Connectome of Autistic Brains, Global Versus Local Characterization

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Abstract. The underlying neural mechanisms of autism spectrum disorders (ASD) remains unclear. Most of the previous studies based on connectomics to discriminate ASD from typically developing (TD) subjects focused either on global graph metrics or specific discriminant connections. In this paper we investigate whether there is a correlation between local and global features, and whether the characterization that discriminates ASD from TD subjects is primarily given by widespread network differences, or the difference lies in specific local connections which are just captured by global metrics. Namely, whether miswiring of brain connections related to ASD is localized or diffuse. The presented results suggest that the widespread hypothesis is more likely.

Keywords: ASD · Connectome · Tractography · Autism · Graph metrics

1 Introduction

A connectome is a mathematical representation of the brain as a network comprising a set of nodes and edges that relate them [17]. Nodes represent distinct homogeneous brain regions generally defined by a brain atlas. Edges represent connectivity, either functional given by co-activation in time of functional signal, or structural given by the fibers physically connecting the areas. Some brain pathologies investigated by using connectomes have been considered either by their effect in specific local connections or by their impact to the global brain network. For instance, with Alzheimer's disease there is an overall disruption of structural and functional connectivity [13]. Schizophrenia is considered the "disconnection" disease with several miswirings between brain areas [20]. Stroke and gliomas are mostly focal lesions and many studies have shown disruptions in structural and functional connectivity related to the focal damage, though subsequent changes on the global organization might be present [9].

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1.1 Connectomes and Autism Spectrum Disorder

Autism spectrum disorder (ASD) is a set of neuro-developmental disorders characterized by impaired social interaction and repetitive behaviors [1]. The underlying neural mechanism of ASD remains unclear. Magnetic resonance imaging-based characterization of ASD has been explored as a complement to the current behavior-based diagnoses [19]. Several studies have proposed biomarkers for discrimination of ASD subjects. Rudie et al. investigated global metrics obtained from functional and structural connectomes [16]. The same metrics have also been used in a support vector machine (SVM) framework to characterize global changes in the connectome of ASD subjects [7]. A *rich-club* refers to a close group of nodes with relatively high degree. Ray et al. used an overall rich-club score for the connectome to discriminate ASD, attention deficit/hyperactive disorder, and typically developing (TD) subjects [14]. At the local level, ASD has been investigated looking for few connections which can be used to discriminate ASD from TD subjects. Promising results have been found using functional connectomes [19], structural connectomes [12], and effective connectivity graphs [3,10]. Lastly, local areas have been studied by using the same global graph metrics used in the aforementioned works but applied to specific local network regions [8], and 10 areas were found statistically different among ASD and TD subject groups. Nevertheless, given the high number of needed connections to discriminate between the two groups in a case-control setting, the question remains whether the most representative biomarkers, which allow the discrimination, are specific local connection differences or ASD is a diffuse global connectome disconnection pathology such as schizophrenia. In this paper we want to investigate whether there is a correlation between these two aspects, and whether one is more predominant than the other. To do so, we compute the most common global metrics and verify if any of them is useful in discriminating ASD from TD subjects. We then seek for the local connections which are different across those two groups and whether there is a correlation between the two types of characterization. In the end, we draw some conclusion considering all these results. The rationale is that if there is statistically significant global metric that discriminate the two groups, there might be a correlation either with single specific local features or with the ensemble of local features.

1.2 Global Metrics

Global metrics are important tools to analyse the network because they allow us to represent with few scalar values the topology and efficiency of a network. Those might represent the segregation, integration, centrality, and resilience of a network. To be in line with previous works on ASD [7,16], we focus on network segregation and integration, using only features which are statistically representative for our dataset.

– Segregation refers to the process of grouping communities such that members of the same community are more densely connected than members of different

communities. This is similar to the concept of clustering and community detection [4].
– Integration refers to the network's ability to propagate information and the efficiency of global communication [4].

