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Multivariate neural connectivity patterns in early infancy predict later autism symptoms.

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Abstract

BACKGROUND: Functional brain connectivity is altered in children and adults with autism spectrum disorder (ASD). Functional disruption during infancy could provide earlier markers of ASD, thus providing a crucial opportunity to improve developmental outcomes. Using a whole-brain multivariate approach, here we asked whether electroencephalography (EEG) measures of neural connectivity at 3 months of age predict autism symptoms at 18 months.

METHODS: Spontaneous EEG data were collected from 65 infants with and without familial risk for ASD at 3 months of age. Neural connectivity patterns were quantified using phase coherence in the alpha range (6–12Hz). Support vector regression (SVR) analysis was used to predict ASD symptoms at age 18 months, with ASD symptoms quantified by the Autism Diagnostic Observation Schedule-Toddler Module.

RESULTS: ADOS scores predicted by SVR algorithms trained on 3-month EEG data correlated highly with ADOS scores measured at 18 months (r=0.76, p=0.02, root mean square error=2.38). Specifically, lower frontal connectivity and higher right temporo-parietal connectivity at 3 months predicted higher ASD symptoms at 18 months. The SVR model did not predict cognitive abilities at 18 months (r=0.15, p=0.36), suggesting specificity of these brain patterns to ASD.

CONCLUSIONS: Using a data-driven, unbiased analytic approach, neural connectivity across frontal and temporo-parietal regions at 3 months predicted ASD symptoms at 18 months. Identifying early neural differences that precede an ASD diagnosis could promote closer

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monitoring of infants who show signs of neural risk and provide a crucial opportunity to mediate outcomes through early intervention.

Keywords

functional connectivity; autism spectrum disorder; infancy; prediction; electroencephalography; machine learning

Introduction

Autism is a disorder of early brain development that is diagnosed based on the presence of social-communication impairments and restricted, repetitive behaviors (1). The behavioral differences that define autism spectrum disorder (ASD) are typically identified after four years of age (2,3), preventing attempts to mediate outcomes before symptoms emerge. Mapping early markers of atypical brain development in ASD represents a promising opportunity to enhance objective and early detection. Identifying autism earlier in life would, in turn, allow interventions to target neurodevelopmental trajectories while they are most mutable, and before infant development is substantially impacted (4–7).

Neural differences in ASD affect how brain regions are structurally and functionally connected with one another (8–12). Social cognition and behavior depend on multiple distributed brain regions that interact in large-scale networks (13,14) by synchronizing their firing patterns (15–17). Microscopic neural changes in ASD are thought to disrupt the brain's ability to generate and sustain coherent oscillatory activity, therefore impacting how information is communicated between neuronal populations. Evidence from postmortem studies supports the presence of fundamental network differences in ASD, demonstrated by changes in neuronal and axonal organization (18–22), myelination (23), and neurotransmitter receptor density (24,25). The large-scale oscillations that emerge from coherent neuronal activity can be measured non-invasively using EEG and fMRI. Direct (EEG) and indirect (fMRI) measures of oscillatory brain activity provide converging evidence that long-range functional connectivity is reduced across the lifespan in ASD (26–32).

Although the majority of connectivity differences in ASD have been studied after a diagnosis is made, emerging evidence suggests that they originate much earlier. The neuronal and synaptic building blocks that scaffold large-scale networks are established during very early brain development. Human neural stem cell models (33) and postmortem studies (34,35) demonstrate that the initial stages of neuronal maturation and organization are abnormal in ASD. ASD-associated genes are also found to converge upon molecular processes that govern neuronal differentiation and synaptic development (36,37). If these early network differences are present in infants who later go on to develop ASD, they could potentially be captured using measures of oscillatory brain activity.

Characterizing early functional connectivity patterns *in vivo* relies on prospective studies of infants who have a heightened risk of developing ASD. The younger siblings of children with ASD (familial-risk infants) have an ASD recurrence risk of nearly 20% (39) with another 30% showing other types of atypical development including the broader autism

phenotype (38). Because these infants are identified based on family history, they can be studied from birth. MRI studies report early brain changes in familial-risk infants who later develop ASD. At 6 months of age, differences in structural brain development include atypical white matter integrity across distributed long-range tracts (40) and major tracts such as the corpus callosum (41,42). In the same sample of infants, fMRI patterns of atypical functional connectivity at 6 months are shown to predict later ASD diagnosis (43). However, as an indirect measure of neuronal activity, fMRI coactivation patterns cannot assay *how* specific neural communication mechanisms are altered. Direct measurement of patterns of functional connectivity using high temporal precision EEG can provide unique mechanistic insight, complementary to MRI techniques, into neural interactions in early infancy.

EEG is particularly well-suited to clinical screening, as it is portable, relatively low cost, and involves a lower testing burden than MRI (44). While EEG has been used to study early neural differences in ASD, there have been no multivariate studies that characterize cortex-wide functional connectivity patterns in infancy that are associated with ASD. Here we aim to address this gap, employing one type of multivariate pattern analysis method, support vector regression. Multivariate pattern analysis broadly refers to data analysis methods that analyze patterns of activity that are based on multiple input features. Multivariate approaches are sensitive to information that is provided by spatial distribution and therefore represents a powerful way to leverage the rich data that is provided by neural time series data.

