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RESEARCH ARTICLE

Disrupted white matter connectivity and organization of brain structural connectomes in tuberous sclerosis complex patients with neuropsychiatric disorders using diffusion tensor imaging

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Abstract

Objective Tuberous sclerosis complex (TSC) is a genetic neurocutaneous syndrome with variable and unpredictable neurological comorbidity that includes epilepsy, intellectual disability (ID), autism spectrum disorder, and neurobehavioral abnormalities. The degree of white matter involvement is believed to be associated with the severity of neurological impairment. The goal of the present study was to evaluate diffusion characteristics of tubers, white matter lesions, and brain structural network alterations in TSC patients using diffusion tensor imaging (DTI), graph theoretical analysis (GTA), and network-based statistical (NBS) analysis.

Materials and methods Forty-two patients with a definitive diagnosis of TSC were recruited for this study. All patients underwent brain DTI examination using a 3 T magnetic resonance imaging system. Mean diffusivity (MD), axial diffusivity (AD), radial diffusivity (RD) values, and fractional anisotropy (FA) mapping in 52 tubers and white matter lesions were measured and compared with those of contralateral normal regions. GTA was performed on the inter-regional connectivity matrix, and NBS analysis was used to identify the significance of any connected subnetworks evident in the set of altered connections. For neurological severity subgrouping, a neurological severity score was assigned to TSC patients including those with ID, seizure, autism, and other neuropsychiatric disorders (NPDs).

Results Significantly higher MD, AD, and RD, and lower FA values, were found in TSC lesions compared with those measured in contralateral normal regions for tubers ($P < 0.05$). GTA and NBS analysis provided better local segregation but worse global integration of the structural network (regular-like network) in TSC patients with ID, seizure, and higher Neurological Severity Score. Disrupted subnetworks in TSC patients with severe status included connections from the frontal lobe to the parietal lobe, temporal lobe to the caudate, and temporal lobe to the insula.

Discussion DTI has the potential to provide valuable information about cytoarchitectural changes in TSC lesions beyond morphological MRI findings alone. Using GTA and NBS, current results provide the information of disrupted white matter connectivity and organization in TSC patients with different neuropsychological impairments.

Keywords Tuberous sclerosis complex (TSC) · Diffusion tensor imaging (DTI) · Graph theoretical analysis (GTA) · Seizure; neurological severity score (NSS) · Developmental disability (DD) · Intellectual disability · Neuropsychiatric disorders (NPD)

Introduction

Tuberous sclerosis complex (TSC) is an autosomal dominant genetic disorder characterized by the formation of hamartomas in multiple organ systems [1]. Pathological manifestations of TSC in the central nervous system involve cortical tubers, subependymal nodules, subependymal giant-cell astrocytoma(s), and cortical tubers, which are the hallmarks of TSC, and result from abnormal neuronal migration during brain development. Cortical tubers represent focal hamartomatous regions of disorganized cortical lamination. Histopathologic examination of tubers typically reveals prominent numbers of glia, neuronal appearing cells, and giant cells that express markers of both neuronal and glial lineages [2]. Mouse models of tuberous sclerosis complex

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indicate decreased myelination throughout the cortex, as well as aberrant topographic projections of axon pathways in the reticulogeniculate tract [3]. Disruption of white matter may contribute to the high incidence of behavioral and cognitive impairments in tuberous sclerosis complex [4]. They play a crucial role in subsequent epilepsy, intellectual disability (ID), autism, and neuropsychiatric disorders (NPDs) in patients with TSC [5, 6].

For the diagnosis and management of TSC, conventional anatomical magnetic resonance imaging (MRI) is routinely used to detect and monitor major intracranial lesions [7]. While this is highly sensitive, it only provides an impression of the extent of intracranial involvement. In recent years, newer MRI techniques, such as diffusion tensor imaging (DTI) and diffusion spectrum imaging (DSI), have been developed with the ability to investigate characteristics of epilepsy, neuropsychiatric phenotype, and microstructural brain lesions, which are seen in TSC [8]. A recent study correlated neurological outcome with cortical tuber burden and transmantle white matter lesions, resulting in a proposed composite clinical scoring system assessing the major neurological features of TSC [9].

DTI is an MRI-based technique, which is able to examine the direction and magnitude of water diffusion, enabling assumptions to be made about the underlying tissue structure [10]. As water does not diffuse equally in all directions within a biological system, anisotropy is used to measure the directional preference of diffusion. DTI is able to describe diffusion and strength according to a tensor at each voxel [4, 8]. The models created using this technique have been shown to be consistent with known neuroanatomy and are also able to demonstrate pathological microstructural changes in tissue in several neurological conditions. Cortical tubers, a hallmark of TSC, exhibit a higher apparent diffusion coefficient, lower fractional anisotropy (FA), and appear to have a greater epileptogenic and neuropsychiatric potential.

A recently proposed framework for brain research describes the connectome, a model of the complex networks of the human brain. It is a widely focused project and numerous hardware and post-processing developments have been made for visualizing and investigating the connectome in human brain in the context of Human Connectome Project (HCP) [11]. This is able to provide novel insights into various brain functions and structural organization and enables researchers to investigate the segregation and integration of information processing [12, 13]. Graph theoretical analysis (GTA), which is a quantitative method of identifying nodes, edges, and disparate topological parameters, has allowed the analysis and modelling of the connection. GTA is also able to quantify clustering coefficients, characteristic path lengths, and small worldness. Recently, GTA along with network-based statistical (NBS) analysis has increased the knowledge and understanding of the functional brain network in TSC by providing network-based information [14].

With cortical tubers, TSC is frequently complicated with neurological comorbidities, such as epilepsy, intellectual disability, and autism spectrum disorder. DTI measures in TSC are abnormal even in structurally normal-appearing white matter. It is demonstrated that TSC with seizures presents alterations of brain connectivity in areas crucial for global cognitive maturation, executive functions, and verbal abilities, implying a higher risk of cognitive impairment, attention-deficit hyperactivity disorder, and autism [15]. For TSC with autism, decreased FA and increased mean diffusivity (MD) have been reported subjects with TSC and autism when compared to subjects with TSC but without autism [16]. It demonstrates that DTI metrics of the corpus callosum are cumulatively associated with comorbid neurological symptoms in TSC and non-syndromic autism. These findings reflect the complex relationship between biological disease burden, and subsequent ID, autism and epilepsy in TSC.

We hypothesized that TSC patients with comorbidities, such as seizures and NPDs, including ID and autism, exhibit fewer reconstructed major white matter tracts. Current study is designed as a cross-sectional study with two subgroups of TSC, all connectivity and network measurements were compared with the presence of comorbidities. The study aimed to evaluate the diffusion characteristics of tubers, white matter lesions, and brain structural network alterations in TSC patients using region of interest (ROI), GTA, and NBS.

