Network Analysis of Brain White Matter Structure in Individuals with Autism Spectrum Disorder

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1 Introduction

In this paper we will be examining and analyzing the white matter structure of pre-teens and adolescent individuals with autism spectrum disorder (ASD) as collected through diffusion tensor imaging and developed with tractography. Given the pivotal nature of axon tracts on coordinating communication among brain regions (Fields, 2008), and the inherent network-like structure of these tracts, we believe that network and graph analysis may provide greater insight and understanding on the relationship between ASD and white matter structure.

More specifically, we will be examining the neural networks of 52 subjects with ASD and 43 under typical development (TD) as unique, weighted, undirected graphs, with nodes being brain regions and edges being the existence and number of neural connections between these regions. Our initial focus is on understanding various features of these regions and their interconnections, including centrality and clustering. Our ultimate goal is to highlight any significant differences between the two subject groups and tie our results back to current medical knowledge on the relationship between ASD and white matter structure in the brain.

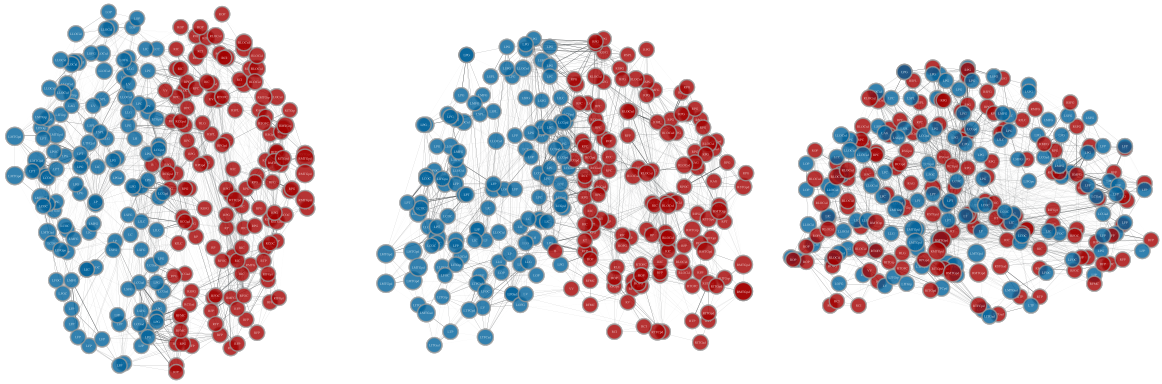
2 Related Work

2.1 DTI and Autism

Diffusion tensor imaging (DTI) tractography is a technique used to represent white-matter neural tracts in the brain — namely, axon tracts and commissures. White matter has an active effect on learning, self-control, and mental illness, controlling the signals that neurons share (Fields, 2008).

Autism spectrum disorder (ASD) is a group of neurodevelopmental disorders with characteristics that include impaired social cognition and reciprocity, and repetitive, restricted behavior (NIMH, 2016; Lord et al., 2000).

There is evidence that a connection between ASD and abnormal white matter structure exists with studies on children and adolescents with autism finding that disruption of white matter tracts in white matter adjacent to the ventromedial prefrontal cortices, in the anterior cingulate gyri and the temporopatietal junctions may be implicated in impaired social cognition for individuals with with ASD (Barnea-Goraly et al., 2004). Developmental studies of white matter in males suffering from ASD has found that there is a reduction in the structural integrity of white matter (namely, lower fractional anistrophy near the corpus callosum and in the right retrolenticular portion of the internal capsul) that may underlie the behavioral pattern observed in autism (Keller et al., 2007). However, it is known that children suffering from ASD often display an increase in postnatal head circumference which may be caused by delayed and prolonged myelination, which is the production of white matter myelin sheath surround nerve cell axons (Volkmar et al., 2005). Thus, recent studies have been placing more attention on analyzing how the nature of abnormality in white matter integrity affects ASD behavioral phenomena, though most work has been kept within the boundaries of biological analysis of white matter fiber tracts (Pryweller et al., 2014; ACE, 2016). We believe



(a) Horizontal plane (b) Coronal plane (c) Sagittal plane

Figure 1: ASD white matter structure from DTI tractography

that representing white matter structure as a graph and using complex network methods and measures to analyze information gathered with DTI scans may help us gain further insight as to how ASD is associated with white matter formation and structure in the brain.