This study maps functional connectivity patterns at 3 months of age that are associated with later ASD symptoms. Functional connectivity is quantified using the phase coherence of alpha oscillations (6–12Hz) (45,46), as alpha coherence is highly sensitive to early neural changes that occur in the context of both typical (47,48) and atypical brain development (49). Further, alpha oscillations are specifically associated with the structural (50,51) and functional (52) properties of long-range connections, and may therefore capture earlier markers of the long-range connectivity differences described in children and adults with ASD. Based on previous findings implicating distributed structural and functional connectivity disruptions infancy in ASD (41,42), we hypothesized that similar patterns of reduced long-range alpha coherence would predict a higher level of ASD symptoms at 18 months.

Methods and Materials

Sample

Participants in the present analyses were part of a larger ongoing study examining the development of infants with and without familial risk for ASD across the first 3 years of life. Exclusion criteria included evidence of a genetic condition or syndrome, gestational age<37 weeks, and prenatal/perinatal complications. Familial-risk infants (N=36) had at least one older sibling with a confirmed ASD diagnosis. Initial parent reports of sibling diagnoses were confirmed by a review of documented evidence. Low-risk infants (N=29) had no reported family history of ASD or other neurodevelopmental disorders within first degree relatives.

Infants were recruited from the community through the UCLA Center for Autism Research and Treatment (CART). Sixty-five infants completed an EEG recording session at 3 months and underwent behavioral assessment at 18 months. Demographic data describing the final 65 participants are presented in Table 1. The study received ethical approval from the relevant institutional review board, and parents provided informed written consent on behalf of all infants in accordance with the Declaration of Helsinki.

ASD Assessment

A trained clinician administered the Toddler Module of the Autism Diagnostic Observation Schedule-Second Edition (ADOS-T) at 18 months (53,54). The ADOS-T is an assessment tool used by clinicians and researchers to assess social-communication and repetitive behaviors associated with ASD (53) in children under 30 months of age (54). ASD symptoms were quantified using dimensional ADOS-T algorithm scores (total score ranging from 0–18). ADOS-T scores ≥ 10 indicate a clinically relevant level of symptoms at 18 months, and are highly indicative of ASD symptoms at later ages (measured using the ADOS) (55). Sample descriptions are provided according to both familial-risk status groupings and ADOS-T cut-off (ASD+ (ADOS-T ≥ 10) & ASD – (ADOS-T<10)) groupings. Of the infants considered ASD+ at 18 months, 11 had familial risk for ASD, and 3 were at low risk.

Cognitive Assessment

Cognitive function was also assessed, in order to distinguish EEG patterns associated with ASD symptoms, rather than general developmental level. The Mullen Scales of Early Learning (MSEL) (56) were administered by trained clinicians at 18 months. The MSEL is a standardized measure of developmental abilities that yields scores five subscales (visual reception, fine motor skills, gross motor skills, receptive language, and expressive language). Subscale *t-scores* (M=50, SD=10) were used in analyses. Receptive language and expressive language subscale *t-scores* were averaged to calculate verbal cognition, and the *t-scores* from the visual reception and fine motor subscales were averaged to calculate non-verbal cognition.

EEG Acquisition

Spontaneous EEG data were recorded using a 129-channel Hydrocel (Electrical Geodesic Net Inc., Eugene, OR), in a dimly lit, sound-attenuated room. EEG was sampled at 500 Hz and referenced to vertex (Cz) at the time of recording. Four electrodes positioned to record electrooculogram (EOG) (located below and lateral to the eyes) were removed from the net to increase comfort for infants. Net Station 4.4.5 software was used to record from a Net Amps 300 amplifier with a low-pass analog filter cutoff frequency of 6 KHz. Data were sampled at 500 Hz and referenced to vertex (Cz) at the time of recording. Electrode impedances were kept below 100 KΩ. Infants were held in a caregiver's lap throughout the recording while bubbles were blown by an unseen experimenter, consistent with widely used spontaneous recording conditions in infant populations (57). EEG data were acquired for at least 3 minutes, with the recording session extended up to 5 minutes if the infant remained calm.

EEG Processing

All offline data processing and analyses were performed using EEGLAB (58) and in-house MATLAB scripts. The experimenter was blind to participant details (including risk status) throughout the data cleaning process. Data were high pass filtered to remove frequencies below 1 Hz and low pass filtered to remove frequencies above 90Hz, using a finite impulse response filter. Continuous data were then visually inspected, and any sections including excessive electromyogram or other non-stereotyped artifacts were removed. Artifact subspace reconstruction (ASR), a data cleaning method that uses sliding window principal component analysis, was then used to remove high amplitude artifacts, relative to artifact-free reference data (59,60). ASR is especially useful for retaining maximum data in infants (where the length of EEG recordings is limited), as it allows artifacts to be removed while retaining the co-occurring EEG activity that is 'clean'. The eeglab function *clean_RawData* was used to implement ASR, with default parameters and rejection threshold k=8 (59).

