Overlaps in Brain Dynamical Functional Connectivity between Schizophrenia and Autism Spectrum Disorder

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Abstract

Autism and schizophrenia share some genotipic and phenotypic aspects as connectome miswiring and common cognitive deficits. Current diagnostics for both disorders include direct reports of relatives and clinical evaluation by a psychiatrist. Several medical imaging biomarkers have been proposed in the past. This work proposes a dynamical functional connectome analysis combined with machine learning techniques to complement the present diagnostic procedure. We used sliding window technique to locate a set of dynamic functional connectivity states and then use them as features to classify subjects as autism/schizophrenia or control. Moreover, by using dynamic functional connectivity measures we investigate the question whether those two disorders overlaps, namely whether the schizophrenia is part of the autism spectrum. The results reveals that both static and dynamic functional connectivity can be used to classify subjects with schizophrenia or autism. Lastly, some brain regions show similar functional flexibility in both autism and schizophrenia cohorts giving further proofs of overlaps.

Keywords: Brain imaging, Schizophrenia, Autism Spectrum Disorder, Connectome, Functional connectivity, FMRI

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1. Introduction

Autism spectrum disorder (ASD) and schizophrenia are neurological disorders. Individuals who are affected by any of these diseases have difficulties with communication and with what is usually considered normal social behavior. Schizophrenia is a psychiatric disorder characterized by having delusion, hallucination, disordered thinking and speech and disorganized behavior [1]. ASD is a set of neuro-developmental disorders characterized by impaired social interaction and repetitive behaviors [2]. Several attempts have been made to understand both diseases from the connectomics perspective. Schizophrenia is found to cause misconnections among brain regions [3] and ASD is identified with patterns of both high and low connectivity among brain regions [4, 2]. Mastrovito et al. compared atypical functional connectivity between ASD to typically developing children and schizophrenia to normal control, highlighting also common connectivity features between ASD and schizophrenia [5]. Recently, a new method is gaining attention to study brain activity: dynamical functional connectivity (dFC), an approach to analyze the functional connectivity from resting state functional magnetic resonance imaging (fMRI), which instead of using time series at once it compares part of them by using sliding windows. In this paper we focus on using dFC features with machine learning tools and novel graph metrics. More specifically we use support vector machine (SVM) for distinguishing either ASD or schizophrenia from control subjects. Moreover we quantify local dynamical differences and how they overlap between the two pathologies using the flexibility index of brain regions. Flexibility of each node/area corresponds to the number of times that it changes module allegiance on time while we move across the dFC representation.

1.1. Functional Connectivity

Functional Connectivity (FC) is an fMRI measure of how temporally dependent brain regions anatomically separated and their neuronal activation interact. FC describes a brain network with edges that define the degree of correlation between brain regions during active periods. Those interactions can be determined by methods such as cross-correlations in the time or frequency domain, mutual information or spectral coherence [6]. *Static Functional Connectivity* is a global measure of functional connectivity of brain activity for the whole time of fMRI scan. It shows how a fixed group of brain regions coordinate and control cognitive processes. It maps a fixed

number of brain regions to a particular mental process. *Dynamic Functional Connectivity* refers to the observed phenomenon that functional connectivity changes over time [7]. Contrary to previous notion that resting state functional connectivity are stationary over time, researchers have observed that when a brain is scanned over a period of time (usually 6 minutes) it reveals a number of functional connectivity states in the brain which are susceptible to variations. The nature of dynamic functional connectivity can be used to distinguish between healthy and diseased brain [8, 9]. This technique has already been used in combination with SVM to classify subjects with traumatic brain injuries with high precision [10].

1.2. Sliding window Technique

Sliding-window analysis (SWA) is a tool for analyzing the dynamic functional connectivity of brain activity taken from fMRI scan. It is the most widely used technique in estimating the dynamics in functional connectivity [11]. The concept of sliding-window is based on taking a time-window of fixed length and compute the functional connectivity of the data point inside of this time-window. After that, the window is moved with a fixed step, until the end of the time-series. Those steps can be defined to give overlapping or consecutive windows. The parameters of SWA include the window length, window step and window shape. The results of any SWA can largely influenced by the choice of these parameters. However, there are no universally recognized values for these parameters and results can be just the consequence of overfitting. The general rules is that the choice of window's size should be large enough to permit robust estimation of functional connectivity and to resolve the lowest frequencies of interest in the signal, and yet small enough to detect potentially interesting transients [12]. The choice of window length may depend on whether the time series changes rapidly. Most researchers use window length between 8 to 240s [9].

