Network-Based Analysis Reveals Stronger Local Diffusion-Based Connectivity and Different Correlations with Oral Language Skills in Brains of Children with High Functioning Autism Spectrum Disorders

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Abstract: Neuroimaging has uncovered both long-range and short-range connectivity abnormalities in the brains of individuals with autism spectrum disorders (ASD). However, the precise connectivity abnormalities and the relationship between these abnormalities and cognition and ASD symptoms have been inconsistent across studies. Indeed, studies find both increases and decreases in connectivity, suggesting that connectivity changes in the ASD brain are not merely due to abnormalities in specific connections, but rather, due to changes in the structure of the network in which the brain areas interact (i.e., network topology). In this study, we examined the differences in the network topology between high-functioning ASD patients and age and gender matched typically developing (TD) controls. After quantitatively characterizing the whole-brain connectivity network using diffusion tensor imaging (DTI) data, we searched for brain regions with different connectivity between ASD and TD. A measure of oral language ability was then correlated with the connectivity changes to determine the functional significance of such changes. Whole-brain connectivity measures demonstrated greater local connectivity and shorter path length in ASD as compared to TD. Stronger local connectivity was found in ASD, especially in regions such as the left superior parietal lobule, the precuneus and angular gyrus, and the right supramarginal gyrus. The relationship between oral language ability and local connectivity within these regions was significantly different between ASD and TD. Stronger local connectivity was associated with better performance in ASD and poorer performance in TD. This study supports the notion that increased local connectivity is compensatory for supporting cognitive function in ASD. *Hum Brain Mapp* 35:396–413, 2014. © 2012 Wiley Periodicals, Inc.

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INTRODUCTION

Autism spectrum disorder (ASD) is characterized by specific impairments in social interactions and communication combined with restricted interests and repetitive behavior [Verhoeven et al., 2010]. According to recent data from the Autism and Developmental Disabilities Monitoring network, an average of 1 in 110 children in the United States is diagnosed with ASD [Rice, 2009]. The increasing number of ASD patients, together with the complex nature of ASD, has attracted greater attention in both the scientific community and in society.

The exact neuropathological abnormalities that define ASD are still being uncovered, but it is clear that ASD is associated with abnormalities in neuroconnectivity [Belmonte et al., 2004; Castelli et al., 2002; Horwitz et al., 1988; Just et al., 2004]. However, the findings from neuroconnectivity studies have been contrary and, sometimes, inconsistent, leaving the exact significance of neuroconnectivity abnormalities in question [Vissers et al., 2012]. In fact, some studies have reported both increases and decreases in connectivity in the same subject populations. For example, resting-state connectivity with the posterior cingulate gyrus has been shown to be increased with some cortical regions and decreased with other cortical regions in individuals with ASD as compared to controls [Monk et al., 2009]. Furthermore, the relationship between connectivity and ASD characteristics is not consistent. For example, worse social skills in individuals with ASD have been correlated with both increases [Anderson et al., 2011a] and decreases [Weng et al., 2010] in resting-state connectivity in the default mode network.

Rather than simply considering these findings as contrary, these findings might suggest that there is another way to look at the connectivity data. For example, instead of considering the ASD brain as being connected less or more than the typically developing (TD) brain, these mixed results suggest that the neural networks in the brain of individuals with ASD are connected and organized differently than the neural networks in the brain of TD individuals. A clear example of this can be seen in another neurodevelopmental disorder, dyslexia. In individuals with a history of dyslexia (i.e., specific reading disability) as a child, brain organization as a young adult appears to be critically important in the eventual development of reading ability [Frye et al., 2010, 2012; Shaywitz et al., 2003]. In a landmark study using functional MRI, Shaywitz et al. [2003] demonstrated that young adults with a history of dyslexia in childhood who develop adequate reading skills demonstrate marked reorganization of the brain's neural network as compared with TD individuals. How-

ever, young adults with a history of dyslexia in childhood who failed to develop adequate reading skills did not demonstrate much brain reorganization and, in fact, demonstrated brain activation that looked more like the TD control group. More recently, using Granger causality to analyze (MEG) recordings, Frye et al. have shown that the organization of the brain network just prior to decoding a phonological stimulus is critically important in individuals who suffered from dyslexia during childhood. Specifically, individuals with a history of dyslexia who performed better on the phonological task in the scanner demonstrated greater top-down control from the inferior frontal gyrus to other brain areas [Frye et al., 2010] and less influence of the right temporoparietal areas on the left temporoparietal area [Frye et al., 2012].

The neuroimaging literature supports the notion of neural network reorganization in ASD. A recent meta-analysis of functional neuroimaging study suggests that, in general, individuals with ASD demonstrate more activity in posterior cortical regions (i.e., temporal, parietal, and occipital areas) and less activity in frontal cortical regions, as compared with controls [Samson et al., 2012]. In addition, this meta-analysis suggests that individuals with ASD have enhanced resource allocation to areas involved with visual processing, suggesting preferential use of visual pathways for information processing [Samson et al., 2012]. The neuroconnectivity literature also supports that idea of alternative network connectivity in ASD. For example, resting-state connectivity with the posterior cingulate gyrus has been found to be decreased with superior frontal cortex but increased with the temporal lobe in individuals with ASD as compared with controls, again suggesting more reliance on posterior cortical regions [Monk et al., 2009]. MEG also supports the notion of reduced connectivity between the frontal areas and the posterior cortical region as well as greater connectivity between posterior regions. For example, during an executive function task, Perez Velazquez et al. [2009] found decreased gamma and beta connectivity between the frontal areas and posterior areas of the brain and increased connectivity between the parietal lobes.