Following interpolation to the international 10–20 system 25 channel montage (61), independent component analysis (ICA) was used to decompose data into maximally independent components (IC) (62), and the power spectral distribution (PSD), scalp topography and time course of each IC were visually examined. IC's that represented non-neural activity (including EMG, EOG, heart artifact and line noise) were removed from the data.

ASR cleaning resulted in an average of 17 channels being removed, and 17.8% of data points being altered. The number of channels removed (P=.438), and data points changed (P=.398), did not vary between ASD outcome groups. The independent components removed during the second stage of cleaning averagely accounted for 24.7% of the EEG variance and did not vary between ASD outcome groups (P=.152). There was no difference between groups in the length of the EEG recording post-cleaning (M=139.54, P=.464).

Alpha Phase Coherence

Cleaned data were transformed to current source density (CSD) estimates, in order to mitigate the effects of volume conduction (46,63). Spherical spline Laplacian transforms were conducted using realistic head geometry, with head radius set at 7cm (representing the average head radius of 3-month-old infants), and flexibility constant m = 3. CSD data were separated into 3-second epochs to obtain coherence metrics. To retain consistent data length across all participants, the first 75 seconds of data were used in all further analyses (representing the minimum data length available across the sample). The newcrossf function provided by eeglab (58) was used to compute phase coherence (ERPCOH) from the aforementioned resting state epochs (for each frequency bin):

$$\mathrm{ERPCOH}^{a,b}(\mathrm{f,t}) = \frac{1}{n}\sum_{k=1}^{n}\frac{F_k^a(f,t)F_k^b(f,t)^*}{\left|F_k^a(f,t)F_k^b(f,t)\right|}$$

where $F_k^a(f,t)$ represents the spectral estimate of channel a in epoch k at frequency f and time t. $F_k^b(f,t)^*$ is the complex conjugate of $F_k^b(f,t)$ (58). For each channel pair, ERPCOH

was averaged across all frequency bins encompassed by alpha band (6–12Hz), resulting in 300 values that represented alpha phase coherence between every possible electrode pair.

Model Fitting

Prediction models were used to assess the relationship between 3-month coherence and 18-month ASD symptoms (ADOS-T total score), with all 300 alpha phase coherence values serving as the initial feature set. A "nested" leave-one-out cross validation (LOOCV) procedure was used to predict the ADOS score of each participant. A nested procedure includes an outer loop that is used to predict N=1, with the remaining N=64 being entered into an inner loop where predictive features are tuned using LOOCV (see Figure 1). Selecting features for each fold with the data of the test subject remaining entirely unseen ensured that feature model performance was not falsely inflated through circularity bias (64).

Model Fitting: Feature Selection

A LOOCV regularized regression approach with an elastic net penalty was used to select a subset of functional connections within each fold. Elastic net regularization is a hybrid approach combining both the ℓ_1 penalty of lasso, and the ℓ_2 penalty of ridge regression (65,66), and it is well suited to remove redundant variables and prevent model overfitting for high dimensional data (67). There are two parameters that impact penalized regression, α and λ. α regulates the degree of mixing between ℓ_1 and ℓ_2 penalties, and effectively determines the compromise between lasso (least absolute shrinkage and selection operator) and ridge regression techniques. Here we implemented α=0.5 to represent an equal balance between ℓ_1 and ℓ_2 penalties. λ is the penalty term and defines the strength of regularization. A geometric sequence of λ values were trialed to determine the λ value that minimized model deviance (mean squared error; MSE), with the final values across all folds averaged to provide a consistent value (λ=1). The *lasso* function in MATLAB was used to implement the regression procedure, and all predictor variables were centered and standardized.

Model Fitting: Support Vector Regression

After conducting feature selection within each inner fold, linear-kernel support vector regression (SVR) models were trained using the default parameters of the *fitrsvm* function in MATLAB. In addition to the advantages of binary classification offered by traditional SVM, support vector machines for regression (SVR) offer an opportunity to assess the value of functional connections for predicting ASD behaviors dimensionally (68). The resulting model was used to estimate the ADOS-T score of the N=1 participant who was left out of the outer loop (validation sample). The procedure was then repeated N=65 times.

Predictive capabilities were examined through the relationship between observed and predicted ADOS-T score. The statistical significance of all LOOCV results was determined using a permutation testing approach (69,70). The null distribution of R^2 was estimated by repeating the entire model fitting procedure (including feature selection within each fold) using 1000 surrogate datasets that were generated under the null hypothesis that there is no relation between 3-month EEG and 18-month ADOS. The final statistical significance of the model was determined by calculating the percentage of null-models that yielded symptom

estimates better than the final model. The reported permutation p values therefore represent the probability of observing the reported R^2 values by chance.