2. Method and Data

The present study seeks to use SVM to diagnose ASD/Schizophrenia and to look for overlaps between the two pathologies. To achieve the first objective, for each subject the fMRI brain data was preprocessed and converted into a FC matrix by using both sliding window technique and Pearson correlation. The second objective is reached by using the flexibility index comparing

either ASD or schizophrenia against control subjects, and then comparing the statistically significant results for between ASD and schizophrenia.

2.1. Data and Experimental settings

We used two different datasets to perform the experiments. The ASD dataset is obtained from the publicly available ABIDE-II dataset [13]. More specifically the San Diego State University cohort comprising 54 subjects (31 ASD and 23 control), of age between 7 and 18 years. For each subject, blood-oxygenation level dependent (BOLD) volumes were acquired in one $6:10$ minute resting state scan consisting of 185 whole brain volumes (TR $= 2,000$ milliseconds, TE $= 30$ milliseconds, flip angle $= 90^o$, matrix size $= 64 \times 64$ matrix, $3.4 \times 3.4 \times 3.4\text{mm}^3$ resolution, 42 axial slices covering the whole brain). The schizophrenia dataset is obtained from the the Center for Biomedical Research Excellence (COBRE) dataset [14]. The dataset included 146 subjects (2 discarded due to artifacts) ranging in age between 18 and 65 (70 with schizophrenia and 74 controls). BOLD volumes were obtained using TR = 2s, TE = 29ms, flip angle $= 75^o$, 32 slices, voxel size $= 3 \times 3 \times 4$ mm^3, matrix size $= 64 \times 64$. Throughout the resting state scan, participants were instructed to relax, and to keep their eyes open and centered on a white fixation cross displayed on black background in the center of a screen, using a rear projection display.

2.2. Pre-processing and Connectome construction

For both fMRI datasets data have been pre-processed according to a standard pipeline: motion correction, mean intensity subtraction, pass-band filtering with cutoff frequencies of [0.005-0.1 Hz] and skull removal. To account for potential noise from physiological processes such as cardiac and respiratory fluctuations, nine covariates of no interest have been identified for inclusion in our analyses [15]. To further reduce the effects of motion, compensation for frame-wise displacement has been carried out [16]. Linear registration has been applied between the Harvard-Oxford atlas [17] and the reference volume by using linear registration with 12 degrees of freedom. The entire brain data set produced a single 96×96 correlation matrix for each subject with rows and columns representing brain regions and the elements of the measures of association between the brain regions defined by the Harvard-Oxford atlas. Due to symmetric correlation matrix duplication was avoided by taking only the upper triangular of the original correlation matrix and the diagonal. For any given symmetric matrix of dimension $N \times N$,

the upper triangular gives a total of $N(N-1)/2$ elements, which for the static FC means a feature vector of 4560 elements. The length of the sliding windows has not been optimized but set sufficiently large. Namely 50 time points and non-overlapping windows, generating 3 time-windows.

2.3. Case-control classification

The used features for the SVM-based classification are the dFC matrices. In our experiments, functional connectivity is defined by using the Pearson correlation between variables A and B being brain region as

$$\rho = \frac{cov(A,B)}{\sqrt{Var(A)}\sqrt{Var(B)}}. \tag{1}$$

In SWA, we define correlation time series $\hat{\rho} = (\hat{\rho}_1, \ldots, \hat{\rho}_L)$ over a functional brain data by successively moving, at a constant rate, a window of predetermined length and shape over the data. We compared results obtained using one static FC matrix per subject with results using several dFC matrices per subject. Given that a correlation matrix is symmetric, only the elements of the upper triangular were considered and flattented into 1D vector for subsequent use as feature vector x_i. Dynamical functional analysis produces a number, depending on the window length and step size, of 1D vectors which are combined to create a single vector as well. In this way, vectors for ASD/Schizophrenia were stacked to create a single data set. The data set was labeled accordingly and used to train and test the selected SVM model. The validity of the model was evaluated using leave-one-out cross validation and Receiver Operating Characteristic (ROC) curve.

