Computational Models for Biomedical Reasoning and Problem Solving

Chung-Hao Chen
Old Dominion University, USA

Sen-Ching Samson Cheung
University of Kentucky, USA

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Chapter 2
Electroencephalogram (EEG) for Delineating Objective Measure of Autism Spectrum Disorder

Sampath Jayarathna
Old Dominion University, USA

Yasith Jayawardana
Old Dominion University, USA

Mark Jaime
Indiana University-Purdue University Columbus, USA

Sashi Thapaliya
California State Polytechnic University – Pomona, USA

ABSTRACT

Autism spectrum disorder (ASD) is a developmental disorder that often impairs a child's normal development of the brain. According to CDC, it is estimated that 1 in 6 children in the US suffer from development disorders, and 1 in 68 children in the US suffer from ASD. This condition has a negative impact on a person's ability to hear, socialize, and communicate. Subjective measures often take more time, resources, and have false positives or false negatives. There is a need for efficient objective measures that can help in diagnosing this disease early as possible with less effort. EEG measures the electric signals of the brain via electrodes placed on various places on the scalp. These signals can be used to study complex neuropsychiatric issues. Studies have shown that EEG has the potential to be used as a biomarker for various neurological conditions including ASD. This chapter will outline the usage of EEG measurement for the classification of ASD using machine learning algorithms.

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INTRODUCTION

Autism Spectrum Disorder (ASD) is characterized by significant impairments in social and communicative functioning as well as the presence of repetitive behaviors and/or restricted interests. According to CDC estimates, the prevalence of ASD (14.6 per 1,000 children) has nearly doubled over the last decade and has a costly impact on the lives of families affected by the disorder. It is estimated that 1 in 6 children in the US suffer from developmental disorders. And 1 in 68 children fall under Autism Spectrum Disorder. ASD is a neurological and developmental disorder that has negative impact in a person's learning, social interaction and communication. It is a debilitating condition that affects brain development from early childhood creating a lifelong challenge in normal functioning. Autism is measured in spectrum because of the wide range of symptoms and severity. The total lifetime cost of care for an individual with ASD can be as high as $2.4 million (Buescher et al. 2014). In the U.S., the long-term societal costs are projected to reach $461 billion by 2025 (Leigh and Du 2015).

One of the main contributing factors for ASD is known to be genetics. And so far, no suitable cure has been found. However, early intervention has been shown to reverse or correct most of its symptoms (Dawson 2008). And this can only be possible by early diagnosis. Therefore, early diagnosis is crucial for successful treatment of ASD. Although progress has been made to accurately diagnose ASD, it is far from ideal. It often requires various tests such as behavioral assessments, observations from caretakers over a period to correctly determine the existence of Autism. Even with this tedious testing often individuals are misdiagnosed. However, there remains promise in the development of accurate detection using various modalities of Biomedical Images, EEG, and Eye movements.

Efforts to identify feasible, low-cost, and etiologically meaningful biobehavioral markers of ASD are thus critical for mitigating these costs through improvement in the objective detection of ASD. However, the phenotypic and genotypic heterogeneity of ASD presents a unique challenge for identifying precursors aligned with currently recognized social processing dimensions of ASD. One approach to unraveling the heterogeneity of ASD is to develop neurocognitive measures with shared coherence that map onto valid diagnostic tasks, like the Autism Diagnostic Observation Schedule Second Edition (ADOS-2) (Gotham et al. 2007), that are the gold standard

in ASD identification. These measures can then be used to stratify children into homogeneous subgroups, each representing varying degrees of impaired social neurocognitive functioning. Despite the need for objective, physiological measures of social functioning, machine learning has not yet been widely applied to biobehavioral metrics for diagnostic purposes in children with ASD.

This chapter focuses on a social processing domain which, according to the NIMH Research Domain Criteria (RDoC), is a central deficit of ASD and lends itself to quantifiable neurocognitive patterns: social interactions during ADOS-2. The ability to socially coordinate visual attention, share a point of view with another person, and process self- and other-related information (Barresi and Moore 1996; Butterworth and Jarrett 1991; Mundy et al. 2009) is a foundational social cognitive capacity (Mundy 2016). Its emergence in infancy predicts individual differences in language development in both children with ASD and in typically developing children (Mundy et al. 1990; Mundy and Newell 2007). Moreover, attention is recognized in the diagnostic criteria of the DSM-V as one of the central impairments of early, nonverbal social communication in ASD. While the empirical evidence on the physiological nature of attention deficits in ASD is emerging that can index attention: social brain functional connectivity (FC) during real-life social interaction.

At the same time, it is well-established in the literature that the neural systems that subserve social cognition are functionally compromised in children with ASD (Baron-Cohen et al. 1985; Lombardo et al. 2011; Hill and Frith 2003; Kana et al. 2009; Mason et al. 2008). The research suggests there is a functional (frontal-temporal-parietal) overlap in neural system activity during ADOS-2 and social cognitive processing (Mundy 2016; Kennedy and Adolphs 2012; Redcay et al. 2012; Schurz et al. 2014; Lombardo et al. 2010; Caruana et al. 2015). Taken together, there is ample evidence to support that aberrant frontal temporal-parietal FC is a potential nexus for latent social cognitive disturbance in early ASD.

