Functional Connectivity Networks in the Autistic and Healthy Brain Assessed using Granger Causality

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Abstract—In this study, we analyze brain connectivity based on Granger causality computed from magnetoencephalographic (MEG) activity obtained at the resting state in eight autistic and eight normal subjects along with measures of network connectivity derived from graph theory in an attempt to understand how communication in a human brain network is affected by autism. A connectivity matrix was computed for each subject individually and then group templates were estimated by averaging all matrices in each group. Furthermore, we performed classification of the subjects using support vector machines and Fisher’s criterion to rank the features and identify the best subset for maximum separation of the groups. Our results show that a combined model based on connectivity matrices and graph theory measures can provide 87.5% accuracy in separating the two groups. These findings suggest that analysis of functional connectivity patterns may provide a valuable method for the early detection of autism.

I. INTRODUCTION

AUTISTIC spectrum disorders (ASDs) comprise the fastest growing class of developmental disabilities, with an incidence of around 6 per 1,000 [1] when higher functioning individuals are included. ASDs are characterized by impaired communication and social interaction, repetitive behaviors, and restricted interests [2,3,4]. Longitudinal studies indicate a generally poor prognosis, as 90% of autistic individuals have clinical deficits that persist throughout adulthood [5], and approximately 60% to 70% have an IQ below 70 [4,5,6].

While the exact neurological basis of ASD is still unknown, early studies reported globally elevated glucose utilization and focal abnormalities in the anterior cingulate gyrus, temporal and parietal lobes, basal ganglia, thalamus, and cerebellum. There are also indications of atypical language dominance and decreased hemispheric functional specialization [3,7,8,9]. Recent studies using behavioral and neuroimaging techniques [10–14] have shown anatomical and functional [15] impairments in several brain regions, including the frontal lobe, medial temporal structures, and the cerebellum. In particular, diffusion tensor imaging has revealed a dispersed pattern of disturbed integrity in the white matter throughout the ASD brain [16], while fMRI studies have shown differences in functional connectivity between ASD and control subjects for social cognition [17], working memory [18], visuomotor coordination [19], and during performance of executive [13] and cognitive tasks, such as sentence comprehension [14]. In the former case, reduced functional connectivity was found between frontal and parietal brain areas.

At the neuronal level, abnormalities in spontaneous neurophysiological activity recorded using electroencephalography (EEG) and magnetoencephalography (MEG) are common in autism, as epilepsy develops in 20% to 30% of autistic individuals [20,21]. EEG and MEG can be used to determine functional relationships between neuronal groups across different brain areas that are disparate in geography yet analogous in context. In particular, several studies have shown the role that synchronous cerebral activation plays in higher cognitive functions in the normal brain [22-25] for associative memory, emotional tone, motor planning [26], and learning [27]. Analysis of resting state EEG functional connectivity in ASD has shown increased theta-band coherence between temporal and frontal regions, reduced alpha coherence between anterior and posterior regions [28], lower intra-hemispheric delta and theta coherences, and reduced inter-hemispheric delta and theta coherences across the frontal and temporal regions [29].

In this study, we analyze Granger causality from MEG activity obtained at the resting state in autistic and normal subjects along with measures of network connectivity derived from graph theory in an attempt to understand how communication in a human brain network is affected by ASDs.

II. MATERIALS AND METHODS

A. Subjects

MEG signals were recorded from 8 subjects with a clinical diagnosis [30,31] of autism (mean age 18.7 ± 0.7 years old) and 8 controls (19.0 ± 1.2 years old). All subjects were right handed [32] and screened for brain injury, seizure disorder, neurotropic infection or disease, bipolar disorder, schizophrenia, or behavior problems that would make accurate and reliable testing difficult. Autistic subjects group were high functioning with full scale and verbal IQs [33] greater than 85. Informed consent was obtained from all participants and/or their parents, under a protocol approved by the University of Texas Medical School at Houston and
the University of Houston.