In our experiments, we tested several metrics of integration and segregation for weighted graphs in discriminating the two groups with a t-test, and we then retained those which are statistically significant (p-value < 0.5). Those are one metric of segregation (Louvain modularity) and one of integration (characteristic path length) both in their weighted version.

The *Louvain modularity* method is a community detection method that partitions the network using a greedy algorithm that optimizes the modularity [15]. The optimization is performed in two steps. First, the method groups individual nodes into "small" communities by optimizing modularity locally. Second, it builds a new network whose nodes are the newly formed communities. These steps are iterated until a maximum of modularity is attained and a hierarchy of communities is produced. For weighted graphs, modularity is defined as

$$Q = \frac{1}{2m} \sum_{ij} \left[A_{ij} - \frac{k_i k_j}{2m} \right] \delta(c_i, c_j), \tag{1}$$

where A_{ij} is the weight of the edge connecting between nodes i and j from the adjacency matrix $\mathbf{A}$, k_i and k_j are the sums of weights of the edges connected to node i and j respectively, $m = 1/(2A_{ij})$, c_i and c_j are the communities of nodes i and j, and δ is a simple delta function.

Weighted characteristic path length measures the integrity of the network and the ease of information flow within the network. The distance d_{ij} is the shortest path between node i and j. It is quantified by the weighted count of edges in this shortest path [15]. The characteristic path length is the average of all the distances between every pair in the network defined as

$$L^W = \frac{1}{n(n-1)} \sum_{i,j \in n, i \neq j} d_{ij}^W, \tag{2}$$

where n is the number of nodes.

1.3 Local Connectivity Differences

We define specific connections which can discriminate between 2 groups of networks as *local connectivity difference*. Local connectivity difference can be found in several ways, as false discovery rate [20], by analyzing the SVM weights trained to discriminate between ASD and TD [6], or by using network based statistics (NBS) [20]. NBS is a nonparametric statistical test used to identify connections within connectivity matrices which are statistically significant different between two distinct populations [20]. In practice, the NBS checks the family-wise error rate, where the null hypothesis is tested independently at each of the edges. This is achieved performing a two-sample t-test at each edge independently using the values of connectivity. The tests are repeated k times, each time randomly permuting members of the two populations.

2 Methods

Our evaluation is carried out with the following steps:

1. For all connectomes of both ASD and TD subjects the aforementioned global metrics are computed.
2. Those metrics are used as features for an SVM classification task.
3. NBS is performed to identify discriminant local connection.
4. Local and global features are then compared.

Beyond the SVM classification, to extract more meaning from the features as in [16] a univariate t-test is performed on the single features assessing their statistical significance independently from the other features. To compare global and local features, univariate and multivariate regressions are performed between the statistically significant global metrics and the local connections.

3 Data and Experimental Settings

The experiments have been performed on the San Diego State University cohort of the ABIDE-II dataset [5]. This cohort was chosen as it was the one with diffusion tensor imaging (DTI) volumes at sufficient resolution to allow acceptable quality tractography. One sample was discarded as it produced too noisy tractography with the used algorithm. The final dataset included 30 ASD and 24 TD subjects matched for age, gender, handedness, and nonverbal intelligence quotient. For each subject, DTI and T1 have been acquired and co-registered. Imaging data were acquired on a GE (Milwaukee, WI) 3T MR750 scanner. T1 data were acquired with repetition time (TR) = 8.108 ms, echo time (TE) = 3.172 ms, flip angle = 8°, 172 slices, 1 mm^3 resolution. DTI volumes were obtained with an echo-planar pulse sequence with full head coverage and encoded for 61 noncollinear diffusion directions with TR = 8,500 ms, TE = 84.9 ms, flip angle = 90°, FOV = 240 mm, 128×128 matrix, $1.88 \times 1.88 \times 2$ mm^3 resolution.