2.2 Brain Neural Network Analysis

The network structure of the brain is a popular topic of research and exploration. The uses and interpretations of a wide array of network measures and tools have been well documented, including measures of segregation and integration, centrality, and resilience (Rubinov and Sporns, 2010). Various mapping techniques, including functional magnetic resonance imaging, electroencephalogram, magnetoencephalography, and susceptibility tensor imaging, which capture different aspects of the functional or anatomical structure of the brain, have been analyzed with various network tools and methods (Sporns et al., 2007; Joyce et al., 2010). For instance, eigenvector centrality has been used to analyze connectivity patterns in temporal fMRI data of the brain, with the authors concluding that the tool is an effective and computationally efficient tool for capturing intrinsic neural architecture at a voxel-wise level (Lohmann et al., 2010).

An effort to evaluate the brain architecture in autism does exist, with the Autism Imaging Data Exchange consortium aggregating and sharing over a thousand resting-state fMRI datasets of male subjects with ASD and TD (Di Martino et al., 2014). However, the structural information captured by fMRI scans is very different to that collected in DTI tractography methods — while DTI tractography attempts to reveal the white matter structure of the brain, fMRI measures brain activity through changes in blood flow (Matthews and Jezzard, 2004). Functional MRI measures and detects changes in blood flow and oxygen metabolism, correlated with neural activation, in the brain, typically while an individual is performing a specific behavioral or cognitive task (Shirley et al., 2005). For this reason, fMRI excels at localizing cortical areas specific to certain functions or behaviors. On the other hand, DTI tractography targets the ansiotropic nature of water diffusion to extract the white matter tracts in the brain. For this reason, representing the results from DTI tractography as a network is a more accurate method of mapping the neural structure of the brain than interpreting fMRI results.

Notably, while local decreases of grey matter, composed of neural cell bodies, neuropil, synapses, capillaries, and glial cells, have been found in individuals with autistic spectrum disorder (Waiter et al., 2004), little work has been done in analyzing and comparing the white matter structure of the brain of individuals with ASD, despite the strong belief that myelination and white matter development in infant and teenage years can be different for people with ASD.

3 Data

We will be working with diffusion tensor imaging (DTI) data collected by the Center for Autism Research and Treatment at UCLA, obtained from the USC Multimodal Conenctivity Database (Brown et al., 2012). The sample consists of 52 subjects with autism spectrum disorders (ASD) and 43 individuals under typical development (TP), all between the ages of 8 and 18. These two groups do not have statistically significant differences in their sex, age, mean and maximum head motion, or their full-scale, verbal, and performance IQ (Rudie et al., 2013). The data was collected on a Siemens 3T Trio scanning device at UCLA. After being asked to relax and keep their gaze focused on a fixation cross on a screen, T2*-weighted functional images were captured, with a TR of 3000ms, TE of 27ms, a 128×128 matrix size, 192mm FoV and 3.0×3.0mm in-plane voxel dimensions. These scans were consequently analyzed and preprocessed, with individuals with excessive motion not included in the final dataset (Rudie et al., 2013). Brain deterministic tractography, which aims to represent the neural tracts collected by the diffusion MRI images, was then preformed on the scans using the Fiber Assignment by Continuous Tracking (FACT) algorithm (Mori and van Zijl, 2002), a state of the art method for fiber tracking from DTI imaging data. The maximum turn angle of fibers propagating from voxels was of 50^o (Zalesky et al., 2010), forcing us to discard fibers shorter than three voxels (no turn angle can be determined from just two voxels). Fibers were consequently smoothed using spline filters (Rudie et al., 2013).

The final data consists of 264 putative functional areas as defined by (Power et al., 2011), where edges between these regions correspond to the number of fibers where one endpoint finished in one region and the other endpoint in the other (Rudie et al., 2013). The data was structured in a 264×264 whole brain structural connectivity matrix. Each of the 94 subjects has a corresponding connectivity matrix. Figure 1 shows the graph for one of the individuals with ASD.

4 Methods

We will survey the various tools and measures we are going to use to analyze the graphs, as well as the statistical methods we are going to use to evaluate the statistical significance of the differences captured by these models on the two subject groups. Some of these measures are on an entire graph, while others capture information on a per-vertex basis.