Many studies reveal either under- or over-connected areas in the autistic brain, depending on whether the subject is at rest or engaged in cognitive processing (Coben et al. 2008; Just et al. 2004; Just et al. 2006; Kana et al. 2014; Koshino et al. 2005; Koshino et al. 2007; Lazarev et al. 2015; Lynch et al. 2013; Uddin et al. 2013; Shih et al. 2010; Noonan et al. 2009; Jones et al. 2010; Damarla et al. 2010; Mohammad-Rezazadeh et al. 2016). Reduced FC within frontal, superior temporal, and temporal— parietal regions—regions that comprise the social brain system—have been consistently reported in most fMRI studies examining FC during social information processing

(Koshino et al. 2007; Castelli et al. 2002; Kleinhans et al. 2008; Rudie et al. 2011; Welchew et al. 2005). The presence of altered social brain system FC in early neurodevelopment can potentially reveal the onset of social difficulties (Keehn et al. 2013), as altered FC disrupts efficient information flow between parallel and distributed neural systems involved in the processing of social and communicative information (Mundy et al. 2009). Thus, children with ASD may develop with limited neurocognitive resources to efficiently deal with the processing demands of dynamic social exchanges. This social deficit may emerge as idiosyncratic patterns of EEG during bouts of joint social attention

LITERATURE SURVEY

Social Interaction Tasks

To date, the few studies that have examined FC during attention have done so using non-clinical paradigms that involve the observation of attention-eliciting videos; however, data from such paradigms may not reflect the true person-to-person interactive nature. More importantly, video paradigms may only tap into one of two facets of attention: responding to joint attention (RJA), which serves an imperative function. What is not represented in JA-eliciting video paradigms is initiating joint attention (IJA), which serves a declarative function and taps into social reward systems that are integral to the social sharing of experiences (Caruana et al. 2015; Schilbach et al. 2010; Gordon et al. 2013). Moreover, RJA and IJA show a developmental dissociation during the first and second years of life (Yoder et al. 2009; Ibañez et al. 2013; Mundy et al. 2007). Although RJA and IJA both have predictive value in infancy, IJA is a more stable marker of ASD than RJA in later childhood (Mundy et al. 1986). Some neuroimaging researchers have dealt with the above issues by using a live face-to-avatar paradigm to simulate IJA bids (Redcay et al. 2012; Gordon et al. 2013). However, the movement constraints inside the MRI scanner create testing conditions that can be difficult for younger children, with and without ASD.

Eye movement behavior is a result of complex neurological processes; therefore, eye gaze metrics can reveal objective and quantifiable information about the predictability and consistency of covert social cognitive processes, including social attention (Chita-Tegmark 2016; Guillon et al. 2014), emotion recognition (Bal et al. 2010; Black et al. 2017; Sawyer et al. 2012; Sasson

et al. 2016; Tsang 2018; Wagner et al. 2016; Wieckowski and White 2017), perspective taking, (Symeonidou et al. 2016) and joint attention (Bedford et al. 2012; Billeci et al. 2016; Falck-Ytter et al. 2012; Falck-Ytter et al. 2015; Swanson et al. 2013; Thorup et al. 2016; Thorup et al. 2018; Vivanti et al. 2017) for children with and without ASD. Eye gaze measurement includes several metrics relevant to oculomotor control (Komogortsev et al. 2013) such as saccadic trajectories, fixations, and other relevant measures such as velocity, duration, amplitude, and pupil dilation (Krejtz et al. 2018a). We believe that combined analysis of fixations and saccades during natural and dynamic joint attention tasks, currently used as a reliable measure of ASD diagnostic criteria, will represent valid biomarkers for objectifying and delineating the dimensionality of ASD diagnosis in the future. Previous work in this area have successfully demonstrated development of Ķ, the coefficient of ambient/focal attention (Krejtz et al. 2016) and previous work has supported the relationship between eye tracking metrics and severity of ASD diagnosis (Frazier et al. 2018; Del Valle Rubido et al. 2018) and communicative competence (Norbury et al. 2009). If visual attention influences stability of fixations dependent upon the demands of dynamic joint attention tasks, a natural next step is to look into how relevance may be reflected in similar neurophysiologic features for atypical social brain systems, such as in the context of ASD (Hotier et al. 2017).

EEG Based Machine Learning for ASD

Studies have shown that EEG has the potential to be used as biomarker for various neurological conditions including ASD (Wang et al. 2013). EEG measures the electrical signals of the brain via electrodes that are placed on various places on the scalp. These electrical signals are postsynaptic activity in the neocortex and can be used to study complex neuropsychiatric issues. EEG has various frequency bands and its analysis are performed on these varying bandwidths. Waves between 0.5 and 4 HZ are delta, between 4 and 8 HZ are theta, between 8 and 13 HZ are alpha, 13 to 35 HZ are beta and over 35 are gamma. Saccadic eye movement plays a big role in the attention and behavior of an individual which directly affects both language and social skills (Fletcher-Watson et al. 2009). Autistic children seem to have different eye movement behaviors than non-autistic children. They tend to avoid eye contact and looking at human face while focusing more on geometric shapes

(Klin et al. 2009). While a typical child doesn't find any interest in geometric shapes and tend to make more eye contact, and human face perception.