Although the idea of reorganization of the brain is large-scale neural network can be compelling, neuroimaging studies support a more complicated picture of brain abnormalities in ASD. Unlike many other neurodevelopmental disorders, there is substantial evidence to suggest accelerated early brain growth in children with ASD [Courchesne, 2004; Courchesne et al., 2011; Hazlett et al., 2011]. This early rapid growth of the brain in individuals with ASD has been suggested to be primarily driven by the radiate compartment of superficial white matter (WM),

which primarily affects intra-hemispheric and cortico-cortical connections [Herbert et al., 2004]. This has led some to suggest that there is an increase in short-range brain connectivity in ASD. Functional neuroimaging data supports this notion. Electroencephalography (EEG) studies have reported increased short-range connectivity, especially in the lateral-frontal areas [Barttfeld et al., 2011], and MEG studies have demonstrated widespread increases in local gamma-band activity suggesting more tightly integrated local neural networks [Braeutigam et al., 2008]. Some have suggested that local over-connectivity is a form of neuroplasticity that compensates for the long-range under-connectivity [Belmonte et al., 2004; Just et al., 2004]. These researchers hypothesize that a disruption of global neural connectivity is the basis of ASD and that changes in connectivity (e.g., high local connectivity) during development compensate for the disruption, resulting in improved cognitive performance on skills associated with core features of ASD, such as language function.

To quantitatively study whole-brain network connectivity, recent studies have applied graph theory to anatomic connectivity data derived from diffusion-tensor imaging (DTI) data [Bullmore and Sporns, 2009; Rubinov and Sporns, 2010; Shu et al., 2011; Xia and He, 2011; Yap et al., 2010]. Such newly emerging multidisciplinary brain network analysis strategies have demonstrated considerable efficacy in comprehensively characterizing large-scale brain connectivity and advancing our understanding of the human brain organization in both healthy subjects and clinical populations [Bullmore and Sporns, 2009; Rubinov and Sporns, 2010; Shu et al., 2011; Yap et al., 2010]. To the best of our knowledge, no studies have used DTI imaging and graph theory to study changes in structural WM neural networks in individuals with ASD.

To apply graph theory to study the neural organization of ASD, it is necessary to measure the structural connectivity strength among different anatomical regions. In DTI-based connectivity analysis, interregional connectivity strengths are usually dependent on the particular tractography algorithms being used [Gong et al., 2009; Hagmann et al., 2008; Iturria-Medina et al., 2007, 2008; Zalesky and Fornito, 2009]. Probabilistic tractography is a commonly used fiber tracking strategy [Behrens et al., 2003; Parker and Alexander, 2003]. However, it can be biased by the probabilities of fiber directions, relatively low image spatial resolution, and the number of fibers extracted. To overcome the shortcomings of fiber tracking, a robust brain connectivity analysis method was proposed based on the improved fast marching (FM) algorithm [Li et al., 2011]. Specifically, in this algorithm, the principal eigenvectors-based FM method [Jbabdi et al., 2008; Parker et al., 2002; Staempfli et al., 2006] was extended to the whole tensor-based FM to calculate the connectivity strength among different brain regions based on the diffusion-time map and diffusion-velocity map. The hypothesis is that faster diffusion along the tensors between anatomical regions indicates stronger WM fiber bundle connectivity and vice

versa. We have showed that the new region-to-region connectivity strength measure is less affected by fiber crossing issue and reflects the neuroanatomical connectivity network more realistically than conventional fiber tracking-based method [Li et al., 2011].

After the whole brain connectivity networks were constructed the network topology was investigated, and statistical analysis was employed to compare ASD with TD using network metrics and connectivity strengths between different anatomical regions. Meanwhile, because language is one of the primary impairments in ASD [Frith, 2003; Huemer and Mann, 2010], and previous studies have showed that such deficits in ASD patients may be due to difficulties in integrating information in context [Just et al., 2004; Kana et al., 2006; Knaus et al., 2008; Wan and Schlaug, 2010], neuropsychological measures of language function were correlated with the connectivity strengths to study the influence of brain organization on cognitive performance in ASD patients.

Our results show that ASD patients had stronger local connectivity compared with TD. Greater local connectivity in the ASD individuals was particularly marked in the left superior parietal lobule, the precuneus and angular gyrus, and the right supramarginal gyrus. Meanwhile, different association patterns of language function and connectivity strengths between ASD and TD groups were observed. In the literature, a dominant finding with respect to the brain connectivity in ASD is that there is a combined pattern of local over-connectivity and long distance under-connectivity [Barttfeld et al., 2011; Belmonte et al., 2004; Casanova and Trippe, 2009; Vissers et al., 2012; Wass, 2011]. Previous studies provided evidence showing that the long-range cortical-cortical functional and structural connectivity appear to be weaker in the ASD compared with TD [Anderson et al., 2011b; Belmonte et al., 2010; Just et al., 2012; Muller et al., 2011]. However, there is less evidence for local over-connectivity [Vissers et al., 2012]. This study can provide great insight to understanding the importance of local brain connectivity in individuals with ASD. Our findings are consistent with the notion that increased local connectivity may develop together with decreased long-range connectivity. Moreover, as summarized in the Discussions, the results may indicate compensatory development in ASD group, which provides useful extension to previous theories of connectivity deficit in ASD.

MATERIALS AND METHODS

Participants

To reduce the risk of heterogeneous pattern in ASD, only high-functioning patients were used, and were matched on age and gender to TD controls. Totally, 20 subjects participated in the study, including 10 high functioning ($IQ > 70$) ASD children (age: 10.7 ± 2.2 , 1F/9M) and 10 TD subjects matched on age (11.4 ± 2.0 , no significant age difference between groups $P = 0.49$) and gender

(1F/9M). All the subjects were enrolled with parental consent approved by the local institutional review board for ethical research and the protection of human subjects. The majority (8) ASD participants were recruited from a local private school providing behavioral and educational services for children with ASD, diagnosed using the standardized Autism Diagnostic Observation Schedule criteria. The other two ASD participants were recruited from the University of Texas Health Science Center at Houston's Medically Based Autism Clinic and had previously been diagnosed using standard criteria by both a psychiatrist and developmental pediatrician. All the subjects were examined by the fourth author (Dr. Frye) and determined to meet the DSM-IV criteria [APA, 1994] for ASD prior to entering the study. Controls were obtained from flyers posted in the University of Texas Health Science Center and by word-of-mouth from the families of the ASD patient tested. Controls had no history of developmental disorders or school problems.