4.1 Clustering

Clustering of brain networks attempts to capture the interconnectivity of groups or clusters within the network. The organization of dependencies captured by these methods may indicate the existence of segregated neural processing (Rubinov and Sporns, 2010). We will be calculating the local clustering coefficient of every node in every graph. This coefficient c is for node n is defined as

$$c_n = \frac{t_n}{k_n(k_n - 1)}$$

where t_n is the number of triangles around a node n and k_n is the degree of node n. We will also be calculating the global clustering coefficient, defined as the average of the clustering coefficients of each node.

4.2 Weighted Transitivity

The weighted transitivity is defined as follows

$$T = \frac{\sum_{n \in N} 2{t_n}'}{\sum_{n \in N} k_n(k_n - 1)}$$

where ${t_n}'$ is the geometric mean of the total weight of triangles around node n (Rubinov and Sporns, 2010; Onnela et al., 2005). This can be thought of as a weighted global clustering coefficient.

4.3 Centrality

We'll be using a number of measures to calculate the centrality of the brain region nodes of our graphs. Each of these centrality measures captures different nuances about the importance and influence of various nodes in our

graphs. We proceed with short introductions of the various centrality measures utilized in this project.

4.3.1 Closeness Centrality

The closeness c of any given vertex n_i is defined as

$$c_{n_i} = \frac{1}{\sum_{n_j} w_{n_i,n_j}}$$

where n_j are the neighbors of n_i and w_{n_i,n_j} is the weight of the edge between nodes n_i and n_j (Opsahl et al., 2010).

4.3.2 Betweenness Centrality

We define the betweenness centrality of a node n as

$$c(n) = \sum_{n_i \neq n_j \neq n} \frac{\sigma_{n_i,n_j}(n)}{\sigma_{n_i,n_j}}$$

where σ_{n_i,n_j} is the number of shortest paths between n_i and n_j, and $\sigma_{n_i,n_j}(n)$ the number of shortest paths between n_i and n_j that pass through n (Brandes, 2001).

4.3.3 Authority and Hubs

Authorities $\mathbf{y}$ and hubs $\mathbf{x}$ are defined as

$$\mathbf{x} = \alpha \mathbf{A}\mathbf{y}$$

$$\mathbf{y} = \beta \mathbf{A}^\top \mathbf{x}$$

where $\mathbf{A}$ is the weighted adjacency matrix and $\lambda = (\alpha\beta)^{-1}$ is the largest eigenvalue of $\mathbf{A}\mathbf{A}^\top$ (Kleinberg, 1999). Since our graphs are undirected, then our adjacency matrix is symmetric along the diagonal. Thus, λ will be the singular value of $\mathbf{A}$ and $\mathbf{x} = \mathbf{y}$. Therefore, the authority and hub value for every node will be the same (we will be reporting a single value for each node). This is equivalent to the eigenvector centrality, which is defined as the eigenvector with the largest eigenvalue λ of a list of vectors $\mathbf{n}$ with weighted adjacency matrix $\mathbf{A}$ (Langville and Meyer, 2005). Namely, it is the solution of $\mathbf{A}\mathbf{x} = \lambda\mathbf{x}$ where λ is the largest eigenvalue.

4.3.4 PageRank

For any node n the PageRank value $R(n)$ is defined iteratively by

$$R(n) = \left(\frac{1-d}{N}\right) + d \sum_{x \in \Gamma(n)} \frac{R(x)A_{n,x}}{\sum_y A_{n,y}}$$

where A is a weighted adjacency matrix, $\Gamma(n)$ are the neighbors of n, and d is a damping factor (Page et al., 1999).