In Grossi et al. (2017), authors use a complex EEG processing algorithm called MSROM/I-FAST along with multiple machine learning algorithms to classify Autistic patients. In this study 15 ASD individuals and 10 non ASD were selected. ASD group comprised of 13 males and 2 females between 7 and 14 years of age. Control group comprised of 4 males and 6 females between 7 and 12 years of age. Resting State EEG of both closed and open eyes were recorded using 19 electrodes. Patients sat in a quiet room without speaking or performing any mentally demanding activity while the EEG was being recorded. The proposed IFAST algorithm consists of exactly three different phases or parts. In the first stage also called Squashing phase, the raw EEG signals are converted into feature vectors. Authors present a workflow of the system from raw data to classification to make comparison between different algorithms such as Multi Scale Entropy (MSE) and the Multi Scale Ranked Organizing Maps (MS-ROM). MSROM is a novel algorithm based on Single Organizing Map Neural Network. In this study, the dataset is randomly divided into 17 training consisting of 11 ASD, 6 controls and eight test records consisting of 4 ASD, 4 control. The noise elimination is performed only on the training set. Also, it completely depends on the algorithm selected for extraction of feature vectors. For MS-ROM features they utilize an algorithm called TWIST. In the final classification stage, they use multiple machine learning algorithms along with multiple validation protocols. The validation protocols are training-testing and leave one out cross validation. For classification purposes they make use of Sine Net Neural Network, Logistic Regression, Sequential Minimal Optimization, kNN, K-Contractive Map, Naive Bayes, and Random forest. With MSE feature extraction the best results were given by Logistic and Naive Bayes with exactly 2 errors. Whereas, MS-ROM with training test protocol had 0 errors (100% accuracy) with all the classification models.

Bosl et al. (2011), conduct a study using mMSE as feature vectors along with multiclass Support Vector Machine to differentiate developing and high-risk infant groups. In this study they use 79 different infants of which 49 were considered high risk and 33 typically developing infants. The 49 infants were high risk based on one of their older siblings having a confirmed ASD diagnosis. The other 39 infants were not high risk since no one in their family ever was diagnosed with ASD. Data was collected from each infant during multiple sessions with some interval. Data extracted from an infant in five different sessions in various months between 6 to 24-month period

were considered unique. Resting state EEG with 64 electrodes was extracted by placing the infant in a dimly lit room in their mother's lap where the research assistant blew bubbles to catch their attention. The raw signals were preprocessed using Modified Multiscale Entropy. Low, high, and mean for each curve from mMSE were calculated to create a feature set of 192 values. The best fit for the classification for High risk and normal infants was at age 9 months with over 90% accuracy.

Abdulhay et al. (2017), use EEG intrinsic function pulsation to identify patterns in Autism. They mathematically compute EEG features and compare ASD with typically developing. In this study they selected 10 children with ASD and 10 non-autistic children within the age group of 4 to 13. They collected resting state EEG using 64 electrodes with a 500 HZ sampling frequency. Initially the signals were band pass filtered and all the artifacts including eye movements were removed by using Independent Component Analysis. Empirical Mode decomposition was applied to extract Intrinsic Mode Function from each of the channels of the participants. Then point by point pulsations of analytic intrinsic modes are computed which is then plotted to make comparison with the counterpart intrinsic mode in another channel. Any existing stability loops are analyzed for abnormal neural connectivity. In addition, they perform 3D mapping to visualize and spot unusual brain activities. In the first IMF of channel 3 versus the first IMF in channel 2 for typically developing and autistic child, it was found that the stability of local pulsation pathways maintained a consistency while it was random in typically developing. Similar patterns were seen in channels 1 and 2 and 36 and 37 of non-autistic and autistic children. Overall this computational method was able to differentiate the abnormal EEG activities between ASD and typically developing children.

Alie et al. (2011) use Markov Models with eye tracking to classify Autism Spectrum Disorder. Unlike most other studies that collected data from children who were 3 years or older, in this study they collect data from 6-month-old infants. There were in total 32 subjects out of which 6 were later at 3 years of age diagnosed with ASD and the rest were not. During the data collection the subjects were placed in front of their mothers and four different cameras from different angles recorded the video for about 3 minutes. The eye tracking was simply based on either the subject looked at the mother's face or not. Through this they get a binary sequence of subjects' eye pattern which is then converted into alphabet sequence of a specific length. Then the sequence was filtered using a low pass filter and down sampled by factor of 18. This is done to enhance Markov Models to produce effective results.

Using this data, they compare Hidden Markov Models and Variable-order Markov Models for the classification of ASD. Hidden Markov Models was able to correctly identify 92.03% of the typically developing subject while identifying only 33.33% of Autistic subject. Whereas the VMM correctly identified 100% of the Autistic and 92.03% of typically developing subjects. It was clear from this result that Variable-order Markov models are superior in finding Autistic eye pattern while both Markov Models are the same in finding typically developing. The authors point out this difference because of various spectrums of Autism with different eye patterns. Nevertheless, the VMM algorithm used in this study looks effective in identifying Autism in an early age. Similarly, Liu et al. (2015) propose a machine learning framework for the diagnosis of Autism using eye movement. They utilize two different datasets from previous studies. One of the datasets had 20 ASD children, 21 typically developing, and 20 typical developing IQ-matched children. The other dataset comprised of 19 ASD, 22 Intellectually disabled, and 28 typical young adults and adolescents. They compute Bag of Words for Eye Coordinates and Eye movement, N-Grams and AOI from the datasets. And they train five different Support Vector machine model with RBF kernel. Each of the model used different form of features like BOW of eye coordinates, BOW of eye movement, combination, N-Grams, and AOI. The result was good for both groups with Combination or fusion data. However, the children dataset with fusion was the best with around 87% accuracy.