Methods

Participants

Forty-two patients (18 male, 24 female; mean [± SD] age 21 ± 10 years) with a definitive diagnosis of TSC were recruited for this study. Written informed consent was obtained from all participants; the study was approved by the Institutional Review Board of Chung Shan Medical University Hospital (Taichung City, Taiwan). All participants were right-handed, none of whom had a history of traumatic brain injury or substance abuse, and none had ever undergone brain surgery. Individuals with metallic implants or other contraindications to MRI were excluded from the study.

Neurologic Severity Score

A Neurological Severity Score (NSS) was assigned to classify the neurological severity of TSC [9], including as follows: ID; seizures (none/controlled or intractable); autism; and other NPDs (except ID or autism), including self-injury, violent behavior, learning disorder, language difficulties, and

anger outbursts. For scoring, ID was assigned 3 points, while intractable seizure and autism were assigned 2 points each. The "other NPD" component—regardless of how many disorders a patient had—and controlled seizure, were assigned one point each. Intractable seizure was defined as failure of seizure control after using two first-line antiepileptic medications, one seizure per month for 18 months, or freedom from seizures for < 3 consecutive months. The NSS of each subject was calculated by summing the points for each of the components.

MRI data acquisition

All diffusion images were acquired using a 3 T scanner (Skyra, Siemens Medical Systems, Erlangen, Germany) equipped with a 20-channel head–neck coil. All the patients who underwent T1 weighted, T2 weighted and DTI are used as conventional anatomical MRI scans for TSC diagnosis, and the target cortical tubers were localized before MRI data acquisition. A three-dimensional magnetization-prepared rapid gradient-echo imaging (3D MPRAGE) sequence was used to obtain T1-weighted images. The images were acquired with the following parameters: repetition time (TR) = 2500 ms, echo time (TE) = 2.27 ms, inversion time (TI) = 902 ms, flip angle = 8°, voxel size (resolution) = 1 × 1 × 1 mm^3, total slices = 160, and scan time = 5.8 min. Diffusion tensor images were acquired using the following parameters: TR = 4800 ms; TE = 97 ms; voxel size = 2 × 2 × 4 mm^3; 35 axial contiguous slices, signal average, 1; 64 non-collinear diffusion weighting gradient direction, with $b = 1000$ s/mm^2; and 12 additional null images without diffusion weighting ($b = 0$ s/mm^2). The phase-encoding direction used in the study was anterior–posterior direction which induced less susceptibility artifact. The scan time was approximately 6 min.

DTI and ROI analysis

After using FSL (FMRIB Software Library, Oxford, United Kingdom) for both eddy currents and subject movement (including *b*-vectors rotation) correction [17, 18], each participant's echo planar image was spatially normalized to the Montreal Neurological Institute T2 template using parameters determined from the normalization of the diffusion null image to the T2 template using Statistical Parametric Mapping (SPM8, Wellcome Department of Cognitive Neurology, London, United Kingdom). Before the analysis of T1 weighted, T2 weighted and DTI are preceded to screen the largest cortical tubers in TSC patients, and subsequently each cortical tuber is selected to be measured and compared with contralateral sites (without lesion). DTI reconstruction was performed using DSI Studio (National Taiwan University, Taipei, Taiwan), and mean diffusivity (MD), axial diffusivity (AD), radial diffusivity (RD) were calculated, and FA was mapped. MD, AD, RD and FA values in 52 tubers and white matter lesions were measured and compared with those of contralateral normal regions with the same region of interest. One or two largest tubers were analyzed per patient. DSI Studio was also used for whole-brain DTI tractography (seeds were placed in the whole brain) with a FA threshold of 0.15 and a maximum angle of 70° (Yeh, Wedeen et al. 2010). Subsequently, the individual structural connectivity matrix (fiber number × FA/mean fiber length) of each participant (size, 90 × 90) could be outputted and the regions of interest inputted based on a standard parcellation template contained in the Automated Anatomical Labeling software package.

GTA

GTA was performed on the inter-regional connectivity matrix using the Graph Analysis Toolbox (Stanford University School of Medicine, Stanford, CA, USA), a Matlab-based package with graphical user interface that integrates the Brain Connectivity Toolbox [14, 17]. The density was calculated by connection with a threshold divided by the connection of random network. The topological measures of structural brain network densities were calculated using different correlation thresholds (0.05−0.2 [in 0.01 increments]), including the clustering coefficient (C), normalized clustering coefficient (γ), characteristic path length (L), normalized characteristic path length (λ), local efficiency (E_{local}), global efficiency (E_{global}), small-worldness index (σ), transitivity, and modularity [14, 17, 19–25]. C and E_{local} reflect local segregation and C quantifies the extent of local interconnectivity in the network, while E_{local} indicates how well the subgraphs exchange information with one another. High scores on the two measures correspond to highly segregated neural processing. L and E_{global} reflect the global integration and L measures the capability for information transfer between brain regions, while E_{global} is a measure of the overall capacity for parallel information transfer and integrated processing. A lower L score or higher E_{global} score indicates more rapid integration of specialized information from distributed brain regions. The γ and λ values are normalized relative to the C and L of 100 random networks. Small worldness (i.e., σ) is calculated by dividing γ by λ. The transitivity is the ratio of triangles to triplets in the network and is an alternative to the clustering coefficient. Modularity is a statistic that quantifies the degree to which the network may be subdivided into clearly delineated groups. To determine the statistically significant differences between the groups in the network topology and regional network measurements, we manually extracted the area under the curve between 0.05 and 0.2 of the density to calculate the p value of the two-sample t test.

NBS analysis

NBS analysis was used to identify the significance of any connected subnetworks evident in the set of altered connections found between the subgroups of TSC patients. NBS analysis attempted to identify any potentially connected structures formed by an appropriately chosen set of suprathreshold links. The topological extent of any such structure was then used to determine its significance. The test statistic (i.e., primary threshold) computed for each pairwise association was used to construct a set of suprathreshold links [26]. The null distribution of the number of edges was empirically obtained using nonparametric permutation (5000 permutations) to assess the significance of each of the connected edges.

Results

Participants and ROI analysis

Demographic characteristics and a summary of cognitive tests are summarized in Table 1. Therefore, age, sex, and years of education were used as covariates for subsequent analyses. Figure 1 was one representative TSC case of DTI analysis, including MD map, AD map, RD map and FA map. In ROI results, as shown in Table 2, significantly higher MD, AD and RD, and lower FA values were found in TSC lesions than those measured in contralateral normal regions for tubers ($P < 0.05$).