3.1 Pre-processing and Connectome Construction

DTI volumes have been pre-processed with eddy current correction and skull stripping. Linear registration has been applied between the automated anatomic labeling (AAL) atlas [18] and the T1 reference volume by using linear registration with 12 degrees of freedom. Tractographies for all subjects have been generated processing DTI data with a deterministic Euler approach stemming from 2,000,000 seed-points and stopping when the fractional anisotropy was smaller than <0.1. Additionally, all the structural connections with fiber lengths <30 mm were also excluded. To construct the connectome, the graph nodes have been determined using the 90 regions in the AAL atlas. The edges have been weighted with the number of tracts connecting two regions.

3.2 Experimental Settings

All features are computed by using the Brain Connectivity Toolbox[1], while the SVM implementation of Scikit-learn[2] was used. Due to the stochastic aspects of the Louvain modularity, experiments were repeated 100 times, averaging the results. NBS was used with $k = 1000$ permutations thresholding the p-value at $\alpha = 0.01$. All results are computed in a leave-one-out cross-validation manner.

4 Results and Discussions

Classification performance by using the global metrics jointly and an SVM classifier can be summarized by the receiver operating characteristic curve (ROC) shown in Fig. 1(a). It can be seen that the mean of 100 runs is significant with a mean area under the curve (AUC) of 0.77 in agreement with similar previous results on another dataset [7]. Performing the SVM classification using only one feature at time, the AUC was 0.70 (mean) for the Louvain modularity, and 0.74 for the characteristic path length. It is worthwhile to mention that the Louvain modularity was producing sometimes relatively high and sometimes relatively low AUC. Table 1 shows the mean and standard deviation for each feature for ASD and TD brain matrices, and the resulting p-values indicate the features where the two classes differ. Those results are in agreement with Rudie et al. [16]. The difference in structural modularity and characteristic path length among ASD and TD subjects can reflect a subtle randomization of the network connectivity as proposed in [15]. Despite using the Louvain modularity and characteristic path length as a representation of segregation and integration can be reductive, giving their significance with the used dataset we used those features jointly with local differences looking for correlations. NBS detected 10 symmetric discriminant structural connections depicted in Fig. 1(b–d), are similar to those obtained with the same dataset and using SVM in [3], and on another dataset using also NBS [8]. However, those are slightly different from the functional connections detected in [19].

Table 1. Mean value and standard deviation of the global metrics for both the ASD and TD population. The last column gives the one-tail p-values comparing the two.

Feature	ASD		TD		p-value
	Mean	Std	Mean	Std	
Louvain modularity	0.542	±0.020	0.532	±0.021	0.047
Weighted characteristic path length	0.0163	±0.0016	0.0155	±0.0010	0.049

It is worthwhile to mention that the detected connections are obtained with a p-value threshold of 0.01 and with a p-value threshold of 0.05 there are approximately 3 times more connections. Those connections are mostly located at the

[1] http://brain-connectivity-toolbox.net.
[2] http://scikit-learn.org/.