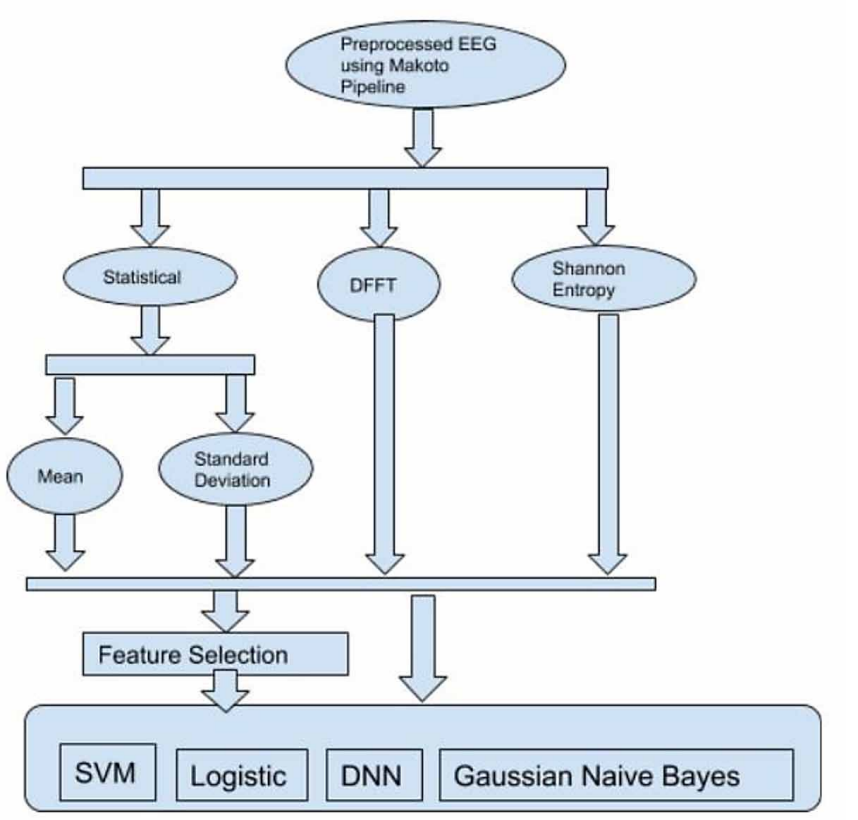
Jiang and Zhao (2017) use eye movement with deep neural networks to identify individuals with Autism Spectrum Disorder. They used dataset from a previous study with 20 ASD and 19 health controls. Here the subjects observed around 700 images from the OSIE database. OSIE database is a popular eye tracking dataset used for image saliency benchmarking. First, they use Cluster Fix algorithm on the raw data to compute fixations and saccades. Next, they work on finding the discriminative images as the OSIE dataset is not specifically built for autism studies. So, both groups might have the same visual pattern for some of the images. For this purpose, they use Fisher score method by which they score each of the images and select only the one with the higher scores to be processed further. After this process of image selection, they compute fixation maps to differentiate fixations between two groups. Fixation maps are simply a probability distribution of all the eye fixations. In addition, they use a Gaussian Kernel for smoothing and normalize by their sum. Normalization is usually done when we are comparing two different fixation maps as is the case here. Then they compute difference of fixation map between the Autistic and non-Autistic group. This is the original

target which they used to train a SALICON network to predict these values. SALICON network is one of the state-of-the-art image saliency prediction algorithms. Image saliency prediction is about predicting the visual pattern of users given an image. SALICON network uses two VGG with 16 layers. One of the VGG uses the original image to detect the small salient regions whereas the other VGG uses the down sampled image to detect the center of large salient regions. At the end both the outputs are combined to get a better result. This only predicts the image saliency. So, to predict the difference of fixation map they add another convolution layer with Cross Entropy Loss function using the original Difference of fixation map. Next, they send the predicted difference of fixation maps to the final prediction layer. In this part they first apply tanh function to the features then concatenate the feature vectors of all fixation to consider dynamic change of attention. After which they reduce the dimension by using local average pooling. At last they train an SVM to make the final classification between ASD and control. They make use of the popular leave-one-out cross validation to measure the performance of their model. The accuracy of this model showed real promise in eye tracking for ASD with about 92% accuracy.

METHODOLOGY

Current techniques in practice for identifying ASD are mostly subjective and prone to error and usually takes a lot of time for final diagnosis. Most of the children with ASD are diagnosed after 3 years of age. Early diagnosis is the key for reversing or treating ASD through early intervention. As time is of an essence we need a method of diagnosis that is fast, and efficient unlike the current practice that could take months to years. Medical Imaging and blood testing (Sparks et al. 2002; Spence et al. 2004) are promising and a lot of work is being done with these modalities to diagnose ASD. However, EEG and Eye movement are cost effective and hence can be accessible in consumer level. The aim of this research is to study the identification of Autism Spectrum Disorder using EEG during ADOS-2. Comparison of the classification performance between EEG features can potentially result in finding the better feature set. We hypothesize as the top performing signal most likely has more of the unique data points and pattern of ASD and similarly, the least performing signals have less of the data points and patterns relating to