B. Granger Causality

Causal relationships among different cortical areas can be assessed by analyzing simultaneously recorded multichannel MEG data that can be modeled as a system of autoregressive (AR) time series. The principle of Granger Causality (GC) is based on the prediction of future values of a signal $X_k$ from past values of self and other signals $X_1, X_2, ...X_N$ that are the time series recorded from $N$ sensors located on the head surface. In general, the system can be represented as

$$X_1(t) = \sum_{j=1}^{p} A_{11}(j)X_1(t-j) + ... + \sum_{j=1}^{p} A_{1N}(j)X_N(t-j) + E_1(t)$$

$$X_2(t) = \sum_{j=1}^{p} A_{21}(j)X_1(t-j) + ... + \sum_{j=1}^{p} A_{2N}(j)X_N(t-j) + E_2(t)$$

$$X_N(t) = \sum_{j=1}^{p} A_{N1}(j)X_1(t-j) + ... + \sum_{j=1}^{p} A_{NN}(j)X_N(t-j) + E_N(t)$$

where $p$ is the maximum number of lags included in the AR model (model order), $A$ contains the estimated coefficients of the model, and $E_1, ...E_N$ are residuals for each time series. The optimum AR model order can be estimated using the Akaike and Bayesian Information Criterion (BIC) [34].

In the above formulation, if the variance of the prediction error $E_2$ is reduced by the inclusion of the $X_2$ term in the first equation, then it is said that $X_2$ causes $X_1$. This definition can be extended to any source signal $X_k \in [X_2, ...X_N]$. Equivalently, $X_h$ causes $X_k$ if the coefficients $A_{hk}(j), j=1,2,..,p$, are not jointly significantly different from zero. The null hypothesis that $A_{hk}$ is zero is tested via an F-test and the strength of each connection is estimated by the logarithm of the F-statistic. GC analysis of $N$ data channels yields an $N$-by-$N$ matrix describing the entire brain network. Finally, the resulting network is thresholded, so that only the strongest links between the various nodes are included.

C. Analysis Procedure

The MEG signals were recorded using a 248-channel whole-head Magnes WH3600 system (4D Neuroimaging Inc., San Diego, CA) with a sampling rate of 1 kHz. Bandpass filtering between 0.1-80 Hz and decimation by a factor of 6 gave an effective sampling rate of 166 Hz. A noise-removal and artifact-rejection procedure was also applied before GC analysis [27]. A connectivity matrix was computed for each subject individually and then group templates were estimated by averaging all matrices in each group. The density of the computed networks was reduced using a common threshold on the strength of the links. Finally, the network structure that was common to both groups was subtracted from the template of each group to enhance the group differences.

Furthermore, we computed several graph measures of the individual networks to extract quantitative features for classification purposes. Namely, we computed the network characteristic path length, eccentricity, graph radius and diameter, average in-, out- and total degree, density,
The set of connections common to both average networks extends practically to the entire head, as shown in Figure 2. After subtraction of this common pattern from each groups’ network, the networks shown in Figure 3 are obtained.

Statistical analysis using t-tests showed that the measure characteristic path length (p<0.031), mean global efficiency (p<0.032), and mean clustering coefficient (p<0.047) were significant. Specifically, the average characteristic path length was higher in the autistic group, while the average global efficiency and clustering coefficient were greater in the normal group.

Classification accuracy using directly the connectivity matrix to separate the two groups is shown in Figure 4 (blue line) as a function of the number of features selected. Furthermore, the best accuracy of the model resulting from the additional 17 features from graph theory is 81.25%. Combining the predictions of these two models with simple averaging gives the results shown in Fig. 4 (red line). As it can be seen, the best performance of the combined model is 87.5%, which is the same as that of using the whole connectivity matrix. However, the former is more robust against the number of selected features while the latter is very sensitive.

**IV. DISCUSSIONS AND CONCLUSIONS**

The aim of this study has been to assess whether autistic subjects have a brain connectivity network which is significantly distinguishable from healthy subjects. We used Granger causality analysis to calculate individual connectivity networks in each subject, and we averaged the resulting maps within each group to obtain a group pattern.

After removal of the common diffuse connections, the resulting network of the autistic group is very sparse and characterized by several long-range connections between the left frontal lobe and the centro-parieto-occipital areas. On the contrary, the connectivity map in the control group is still populated with an extended network of local peripheral connections around the entire head along with long-range connections between left temporal and right frontal areas.

Statistical analysis indicates that several connectivity features derived from graph theory are significantly different.
in the two groups. Specifically, the characteristic path length was found to be lower in the normal group, confirming the prevalence of local connections over long-range ones. Likewise, the mean clustering coefficient, which reflects the prevalence of clustered connectivity around individual nodes, was significantly higher in the normal group. The global efficiency, which represents a measure of network integration, was found to be higher in the normal group. The overall classification performance using the 20 best ranked features and 17-graph connectivity measures led to an accuracy rate of 87.5%.

In conclusion, the autistic and normal groups are separable by analyzing the connectivity maps obtained with Granger causality. Moreover, the classification performance indicates that functional connectivity patterns may represent a valuable tool for the early diagnosis of autism disorders.

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