GTA

GTA revealed that TSC patients with ID had a higher normalized clustering coefficient, modularity, transitivity and normalized characteristic path length than the ones with normal intelligence ($P < 0.05$) (Fig. 2), which indicated better local segregation but worse global integration was found. TSC patients with intractable seizure status demonstrated a higher clustering coefficient, local efficiency, modularity, transitivity and normalized characteristic path length than those who with seizure status of none/controlled ($P < 0.05$) (Fig. 3), which indicated better local segregation but worse global integration was obtained. TSC patients with higher NSS (6–8) demonstrated a higher clustering coefficient, modularity, transitivity and normalized characteristic path length than those with lower NSS (0–5) ($P < 0.05$) (Fig. 4), which indicated better local segregation but worse global integration was observed. However, there were no significant differences in other topological parameters in TSC patients with autism or other NPDs.

Table 1 Demographic data of TSC patients, $n = 42$

Variable	Numbers	%
Age	29 (5–51)	
Sex (male: female)	18:24	
Gene		
TSC1	7	16.7
TSC2	23	54.6
NMI/ND	12	28.6
Neurological Severity Score		
ID		
Yes	25	59.5
No	17	40.5
Seizure		
None/controlled	24	57.1
Intractable	18	42.9
Autism		
Yes	4	9.5
No	38	90.5
NPD		
Yes	23	54.8
No	19	45.2
Sum of score		
0–5	26	61.9
6–9	16	38.1

NMI no mutation identified, *ND* not done, *DD* developmental disability, *ID* intellectual disability, *NPD* other neuropsychiatric disorders, *NSS* Neurological Severity Score. NSS equal to sum of ID, seizure, autism and NPD

NBS analysis

In NBS, there were several disruptions in the connectivity between the subgroups of TSC patients (TSC patients with ID vs. patients with normal intelligence, patients with intractable seizure vs. patients with none/controlled seizure, patients with higher NSS vs. patients with lower NSS). NBS analysis revealed a disrupted subnetwork in TSC patients with ID compared with those who with normal intelligence (ID < intelligence; $P < 0.05$) (Fig. 5), including connections from the temporal lobe to the insula. NBS analysis was also used to compared the edges of the brain networks between TSC patients with intractable or none/controlled seizures (Fig. 6). One subnetwork exhibited more edges in the none/controlled when compared with intractable seizure (NR > AR; $P < 0.05$), including the connections from the frontal lobe to the parietal lobe. Figure 7 illustrates the disrupted subnetwork in TSC patients with higher NSS (6–8) compared with who with lower NSS (0–5) (higher NSS [6–8] < lower NSS [0–5]; $P < 0.05$), including connections from the temporal lobe to the caudate. The structures marked

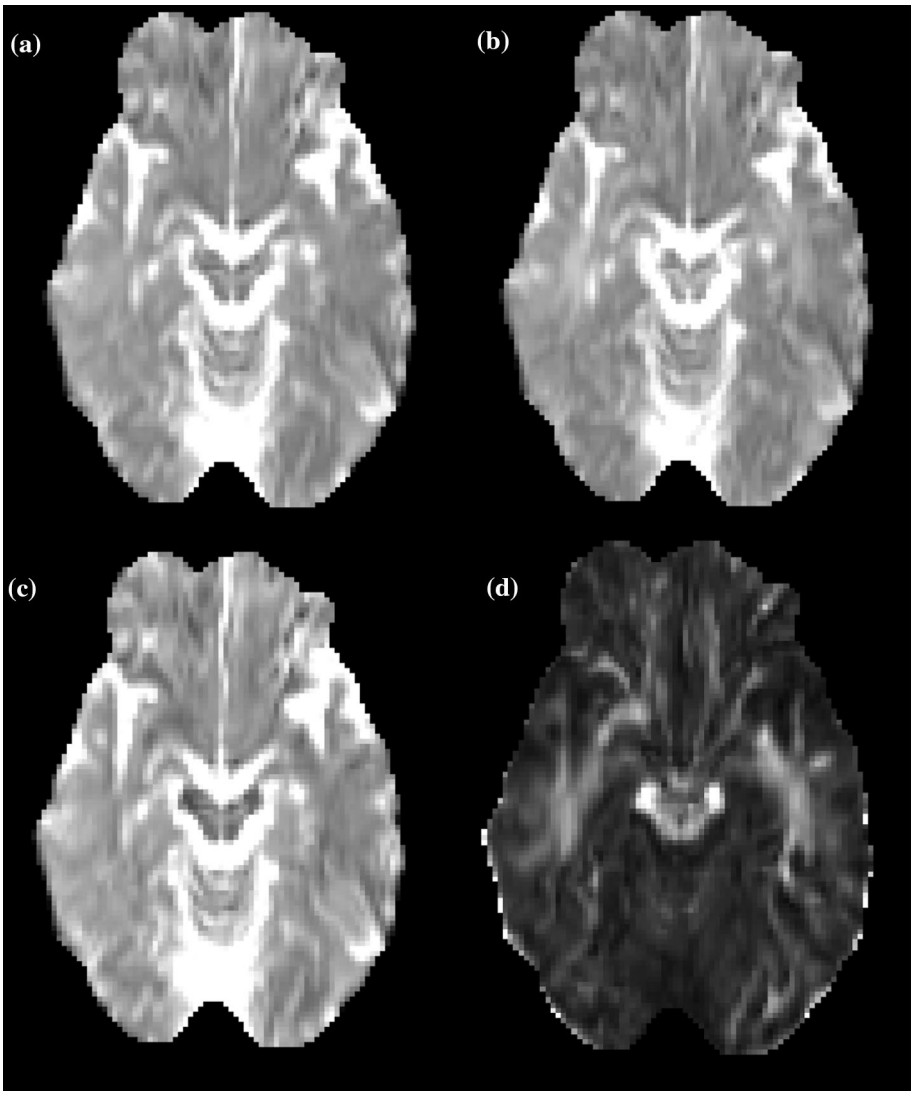

Fig. 1 One representative TSC case of DTI analysis, including **a** MD map, **b** AD map, **c** RD map and **d** FA map

Table 2 Comparison of diffusion indices values between tubers lesions and contralateral normal regions

	TSC lesion	Contralateral normal region	*P* value
MD (10^{-3} mm^2/s)	2.151 ± 0.095	1.736 ± 0.106	< 0.05
AD (10^{-3} mm^2/s)	2.334 ± 0.100	1.927 ± 0.111	< 0.05
RD (10^{-3} mm^2/s)	2.060 ± 0.09	1.648 ± 0.102	< 0.05
FA	0.091 ± 0.006	0.119 ± 0.009	< 0.05

TSC tuberous sclerosis complex, *MD* mean diffusivity, *AD* axial diffusivity, *RD* radial diffusivity, *FA* fractional anisotropy

with different colors stand for the different modularity. The abbreviation of node stands for the brain region based on a standard parcellation template contained in the Automated Anatomical Labeling software package.