Neuropsychological Testing

All the subjects completed neuropsychological testing. This included a measure of nonverbal IQ (NVIQ) to ensure that subjects were high-functioning and a measure of language function. The NVIQ was assessed with the computerized version of the Comprehensive Test of Nonverbal Intelligence (CTONI), which does not require oral responses, reading, writing, or manipulation of objects, thus it is useful for testing individuals with difficulties in language or fine motor skills or other neurological disabilities [Hammill et al., 1997]. Language function was assessed with the Gray Oral Reading Test-Fourth Edition (GORT-4) [Wiederholt and Bryant, 2001], which was used for language function assessment in ASD study [Huemer and Mann, 2010]. This oral reading test assesses both reading and expressive language ability, one of the primary impairments in ASD. Measurement of expressive language ability provides a measure of the common language disability associated with ASD using a standardized script, and it provides a measure of comprehension, another ability that is limited in children with ASD. The test also provides measures of reading rate, accuracy, fluency, and comprehension as well as a summary score known as the oral reading quotient (ORQ). Table I lists the details.

Brain Imaging Data Acquisition

All the subjects underwent a single MR imaging session at 3T (Philips Intera) in University of Texas Health Science Center at Houston. Each scan consists of T1-weighted MRI (TR/TE = 8.4/3.9 ms; FA = 8°; matrix size = 256 × 256; FOV = 240 mm; slice thickness = 1.0 mm sagittal slices) and a 32-direction diffusion imaging sequence (TR/TE = 8500/67 ms; FA = 90°; 2 mm axial slice thickness, max. *b*-value of 800 s/mm²).

TABLE I. Demographics and neuropsychological characteristics of all participants

Characteristics	ASD (<i>n</i> = 10)	TD (<i>n</i> = 10)	<i>P</i> value
Mean age (range; year)	10.7 (7–15)	11.4 (8–15)	0.57
Gender (F/M)	1/9	1/9	
CTONI-NIQ	85.3 ± 4.0	108.4 ± 5.4	0.003
GORT: Rate	8.1 ± 1.3	12.3 ± 0.9	0.01
GORT: Accuracy	7.8 ± 1.4	12.5 ± 1.2	0.01
GORT: Fluency	7.6 ± 1.5	13.1 ± 1.4	<0.001
GORT: Comprehension	7.4 ± 1.7	11.7 ± 1.4	0.03
GORT: ORQ	89.0 ± 8.7	113.5 ± 5.6	0.02

Image Processing and Network Construction

The FMRIB's diffusion toolbox [Smith et al., 2004] was used for eddy current correction and motion correction. Meanwhile, an analysis of 6-axis translational and rotational motion during the acquisition of the 32 individual diffusion-weighted image volumes was conducted based on the output realignment parameters of motion correction to determine if the autism subjects moved more than the TD subjects. Overall, the mean range of translational displacement was small and was not significantly greater for the ASD group (1.22 ± 0.68 mm) compared with the TD group (2.06 ± 0.26 mm). The mean range of angular displacement was also small and was not significantly greater for the ASD group (0.98 ± 0.58°) compared with the TD group (0.47 ± 0.28°).

DTIStudio [Jiang et al., 2006] was applied to generate the channel images, including ADC, FA, eigenvalues of the tensor, relative anisotropy, and volume ratio. A multi-channel DTI segmentation method [Liu et al., 2007] was adopted to perform tissue segmentation based on DTI data, which classified DTI data into WM, gray matter (GM), and cerebrospinal fluid (CSF). This method classified the brain into two compartments by utilizing the tissue contrast existing in each channel. For example, using ADC the brain tissues were separated into CSF and non-CSF while FA was used to separate WM from non-WM tissues. Finally, the STAPLE algorithm [Warfield et al., 2004] was used to combine the two-class maps to obtain a complete segmentation of CSF, GM, and WM.

After segmenting the DTI images, a deformable warping method was used to register the JHU-DTI-MNI atlas [Oishi et al., 2009] onto each subject image [Xue et al., 2010] with the whole tensor information in DTI space. In this way, the regions of interest (ROIs) in the atlas were superimposed on to each DTI image, and a map of labeled anatomical regions for each subject was obtained. To focus on the connectivity defined by WM tracts, the segmented images were then used to mask out the GM and CSF for each subject. Forty-six cortical ROIs (Table II) were extracted and used for constructing the brain connectivity network. The automatically labeled cortical regions were refined based on the tissue segmentation results.

TABLE II. Cortical regions of interest defined in the study

Index	Abbreviation	Regions	Index	Abbreviation	Regions
1, 24	SPG	Superior Parietal Lobule	13, 36	SOG	Superior Occipital Gyrus
2, 25	CGC	Cingulate Gyrus	14, 37	IOG	Inferior Occipital Gyrus
3, 26	SFG	Superior Frontal Gyrus	15, 38	MOG	Middle Occipital Gyrus
4, 27	MFG	Middle Frontal Gyrus	16, 39	STG	Superior Temporal Gyrus
5, 28	IFG	Inferior Frontal Gyrus	17, 40	ITG	Inferior Temporal Gyrus
6, 29	PrCG	Precentral Gyrus	18, 41	MTG	Middle Temporal Gyrus
7, 30	PoCG	Postcentral Gyrus	19, 42	LFOG	Lateral Fronto-Orbital Gyrus
8, 31	AG	Angular Gyrus	20, 43	MFOG	Middle Fronto-Orbital Gyrus
9, 32	PrCu	PreCuneus	21, 44	SMG	Supramarginal Gyrus
10, 33	Cu	Cuneus	22, 45	RG	Gyrus Rectus
11, 34	LG	Lingual Gyrus	23, 46	Ins	Insular
12, 35	Fu	Fusiform Gyrus			

Specifically, every labeled GM region is dilated by a kernel with size of $2 \times 2 \times 2$ voxels, so that they overlapped with the WM regions, in which the brain connectivity was defined.