Figure 1. EEG Processing Pipeline for Study 1. EEG Data preprocessed using Makoto Pipeline follows this pipeline to train SVM, Logistic, DNN and Gaussian Naïve Bayes Models

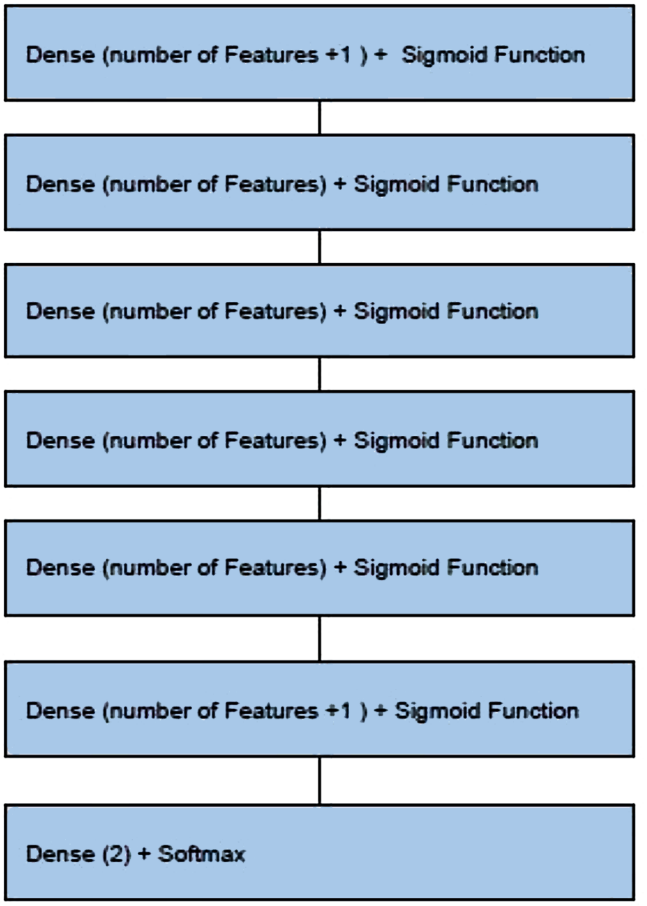


ASD. The secondary goal is to compare various machine learning algorithms for the classification purposes. Conditions like ADHD, and other learning disabilities can also share similar comparative patterns for different features.

Machine Learning With EEG Measures During Joint Attention

We have recently employed preliminary feature analysis on acquired raw EEG data from the work of Jaime et al. (2016), wherein the EEG was recorded from adolescents with ASD (N=24) and typically developing adolescents (N=28) while they watched a series of 30-second joint attention eliciting video clips.

Figure 2. EEG Feature Processing Pipeline for Deep Neural Network. Each layer of the deep neural network is shown in the figure, with its functionality



First, we applied the pre-processing pipeline (described in §3.3.1) on the raw EEG time series to remove noisy channels and data segments containing movement and ocular artifacts from the EEG data. The pre-processed data was then classified using *EEG Analytics Pipeline* (implemented in Python) (Thapaliya et al. 2018).

Joint attention is the ability to socially coordinate visual attention, share a point of view with another person, and process self and other-related information. Hence the data retrieval was performed while making the subjects watch video clips that would help in examining joint attention. There was a total of 12 videos each of which was 30 seconds. About one second gap was provided between each video. Both the EEG and Eye movement were

collected while the participants watched the video. A total of 34 participants EEG data was used in this paper after the preprocessing step.

There are many ways to extract feature from EEG data. Entropies, wavelets, FFT and various other statistical methods are commonly computed features (Al-Fahoum and Al-Fraihat 2014). In this work we use Statistical and Entropy values. Statistical features comprise of Mean, Standard Deviation, and combined mean and standard deviation of the filtered data. For the feature analysis, we used statistical and entropy values including mean, standard deviation, and combined mean and standard deviation on the pre-processed data. Entropy is computed by using Shannon entropy function (Lin 1991), which is the average rate at which information is produced by a stochastic source of data given by, $H_e = -\sum p_i \log_2 p_i$. Mean function takes in a 2D matrix consisting of the EEG signal of a person and returns a feature vector with mean values for each channel over windows of signal. For the mean, each of the 128 channels were computed. For each subject a feature vector consisting of mean of single channel was created. So, the mean function takes in a 2D matrix consisting of the EEG signal of a person and returns a feature vector with mean values for each channel. For the standard deviation, each of the 128 channels were computed. For each subject a feature vector consisting of mean of single channel was created. So, the deviation function takes in a 2D matrix consisting of the EEG signal of a person and returns a feature vector with standard deviation values for each channel. This is shown in the Figure 1.

For classification SVM, Logistic, Deep Neural Network (DNN), and Gaussian Naive Bayes is used. For the deep neural network (see Figure 2) with five hidden layers with sigmoid activation function is used. For optimization categorical cross entropy for loss and Adamax optimizer (Freivalds and Liepins 2017) is used. We captured three different feature set; entropy features, FFT

Table 1. Classification Accuracy of EEG during Joint Attention Study. The Entropy, FFT, Mean and Standard Deviation values are given for each classifier used for this study

Classifier	Entropy	FFT	Mean	Std.
Gaussian Naive Bayes	0.26	0.53	0.55	0.55
Logistic Regression	0.11	0.78	0.58	0.50
SVM	0.11	0.56	0.55	0.55
DNN	0.20	0.52	0.58	0.45

and statistical features. We also calculate mean, and standard deviation. In total there are 4 different features from EEG and 4 different models for each type of classifier and, overall there are 16 different model variations based on the features (4 feature set x 4 classifiers). For each feature there are three models for each algorithm, two models using Feature Selection and the third one without using any feature selection. For Feature selection PCA and sequential feature selection is used.