Discussion

In healthy individuals, brain networks exhibit small-world properties, showing a balance between local segregation and global integration between brain regions and networks [27]. The results of our study revealed a trend toward decreased global integration and increased local segregation among TSC patients, which may indicate changing in the brain networks, shifting toward structural regularity and leading to impaired organization for efficient information transfer in these patients. The results from the DTI analysis have the potential to provide valuable information on cytoarchitectural changes in TSC lesions beyond basic morphological MRI findings. This study also provides information on disrupted white matter connectivity and organization in TSC patients with different neuropsychological impairments using GTA. Using NBS analysis, which helps detect abnormal connections between specific pairs of brain regions, the

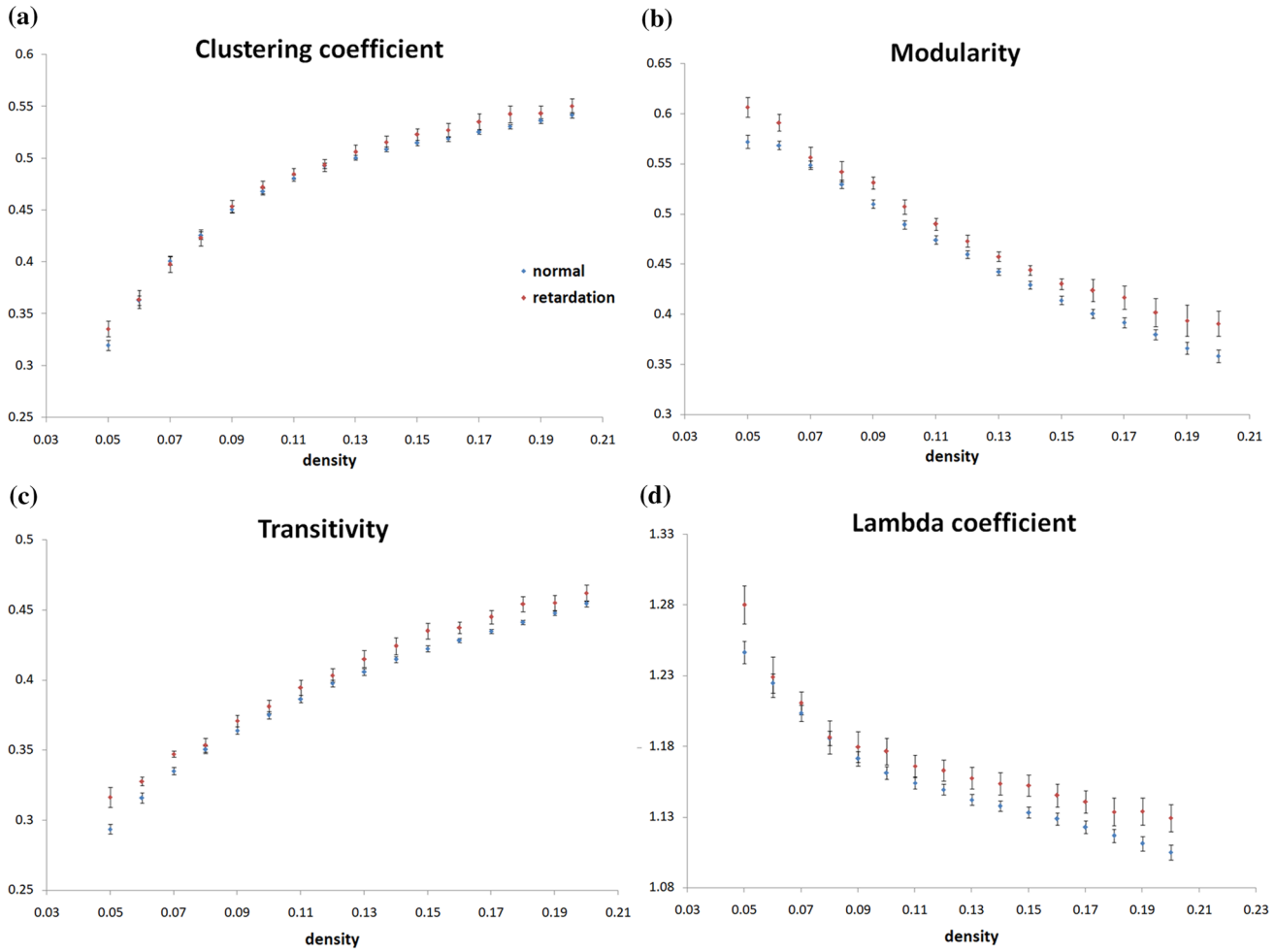

Fig. 2 TSC patients with intellectual disability have higher **a** clustering coefficient, **b** modularity, **c** transitivity and **d** normalized characteristic path length than who are negative of intellectual disability

results of the current study revealed the connections in subnetwork connectivity in TSC were complicated by NPDs. Our findings may help to better understand the variable clinical phenotypes of TSC patients and the underlying physiological mechanisms.

Among the current DTI analysis methods, tract-based spatial statistics (TBSS), as a pioneering approach for the voxel-wise analysis of DTI data, have gained a lot of popularity due to its user-friendly framework and may provide more robust normalization and diffusion analysis results [28]. However, in recent years, the reliability and interpretability of TBSS have been challenged by several works, and several improvements over the original TBSS pipeline have been suggested. GAT and NBS analyses do not rely on the accurate alignment of fractional anisotropy (FA) images for population analysis and get rid of the skeletonization procedures of TBSS, which have been indicated as the major sources of error. GAT provides the detailed information of local segregation and global integration of structural network, and to evaluate the small-worldness property. Furthermore, NBS improves the interpretability of results by directly reporting the resulting statistics on structural network based on white matter tracts, waiving the need of a white matter atlas in the interpretation of the results. Through our results, it is validated that GAT and NBS can provide detailed statistical results in a comprehensive and easy-to-understand way.