To construct the brain connectivity network, the tensor-based FM method [Li et al., 2011] was employed to simulate the diffusion dynamics to define the connectivity strength between each anatomical region pair. Specifically, the tensor-based FM algorithm started from one region and simulated the diffusion until the entire brain was filled. Such diffusion is based on the tensor itself so that the marching front moved faster if the projection of the tensor along marching direction is bigger, otherwise the move is slower. In this way, an arrival time map and an average velocity map were obtained. These maps define the speed of the diffusion when starting from the selected anatomical region. Thus, by superimposing the automatically labeled anatomical regions onto the brain, the connectivity strength between the anatomical region where the FM algorithm starts and every other brain region can be defined. Faster diffusion between a region pair indicates denser, more highly oriented fibers or stronger connectivity between them. This translates to shorter arrival time and higher average velocity. Therefore, the arrival time map and the average velocity maps can be combined together using a sigmoid function to calculate the connectivity strength. Finally, by performing FM from each of the forty-six regions, the connectivity strengths among them were quantified to construct the brain neuroanatomical connectivity network. The resolution of the grid for FM is the same as the image resolution, and 26 propagation directions were considered given a current active point in the implementation. Figure 1 shows the framework of the FM-based brain connectivity network construction using DTI.

Network Metrics

After construction of the whole brain connectivity network, a weighted graph $G = \{V, C\}$ was obtained to reflect

the brain structural connectivity for each subject. The vertex set V represents the cortical region listed in Table II. The edge of the graph is represented by the symmetric connectivity matrix $C = [c_{m,n}]_{N \times N}$, where $c_{m,n}$ is the connectivity strength between cortical region m and cortical region n . N is the number of cortical ROIs.

The calculated network metrics consist of the connectivity strength of each pair of anatomical regions, weighted clustering coefficient (CC), and weighted characteristic path length (CL) [Watts and Strogatz, 1998]. Briefly, connectivity strength measures the diffusion-based connection of WM fiber bundles based on the FM algorithm, while CC and CL capture the information about how the network is organized. High connectivity strength between any two anatomical regions indicates dense WM fiber bundles and strong connection between them. A node with high CC means there is strong local connection network around the node itself. A node with high CL means it has, on average, short network distance from other nodes.

Network connectivity strength

The connection strength between two ROIs reflects the overall diffusion integrated by microstructure of neural fibers between them. Meanwhile, any possible change of graph metrics is substantially induced by the alteration of such connections. Thus, the analysis of the connection strength not only provides valuable insight about where and how the deficit of the connection occurs, but also provides insight about the change of network topological structure.

Weighted CC

CC measures the local aggregation or cliquishness of a typical neighborhood. High CC value means good local connectivity of a network, as shown in Figure 2a [Watts and Strogatz, 1998]. For a weighted graph, the weighted CC of a vertex i is defined as [Onnela et al., 2005]:

Figure 1.

The framework of brain connectivity network construction based on diffusion tensor imaging. By automatically registering the JHU-DTI-MNI atlas (a) onto each subject's DTI data (b), the anatomical regions of the subject are labeled; then, the inter-regional connectivity strength can be calculated by using the tensor-based fast marching algorithm and by combining the diffusion-time map (c), and the diffusion-velocity map (d); finally,

the brain connectivity matrix (e) is constructed and network analysis (f) can be performed for quantitative analysis of ASD. The yellow arrows in (c) and (d) point to the ROI (middle frontal gyrus, mauve region), and morphological operation is used to dilate the ROI to its adjacent WM regions (green) where the FM algorithm starts. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

$$CC_i = \frac{1}{k_i(k_i - 1)} \sum_{m,n \in V} (\tilde{c}_{i,m} \cdot \tilde{c}_{m,n} \cdot \tilde{c}_{n,i})^{1/3}, \quad (1)$$

where, k_i is the number of links connecting with node i , and the connectivity strengths are normalized for each subject to remove potential differences of connectivity

Figure 2.

Illustrations for network measures in Eqs. (1) and (3). (a) Weighted CC for center node i is calculated based on its connected neighbors linked by the bold dotted lines, and CC for node i , CC_i , is the ratio of total connectivity strength of the triangles that contain node i to the total connectivity strength of all possible triangles comprised with node i and two of its neighbors.

The bold solid lines represent the links among those four neighbors; (b) the geodesic length between node i and node j can be calculated as the sum of the edge lengths along the geodesic path between i and j , represented as bold solid lines in the picture. In this case, the geodesic length $d_{ij} = l_{i,g} + l_{g,k} + l_{k,j}$.

strengths across subjects, $\tilde{C}_{m,n} = C_{m,n}/\max(C)$. The average and standard deviation values of $\max(C)$ was not significantly different between the two groups ($P = 0.83$). As shown in Figure 2a, CC_i assesses the connectivity within its immediate neighborhood. Thus, a larger CC_i means stronger average connectivity among node i and its neighbors, and vice versa. The CC for the whole graph G is defined as the average of CC around each node:

$$CC = \frac{1}{N} \sum_{i \in V} CC_i. \quad (2)$$

In this work, CC was used as one of the network metrics to characterize the network properties, and CC_i was used to calculate the weighted CC of the subnetwork related to vertex i .

Weighted CL

Weighted CL measures the average distance between node pairs in the network. The CL for every region of the brain is defined as:

$$CL_i = \frac{1}{N-1} \sum_{\substack{j \in V \\ j \neq i}} d_{i,j}, \quad (3)$$

where $d_{i,j}$ is the geodesic length between node i and j , which is calculated as the sum of the edge lengths along the geodesic path, as shown in Figure 2b [Boccaletti et al., 2006; Watts and Strogatz, 1998]. In this work, the edge length of each link along this geodesic path is defined as the inverse of connectivity strength, that is, $l_{i,j} = 1/c_{i,j}$ [Boccaletti et al., 2006]. In this way, a stronger connection between two nodes means that the edge length between them is shorter. According to Eq. (3) and Figure 2b, smaller characteristic length for a node i , CL_i , indicates that the average distance from node i to other nodes is small, or in another word, the average connectivity from node i to its other nodes is strong.

Similar to CC , the CL can be calculated for the whole graph G as the average of the CL for each node:

$$CL = \frac{1}{N} \sum_{i \in V} CL_i. \quad (4)$$

CL measures the average geodesic distance between any pair of vertices in the network and thus represents the typical separation between these two vertices.

