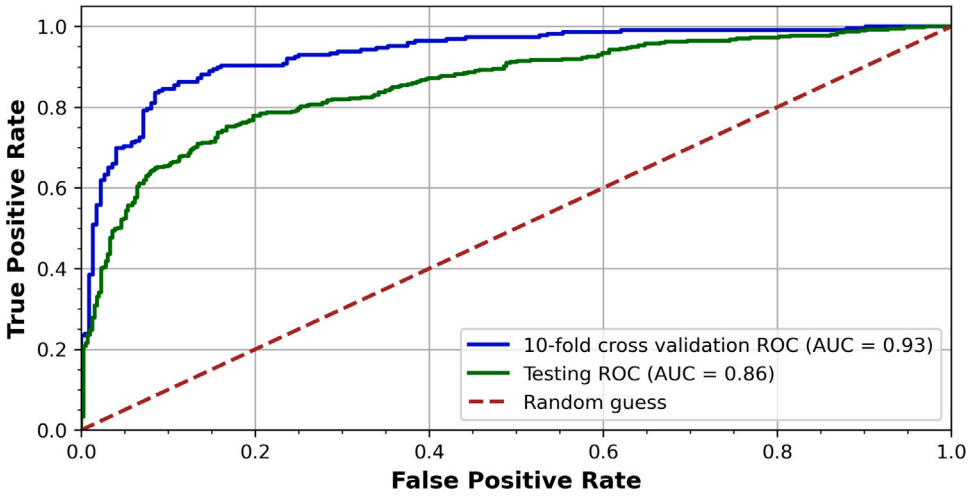

Fig. 4. Comparison of ROC curves. The AUC for the 10-fold cross-validation on the first dataset is 0.93, indicating high performance, while the AUC for the test dataset is 0.86, indicating generalizability.

connections were primarily situated within the frontal lobe (Fig. 7). Table 2 details the name of connections in both original and reconstructed networks. Moreover, we observed weaker strength in those connections for ASD group compared with neurotypical children ($\alpha = 0.05$, $p \leq 1e^{-6}$, $t_{296} = -9.2833$, $SD = 0.0322$).

Table 3 presents the performance score of our proposed pipeline on independent test dataset with 171 and Top-23 features while Fig. 4 shows the ROC curve. The scores and the curve verify the generalizability of our trained pipeline.

Table 3
Performance scores of the proposed pipeline on the test dataset. "All" refers to 171 features, while "Top-23" refers to 23 features extracted by the mRMR algorithm. Although the performance decreased by ≈10%, it is still under reasonable margin.

Input features	Accuracy, %	Precision, %	Recall, %	F_1, %
All	86.41	85.58	87.25	86.46
Top − 23	84.47	85.00	83.33	84.10

4. Discussion

The current study primarily sought to determine if contrastive learning could disentangle abnormal functional connectivity in EEG associated with autism from the broader spectrum of EEG variations in neurotypical development. Additionally, this study represents the first known application of Icoherency as a functional connectivity measure for detection of ASD-associated features in EEG. The cVAE generated functional connectivity enabled a simple shallow neural network classifier to achieve substantial accuracy above 90%. Furthermore, the small subset of critical connections identified via feature engineering gave

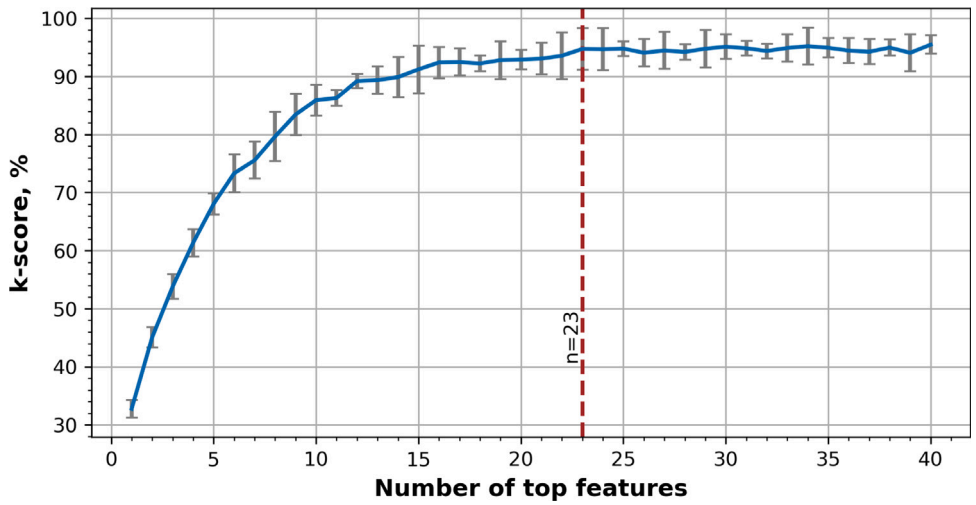

Fig. 5. K-fold cross validation score (accuracy) vs. number of top features. After $n \geq 23$, classifier performance experiences saturation. Whiskers represent standard deviation (SD).

