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Graph theoretical approaches towards understanding differences in frontoparietal and default mode networks in Autism

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Abstract

Autism Spectrum Disorder is a complex developmental disorder affecting 1 in 68 children in the United States. While the prevalence may be on the rise, we currently lack a firm understanding of the etiology of the disease, and diagnosis is made purely on behavioral observation and informant report. As one method to improve our understanding of the disease, the current study took a systems-level approach by assessing the causal interactions among the frontoparietal and default mode networks using structural covariance of a large Autism dataset. Although preliminary, we report diffuse yet subtle changes throughout these networks when comparing age and sex matched controls to ASD patients.

Index Terms

Autism; MRI; Networks; Machine learning

1. INTRODUCTION

As a complex disorder rooted in disturbances of typical brain development, Autism Spectrum Disorder (ASD) affects 1 in 68 children in the United States [1]. This disorder often occurs during a critical period of brain development that includes synaptic formation and maturation of structurally co-varying regions, possibly leading to co-variance at the macroanatomical level [2]. Widespread disruptions in inter-regional volumetric correlations in children with ASD have been observed, particularly in regions subserving aspects of social function, such as the default mode network and the frontoparietal control hub [3–4]. Critically, it has been shown that the frontoparietal network displays a high degree of between-network connectivity, especially in regulating task switching between internally and externally driven states involving the default mode network [5]. Behavioral and cognitive abilities have also been associated with both regional morphometric proportions and co-variance between other regions. For example, higher IQ has been associated with stronger correlations between the inferior frontal gyrus and thickness of other frontal and parietal regions [6]. Furthermore, studies of brain development have identified that structurally co-varying regions show correlations in terms of their rate of change over time [7].

Just as strong functional connectivity can arise in the absence of direct white matter connectivity, this pattern of inter-regional structural covariance has been shown to likely be more akin to a pattern of functional connectivity [8]. For example, the correlation between brain regions in intrinsic brain activity measured with blood oxygen level dependent (BOLD) imaging fMRI has shown significant overlap between population based measurements of gray matter covariance in the same regions [9]. Importantly, studies that target brain connectomics can also be prohibitively expensive, while structural MRI scans that are often acquired for clinical purposes may remain unanalyzed. Therefore, the goal in our study was to apply what is known about brain networks from functional imaging, to a large dataset of ASD patients using structural imaging. We sought to determine whether or not this network approach would improve our ability to detect subtle differences between ASD patients and controls.

2. METHODS

2.1. Network Atlas

In order to better understand network level structural covariance in ASD, we sought to apply a functionally defined atlas consisting of 7 networks of the brain. Here we focused on two of these: the default mode network and the frontoparietal network. The particular networks show documented interactions in healthy controls, as well as possible disruptions due to ASD and other development disorders. More detailed information on the construction of this comprehensive network atlas can be found in [10]. Briefly, this atlas was created using resting-state functional imaging data from 1,000 healthy young adults, aged 18–35. In order to create the atlas, subjects were divided into a discovery and replication cohort of equal size, age, and sex distribution. All subjects were scanned at the same site, with equivalent acquisition parameters. Any unclear network boundaries were further delineated using histopathological atlases, and immunohistochemistry. The discovered networks consist of largely parallel interdigitated circuits distributed across the brain. More traditional regions of interest, such as the posterior cingulate, were divided into multiple networks. The frontoparietal and default mode networks as defined through this atlas are shown in Figure 1 below.

2.2. Participants

Data were collected from 1,082 sex-, age-, and FIQ-matched ASD patients and healthy controls across 21 sites participating in ABIDE I or II. As autism is a developmental disorder, we chose to focus on participants that were younger than 21 years of age. Basic subject demographics are summarized in Table 1.