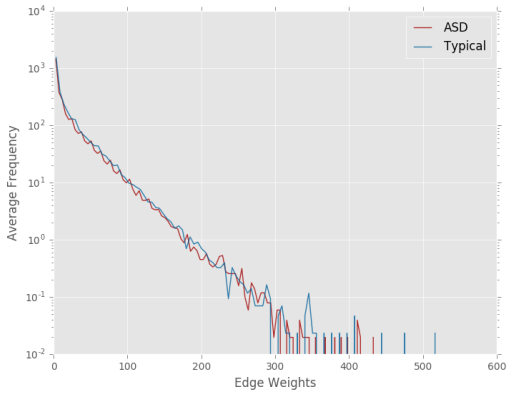


Figure 2: Average edge weight distributions for TD and ASD individuals

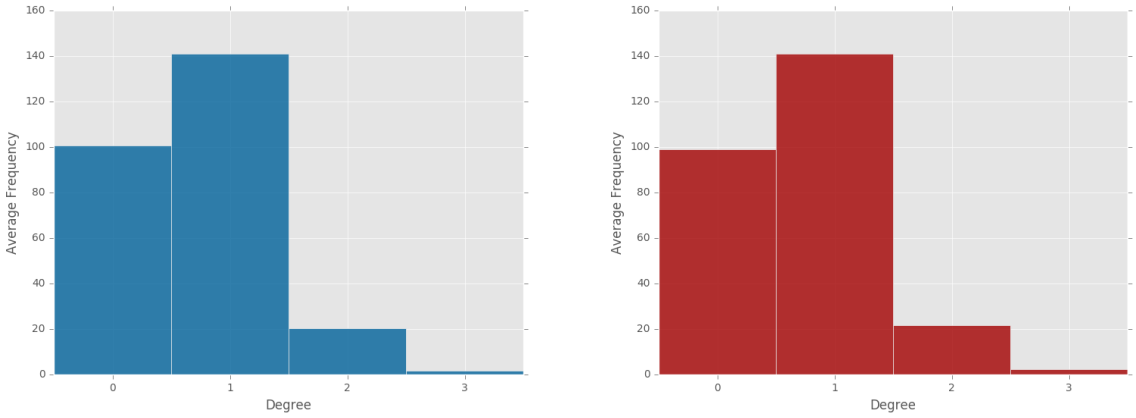
4.4 Statistical Tests

We will be using statistical tests to capture the statistical significance between any differences found between the two subject pools, while controlling for multiple testing error. We proceed by highlighting the various statistical tools and procedures used in this project.

4.4.1 Mann-Whitney U Test

The Mann-Whitney U non-parametric test will help us test the statistical significance of the means of the metrics calculated from the graphs of both ASD and TD groups.

The principal reason why we are using the Mann-Whitney U test rather than the Student's t-test is because it does not require us to assume that our distribution is sampled from a normal distribution (Fay and Proschan, 2010). Given that we have a relatively small number of examples, we do not want to rely on the central limit theorem. In the case that our data is normally distributed, it is nearly as efficient as the t-test.



(a) TD

(b) ASD

Figure 3: Average degree distributions for TD and ASD individuals

4.4.2 Kolmogorov-Smirnov Test

The Kolmogorov-Smirnov, or KS test, is a non-parametric test of the equality of a hypothetical cumulative and continuous probability distribution with an empirial distribution function (Massey Jr, 1951). It is sensitive to differences of location and shape of the distributions provided, making it a desired test for comparing per-node metrics across both datasets. Similar to the Mann-Whitney U test, it does not rely on the assumption of normality.

4.4.3 Benjamini-Hochberg Procedure

Given the large number of statistical tests that we plan on running in this project, it is imperative that we control the false discovery rate of our results. The Benjamini-Hochberg procedure does exactly that, controlling for multiple testing error by essentially decreasing the rejection threshold of the null hypothesis (Benjamini and Hochberg, 1995).

5 Results

5.1 General Metrics

We begin by extracting and analyzing some general network metrics of both sets of graphs. We calculated simple global characteristics of our networks, presented in Table 1, including the number of edges and nodes, the number of triangles, the global clustering coefficient, the weighted transitivity, and the global efficiency. Each of these metrics is the average over all graphs in that dataset. There are not, at first glance, any drastic differences between both groups.

Metric	ASD	TD
$\|E\|$	3210.8	3159.7
$\|V\|$	264.0	264.0
Number of Triangles	12121	11691
Global Clustering	0.4014	0.4026
Weighted Transitivity	0.4427	0.4434
Global Efficiency	0.08571	0.0856

Table 1: Average graph statistics for ASD and TD datasets

We also calculated the degree distributions for both groups, as can be seen in Figure 3, as well as the edge weight distributions, presented in Figure 2. Both of these metrics seem to be quite similar between both groups. Interestingly,

We used the Mann-Whitney U test to vertify whether there is a statistically significant difference between these values. We then used Benjamini-Hochberg to correct for multiple hypothesis testing. However, even at an alpha level of 0.1, none of the tests are significant.