2.4. Support vector machine

Here we review the main concept of SVM [18]. SVM is a supervised learning method which constructs a hyperplane or set of hyperplanes in a high- or infinite-dimensional space used for classification. Considering the problem for binary classification, such as ASD versus control, we have two classes of objects (samples) and we want to separate (classify) them. The data are given as $(x_1, y_1), (x_2, y_2), ..., (x_m, y_m) \in X \times \{\pm 1\}$. Such that X is a non-empty set in the domain of x_i features, and y_i are the targets or labels. We assume that the data are into the Hilbert product space $\mathcal{H}$ to allow us to measure the distance of the vectors in that space. Among all hyperplanes we seek for the optimal separable hyperplane that maximize the

distance between the data points (vectors). This can be achieved by using the hyperplane decision function

$$f(x) = sgn(\sum_{i=1}^{m} y_i \alpha_i < x_i, x_j > +b) \tag{2}$$

where α_i are Lagranger multiplier and b is a threshold which can be computed by convex optimization [18].

2.5. Functional connectivity differences

As we are mostly interested in dynamic functional connectivity, we used a metric quantifying changes in it. The flexibility index for each node of a connectome defined at different time points is defined as the number of times that it changes community allegiance, normalized by the total possible number of changes. In temporal networks, we consider changes possible only between adjacent time points. The flexibility index has been introduced by Bassett et al. [19] to quantify changes in connectomes related to learning at different time points. Biologically, a network flexibility could be driven by physiological processes that facilitate the participation of cortical regions in multiple functional communities (clusters) [19]. As communities organization change smoothly with time, the flexibility index displays coherent temporal dependence also in dynamical functional changes within the same session. Fig. 1 gives a schematic representation of changes in community for two nodes along time. Our rationale is that ASD and schizophrenia subjects due to their connectome miswiring have some brain region with different flexibility from healthy control subjects. Moreover, we are interested in seeing if some of these difference are shared between ASD and schizophrenia subjects. To validate this, we assessed the number of clusters in all our dFC connectomes using the eigengap techniques related to spectral clustering [20] as a mean eigengap for all connectomes. This led to a mean rounded value k=6. Once the number of clusters is known, spectral clustering based on k-means was performed, and subsequently the changes of each brain region according to communities as the flexibility of a node f_i normalized by the total number of changes that were possible. Given all f_i index for each brain region and subjects, a statistical framework based on two-tail t-test was used to find statistical difference between the groups (ASD vs control, schizophrenia vs control, and ASD vs schizophrenia). T-test values were then converted into p-values to check which are statistically significant under the threshold $\alpha = 0.05$.

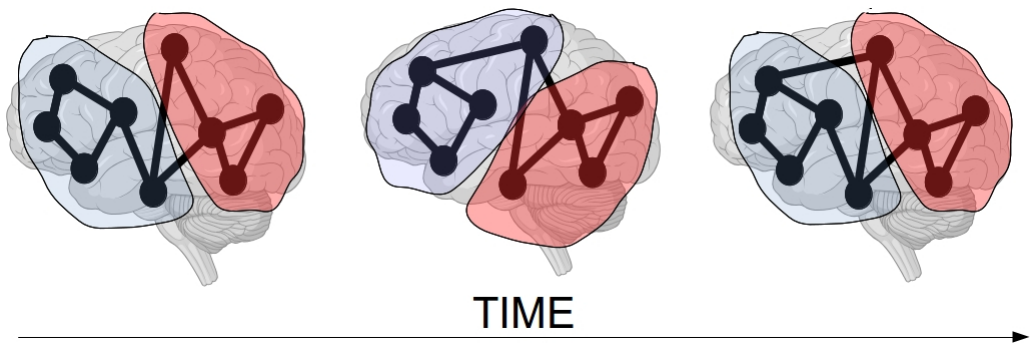
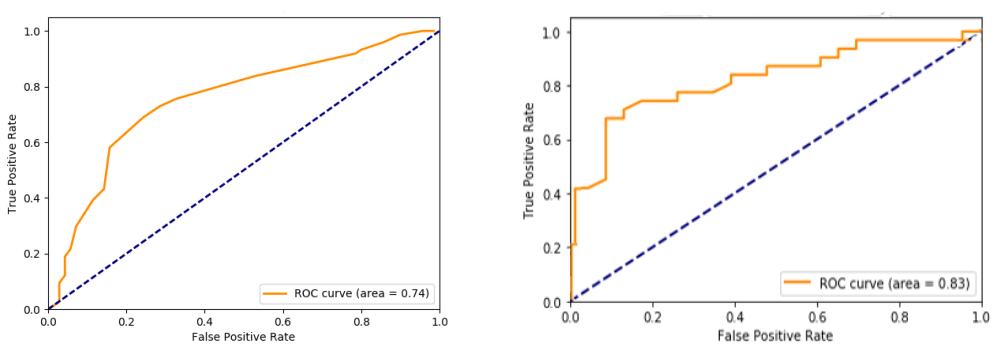


Figure 1: Schematic representation of 2 nodes which change community across time twice.