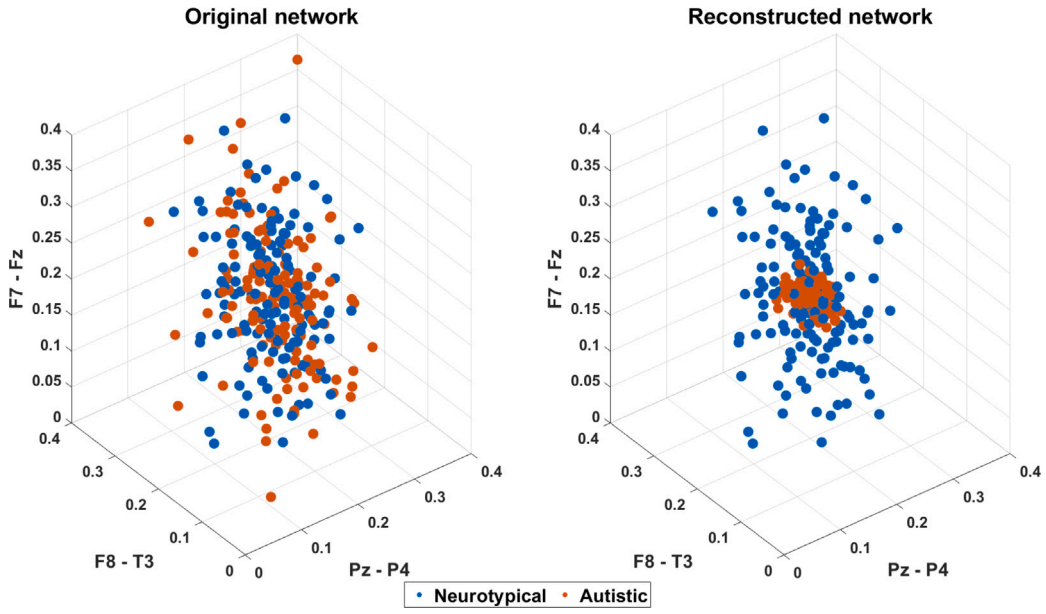

Fig. 6. Disentanglement of autism-specific connectivity. Scatter plot of top 3 features that contributed most in ASD classification. It is apparent how original autism-specific connectivity is entangled with neurotypical in original network while opposite can be seen in reconstructed network.

almost equivalent performance compared to using all connections. Most informative connections were localized in the frontal lobe and showed reduced strength in autistic individuals as compared to neurotypical ones.

Most studies employ traditional connectivity metrics which suffer from volume conduction contamination. Volume conduction also known as field spread problem refers to the complex effects of sensing electrical potentials at a distance far from their sources. Volume conduction has major effects on interpreting the results of EEG experiments and [40] provides a detailed discussion on these issues. To the best of our knowledge, this is the first study which uses Icoherency as a functional connectivity measure to recognize EEG of children with ASD.

The cVAE method helps to identify salient features that may be otherwise entangled with dominant non-salient features. In case of ASD, several studies hinted that autism-specific variations are concealed within broader spectrum of variability in neurotypical development [8,9,39]. In this study, we disentangled autism-specific variations from dominant neurotypical characteristics by treating the autistic functional connectivity as a target data and neurotypical functional connectivity as a background data. Using reconstructed functional connectivity enriched with the autism-specific variations, we achieved a discriminatory accuracy of ≈95% compared to ≈50% when autism-specific functional connectivity was entangled with neurotypical.

Using feature engineering, this study also identified the small subset of critical functional connections that provides almost equivalent performance as that of 171 functional connections. It emphasizes the significance of choosing and interpreting input features for building classifiers (development of interpretable machine learning algorithms). The captured functional connections are not only most informative in classification but are also physiologically interpretable. Moreover, these physiologically interpretable connections reinforce that cVAE successfully isolates distinguishing features rather than extracting trivial dissimilarities. This engineering of features has been proven quite useful in our previous works [15,45].