Classification of EEG During Joint Attention: Results

The Table 1 presents an analysis and comparison of EEG data. Note that two models were created for each model with only EEG and combined data by using PCA and without using PCA. Like SVM with PCA and without PCA. For some models with PCA did better while for some without PCA did better. For example, DNN almost always without using PCA did worse because of the curse of dimensionality. The highest performing SVM with about 56% accuracy was using FFT with all the features without PCA. The highest performing Logistic regression with 78% accuracy was using FFT without PCA. SVM, Logistic Regression, and Gaussian Naive Bayes do better without PCA which means that with PCA it loses data points that these models find useful. This is interesting because PCA is supposed to find the most discriminant features and remove redundant or noisy features. And this is supposed to help machine learning models produce better results. For SVM most models with PCA did better except the highest performing model. This might mean that the Entropy data is more linear than the other datasets. For DNN the curse of dimensionality is obvious. Whereas for Gaussian Naive Bayes all the high performing models did not use PCA except the one with EEG mean. This is an exception and must be due to the nature of the EEG mean data. But in general case Naive Bayes does better without PCA. This might be since probabilistic models are able to make sense of higher dimensional dataset much easier than other models like DNN. Then with using Sequential Feature Selection algorithm almost all the models performed better than either PCA or no Feature Selection.

In this study we have used PCA, and Sequential Feature Selection algorithms. There are other Feature Selection algorithms like Genetic algorithm, Particle Swarm Optimization, and TWIST which can be compared to find features to optimize the performance of the models. Also, this will tell us which feature selection algorithm will work better for the combined

data sets. Gaussian Naive Bayes with some of the features had perfect score. But we need to reproduce this result with large number of participants to be able to use this in a clinical setting. Current number of 34 participants is too low to confirm our results. However, this is a first step towards developing an optimal Autism Diagnosis system.

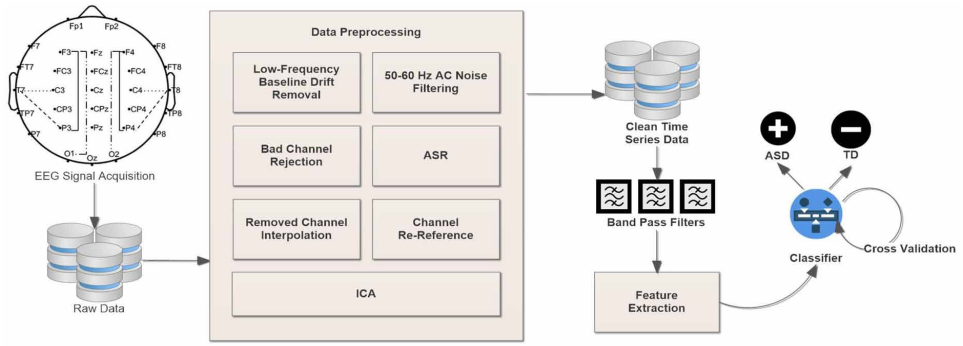
EEG Coherence During Live Social Interaction

The notion that social brain system FC may be a useful index of social impairment is suggested by both the literature (Mundy 2016; Jaime et al. 2016) and by our preliminary findings obtained from our pilot sample composed of individuals between the ages of 5 and 17 years who completed an ADOS-2 assessment while we simultaneously recorded their EEG. Despite a small sample size (ASD = 8; TD = 9), our preliminary results indicate a trending negative association between right hemisphere delta and theta band EEG coherence and level of social symptom severity (according to the ADOS-2 algorithm scoring) in children with ASD (see Table 2 below), but not in our pilot sample of typically developing (TD) children. Our preliminary results paint a conceptual picture that is in line with our prior work evaluating EEG coherence during joint social attention perception in ASD (Jaime et al. 2016), that there are diagnostic group differences in the association between right hemisphere frontal–temporal–parietal FC and standardized measures of social functioning. Such diagnostic group differences in FC association patterns reflect a tendency for children with impaired social capacity to have idiosyncratic patterns of social brain system functional organization relative to typical neurodevelopment. Thus, EEG measures of social brain system FC acquired during live social interaction shows promise as a candidate non-invasive biomarker of early emerging aberrant social neurocognitive dysfunction in ASD.

EEG Acquisition and Pre-Processing

Our preliminary FC measures were analyzed from each pilot subject's EEG recording, acquired throughout the entire duration of the ADOS-2. We used a 32-channel LiveAmp wireless EEG system with active electrodes and a digital sampling rate of 250 Hz (Brain Products GmbH) for EEG time series acquisition. Use of a wireless EEG system allowed for head movements

Figure 3. EEG Feature Processing and Classification. The raw signals acquired from an EEG are stored and is subjected to preprocessing to obtain clean time-series data. Once this completes, the clean data is passed through band pass filters and feature extraction is performed. Then the extracted features are fed into a classifier, which uses cross validation to evaluate its performance depending on how it predicts ASD and TD class labels.



and the active electrodes increased speed of application thereby increasing probability of successful EEG data acquisition with special populations.