Statistical Analysis

To determine whether there is significant difference between the ASD and TD groups, a two-tailed t-test was used to calculate the statistical differences of the network metrics (CC , CL , CC_i , and CL_i) and the connectivity strengths themselves. Power analysis was adopted to guar-

antee the reliability of the statistical judgment [Cohen, 1988]. The false discovery rate (FDR) was used to correct for Type I error due to multiple comparisons [Genovese et al., 2002]. To visualize the location of significantly different connectivity between ASD and TD group, a matrix reordering algorithm [Rubinov and Sporns, 2010] was adopted. This algorithm rearranges the connectivity matrix so that the regions strongly connected to each other are now displayed as neighboring nodes.

A multivariate linear regression model in Eq. (5) was used to examine the interaction effect between groups (ASD and TD) and neuropsychological test scores on the connectivity strength [Frye et al., 2010, 2011]. Let $c_{i,m,n}$ be the connectivity strength of a pair of anatomical regions (m,n) for subject i , the following linear regression model can be used by considering the group effects, neuropsychological test scores, and group-neuropsychological interaction:

$$c_{i,m,n} = \beta_0 + \beta_1 S_i + \beta_2 g_i + \beta_3 S_i g_i + \varepsilon_{i,m,n}, \quad \text{for all the subjects, (5)}$$

where, S_i is the neuropsychological test score for subject i , g_i is the group dummy variable (i.e., $g_i = 1$ for ASD, and $g_i = 0$ for TD), $\varepsilon_{i,m,n}$ represents the residual error. β_0 is the regression constant, and β_1 , β_2 , β_3 are the linear regression coefficients. After linear regression, the presence of a significant interaction (i.e., term $\beta_3 S_i g_i$) indicates that the effect of the neuropsychological scores on the connectivity strength values is significantly different for different groups.

Using this approach, we can test, for each connection of interest, whether the correlation between neuropsychological variables and connectivity strengths is significantly different between the ASD and TD groups. Only the connections with significantly different connectivity strengths between the two groups were further analyzed using the multivariate linear regression model. Because multiple comparisons were performed, FDR was used for statistical correction.

Finally, for each multivariate linear regression model result showing significant group differences, independent linear regression analysis was employed to examine the correlation between the connectivity strengths and the neuropsychological variables in each group. The results further identifies whether the connectivity strengths and the neuropsychological variables were correlated.

RESULTS

CC and CL of the Brain Network

As shown in Figure 3, CC was higher, and CL was smaller in the ASD group as compared with the TD group. T-tests between these two groups showed that these network topological characteristics were significantly different, and the P -values were $P = 0.0024$, and $P = 0.0273$ for CC and CL , respectively. For CC , statistical analysis

Figure 3.

Comparison of CC and CL for ASD and TD groups. (a) Average and stand deviation of CC for the whole brain connectivity network; (b) average and standard deviation of CL for the whole brain connectivity network.

confirmed that the observed effect size was 2.1. At an alpha-probability level of 0.05, this effect size provides a statistical power for two-tailed t-test close to 100%. Similarly, for CL the observed effect size was 0.92, and the statistical power was 49%. Therefore, CC provides a more powerful measure as compared to CL in our study.

For the CC and CL associated with each anatomical region, that is, CC_i and CL_i , $i = 1, \dots, 46$, the two-tailed t-test was also used. Figure 4 shows the results of these tests. Regions with significant differences both for CC and CL (higher CC and lower CL) in the ASD group compared with the TD groups included left and right supramarginal, superior occipital, middle occipital, precuneus gyri, and the left angular, superior parietal gyri. P-values for these regions are summarized in Table III.

Connectivity Strength of the Brain Network

Two-tailed t-tests were performed on the connectivity strengths of each pair of anatomical regions. Figure 5a is the mean connectivity matrix over all the subjects. Figure 5b shows the statistical test results, where the red dots indicate the links with significant difference between the ASD and TD groups. It should be noted that all the significantly different links have larger connectivity strength in the ASD group than that in the TD group.

A matrix-reordering algorithm was applied on the mean connectivity matrix. Figure 5c is the reordered mean connectivity matrix, and the name of anatomical regions for every row or column can be found according to the matrix index value, which is consistent with Table II. From the reordered matrix, it can be noted that there are three clusters in the whole brain; these include the left occipital, temporal, and parietal lobes (cluster 1), the left and right frontal lobes (cluster 2), and the right occipital, temporal parietal lobes (cluster 3).

To visualize the location of increased connectivity, the statistical test results in Figure 5b can also be reordered

accordingly, and Figure 5d shows the results corresponding to Figure 5c. Compared with the TD group, the ASD group exhibited a widespread increase of connectivity strength in many brain regions [$P < 0.05$, FDR corrected], and most of the abnormal links were locally organized in clusters 1 and 3. In total, there were 36 abnormal links in the whole brain, and 29 anatomical regions were involved in cluster 1 and 3; 78.8% of the abnormal links connected regions within cluster, while 22.2% of the abnormal links connected regions outside the clusters. The results suggest that most of the abnormal links are over-connected and are locally organized within the two clusters.

Given that the connections associated with intergroup differences appear to be organized into distinct clusters, it is also interesting to see whether the subnetworks formed from these connections are stable and significant between ASD and TD. The network-based statistics (NBS) [Zalesky et al., 2010a] was employed for this purpose. Based on the FDR corrected statistical analysis results (i.e., the nodes in Fig. 5b), the T-threshold was set to 3.68 so the selected suprathreshold links were consistent with the FDR corrected results. Three connected subnetworks, comprising 22, 13, and 1 links, were identified, as shown in Figure 6. Then, we performed the permutation tests for 1000 times, and the P-values for the sizes of these three sub-networks were 0.002, 0.004, and 0.498, respectively. The results showed that the two larger subnetworks obtained from the connectivity matrices were significant based on NBS analysis.

Meanwhile, the number of significantly different connections for every region was calculated. The first four regions with the most abnormal links include the left superior parietal lobule (SPG_L, 7 significantly different links), the left precuneus (PrCu_L, 6 significantly different links), the left angular gyrus (AG_L, 6 significantly different links), and the right supramarginal gyrus (SMG_R, 5 significantly different links).