It has been hypothesized that tubers disrupt local cerebral architecture, resulting in impaired brain function. The DTI-ROI analysis of TSC tubers that appear normal on conventional MRI has identified abnormalities suggesting abnormal myelination and astrogliosis. The disruption of the normal development of brain function in patients with TSC was caused by alterations in the microstructural integrity of axons and myelination. However, the inter-regional connectivity and altered subnetwork connections need to be addressed. In GTA and NBS analyses, we compared TSC patients with severe status and mild status to further

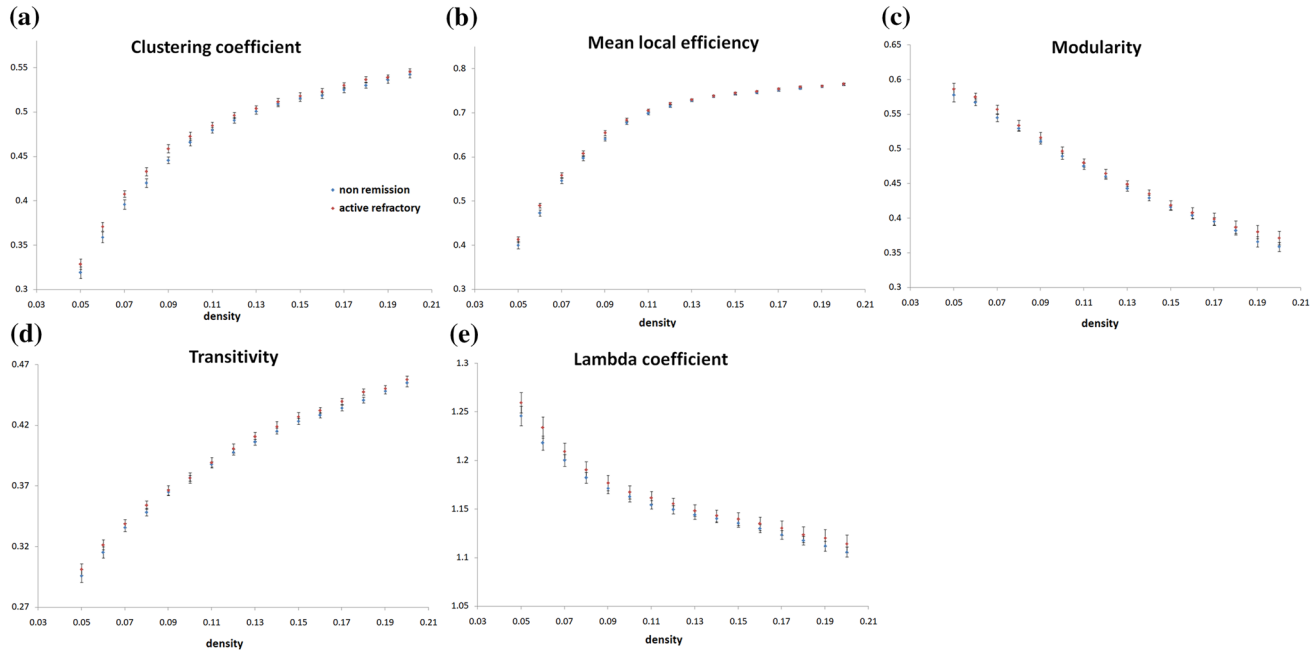

Fig. 3 TSC patients with intractable seizure have higher **a** clustering coefficient, **b** local efficiency, **c** modularity, **d** transitivity and **e** normalized characteristic path length than who are none / controlled

characterize abnormal white matter microstructure and aberrant connectivity in TSC. We found an increase in loss of white matter global integration in TSC patients with severe status would lead to an increase in cognitive and social behavioral deficits. Disrupted subnetworks in TSC patients with severe status included connections from the frontal lobe to the parietal lobe, temporal lobe to the caudate, and temporal lobe to the insula, which may reflect the location of the load of tubers.

The range of diverse phenotypes seen in TSC patients derives from abnormal neural connections, which are independent of the benign hamartomas [10, 29]. Studies into DTI findings for TSC have shown decreased FA and increased MD values in certain brain structures, including the corpus callosum and the internal and external capsule [30, 31]. DTI is able to provide imaging data that determine associations between altered white matter microstructures and abnormal brain function in the TSC population. Makki et al. [32] report DTI abnormalities in individuals with TSC, these included normal-appearing white matter, indicating foci of microstructural abnormalities, depending on sample size and technique. These data suggest that microstructural changes are likely present throughout the cerebral white matter in those with TSC. Our results demonstrated significantly higher MD, AD, RD, and lower FA indices in TSC lesions than those of contralateral normal regions. Moreover, the changes in MD in the TSC lesions indicate microstructural changes resulting in increased water diffusion in axonal fibers. Elevated AD is related to axonal injury, or a disarray of axons, while increased RD and decreased FA are related to demyelination or abnormal myelin. This attributes to hamartomatous proliferation along with depleted and disordered myelin sheaths.

The altered brain connectivity in TSC is correlated with qualitative assessments of tuber load [33]. Both short- and long-association fibers are affected in TSC, and subsequently interhemisphere connectivity is reduced, leading to increased network clustering within hemispheres [10]. The current results revealed improved local segregation and reduced global integration of the structural network in TSC patients with normal intelligence in comparison to those with ID, as well as in TSC patients with no/controlled seizures compared with those who were intractable. Both structural networks in TSC patients with ID and intractable seizure were more comparable to regular networks. Therefore, our ROI and GTA results were able to distinguish the differences in microstructural tissue water diffusion properties among different intellectual and/or seizure groups, thus reflecting underlying microstructural abnormalities in TSC.

Modules are defined as sets of nodes that are more strongly connected to one another than to the remainder of the network [27]. Using GTA, we revealed that TSC patients with ID, intractable seizures, and higher NSS exhibited increased local segregation and decreased global integration of the network [34]. In GTA, the clustering coefficient quantifies the extent of local interconnectivity in the network, and the transitivity refers to the extent to which the relationship between two nodes in a network that is connected by an edge