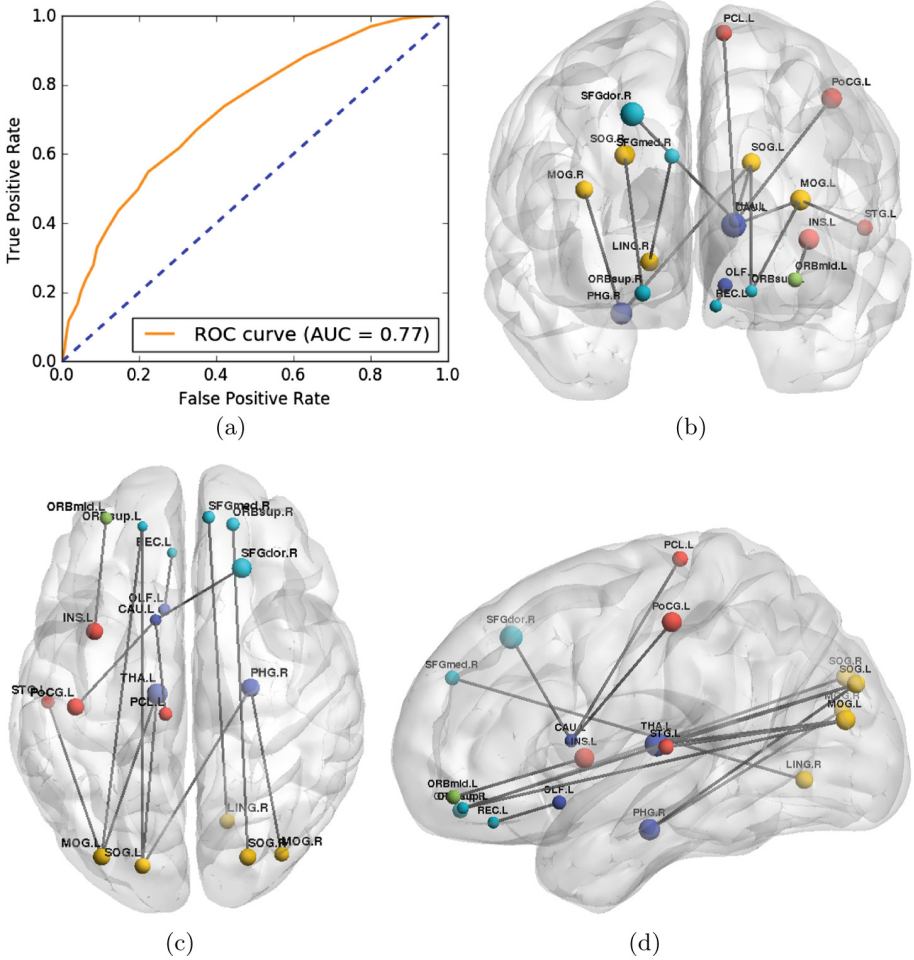

Fig. 1. (a) Mean ROC and AUC for the classification task with both features obtained averaging 100 times the ROC with different Louvain modularity computed. (b) axial, (c) coronal and (d) sagittal view of the statistical different connections between the ASD and TD subjects. The used abbreviations are MOG = middle occipital gyrus, SOG = superior occipital gyrus, PoCG = posterior cingulate gyrus, THA = thalamus, SFG = superior frontal gyrus, INS = insula, PCL = Paracentral lobule, CAU = caudate, PHG = para hippocampal gyrus, L = left, and R= right.

occipital gyrus on both sides going to the orbitofrontal cortex, thalamus and caudate left, para-hippocampal gyrus, in agreement with former studies [8,11]. The accuracy of the SVM classification using the 2 global features was 65% while using the 10 discriminant connection was 61%. This is in line with previous studies [7], which are also suggesting that accuracy can be increased if functional rather than structural connectivity is used [19].

The univariate correlation between the mean Louvain modularity or weighted characteristic path length and single connections detected by the NBS was not so strong. In fact, all the computed r^2 score were between 0.01 and 0.2, when 0 is no correlation and 1 is perfect correlation. Instead, performing a multivariate regression between the Louvain modularity or path length and all connectivity values jointly gave respectively a mean $r^2 = 0.49$ and $r^2 = 0.48$, suggesting a stronger meaning in using all connections jointly. Moreover, given also the high number of different connections between the two groups (10 and 31 for the $\alpha = 0.01$ and $\alpha = 0.05$ p-value threshold respectively), and their location spread across the brain, we conclude that ASD is more characterized by spread miswiring similar to schizophrenia rather than few representative disconnections. Therefore, we agree with previous hypothesis that a global disruption of connectivity is the basis of ASD, and that changes during development compensate for the disruption [2], although the experiments should be repeated with larger sample sizes.

5 Conclusion

In this paper we have shown that the structural connectome of ASD and TD subjects can be classified by either using the Louvain modularity and characteristic path length or a set of structural connections, giving similar accuracy. Lastly, given still the high number of connections and their heterogeneous location within the brain of structural connection, ASD could be considered as a widespread miswiring of the brain. Future work comprises the use of functional connectivity in the analysis, the inclusion of other global metrics beyond segregation and integration, and investigating different settings for classification.

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