To better visualize the significantly different connectivity, the results were plotted in Figure 7 by superimposing

Figure 4.
CC and CL for every anatomical region.

them onto the brain and rendering them in different views. Each line in Figure 7 shows a connection with a significant difference between ASD and TD. Thus each red point in Figure 5b,d corresponds to a line in Figure 7. Each node was placed in the brain according to its anatomical location, and the size of the node reflects the number of significantly different connections for that region. Interestingly, despite the fact that such significantly different connections were widely distributed in the brain, most of the significantly different connections were found on the posterior part of the brain, and more in the left hemisphere than the right hemisphere.

Analysis of Local Network with Significantly Different Connections

The above results showed that the number of significantly different connections for left superior parietal lobule (SPG_L), left precuneus (PrCu_L), left angular gyrus (AG_L), and right supramarginal (SMG_R) ranked higher. In fact, it is clear that most of the regions with large number of significantly different connections also appear in the network characteristic analysis results as shown in Table III.

Figure 8 shows the significantly different connections associated with the four aforementioned regions. Figure 8a

illustrates that there are eight significantly different connections linked with left superior parietal lobule (SPG_L), and the histogram on the left shows their connectivity strengths in the ASD and TD groups. The size of the node represents the number of significantly different connections related to that node, and the weight of the lines indicates the average connectivity strength of the TD group. The same convention applies to Figure 8b,c, showing significantly different connections associated with left precuneus (PrCu_L), left angular gyrus (AG_L), and right supramarginal (SMG_R).

TABLE III. Regions with significantly different CC and CL ($CC_{ASD} > CC_{TD}$ and $CC_{ASD} < CC_{TD}$)

Index	Region	$P(CC_{ASD} > CC_{TD})$	$P(CC_{ASD} < CC_{TD})$
44	SMG_R	0.0001	0.0066
36	SOG_R	0.0013	0.0032
8	AG_L	0.0025	0.0002
21	SMG_L	0.0025	0.0034
38	MOG_R	0.0026	0.0090
13	SOG_L	0.0036	0.0029
9	PrCu_L	0.0041	0.0020
15	MOG_L	0.0064	0.0060
24	SPG_R	0.0100	0.0073
32	PrCu_R	0.0104	0.0038

Figure 5.

Statistical analysis of connectivity strengths. (a) Average connectivity matrix; (b) matrix of significantly different connectivity; (c) reordered mean connectivity matrix; (d) reordered matrix of significantly different connectivity. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Correlation of Connectivity Strength with Neuropsychological Variables

For each of the 36 significantly different connections found above (i.e., the nodes in Fig. 5b or the lines in Fig. 7), we performed a multivariate regression analysis according to Eq. (5) with the four GORT scores. For multivariate regression, the purpose was to determine whether

the correlations between connectivity and the neuropsychological variables were significantly different between the groups. Figure 9 shows all the connections with significant different association (P -value < 0.05 , FDR corrected) of neuropsychological variable and connectivity strength across the two groups, among all the $36 \times 4 = 144$ tests. The results of independent linear regression, that is, the R^2 and P -value for linear regression of each group, are shown

Figure 6.

Connected components/subnetworks identified by NBS algorithm. After permutation test, the *P*-values for the sizes of the identified subnetworks were calculated. The results are: Group 1 (marked with “*”) comprises of 22 links, and *P*-value = 0.002; Group 2 (marked with “+”) consists of 13 links, and *P*-value = 0.004; Group 3 (marked with “o”) has 1 link, and *P*-value = 0.498. Therefore, the two larger subnetworks obtained are significant by comparing ASD and TD.

in the figure. They indicate whether the connectivity is linearly correlated with a GORT score for ASD or TD group. For example, in Figure 9h, individual group linear regression shows the correlation is not significant for ASD and TD (*P*-value = 0.061 for ASD and 0.1399 for TD), but it turned out that two-group multivariate linear regression was significant (*P*-value < 0.05 and FDR corrected). Therefore, even though the relationship between connectivity and a GORT score was significantly different from zero for each group individually, the relationship between connectivity and GORT scores were significantly different, particularly because the relationships were in opposite directions. The lack of significance in the linear regression was most likely due to the smaller sample size of the individuals groups (half) as compared with the complete group of subject. Indeed, linear regression as a follow up to multivariate regression is commonly used in more of a descriptive manner rather than to provide significance.

Overall, the significantly different associations involved four connections and four GORT scores. In particular, the connection between the left cingulate gyrus (CGC_L) and left angular gyrus (AG_L) correlates with GORT fluency, GORT comprehension, GORT ORQ, and GORT accuracy differently between ASD and TD; the connection between left cuneus (Cu_L) and left superior occipital gyrus (SOG_L) correlates with GORT comprehension and GORT

ORQ differently between ASD and TD; and the connections between right precentral (PrCG_R) and right supramarginal gyrus (SMG_R) and between right postcentral gyrus (PoCG_R) and right supramarginal gyrus (SMG_R) correlate with GORT comprehension differently between ASD and TD.

The connectivity strength tended to increase as GORT scores increase in the ASD group, and in the TD group such tendency was reversed. This can be determined from the regression lines for each group in Figure 9. The dashed lines were calculated from ASD, showing a positive correlation between connectivity strength and GORT scores, while the solid lines from TD indicated negative correlation between connectivity strength and GORT scores.

DISCUSSIONS

ASD is considered a disorder of neuroconnectivity [Belmonte et al., 2004; Castelli et al., 2002; Horwitz et al., 1988; Just et al., 2004]. In this article, the structural brain connectivity networks of ASD patients and matched TD controls were analyzed using DTI and graph theory. Connectivity results were correlated with the neuropsychological variables of language function.

The network topology of ASD was found to be significantly different compared to the TD group. Overall analysis for the whole brain showed stronger local network connectivity and shorter average distance among anatomical regions in ASD patients compared with TD patients. Meanwhile, statistical analysis of interregional connectivity strengths showed significantly different connections in ASD especially within the left and right occipital, temporal, and parietal lobes. The connectivity strengths were higher in the ASD as compared with the TD group.