Predictive Model Features

A major benefit of multivariate pattern analysis is the ability to examine the features that drive the predictive capability of the SVR algorithm. We analyzed the final consensus feature set that consisted of 22 functional connections that had non-zero coefficients in 100% of folds (69,71), extracting the weight value assigned to each feature. Interpreting the weights from linear models in terms of neural activity patterns can be misleading (72,73). To allow neurophysiological interpretation of individual features in the model, SVR weights were transformed into activation patterns using the method described by Haufe and colleagues (73). Specifically, the activations are derived by,

$$A = \sum_x W \sum \hat{S}^{-1}$$

where Σ_x denotes the covariance of the data, W represents the regression weights, and Σ_s^{-1} is the inverse covariance of the latent factor.

Results

Model Performance

Alpha phase coherence at 3 months predicted ADOS-T scores. Specifically, the SVR model estimated ADOS-T total scores that significantly correlated with actual ADOS-T scores measured at 18 months (Pearson's $r = 0.76$; $R^2 = 0.58$; $p = 0.02$; see Figure 2). Reported significance values were corrected to represent permutation testing (described in methods section). The average root mean square error across the sample was 2.38 (SD=2.08). Independent t-tests indicated that prediction errors did not vary according to familial-risk group ($p = 0.20$), ADOS outcome group (p=.19), or sex ($p = 0.16$).

To determine its specificity, we assessed the ability of the model to estimate cognitive function. Trained on the same input features, the SVR model was unable to predict verbal and non-verbal cognitive scores at 18 months. While there was a stronger relationship with verbal cognitive abilities (Pearson's r =0.31, p =0.01, corrected p =0.91) than non-verbal cognitive abilities (Pearson's $r = 0.15$; p =0.36, corrected p=0.99), neither of these relationships were significant.

Feature Activations

As described above, the contribution of individual functional connections to the SVR model was quantified using activation patterns, which are defined as transformed SVR weights that allow neurophysiological interpretation (but do not represent activation patterns as conventionally described in MRI work). Functional connections that contributed to the SVR model represented a mix of positive and negative features (See Figure 3 & 4).

Discussion

The present study characterizes functional connectivity patterns during early infancy that predict individual differences in later ASD symptoms. Early connectivity differences that predicted ASD symptoms were multivariate, highlighting the importance of studying patterns of activity rather than specific functional connections. The regional distribution of predictive connections shows that decreased connectivity across frontal connections and increased connectivity across temporo-parietal areas are associated with a higher level of ASD symptoms at 18 months. Due to the limited spatial resolution of EEG, the precise cerebral structures driving these results cannot be determined. However, guided by an infant EEG-MRI localization study, we can consider general structures that underlie electrode locations (75).

Decreased frontal alpha phase coherence

Decreased alpha phase coherence across fronto-frontal, fronto-temporal and fronto-parietal connections predicted higher ASD symptoms. Early disruptions in frontal connectivity are particularly relevant, given the extensive previous literature that implicates frontal neuropathology in ASD. At a cellular level, postmortem studies show disruptions in neuronal (22,34,76), axonal (23), laminar (35), and minicolumn (18,77) organization in the frontal cortex of individuals with ASD. Differences in large scale frontal connectivity (often fronto-posterior hypoconnectivity) are also highly supported by EEG and fMRI studies of children and adults with ASD (30,78–83). We extend these findings to show that frontal disruptions occur prior to behavioral symptoms, suggesting that they represent core pathophysiology of the disorder, and not simply a consequence of ASD symptoms.

Frontal cortex may be particularly vulnerable to connectivity disruptions in ASD for several reasons, especially given its protracted development (84). For instance, ASD-associated risk genes are shown to converge upon co-expression networks in frontal cortex during fetal brain development (36). By disrupting key neurobiological processes (such as neuronal migration, synaptogenesis, and myelination) in frontal cortex, ASD-risk genes may particularly impact frontal functional connectivity (85). Further evidence linking ASD-risk genes to specific frontal disruptions comes from copy number variations and single gene disorders that confer susceptibility for ASD and are also associated with decreased fronto-temporal and fronto-parietal connectivity (86–91). The present data suggest that, in addition to the changes seen in syndromic ASD (91), early frontal dysconnectivity arising from familial risk may similarly predispose infants to the emergence of later ASD symptoms.

Increased temporo-parietal alpha phase coherence

Positively weighted predictors describe connections for which increased coherence is associated with higher levels of ASD symptoms at 18 months. These connections mainly bridged temporal and parietal areas in the right hemisphere and were localized above brain structures that subserve social information processing (13), including the superior temporal sulcus, as well as postcentral, supramarginal, temporal and angular gyri (75). These results implicate the right temporoparietal junction (rTPJ) (92), a social hub (93) that coordinates social information processing (94,95), and shows atypical function in ASD (96). Alpha

phase coherence differences in these regions may reflect the network inefficiencies (40) and structural differences in temporal and parietal white matter tracts that have been identified at 6 months of age in ASD (41), especially given that white matter integrity is associated with alpha phase coherence (97).

In addition to revealing early connectivity differences during infancy, increased alpha phase coherence in temporal parietal areas may shed mechanistic insight into reports of hypoconnectivity that are observed following infancy in ASD. The deleterious effects of increased regional connectivity are well-described in neurocognitive disorders, where periods of increased connectivity are shown to precede decreased connectivity, a pathological process described as hub-overload (98). Increased alpha phase coherence may lead to hub-overload in ASD (99), and could underlie the transition from over- to under-connectivity that is seen in both alpha phase coherence and white matter integrity from around 2 years of age in ASD (41) (27), as well as widely described reductions in rTPJ activation and connectivity (31,96,100–106).