5.2 Node Metrics

We proceed at looking at statistics at a vertex level. For each different metric (i.e. node

betweenness centrality) we check whether the values for each node are statistically significant from its corresponding node in the other dataset using the Mann-Whitney U test. We specifically calculated the authority, betweenness centrality, closeness centrality, and PageRank of each node in each graph.

On an alpha level of 0.1, we find that only one test is statistically significant—namely, the authority of the anterior division of the Left Inferior Temporal Gyrus (LITGad). We proceed by using the Kolmogorov-Smirnov test to check whether these distributions are the same or not. Ideally, we would treat each metric as a draw from a multi-dimensional distribution and then compare each. Good 2- and 3-dimensional versions of the KS test exist (Fasano and Franceschini, 1987; Loudin and Miettinen, 2003) — however, we would require a 94-dimensional test given that our data would be sampled from a 94-dimensional distribution. Therefore, we instead treat each node's statistic as if it were from a univariate distribution and then test to see if there is a statistically significant difference between the ASD and TD datasets.

We find that the authority of the anterior division of the Left Inferior Temporal Gyrus is different at a statistical level between the ASD and TD groups at an alpha level of less than 0.002. This allows us to reject the null hypothesis that the authority of this node is from the same distribution for both groups.

5.3 LITGad Centrality

Given the results on LITGad's authority, we decided to investigate the node with greater detail. Table 2 presents all centrality measures for the LITGad node. For all centrality measures except closeness the node has a higher value in the ASD dataset than in the TD dataset, even though this is only statistically significant for authority.

5.4 LITGad Neighborhood Analysis

We proceed by analyzing the 1-hop neighborhood of the LITGad node. This consists of extracting the subgraph of all nodes that LITGad is connected to in every graph. Sample LITGad 1-hop neighborhoods for both ASD and TD are presented in Figure 4 and Figure 5, respectively.

Metric	ASD	TD
Authority	0.001984	0.001831
Betweenness	0.008243	0.006266
Closeness	0.2335	0.2420
PageRank	0.002304	0.002135

Table 2: Average LITGad node metrics for both ASD and TD groups

Metric	ASD	TD
LITGad Clustering	0.007939	0.006226
3-edge motif	0.2085	0.2177
2-edge motif	0.7915	0.7823
1-edge motif	0.0000	0.0000
0-edge motif	0.0000	0.0000

Table 3: Average LITGad neighborhood graph metrics for ASD and TD datasets

For all of these 1-hop neighborhoods for both the ASD and TD sets of graphs we calculated the average clustering and 3-node motif proportions, presented in Table 3.

The presence of the two predominant motifs does not seem to vary between the two sets. However, the local clustering for LITGad node within its neighborhood in ASD is higher than in TD individuals. These results are aligned with the results founds previously, where the LITGad node had a higher centrality in ASD individuals than in typical development individuals when analyzing the complete DTI tractography networks.

6 Conclusions

The inferior temporal gyrus is commonly associated with the representation of complex objects, and may play an important part in face perception (Haxby et al., 2000) and number recognition (Shum et al., 2013). The anterior region is principally connected with the fusiform gyrus, an area related to recognition, the middle temporal gyrus, known to play a part in for face recognition and word meaning