In addition, the local connectivity strengths were correlated with neuropsychological variables of language function. The results showed significantly different associations of neuropsychological variables and connectivity strengths between ASD and TD groups. In general, stronger short-range connectivity was associated with better language performance in individuals with ASD and lower performance in TD individuals. These results suggest that connectivity is altered in widespread pathways in individuals with ASD and that some of the changes in connectivity in individuals with ASD may be compensatory, resulting in relatively good performance in language function.

Altered Network Topology of ASD Patients

Overall, the network topology was explored in terms of CC and CL in ASD patients using graph theory and DTI images. A significantly larger CC and smaller CL were found in ASD subjects compared with TD subjects. Larger CC in ASD indicates a higher level of local network connectivity. Since CL is calculated based on the connectivity strength, smaller CL in the ASD group may indicate higher

Figure 7.

3D visualization of the significantly different links in different views. Each line indicates a significantly different connectivity between ASD and TD groups; each black node represents an anatomical region; the size of the node represents the number of significantly different connections from the node itself.

Figure 8.

Significantly different connections associated with SPG_L, PrCu_L, AG_L, and SMG_R.

Figure 9.

Connections with significantly different association of neuropsychological variables and connectivity strengths between the ASD and TD groups. * indicates that the association of neuropsychological variable and connectivity strength between the ASD and TD groups is significantly different [$P < 0.05$, FDR corrected]. The results of independent linear regression, that is, R^2 value and the P -value for linear regression of each group are also shown in the figure.

connectivity strength. Previous histological studies on apical dendrite samples of pyramidal cells found increased dendritic spine densities in ASD patients [Hutsler and Zhang, 2010]. Meanwhile, neurobiology studies show that ASD patients have more densely packed and smaller columns of neuronal cells [Casanova and Trippe, 2009; Hughes, 2007]. Both the abnormal patterns of dendritic spines and neuronal columns may contribute to the altered network characteristics and enhance local connectivity in ASD patients.

CC and CL associated with each anatomical region are also compared in this study. Significant differences are found in the left and right supramarginal, superior occipital, middle occipital, and precuneus gyri, and the left angular, and superior parietal gyri. These regions are associated with language and visual processing. For example, the supramarginal gyrus has been reported to be involved in phonological and articulatory processing of words, whereas the angular gyrus and precuneus gyrus seem more involved in semantic processing [Ben-Shachar et al., 2007; Booth et al., 2004; Graves et al., 2010; Joubert et al., 2004]. The cortices, such as the superior and middle occipital gyri, which enable us to see and read words, are also crucial for language processing [Ben-Shachar et al., 2007]. These findings indicate that the language-associated anatomical regions exhibit abnormal connectivity characteristics in ASD patients, potentially underlying abnormal communication in the ASD group.

Abnormal Links with Increased Connectivity in ASD Patients

Statistical analysis of the connectivity strength between each anatomical region pair showed significantly stronger connections in the ASD group than in the TD group. The average connectivity matrix is reordered by permuting rows and columns such that highly connected regions are rearranged as neighboring indices. Three local clusters were clearly seen from the reordering connectivity matrix, in which a majority of significantly different connections fell into these clusters, indicating a short-range increased connectivity pattern within left and right occipital, temporal, and parietal lobes. Recalling the hypothesis of the FM-based network construction algorithm, we may speculate that there is increased fiber volume and high fiber density, especially within intrahemispheric WM fibers, in ASD patients. Such findings are also consistent with previous studies about overgrowth of localized cortical connections. For instance, Herbert et al. [Herbert et al., 2004] showed that the brain volume growth in ASD patients was mainly driven by superficial WM, which primarily affected intrahemispheric and cortico-cortical connections during ongoing postnatal process in individuals with ASD.

Based on the number of significantly different connections linked to each ROI, the connections associated with the left superior parietal lobule (SPG_L), left precuneus

(PrCu_L), left angular gyrus (AG_L), and right supramarginal gyrus (SMG_R) showed significantly stronger connectivity. These regions are related to visual and language processing, and they are consistent with the results of network topology.

Different Association of Neuropsychological Variables and Connectivity

Multivariate correlation analysis shows that the associations between connectivity strengths and four neuropsychological variables of language function are significantly different between the ASD and TD groups. As shown in Figure 9, the connection between the left cingulate gyrus (CGC_L) and the left angular gyrus (AG_L) is associated with all four of these different GORT scores (Fig. 9a,e,g,h), indicating its important role in oral reading-related tasks.

In addition, all the connections showed positive relationships with neuropsychological variables of language function in the ASD group. In contrast, a negative relationship was observed between connectivity strength and neuropsychological variables in the TD group. Such different diffusion-based connectivity patterns and correlation results suggest that DTI connectivity may be an indicator of the developmental differences between ASD and TD in neurocognitive networks, especially for language skills.

It has been found that individuals with ASD have greater local connectivity as compared with TD. However, the significance of these connectivity changes is not completely understood. Using the data from high functioning ASD patients the findings of this article suggest significantly different association patterns of connectivity strengths and neuropsychological variables of language function between ASD and TD groups. Specifically, although these language functions are weaker for ASD than those in TD, greater local connectivity in specific cortical regions was associated with better language performance in individuals with ASD and lower performance in TD individuals. These data are consistent with the underconnectivity and compensatory theory used to understand the development and recovery of autistic brains [Belmonte et al., 2004; Just et al., 2004]. This theory states that disruption of global neural connections of the brain is the basis of ASD, and during the development and recovery, reorganization of neural network (e.g., high local connectivity) may occur in tandem with such disruption, to compensate for the disruption and result in better performance in tasks of language function.

Methodological Issues and Future Work

Heterogeneity prevalent in ASD patients presents a significant challenge to network analysis. In this study, to reduce the risk of heterogeneous pattern in ASD, only high-functioning patients were used, and the age and gender were matched for the TD controls. Future work on

Figure 10.

Distribution of the anatomical length of abnormal connections. All the results are obtained from one-tailed t-test with threshold $P < 0.05$. Blank bars show stronger connections in ASD group, while black bars show weaker connections in ASD group.

large patient sample sizes is expected to test if current findings can be extended to different phenotypic subgroups of ASD patients. The phenotypic subgroup classification of ASD patients can be obtained via a recently developed clustering analysis method [Hu and Steinberg, 2009].