Moreover, we looked at static FC differences using the network based statistics (NBS) [3]. As noticed empirically that the NBS was producing about 300 connection using a threshold of $\alpha = 0.05$ (proportionally in agreement with Mastrovito et al. [5]), we lowered the NBS threshold to $\alpha = 0.01$ to allow visual inspection of those results.

3. Results

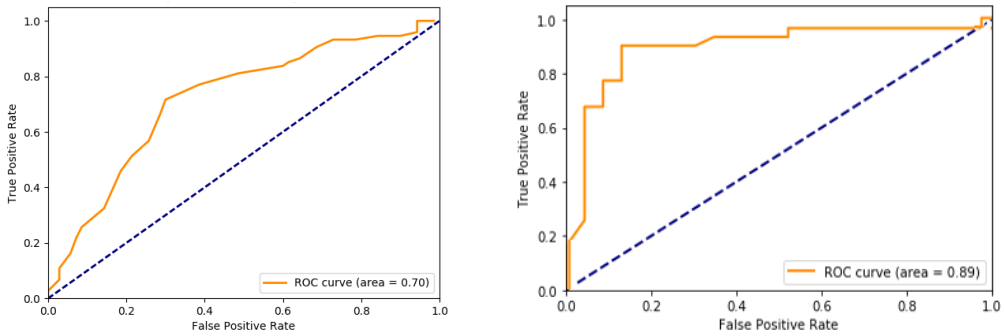
Static Functional Connectivity: For the ASD dataset, the area under the ROC (AUROC) gave us a value of 0.825 using the static FC matrix (see Figure 2(a)). While using the schizophrenia features AUROC curve with value was 0.74 (Figure 2(b)). *Dynamical Functional Connectivity:* For



(a) (b)

Figure 2: ROCs for static functional connectivity analysis. (a) Schizophreana and (b) ASD.

dynamic analysis, the AUROC value was 0.895 for the ASD experiment (see Figure 3(a)), and 0.70 for the schizophrenia (Figure 3(b)).



(a) (b)

Figure 3: ROC for dynamic functiuonal connectivity analysis. (a) Schizophreana and (b) ASD.

The statistically significant areas ($\alpha = 0.05$) according to the flexibility index were, for the ASD group, the cingulate gyrus, the frontal orbital cortex, and central opercolum cortex. While for the schizophrenia dateset the significant different areas were the inferior frontal gyrus, pars opercularis, the post-central gyrus, inferior temporal gyrus, paracingulate gyrus, supracalcarine cortex and the cingulate gyrus. The experiments with both datasets highlighted the cingulate gyrus as a different region from the flexibility point of view.

The local differences detected by using NBS however were not directly comparable between the ASD and schizophrenia cohorts, apart the presence of DMN related connections to the posterior cingulate gyrus (CGp) and medial frontal cortex (FMC) as depicted in Fig. 4.

4. Discussions

Several studies support the idea of continuum between schizophrenia and ASD. Previous investigations showed that subjects with high-functioning ASD shared similar but more severe impairments in verbal theory of mind than schizophrenia patients [21]. More recently the analysis of the co-atrophy network of schizophrenia, ASD, and obsessive compulsive disorder showed