All 32 channels were continuously recorded using the FCz electrode as reference. To maximize the consistency of the recording quality across conditions, a single epoch was recorded per experimental condition. In between epoch recordings an impedance check will be performed. This was resulted in 6 different epochs per subject. Prior to the recording of each experimental epoch, a 90 second epoch of eyes closed while resting will be recorded. This served as a necessary baseline metric for the EEG analysis. After acquisition, the raw EEG data output was imported into the open-source MATLAB toolbox: EEGLAB (Delorme and Makeig 2004). Next, following preprocessing pipeline is applied:

1. Remove low frequency baseline drift with a 1 Hz high-pass filter.
2. Remove 50-60 Hz AC line noise by applying the CleanLine plugin.
3. Clean continuous raw data using the clean_rawdata plugin (Mullen et al. 2015). The clean_rawdata plugin first performs bad channel rejection based on two criteria: (1) channels that have flat signals longer than 5 seconds and (2) channels poorly correlated with adjacent channels. It

then applies artifact subspace reconstruction (ASR) — an algorithm that removes nonstationary, high variance signals from the EEG then uses calibration data (1 min sections of clean EEG) to reconstruct the missing data using a spatial mixing matrix.

4. Interpolate removed channels.
5. Re-reference channels to average reference.
6. Separate non-brain artifacts from the EEG recording via EEGLAB's Independent Component Analysis (ICA)[1]. Briefly, ICA involves the linear decomposition of the aggregate channel activity into a series of independent components that are spatially filtered from the recorded EEG time series. Components representing eye, cardiac, and muscle artifact are removed and components representing genuine brain activity are retained.

Table 2. ADOS-2 Score of the ASD vs TD subjects. Here, 8 subjects were diagnosed with ASD (above horizontal line) and the others were typically developing (TD)

Participant	Sex	Age	ADOS-2	ASD Diagnosis
2	M	10	19	ASD
4	M	17	12	ASD
11	M	6	11	ASD
12	M	16	16	ASD
13	F	11	16	ASD
15	F	10	7	ASD
18	M	5	20	ASD
20	M	15	9	ASD
5	M	11	5	TD
7	F	9	0	TD
8	F	6	5	TD
14	F	16	0	TD
16	M	8	4	TD
17	F	6	0	TD
19	M	15	2	TD
21	M	6	4	TD
22	F	8	0	TD

EEG Measures of Functional Connectivity

We first extracted 180-second epochs beginning from the middle one-third portion of each subject's pre-processed EEG time series to calculate a functional connectivity (FC) measure of the engaged social brain system. With each subject's epoched EEG time series treated as a discrete-time signal $u = x_i\left(t\right)$ for EEG channel i, we used EEG coherence as a variable of FC. EEG coherence, or normalized magnitude-squared coherence (MSC), $C_{uv}^2\left(\omega\right)$, is a statistical estimate of the amount of phase synchrony between two EEG time series, u and v : $C_{uv}^2\left(\omega\right) = \left|\phi_{uv}\left(\omega\right)\right|^2 / \left(\phi_{uu}\left(\omega\right)\phi_{vv}\left(\omega\right)\right)$ where the squared magnitude of the cross spectrum density $\left|\varphi_{uv}\left(\omega\right)\right|^2$ (a measure of co-variance) between the two signals u and v at a given frequency ω, is normalized by the Power Spectral Densities (PSDs) (variance) of each channel φ_{uu} and φ_{vv} so that $0 \le C_{uv}^2\left(\omega\right) \le 1$. Higher values represent greater synchronous activity between distinct channels whereas lower values represent reduced or non-synchronous activity (Nunez and Srinivasan 2006). Coherence is a function of frequency; to compute a single similarity metric between a pair of signals, we integrate over frequency to obtain total power (or variance in a statistical sense) $P_{ij} = \frac{1}{T}\int_0^T C_{uv}^2\left(\omega\right)$ where T is the extent of frequency components sampled. The MSC of a signal which itself produces no variance (in the statistical sense) and hence $P_{ii} = 1$, gives a convenient, normalized metric of similarity.

Accordingly, intra-hemispheric MSC between electrode positions that are spatially collocated over areas comprising the social brain system (Saxe 2006; Adolphs 2009) were examined. Electrode pairs were selected based on Homan et al.'s [1987] electrode placement correlates of cortical location. Using the international 10/20 placement system (Klem et al. 1999), the following electrodes were selected: F7, F8, T7, T8, TP9, TP10, P7, P8, C3, and C4.

Classification of EEG During ADOS-2: Results

We generated five feature sets categorized according to the frequency bands: 1) delta, 2) theta, 3) alpha, 4) beta and 5) gamma with each set representing the amplitude and power of the signal from each electrode. These feature

sets were entered to 43 different classifiers yielding precision rates, recall rates, F1 scores, and percent accuracy. We identified six the top performing classifiers: Random Forest, Logistic, Bagging, JRIP, LMT and AdaBoostM1.