Scalability

EEG measures of early brain network function can serve as scalable and clinically actionable predictors of ASD in early infancy, at a time when behavioral signs of atypical development remain unclear. The portability, relatively low cost and low testing burden of EEG renders it practical for community screening in large populations (44). To translate laboratory-based EEG studies to community settings, a neural signal of interest must be accurately measured under task-free conditions in less controlled environments. Alpha phase coherence, in particular, represents a highly scalable metric. Alpha oscillations are dominant in spontaneous brain activity and are less susceptible to biological and environmental artifacts (107,108), thus facilitating its measurement in larger, clinical or community samples (109).

Early Identification & Intervention

Behavioral features that can consistently predict later ASD diagnosis have not been identified in the first year of life, and predominantly emerge after 12 months of age (110–115). Although EEG is not intended to replace behavioral assessment of ASD, EEG markers are uniquely positioned to elucidate individual differences that confer neural risk for ASD. By examining dimensional risk (rather that binary diagnostic labels), the present study highlights that early network disruptions in ASD occur along a continuum. This approach will facilitate the identification of neural risk associated with milder/borderline ASD symptoms, a clinical group that elude early behavioral identification (3), but may be particularly responsive to prompt intervention (116,117).

Early disruptions in brain activity may also impact how an infant responds to their environment, causing a cascading brain-behavior-environment interaction (76,118–122) that will further impact brain development (123,124). Identifying individuals using objective EEG markers will facilitate a shift from reactionary interventions that focus on modifying established behaviors, towards preemptive interventions that may mitigate the effects of early disruptions (125,126).

Strengths, Limitations & Future Directions

The present study leveraged the benefits of machine learning to model multivariate data. However, in order to retain interpretable links between neurobiology and behavior (127,128), we employed a hypothesis-driven modelling approach that reflects our prioritization of interpretability over prediction. For instance, although the inclusion of additional EEG features may capture interactions leading to better model prediction, by focusing on one neurobiologically- and clinically-relevant EEG metric (alpha phase coherence), we retain the ability to map predictive model features back on to EEG data (129). These links were also preserved through the use of linear modelling, as well as forward modelling transformations (73,130). These steps allow us to understand very early brain differences that precede ASD, and ultimately optimize the translatable clinical utility of machine learning methods in ASD.

As with many prior EEG studies of familial-risk infants, a relatively small sample size and lack of independent validation limits the generalizability of this study. To determine if alpha phase coherence patterns can provide a clinically applicable biological marker of risk, we need studies in diverse participant samples representing wider etiological factors beyond familial risk, such as infants with known genetic syndromes or preterm infants, as well as a community screened cohort. Although the patterns of functional connectivity described here were not associated with later verbal cognition, it may be the case that they are predictors of general language delays that are not specific to ASD. In order to ascertain the specificity of the present findings to ASD, future studies will examine social communication impairments and restricted repetitive behaviors using separate assessments. Disentangling ASD symptom domains will elucidate whether the patterns described here are equally predictive of restricted and repetitive behaviors and social communication impairments.

The present study also focused on one measurement technique. Since EEG and fMRI provide complementary information about brain function (131), a recently initiated study by our group integrates both methods to examine how the timing of structural and functional brain changes are related to one another during the first year of life in ASD. Finally, longitudinal monitoring of behavior, environment, and brain development will broaden our understanding of dynamic early changes in ASD and inform decisions around the exact timing and targets of preventative interventions to ultimately improve developmental outcomes.