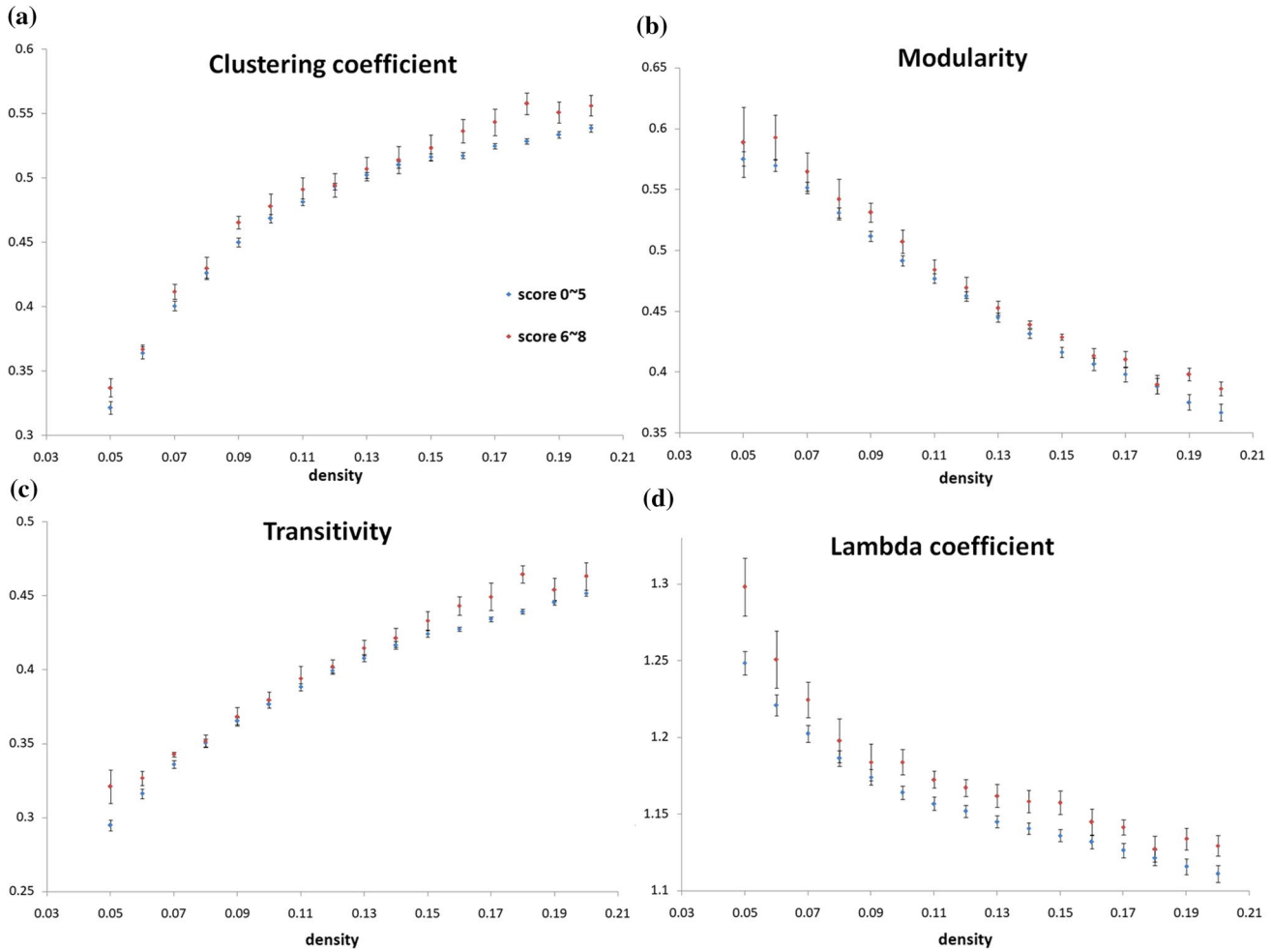

Fig. 4 TSC patients with higher NSS (6–8) have higher **a** clustering coefficient, **b** modularity, **c** transitivity and **d** normalized characteristic path length than who have lower NSS (0–5)

is transitive. The results revealed that TSC patients with ID, intractable seizure, and higher NSS exhibited a significant difference in clustering coefficient and transitivity in GTA. These measures reflect the extent of local segregation of the neural network; more specifically, higher scores of these measures correspond to a higher extent of segregated neural processing with higher local interconnectivity, higher efficiency of local information exchanges, and higher transitivity between nodes. The current results suggest that TSC patients may have improved segregation but reduced global integrated neural processing with a higher clustering coefficient, local efficiency, and transitivity when complicated with ID, intractable seizures, or higher NSS. Alternatively, the results could exhibit poor global integration of the neural network with a larger normalized characteristic path length. Path length is defined as the minimum number of edges between all pairs of nodes. An increased path length indicates a reduction in global integration of the network, indicating an essential balance between local segregation and global integration within brain regions and networks [13, 19]. We propose that TSC patients with ID, intractable seizure, or higher NSS exhibit increased local segregation and relatively decreased global integration, which may lead to reduced specificity of particular processing functions mediated by distinct neural structures.

In addition to seizures and ID, cortical tubers in TSC appear to be related to serve as foci, and neuroimaging enables the early identification and characterization of these brain abnormalities [35]. Lewis et al. [36] demonstrated microstructure integrity in FA was associated with autism in TSC patients, indicating a possible relationship between aberrant white matter, microstructural integrity, and TSC associated NPDs. Despite our results demonstrating cytoarchitectural changes, they also reveal disrupted white matter connectivity and organization in TSC patients with complications of ID and intractable seizure beyond morphological findings based on MRI alone. There were no significant correlations in comorbidies in TSC with autism

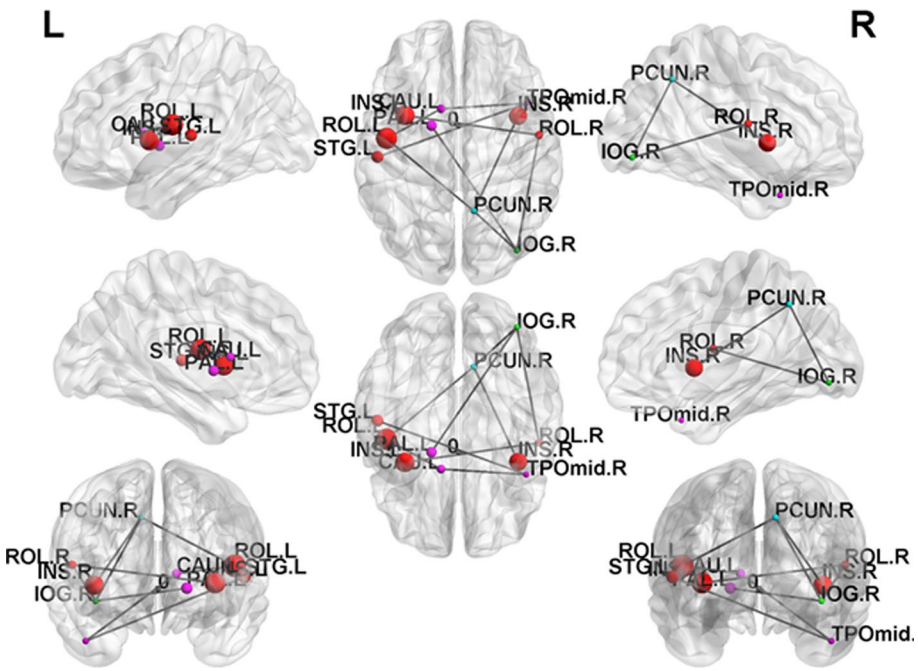

Fig. 5 The NBS result showed the disrupted subnetwork in the TSC patients with intellectual disability compared with who have normal intelligence (ID < normal)