The six top performing classifiers for the 5-band feature set are listed in Table 3. The JRIP classifier yielded the highest percent accuracy with 98.06% indicating that a 5-band feature set collected during an ADOS-2 test classifies a diagnosis of ASD with greater than 90% accuracy. From these six classifiers, the AdaBoostM1 classifier yielded the lowest percent accuracy at 92.14%.

The evaluation results in Table 3 were calculated based on features from all electrodes. We also conducted an evaluation by selecting only F7, F8, T7, T8, TP9, TP10, P7, P8, C3 and C4 electrodes based on Homan et al.'s [1987] electrode placement correlates of cortical location. The results of this evaluation are listed in Table 4. When comparing the results, it was observed that the Random Forest classifier yielded the highest percent accuracy with 97.04%. The AdaBoostM1 classifier yielded the lowest percent accuracy at 79.75%.

Table 3. Precision, Recall, F1 and Accuracy of six classifiers used for classification of EEG during ADOS-2

Classifier	Precision	Recall	F1	Accuracy
Random Forest	0.98	0.98	0.98	**98.00%**
Logistic	0.96	0.96	0.96	96.63%
Bagging	0.95	0.95	0.95	95.66%
JRIP	0.98	0.98	0.98	**98.06%**
LMT	0.95	0.95	0.95	95.79%
AdaBoostM1	0.92	0.92	0.92	92.14%

Table 4. Precision, Recall, F1 and Accuracy of six classifiers used for classification of EEG during ADOS-2 using only a selected set of features

Classifier	Precision	Recall	F1	Accuracy
Random Forest	0.97	0.97	0.97	**97.04%**
Logistic	0.84	0.84	0.84	84.72%
Bagging	0.95	0.95	0.95	**95.50%**
JRIP	0.94	0.94	0.94	94.57%
LMT	0.83	0.82	0.82	82.94%
AdaBoostM1	0.80	0.79	0.79	79.75%

DISCUSSION AND FUTURE OUTLOOK

Due to its low cost and feasibility, electroencephalography (EEG) shows potential as an effective neurophysiological instrument in the classification of ASD (Lenartowicz and Loo 2014; Snyder et al. 2015; Gloss et al. 2016), and there is emerging evidence that——combined with machine learning approaches——quantitative measures of EEG can predict ASD with high levels of sensitivity and specificity (Bosl et al. 2018; Grossi et al. 2017; Djemal et al. 2017). An advantage of EEG is its ability to be applied to ecologically valid contexts (i.e., person-to-person social interaction) via wireless solutions thus allowing for the simultaneous acquisition of data from multiple participants in real-world settings.

To establish proof of concept—that our classifiers show utility to predict features in line with diagnostic criteria of ASD—we collect biobehavioral metrics within the context of standardized tasks used in a gold standard assessment of ASD symptomatology: The Autism Diagnostic Observation Schedule Second Edition (ADOS-2) (Gotham et al. 2007). The ADOS-2 has been carefully developed to create snapshots of naturalistic social scenarios that can reveal observable features central to ASD (i.e., joint attention, social overtures), thereby allowing us to measure brain activity that are temporally concurrent with these observable ASD features within relatively brief periods. It is also important to note that we did not use these ADOS-2 tasks as a clinical tool to diagnose participants; rather, we capitalized on the semi-structured and standardized nature of these social tasks in the ADOS-2 to create a context that engages the social brain system and elicits joint visual attention behavior for acquisition of biobehavioral metrics. Thus, participants recruited for this study have already received a diagnosis of ASD by a clinical professional prior to enrolling in this study.

Due to its high temporal resolution and feasibility, electroencephalography (EEG) shows potential as an effective neurophysiological instrument in the classification of ASD (Lenartowicz and Loo 2014; Snyder et al. 2015; Gloss et al. 2016). An advantage of EEG is its ability to be applied to ecologically valid contexts via wireless solutions that allow for the simultaneous acquisition of data from multiple participants. This makes EEG an appropriate choice for examining relevant neurophysiological features of ASD in real-world settings (Lee and Tan 2006). Despite these advantages, most EEG research occurs in highly controlled experimental environments, requiring data collected over

many trials with minimal head movement. We will address this deficiency by combining EEG and eye tracker usage in the future studies.

Early diagnosis is crucial for successful treatment of ASD. Although progress has been made to accurately diagnose ASD, it is far from ideal (Dawson 2008). It often requires various subjective measures, behavioral assessments, observations from caretakers over a period to correctly diagnose ASD. Even with this tedious testing often individuals are misdiagnosed. However, there remains promise in the development of accurate detection using subjective modalities of EEG, and Eye movements. In the future we will obtain two sets of biobehavioral measures representing joint attention: functional integration of neurocognitive networks associated with the social brain (i.e., EEG metrics) and visual behavior (i.e. eye tracking metrics). Regarding visual behavior, we will collect, analyze, and produce a battery of traditional positional eye movement metrics thought to be potential indicators of joint attention, including number of fixations (Jacob and Karn 2003), fixation durations (Fitts et al. 1950; Just and Carpenter 1976), and number of regressions (Azuma et al. 2014), during naturalistic, dynamic communication tasks.

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ENDNOTE

[1] Details regarding performing ICA in EEGLAB can be found here: Swartz Center for Computational Neuroscience (2018, September 19). Chapter 09: Decomposing Data Using ICA. EEGLAB Wiki. https://sccn.ucsd.edu/wiki/Chapter_09:_Decomposing_Data_Using_ICA