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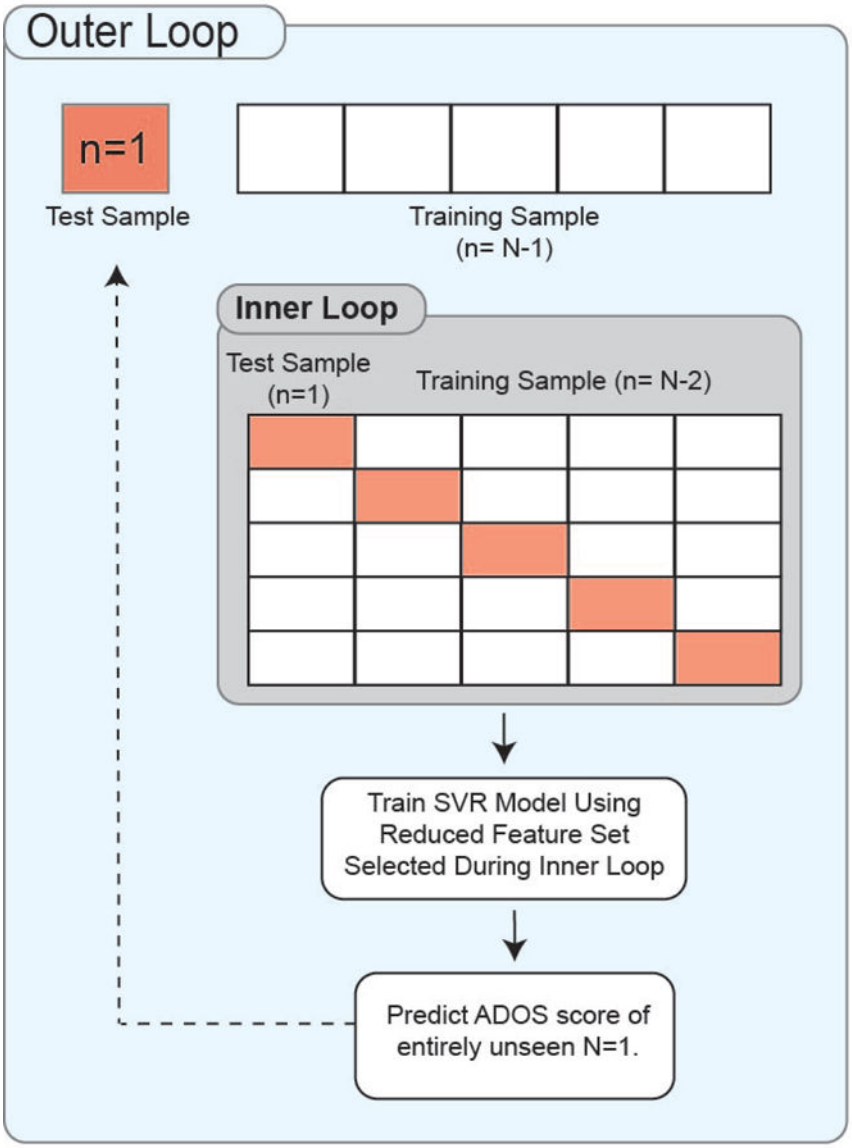

Figure 1.
A schematic representation of the machine learning approach used to predict ASD symptoms at 18 months.