We have seen that the most informative connections exist in frontal lobe. This demonstrates that alpha band functional connectivity in frontal lobe region of autistic individuals is abnormal as compared to neurotypical peers. This result aligns with several previous studies that

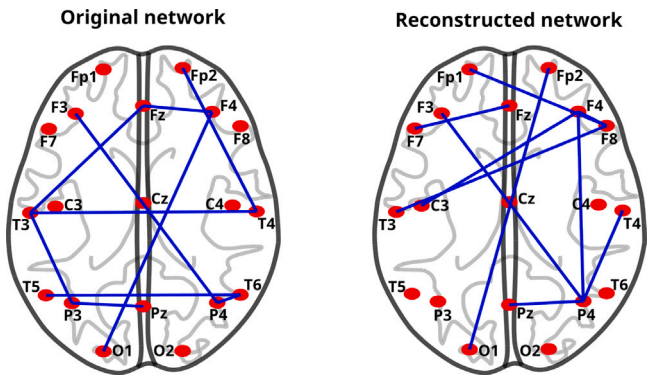

Fig. 7. Functional connectivity structures. Top-10 functional connections that contributed most in the ASD classification computed via mRMR. Connections in original network encompass the whole brain, whereas in reconstructed network, 8 out of 10 connections are in frontal lobe.

demonstrated an alteration in alpha band functional connectivity in frontal lobe of autistic individuals [15,46–55]. Although several other studies concluded that it is difficult to generalize that either hyper- or hypo-connectivity is present in frontal lobe [56–63]. It should be noted that these conflicting findings can originate from differences in experimental methods. Variations exist in how studies define frequency bands, the age of participants, and the metrics used to measure functional connectivity. Nevertheless, it is evident that frontal lobe plays a decisive role in autism.

The altered functioning of the frontal lobes could be highly associated to the neurodevelopment disorders [64]. According to the previous findings human brain develops from the sensory lobes (occipital, temporal and parietal) to the frontal lobe of the brain — the last area of the brain to mature [65]. The relatively late development of prefrontal cortex in children are related to the protracted development of prefrontal-dependent "executive functions" such as planning, decision-making, working memory, cognitive and impulse control, which continue to develop through the all childhood [66,67]. From the other hand, the maturation of prefrontal cortex continues from the early infancy and played a very big role in the development of infant social and emotional functions; so, the frontal lobes could be described as a brain area with later periods of extended refinement [68] and not discerned sensitive periods [69]. In spite of early individual deficits in prefrontal cortex-dependent behaviors had shown high predictive value in the development of social competence, stress resilience, and emotional disorders [70,71], it may not be easily assessed and emerged until the later childhood and especially in the case of altered development in children with ASD. Based on our findings, we suggest that increased focus on efficient frontal lobe EEG sampling could enable more accessible diagnostic functional biomarkers versus blanket scalp coverage.

Since the last decade, machine learning has been playing a significant role in automating autism diagnosis. Unfortunately, much attention was paid to increase performance measure with using complex state-of-the-art deep learning models. Although quite high performance was documented, the results were difficult to generalize. To overcome this problem, we suggest that focus should be given to improve the interpretability of developed models that can provide an explanation of neural mechanisms of autism.

5. Conclusion

We demonstrated the applicability of contrastive machine learning in disentangling autism-specific functional connectivity from the broader spectrum of neurotypical connectivity. Additionally, we captured a set of informative and physiologically interpretable functional connections by utilizing feature engineering technique. Their importance for discrimination autism-specific connectivity from neurotypical connectivity was verified using a shallow neural network that achieved F1-score up to 95%.

Our study reveals the alterations in alpha band functional connectivity of autistic children. We observed a weaker connectivity in frontal lobe for ASD. Based on this finding, we suggest to place greater emphasis on sampling EEG data from the frontal lobe. Our study highlights the critical role of thoughtful selection and interpretation of input features when constructing classifiers. Moreover, the obtained results have proven a contrastive variational autoencoder to be a promising approach for discovering latent patterns and features in complex networks.

We believe our findings could offer a new perspective on using contrastive machine learning with feature engineering to understand neurological disorders. We further expect a shift in focus from performance metrics to utilizing machine learning to explain the underlying mechanisms of neurological disorders.

6. Limitations and future work

While this study demonstrates promising results, it suffers from some limitations that require further work. This study is focused on autistic children and thus limits the applicability of the findings to other age groups. Additionally, the current study primarily focuses on the methodological aspects and does not explore the clinical implications or translational applications of our findings. In perspective, the proposed method may help to elaborate the medical decision support system for ASD diagnosis [72].

In our future work, we aim to address above limitations and expand the scope of our research. One key objective is to replace the supervised classifier in our methodology with an unsupervised classifier. A fully unsupervised pipeline can potentially diagnose autism without relying on labeled data. Furthermore, we suppose to investigate the potential of dynamic functional connectivity analysis and task-based EEG data, which may offer valuable insights into the temporal dynamics and task-related neural patterns associated with ASD.

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CRediT authorship contribution statement

Muhammad Salman Kabir: Writing – original draft, Visualization, Software, Methodology, Investigation, Formal analysis. **Semen Kurkin:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Formal analysis, Conceptualization. **Galina Portnova:** Writing – review & editing, Validation, Resources, Investigation, Formal analysis, Data curation, Conceptualization. **Olga Martynova:** Writing – review & editing, Validation, Resources, Investigation, Formal analysis, Data curation. **Zhen Wang:** Writing – review & editing, Validation, Methodology, Conceptualization. **Alexander Hramov:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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