2.3. Neuroimaging Processing

All images were processed through FreeSurfer's validated surface-based pipeline for brain image skull stripping, reconstruction, alignment, and parcellation. More detailed information may be found in [11]. For the purpose of this study, the Yeo et al., network labels were spherically mapped using annotation files in freesurfer's average space and then converted to subject specific volumetric labels. In order to address distortions in the between subject registration, holes were filled by dilating and eroding the mask for the corresponding

network, and finally cleaned using the subjects hemispheric ribbon. All images were assessed for quality control by viewing the subjects processed brain image with their corresponding network masks. These masks were then used to calculate volumetric statistics corresponding to the original FreeSurfer parcellations within the boundaries of the given network mask. This was done to represent that most native freesurfer parcellations fall within multiple networks, and likely have inter-related albeit differing functions. Regions that inconsistently appeared within the default mode or frontoparietal network boundaries across subjects were excluded from the structural covariance analysis.

2.3. Network Formation

In order to take into account the likelihood for mutual dependencies, reduce multicollinearity, and more fully understand how these networks might interact with each other in ASD compared to controls, we constructed a sparse partial correlation matrix of the results within each diagnostic group separately (ASD vs controls). We then applied graphical least absolute shrinkage and selection operator (LASSO) in order to visualize and interpret the results. LASSO helps to ensure the output is a parsimonious and stable network that more likely reflects the underlying relationships than the partial correlation does alone. Only the relevant edges are retained in the network, avoiding spurious edges simply due to chance, and reducing the overall number of parameters that must be estimated. An extended bayesian information criterion (EBIC) is used to determine the optimal overall network. EBIC selects the optimal value of the tuning parameter λ based on minimising the EBIC over a range of 100 λ values. Many models are generated and the one with the best fit is selected. Likewise, the γ hyperparameter decides how many edges are recovered. Unlike more traditional graph measures, smallworldness and global clustering are less useful because they're not typically derived from weighted networks as is the output here [12]. Here, each node represents a volumetric region within one of the two networks, and the edges indicate the strength of the correlations between regions. Red edges indicate a negative correlation, while blue indicate positive. The proximity of each node indicates how strongly a node is connected to the others, and the most central nodes are typically those with the greatest overall connections. Finally, we calculated graph measures on group centrality scores.

3. RESULTS

Resulting networks are summarized in Figure 3 along with a list of regions included in each network. Upon visualization, it appeared that there were not many differences between the controls and ASD groups on the edges maintained following normalization by LASSO. It is possible that a reduced sparsity would yield more interesting results. We also calculated measures on group centrality. We did not find overall statistical differences following 1,000 permutations comparing group distributions on the total network as a whole. However, we also conducted permutation tests after identifying that node 13 - the left middle temporal gyrus of the default mode network was consistently implicated as an important node in the group centrality measures for the normal controls. Here we found that there were significant differences in the edge strength between this measurement and the left supramarginal of the default mode network between groups. The relationship between these regions was not

strong enough to appear in the ASD network, while it showed a moderate positive association in the control network.

4. DISCUSSION

This study is one of the largest conducted geared towards understanding the effects of structural covariance in Autism disease. While we did not find robust differences between groups, there are variations in edge strengths throughout the network indicating mild and diffuse network differences. These diffuse differences point to the importance of a systems approach for understanding the etiology of Autism. Given that certain regions showed complete isolation, it is likely that inclusion of additional networks will yield further insights. It is also possible that finding a way to incorporate diagnosis in construction of the network, rather than stratification by groups will lead to additional insights. We plan on follow-up studies focused specifically on sex differences within these networks. As both brain networks and ASD show sex differences, we expect these techniques to reveal greater insights using this stratification.

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Figure 1.
Default mode (blue) and frontoparietal (green) networks as defined in [10].

Figure 3. Results from graphical LASSO for control and ASD networks separately. Each number corresponds to a brain region, and the corresponding region can be identified using the legend on the right.

Table 1

Demographics of the ABIDE participants included in this study. FIQ: Full Scale Intelligence Quotient.

Demographic Characteristics of Autism and Healthy Controls				
		Total	Age (Mean $\pm$ SD)	FIQ
Controls	<i>N = 541</i>		12.7 (3.5)	112 (12.7)
	Males	467	12.9 (3.5)	112.3 (3.5)
	Females	74	11.6 (3.2)	110.1 (12.2)
ASD	<i>N = 541</i>		13.2 (3.7)	105.3 (17.4)
	Males	467	13.4 (3.7)	105.5 (17.5)
	Females	74	12.3 (3.7)	103.8 (17.3)