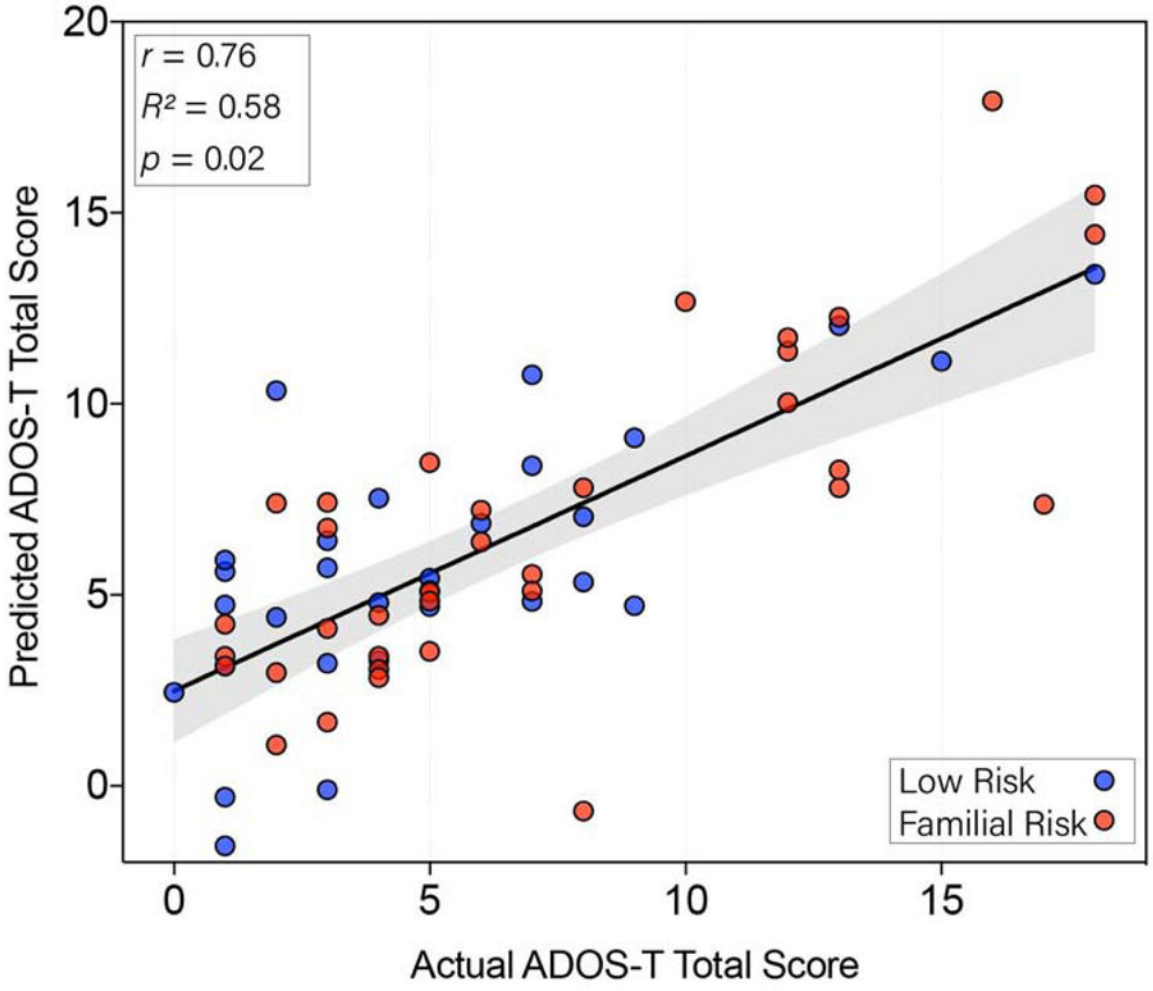

Figure 2.
Correlation between actual ADOS-score (X axis), and the predicted ADOS score (Y axis) for each participant, with 95% confidence intervals.

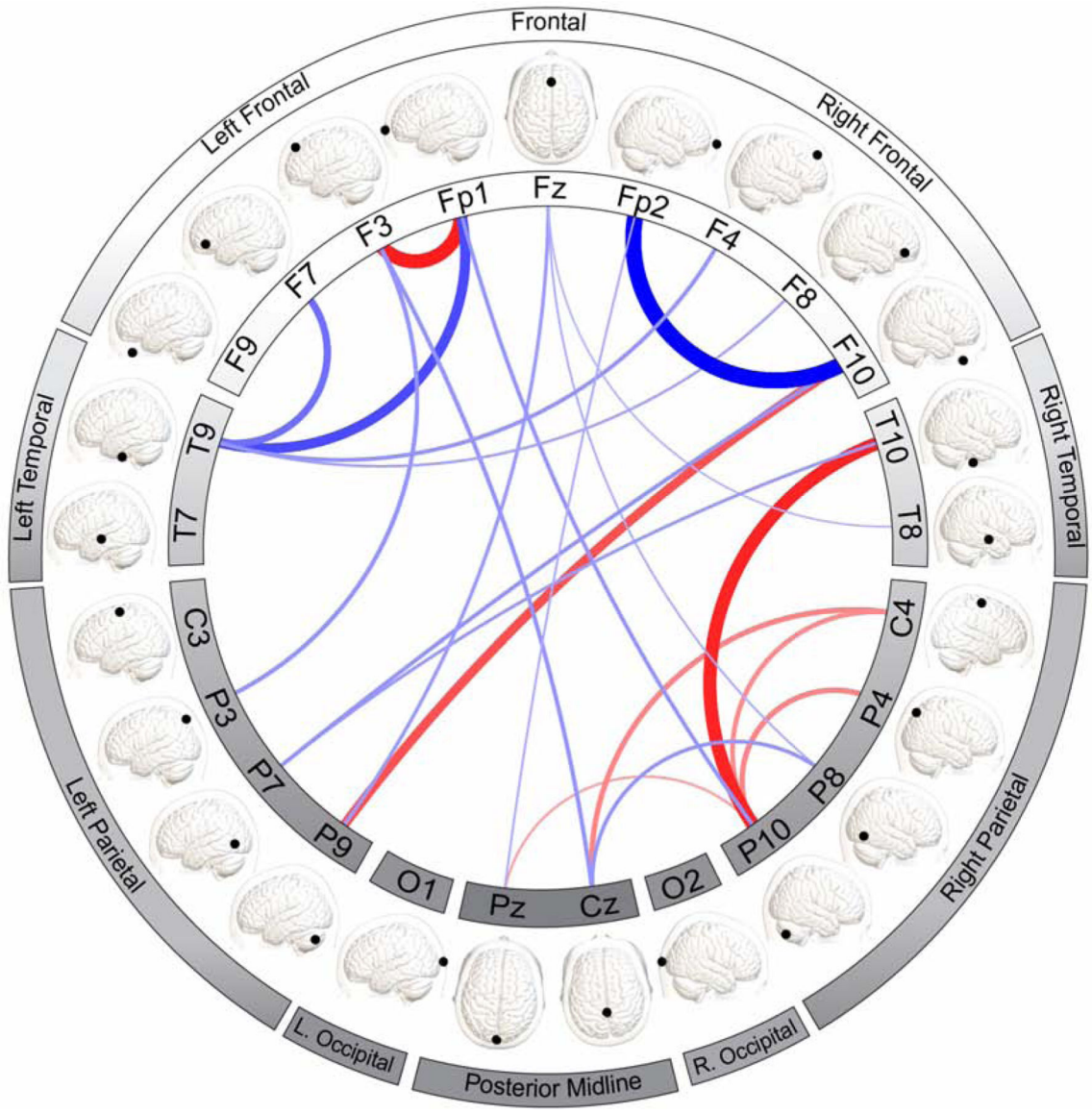

Figure 3.

Mean feature activations for each of the 22 predictive function connections that defined the consensus feature set. Red lines represent a positive activation value (higher alpha phase coherence = higher ADOS-T score), and blue lines represent a negative activation value (lower alpha phase coherence = higher ADOS-T score). Wider lines indicating a larger contribution to the model (greater absolute activation strength). Graphical representations indicate the location of each measurement channel. White-gray shading of electrode labels indicates the anterior (white) – posterior (gray) location of each channel.