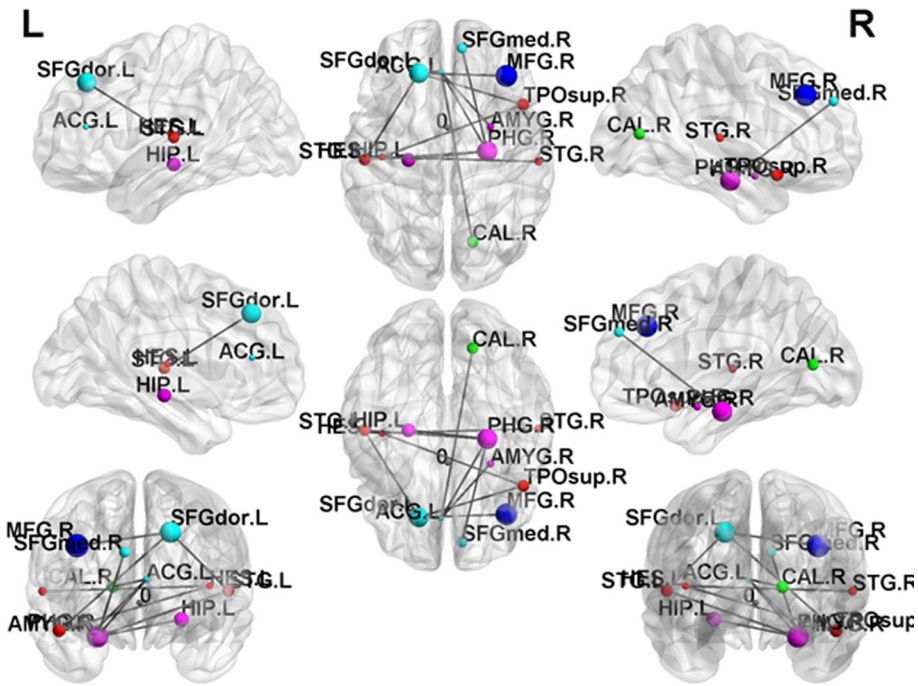

Fig. 6 The NBS result showed the disrupted subnetwork in the TSC patients with intractable seizure of intractable compared with who are none/controlled (active + refractory < none + remission)

or other NPDs. We speculate that it is potentially related to the limited number of autism patients and the heterogeneity of other NPDs.

The sample size was limited in this study due to the rarity of this disease, which may affect the generalizability of the results. Despite autism being common in TSC, the current study enrolled a limited number of TSC patients with autism, resulting in negative findings in the protocols with autism. As a cross-sectional study, here it precluded us from observing longitudinal changes in intracranial lesions in TSC participants; as such, longitudinal studies are required to examine such effects. Previous studies indicated that compared to healthy controls, there exist global white matter changes in TSC patients, which suggests that there exist potential limits using contralateral normal-appearing white matter as the reference in the analysis. The relatively thick slice was used in the DTI study because we want to have large coverage of brain

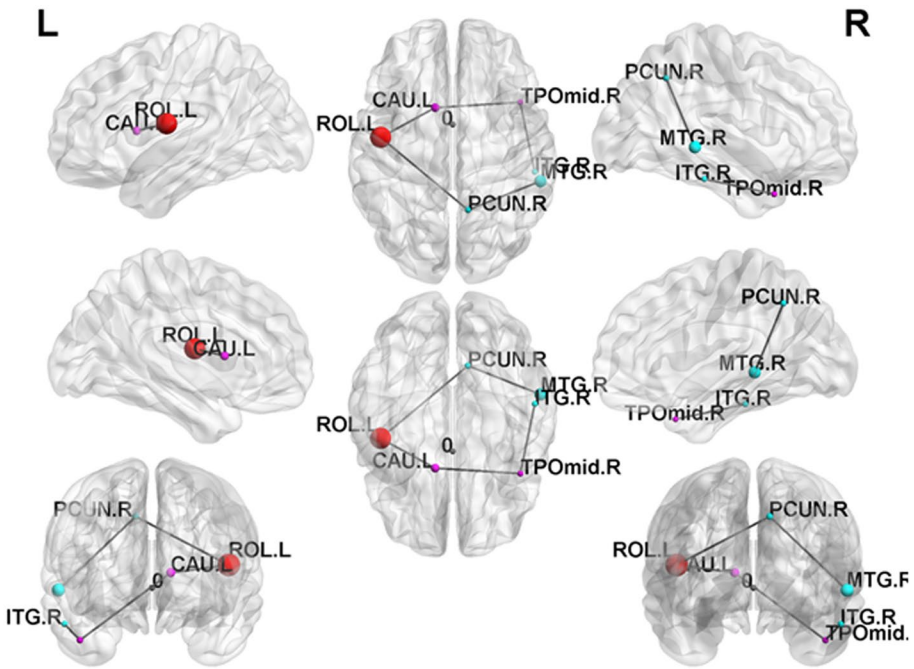

Fig. 7 The NBS result showed the disrupted subnetwork in the TSC patients with higher NSS (6–8) compared with who have lower NSS (0–5) (higher NSS (6–8) < lower NSS (0–5))

region under relatively short scan time, i.e., 6 min, and to increase the cooperation of tuberous sclerosis complex patients. However, the effect of relatively large voxel size could be ignored since the analysis method, i.e. GAT and NBS, we used.

Conclusion

The current results suggest that DTI has the potential to determine valuable information about cytoarchitectural changes in TSC lesions beyond morphological MRI findings, and provides information regarding disrupted white matter connectivity and organization in TSC patients with different neuropsychological impairments using GTA and NBS. Our current findings may help better understand the variable clinical phenotypes seen in TSC patients and the underlying physiological mechanisms.

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Author contributions J-DT conceived and designed the experiments, authored or reviewed drafts of the paper, and approved the final draft. M-CH, H-YL, and C-YS contributed reagents/materials/analysis tools and analyzed the data. J-YL analyzed the data and prepared figures and/or tables. J-CW conceived and designed the experiments, contributed reagents/materials/analysis tools, authored or reviewed drafts of the paper, and approved the final draft.

Compliance with ethical standards

Conflict of interest None of the authors of this work have any conflict of interest to declare.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of our institutional review board (IRB) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standard.

Informed consent Informed consent was obtained from all individual participants included in the study. All applicable international, national, and institutional guidelines were followed.