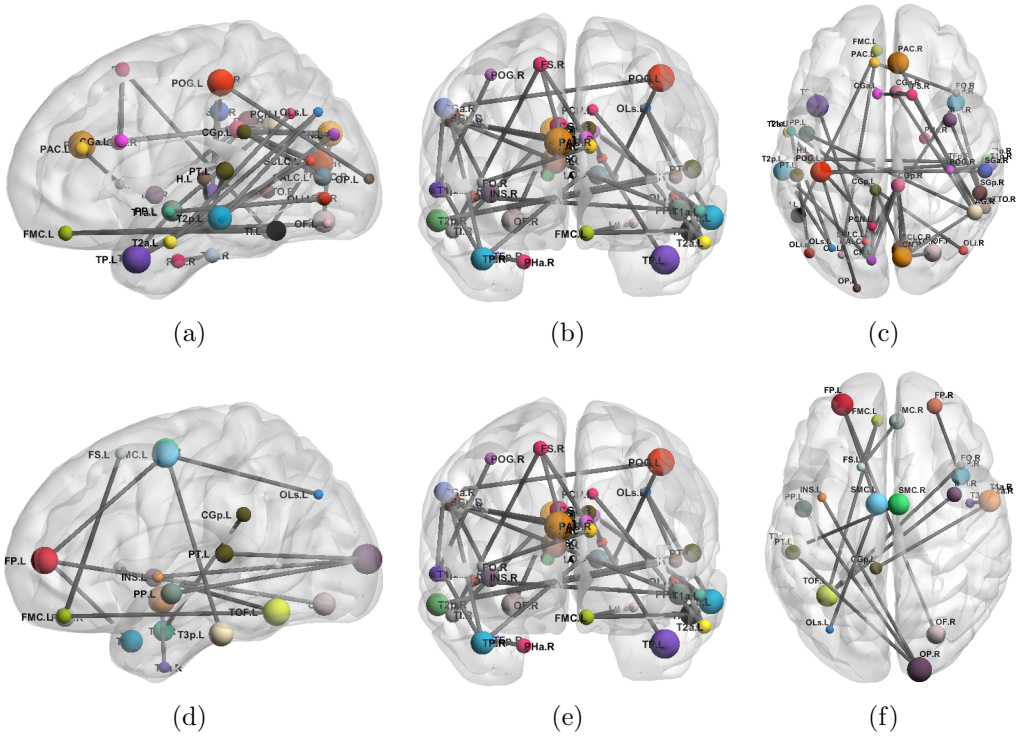


Figure 4: Statistically significant connection detected on the static FC matrices respectively for the schizophrenia (a) sagittal, (b) coronal, and (c) axial view. Statistically significant connection of the ASD cohort against respective control (d) sagittal, (e) coronal, and (f) axial view.

that alterations in certain grey matter ROIs appear to be statistically related to alterations of other grey matter ROIs consistently in all three disorders [22]. From a diagnostic point of view, it could be useful identifying biomarkers for psychiatric disorders such as ASD and schizophrenia. It has been already hypothesized that schizophrenia subjects present higher flexibility indices than control in their connectomes probably due to mechanism modulated by N-methyl-D-aspartate receptors [23]. In line with this work, our experiments with both datasets highlighted the cingulate gyrus as a different region from the flexibility point of view. Namely that the cingulate gyrus for both ASD and schizophrenia subjects manifest an altered reconfiguration compared to control subjects. This can be explained by the fact that this region is one of the main hub of the default mode network (DMN)

which is known to be different for both ASD and schizophrenia subjects compared to healthy controls [5]. Many studies have identified the DMN as a collection of areas that are structural and functional hubs related to supplementary motor-areas, frontal eye fields involved in control of visual attention [24, 25]. Although the two diseases are known to exhibit significant changes in connectivity in the DMN, the two disorders display different connectivity alterations. ASD subjects exhibit a greater proportion of within-network changes in the DMN and reduced connectivity between DMN and language areas. Conversely, schizophrenia changes between DMN and language areas are increased in connectivity [26].

Despite the local differences identified by NBS were not directly comparable between the ASD and schizophrenia cohorts, the detected discriminant connections individually for ASD and schizophrenia are in line with connections detected by other works [27, 5]. Nevertheless, the general spread miswiring for both pathologies yet suggests the hypothesis that schizophrenia is part of the autism spectrum as the two pathologies clearly overlap at some aspects [28].

A limitation of the study is given that the two cohort (ASD/control and schizophrenia/control have been acquired by different centers with slightly different protocol. Moreover, the AUC for the dFC using the schizophrenia dataset was worse than using the static FC matrix. This can be related to the high dimensionality of the data suggesting that dimensionality reduction or independent component analysis might be necessary for this dataset, as shown in [29]. Future works include those aforementioned techniques and the use of generalized Louvain modularity [30] as multilayer network instead of window-wise spectral clustering.

5. Conclusions

This work recommend SVM as a potential further tool for discriminating both ASD and Schizophrenia from healthy subjects. Both static and dynamic functional connectivity can be used as features for this discrimination. Lastly, flexibility index and NBS highlighted the impact of the posterior cingulate gyrus for both pathologies compared to healthy control. These results are further proofs that overlaps between the two pathologies exist.

Statements

No actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within three years of beginning the submitted work exists.

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