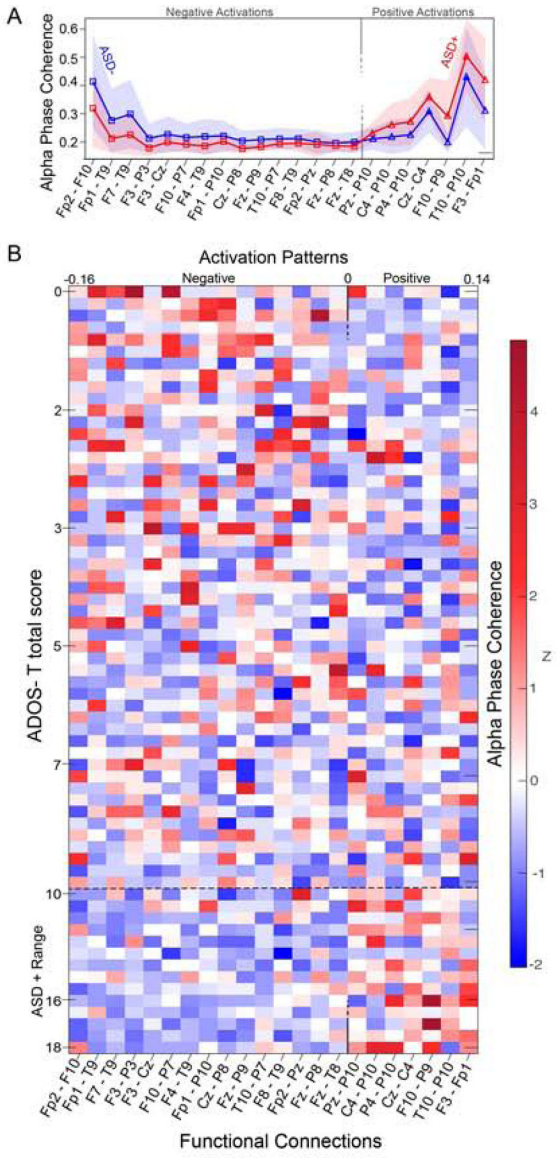

Figure 4.

(A) Mean alpha phase coherence for each of the 22 predictive function connections that defined the consensus feature set for ASD+ (red) and ASD- (blue) groups. Shaded regions represent SD. (B) Individual alpha phase coherence values (z scores) for each participant (arranged from low to high ADOS score) for each predictive function connection (with activation patterns arranged from negative to positive).

Table 1.

Demographic participant details grouped by familial risk status, and ASD symptoms at 18 months.

	Familial Risk (N=36)	Low Risk (N=29)	*P Value*[a]	ASD+ (N=14)	ASD− (N=51)	*P Value*[a]
Sex n female (% female)	13 f (36.1%)	11 f (37.9%)	.54	2 (14.3%)	22 (43.1%)	0.60
Race n (%)						
White	21 (58.3%)	18 (62.1%)		4 (28.6%)	35 (68.6%)	
More than one race	9 (25%)	10 (34.5%)	.21	6 (42.9%)	13 (25.5%)	.01*
Asian/Black/Pacific Islander	6 (16.7%)	1 (3.4%)		4 (28.6%)	3 (5.9%)	
Ethnicity n (%)						
Hispanic	16 (44.4%)	4 (13.8%)	.01*	5 (35.7%)	15 (29.4%)	.65
Non-Hispanic	20 (55.6%)	25 (86.2%)		9 (64.3%)	36 (70.6%)	
Maternal Education n (%)						
Some college or less	2 (6.9%)	2 (6.9%)		2 (14.3%)	2 (3.9%)	
College Degree and above	28 (77.8%)	24 (82.8%)	.756	9 (64.3%)	43 (84.3%)	.20
Unreported	6 (16.7%)	3 (10.3%)		3 (21.4%)	6 (11.8%)	
Precise 3 Month EEG age Mean (SD), Range	3.18 (0.35), 2.57–3.90	3.17 (0.32), 2.63–4.13	.87	3.05 (.23), 2.57–3.43	3.21 (.36), 2.63–4.13	.117
18 Month MSEL Verbal T-score Mean (SD), Range	43.39 (9.61), 21–63.5	49.07 (10.63), 25–66	.030*	31.75 (5.82), 21–40.50	49.95 (7.43), 35.5–66	<.001*
18 Month MSEL Non-verbal T-score. Mean (SD), Range	46.07 (7.51), 24.5–64	51.54 (9.08), 25–66	.011*	40.96 (9.70), 24.5–59.5	50.65 (7.02), 34–66	<.001*
18 Month ADOS-T Total Score Mean (SD), Range	7.17 (5.12), 1–18	5.21 (4.44), 0–18	.11	14.28 (2.67), 10–18	4.09 (2.46), 0–9	<.001*
18Month ADOS-T Total Score >10 n >10 (%>10)	11 (30.6%)	3 (10.3%)	.07			

[a]Group differences assessed using independent samples t-tests or chi-square analyses.