References

1. Orlova KA, Crino PB (2010) The tuberous sclerosis complex. Ann N Y Acad Sci 1184:87–105
2. Ess KC (2006) The neurobiology of tuberous sclerosis complex. Semin Pediatr Neurol 13(1):37–42
3. Meikle L, Talos DM, Onda H et al (2007) A mouse model of tuberous sclerosis: neuronal loss of Tsc1 causes dysplastic and ectopic neurons, reduced myelination, seizure activity, and limited survival. J Neurosci 27:5546–5558
4. Krishnan ML, Commowick O, Jeste SS, Weisenfeld N, Hans A, Gregas MC, Sahin M, Warfield SK (2010) Diffusion features of white matter in tuberous sclerosis with tractography. Pediatr Neurol 42(2):101–106
5. Wei CC, Sheu JN, Liu JT, Yang SH, Chou IC, Tsai JD (2018) Trend of seizure remission in patients with tuberous sclerosis complex: a retrospective medical review. J Chin Med Assoc 81(8):724–728
6. Curatolo P, Moavero R, de Vries PJ (2015) Neurological and neuropsychiatric aspects of tuberous sclerosis complex. Lancet Neurol 14(7):733–745

7. Tsai JD, Wei CC, Tsao TF, Hsiao YP, Tsai HJ, Yang SH, Tsai ML, Sheu JN (2016) Association between the growth rate of subependymal giant cell astrocytoma and age in patients with tuberous sclerosis complex. Childs Nerv Syst 32(1):89–95
8. Kassiri J, Snyder TJ, Bhargava R, Wheatley BM, Sinclair DB (2011) Cortical tubers, cognition, and epilepsy in tuberous sclerosis. Pediatr Neurol 44(5):328–332
9. Wong AM, Wang HS, Schwartz ES, Toh CH, Zimmerman RA, Liu PL, Wu YM, Ng SH, Wang JJ (2013) Cerebral diffusion tensor MR tractography in tuberous sclerosis complex: correlation with neurologic severity and tract-based spatial statistical analysis. Am J Neuroradiol 34(9):1829–1835
10. Im K, Ahtam B, Haehn D, Peters JM, Warfield SK, Sahin M, Ellen GP (2016) Altered structural brain networks in tuberous sclerosis complex. Cereb Cortex 26(5):2046–2058
11. Glasser MF, Smith SM et al (2016) The human connectome project's neuroimaging approach. Nat Neurosci 19:1175–1187
12. Chen VC, Liu YC, Chao SH, McIntyre RS, Cha DS, Lee Y, Weng JC (2018) Brain structural networks and connectomes: the brain-obesity interface and its impact on mental health. Neuropsychiatr Dis Treat 26(14):3199–3208
13. Bullmore ET, Bassett DS (2011) Brain graphs: graphical models of the human brain connectome. Annu Rev Clin Psychol 7:113–140
14. Hosseini SM, Hoeft F, Kesler SR (2012) GAT: a graph-theoretical analysis toolbox for analyzing between-group differences in large-scale structural and functional brain networks. PLoS ONE 7(7):e40709
15. Moavero R, Napolitano A, Cusmai R et al (2016) White matter disruption is associated with persistent seizures in tuberous sclerosis complex. Epilepsy Behav 60:63–67
16. Baumer FM, Peters JM, Clancy S et al (2018) Corpus callosum white matter diffusivity reflects cumulative neurological comorbidity in tuberous sclerosis complex. Cereb Cortex 28(10):3665–3672
17. Leemans A, Jones DK (2009) The B-matrix must be rotated when correcting for subject motion in DTI data. Magn Reson Med 61(6):1336–1349
18. Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE et al (2004) Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage 23(Suppl 1):S208–219
19. Rubinov M, Sporns O (2010) Complex network measures of brain connectivity: uses and interpretations. Neuroimage 52(3):1059–1069
20. Watts DJ, Strogatz SH (1998) Collective dynamics of 'small-world' networks. Nature 393(6684):440–442
21. Onnela JP, Saramaki J, Kertesz J, Kaski K (2005) Intensity and coherence of motifs in weighted complex networks. Phys Rev E Stat Nonlin Soft Matter Phys 71(6 Pt 2):065103
22. Bassett DS, Bullmore E (2006) Small-world brain networks. Neuroscientist 12(6):512–523
23. Saramaki J, Kivela M, Onnela JP, Kaski K, Kertesz J (2007) Generalizations of the clustering coefficient to weighted complex networks. Phys Rev E Stat Nonlin Soft Matter Phys 75(2 Pt 2):027105
24. Bullmore E, Sporns O (2009) Complex brain networks: graph theoretical analysis of structural and functional systems. Nat Rev Neurosci 10(3):186–198
25. Bassett DS, Gazzaniga MS (2011) Understanding complexity in the human brain. Trends Cogn Sci 15(5):200–209
26. Zalesky A, Fornito A, Bullmore ET (2010) Network-based statistic: identifying differences in brain networks. Neuroimage 53(4):1197–1207
27. Weng JC, Kao TW, Huang GJ, Tyan YS, Tseng HC, Ho MC (2017) Evaluation of structural connectivity changes in betel-quid chewers using generalized q-sampling MRI. Psychopharmacology 234(13):1945–1955
28. Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, Watkins KE, Ciccarelli O, Cader MZ, Matthews PM, Behrens TEJ (2006) Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. NeuroImage 31(4):1487–1505
29. Tsai P, Sahin M (2011) Mechanisms of neurocognitive dysfunction and therapeutic considerations in tuberous sclerosis complex. Curr Opin Neurol 24(2):106–113
30. Peters JM, Sahin M, Vogel-Farley VK, Jeste SS, Nelson CA 3rd, Gregas MC, Prabhu SP, Scherrer B, Warfield SK (2012) Loss of white matter microstructural integrity is associated with adverse neurological outcome in tuberous sclerosis complex. Acad Radiol 19(1):17–25
31. Peters JM, Taquet M, Prohl AK, Scherrer B, van Eeghen AM, Prabhu SP, Sahin M, Warfield SK (2013) Diffusion tensor imaging and related techniques in tuberous sclerosis complex: review and future directions. Future Neurol 8(5):583–597
32. Makki MI, Chugani DC, Janisse J, Chugani HT (2007) Characteristics of abnormal diffusivity in normal-appearing white matter investigated with diffusion tensor MR imaging in tuberous sclerosis complex. Am J Neuroradiol 28(9):1662–1667
33. Yogi A, Hirata Y, Karavaeva E, Harris RJ, Wu JY, Yudovin SL, Linetsky M, Mathern GW, Ellingson BM, Salamon N (2015) DTI of tuber and perituberal tissue can predict epileptogenicity in tuberous sclerosis complex. Neurology 85(23):2011–2015
34. Weng JC, Chou YS, Huang GJ, Tyan YS, Ho MC (2018) Mapping brain functional alterations in betel-quid chewers using resting-state fMRI and network analysis. Psychopharmacology 235(4):1257–1271
35. Asano E, Chugani DC, Muzik O, Behen M, Janisse J, Rothermel R, Mangner TJ, Chakraborty PK, Chugani HT (2001) Autism in tuberous sclerosis complex is related to both cortical and subcortical dysfunction. Neurology 57(7):1269–1277
36. Lewis WW, Sahin M, Scherrer B, Peters JM, Suarez RO, Vogel-Farley VK, Jeste SS, Gregas MC, Prabhu SP, Nelson CA 3rd, Warfield SK (2013) Impaired language pathways in tuberous sclerosis complex patients with autism spectrum disorders. Cereb Cortex 23(7):1526–1532

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