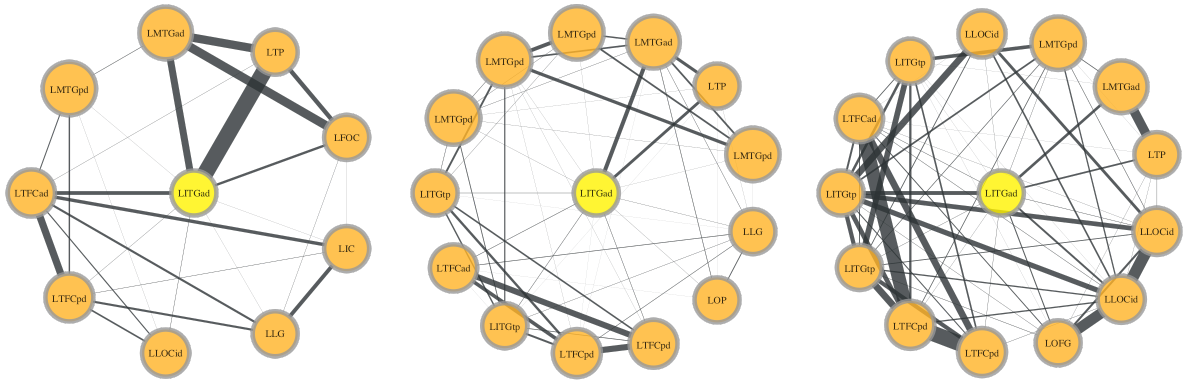


Figure 4: Sample ASD LITGad 1-hop neighborhood subgraphs

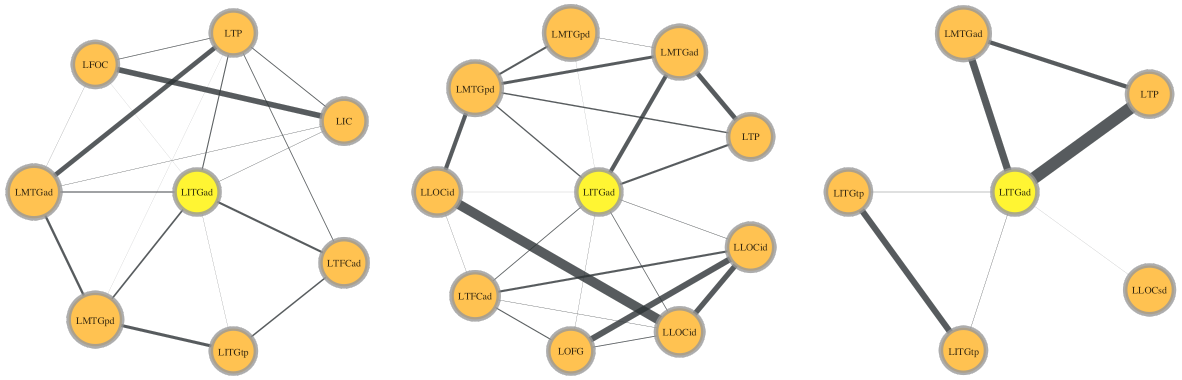


Figure 5: Sample TD LITGad 1-hop neighborhood subgraphs

access during reading (Acheson and Hagoort, 2013), and the superior temporal gyrus, which contains several important areas responsible for sound and language processing and recognition.

Previous studies have found increases in grey matter volume in ASD subjects in the fusiform gyrus, the superior temporal sulcus (the sulcus separating the superior temporal gyrus from the middle temporal gyrus), and the superior temporal gyrus (Waiter et al., 2004). However, we were unable to find studies that uncovered the effects that ASD has on the white matter connectivity of the anterior division of the left inferior temporal gyrus, leading us to believe that our results may be novel findings. Given that many of the behavioral differences of individuals suffering from autism spectrum disorder are related to those governed by this brain region and its immediate neighbors — including problems developing and understanding nonverbal communication — these results may shed light on how the structure of white matter in the brain can have cognitive and behavioral effects in individuals suffering from autism spectrum disorder.

Furthermore, the fact that we evidenced an increase in the connectivity and clustering of the area around the anterior division of the left inferior temporal gyrus is aligned with current belief that ASD is correlated with increased and delayed myelination, although further research needs to be done to make this conclusive.

7 Future Work

The results and findings presented in this paper are a glimpse into the rich field of research of brain white matter structural analysis using graph theory. There are many directions and dimensions further work in this subject may take. First, autism spectrum disorder describes a wide range of neurodevelopmental disorders that span from mild social

impairments to severe impairment of reciprocal social interaction. Developing conclusions on such a wide berth of disorders, particularly with relatively small sample sizes, is difficult. Future studies and research on white matter structure of a specific ASD condition, or of individuals experiencing very similar symptoms, may be more fruitful. Second, the same principles and techniques presented and used in this project may be applied to understanding the effects that other neurodevelopmental disorders, including down syndrome, attention deficit hyperactivity disorder, and schizophrenia, have on the brain's white matter structure. Ultimately, we believe that this project hints at the potential that using network analysis on white matter neural structure has on furthering our understanding of the human brain.

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