All the abnormal links shown in Figure 5b demonstrate increased connectivity. Most of such abnormal links are located in the posterior part of the brain, and the frontal lobes were seldom implicated. However, previous studies showed that, in addition to the increased short-range connectivity, there is also reduced connectivity in ASD patients, especially those long-range connections within the frontal areas and the fusiform face area [Sundaram et al., 2008; Zikopoulos and Barbas, 2010]. This may be due to the limited statistical power of univariate statistical analysis methods used in the multicomparison analysis procedure. To improve the statistical power of network-based analysis, intrinsic multivariate nature of the human brain connectivity network should be considered [Wickelgren, 2005]. Newly developed network-based statistical analysis methods [Li et al., 2012; Zalesky et al., 2010a] can be applied for further analysis and to improve the statistical power.

Actually, both increased and reduced connections in ASD group are found without FDR correction ($P < 0.05$). Figure 10 shows the distribution of the anatomical lengths of these connections (distance between ROIs). It can be seen that the strength-reduced connections (black bars) trend to be longer than the increased ones, indicating deficit of long-range fibers in ASD. In fact, such reduced long-range connections could affect the integration of different source of information into coherent behavior and cognition [Friston, 2002; Sporns and Zwi, 2004]. Also, the largest number of reduced links are associated with the Broca's area (left inferior frontal gyrus), which is thought to serve as a coordinating center for information integration and synchronization across the large-scale cortical network for

language processing [Gabrieli et al., 1998; Just et al., 2004; Michael et al., 2001; Schnur et al., 2009], as well as social cognition [Enticott et al., 2012]. This may explain the lower language scores of ASD (Fig. 9).

It is known that conventional fiber tracking-based connectivity analysis might be biased by the assumption of fiber tracking and often fails to resolve the fiber crossing problem. With no explicit fiber tracking, the FM-based analysis method can identify anatomical connectivity from the original tensor field. However, since the evolving front can always grow from one region into another by crossing even unconnected regions, false positive can be induced when calculating the connectivity strength. In our study, the marching velocity and time are combined to determine the connectivity strength, thus to allay the effort of false positive. Our rationale is that, the connectivity strength between two brain regions is strong only if the average marching time is small and the average marching velocity is large. The FM-based analysis method has been shown to be more robust and suitable for analyzing DTI connectivity than the conventional tractography-based method [Lazar et al., 2003; Li et al., 2011]. Nonetheless, the analysis should be performed on a new and large dataset to validate the reproducibility of our method. Additionally, comparison with other connectivity indexes, such as anatomical connection probabilities [Iturria-Medina et al., 2008], maximum number of link-disjoint paths [Zalesky and Fornito, 2009] will also be performed.

Only structural DTI was adopted to reconstruct the human brain connectivity networks in this article. Although DTI is a promising technology to provide important insight into the structural basis of ASD, other techniques, such as fMRI or EEG, can provide complementary functional information for ASD patients. For example, EEG can be used to directly measure the transmission time of interhemispheric signals [Whitford et al., 2011]. As DTI-based structural connectivity analysis mainly focuses on the diffusion patterns, and functional connectivity studies mainly focus on spatial-temporal activity correlations, it is desirable to perform joint structural and functional connectivity studies in the future.

The JHU-DTI-MNI atlas was used as a reference map for brain parcellation. The accuracy of the brain parcellation algorithm will certainly have an influence on the accuracy of the tensor-based network reconstruction. Although the elastic deformable DTI registration method used in this article has reasonably good performance in parcellating human brains, improved brain parcellation and recognition algorithms in the future would further improve the quality and robustness of the reconstructed network [Destrieux et al., 2010; Killiany et al., 2006].

Both the network topology analysis and the connectivity strength analysis are adopted to study the brain connectivity change in ASD group, and stronger local connectivity can be observed in the ASD. However, the meaning of the word "local connectivity" has different meanings in these two cases. In the first case, "local connectivity" is a term

derived from the network theory regardless of the location of the regions or their distance. A network with high CC, as the situation in the ASD group in our study, indicates that the strongly connected ROIs of the graph tend to be clustered together. In the second case, it is related to the physical distance among ROIs. This could be in different scales such as among different gyri, or within a gyrus if high resolution images are captured. By using DTI, this study focuses on a macroscopic scale of the brain network and only 46 cerebral cortical regions were considered for the construction of the connectivity network. Therefore, local connectivity is mainly used to describe connectivity among subregions of the same lobe or adjacent lobes, for example, including but not limited to U-fibers. In the future, fine parcellation algorithms, such as work in [Hagmann et al., 2007], will be adopted to study the influence of the spatial scale on the network characteristics of ASD [Zalesky et al., 2010b]. Because the same spatial scale is used in both groups, we believe that the measurements of network characteristics are comparable between groups, and the inference based on these measurements is reasonable and can provide great insight on the neurobiological basis from the perspective of network organization.

Finally, as a highly heterogeneous disease, a combined multiscale study involving genetics, microscopic and macroscopic level of imaging is desirable to understand the difference between ASD subgroups and to understand the mechanisms of functional recovery of ASD. For example, the combined approach can be used to study the interaction of affected neurons in local circuits and to incorporate local circuits into large scale cortical networks, as well as their genetic mechanisms [Casanova and Trippe, 2009].

CONCLUSIONS

DTI-based brain network analysis is used to analyze the difference of brain connectivity between ASD patients and matched TD subjects. Network connectivity metrics were also correlated with neuropsychological measures of language function using multivariate statistical analysis. The results demonstrated increased local network connectivity in ASD as compared with TD. Although significantly different connections were found to be widely distributed, more abnormal connections were primarily located in the parietal regions, specifically in the left superior parietal lobule, the left precuneus, the left angular gyrus, and the right supramarginal gyrus. In addition, significantly different associations between the connectivity strengths and the GORT scores were found in ASD and TD. The results suggest that DTI connectivity may be an indicator of the differences between network reorganization associated with ASD patients and normal neurodevelopment. These results illustrate paradigms for understanding the neurobiological basis of social function deficits and communication difficulties in ASD patients.

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