White Matter Network Abnormalities Are Associated with Cognitive Decline in Chronic Epilepsy

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Patients with chronic epilepsy frequently display cognitive comorbidity and might have widespread network abnormalities outside the epileptic zone, which might affect a variety of cognitive functions and global intelligence. We aimed to study the role of white matter connectivity in cognitive comorbidity. Thirty-nine patients with nonsymptomatic localization-related epilepsy and varying degrees of cognitive impairment and 23 age-matched healthy controls were included. Whole brain white matter networks were constructed from fiber tractography. Weighted graph theoretical analysis was performed to study white matter network abnormalities associated with epilepsy and cognition. Patients with severe cognitive impairment showed lower clustering (a measure of brain network segregation) and higher path length (a measure of brain network integration) compared with the healthy controls and patients with little or no cognitive impairment, whereas whole brain white matter volume did not differ. Correlation analyses revealed that IQ and cognitive impairment were strongly associated with clustering and path lengths. This study revealed impaired white matter connectivity, associated with cognitive comorbidity in patients with chronic epilepsy. As whole brain white matter volumes were preserved in the patient group, our results suggest an important role for the network topology rather than volumetric changes, in epilepsy with cognitive decline.

Keywords: cognitive impairment, epilepsy, network efficiency, tractography, white matter fiber pathways

Introduction

Patients with chronic epilepsy frequently display comorbid cognitive problems, ranging from memory deficits, mental slowing (Elger et al. 2004) and language problems (Vlooswijk et al. 2010), to global cognitive deterioration (Oyegbile et al. 2004). Patients with epilepsy often have lower intelligence levels than expected compared with healthy controls (Helmstaedter and Kockelmann 2006; Bonelli et al. 2010) even in studies that exclude symptomatic epilepsy (Hermann et al. 1995).

There is recent consensus that many cognitive functions result from the concerted interaction between brain areas in large-scale networks (Bressler and Menon 2010; Deary et al. 2010). The functioning of these networks is constrained by the organization of the associated axonal bundles of the white matter (WM). Magnetic resonance imaging (MRI) studies on WM and functional networks (Li et al. 2009; van den Heuvel et al. 2009) furthermore show that network efficiency plays an important role in intelligence. Therefore, any abnormality in the axonal network organization, associated with epilepsy, may explain cognitive decline in a much more sensitive way than changes in specific brain structures, as the location of the affected structures may vary from patient to patient.

The extent to which brain abnormalities manifest beyond the epileptic zone is currently a matter of debate (Meador and Hermann 2010). For instance, there is growing evidence from diffusion tensor imaging (DTI) that microstructural WM abnormalities are present outside the epileptic focus in temporal lobe epilepsy (TLE) (Focke, Yogarajah, et al. 2008; Meng et al. 2010; Riley et al. 2010) and that distant fiber bundles are affected (Powell et al. 2007; Yogarajah et al. 2008) and associated with cognitive comorbidity (Diehl et al. 2008; McDonald et al. 2008; Yogarajah et al. 2008; Riley et al. 2010).

For cryptogenic epilepsy, the imaging of WM abnormalities focused on predefined brain regions or connections gives rise to interpretational ambiguities because the precise anatomical location of the epileptic zone often remains uncertain and may vary between patients. A method that adequately deals with these problems is graph theoretical analysis (Stam and Reijneveld 2007; Bullmore and Sporns 2009). Graph theoretical analysis typically captures topological properties of the brain network in a few summary measures, which provide information on the amount of segregation and integration among brain regions. With graph theoretical analysis, it is possible to investigate the whole brain network, dividing it into a large number of regions (nodes) with an even larger number of possible connections (edges). It can then be calculated how the network is organized. One distinction that can be made is between a “small-world” and a random topology. A small-world network is characterized by a high degree of local clustering and short path lengths that globally link all the regions of the network. On the contrary, in a random topology, all links in the graph have an equal probability connecting any 2 nodes. This methodology has recently been shown to provide more sensitive measurements than conventional DTI indices in stroke (Crofts et al. 2011) and in schizophrenia (van den Heuvel et al. 2010; Zalesky, Fornito, Seal, et al. 2010). Graph theoretical analysis of WM networks has not been performed in epilepsy and might provide valuable insights into the extent and nature of WM network abnormalities and their potential relation with decline in cognitive performance (cognitive comorbidity).

Our objective was to investigate the integrity of white matter network organization using graph theoretical network analysis in patients with cryptogenic, localization related, epilepsy with frontotemporal focus in comparison to age.
matched healthy controls. We investigated to which extent patients with epilepsy show abnormal white matter network properties and whether these relate to cognitive impairment.

Materials and Methods

Study Population

All patients were included from the tertiary referral epilepsy center Kempenhaeghe (Heeze, the Netherlands) and the outpatient clinic neurology of Maastricht University Medical Centre (Maastricht, the Netherlands). Inclusion criteria for the patients were: cryptogenic (i.e., nonsympathomimetic) localization-related epilepsy with a temporal and/or frontal epileptic focus, no history of status epilepticus, and no other underlying disease that could possibly cause cognitive decline. Healthy controls were family members and acquaintances of the patients without a history of brain injury or cognitive problems. Thirty-nine patients (19 males, age 40 ± 12 years) and 23 age-matched healthy controls (9 males, age 40 ± 13 years) were included. Post hoc analysis confirmed that the patient and healthy group control did not differ in age (t-test, P = 0.65) or group composition of gender (Chi-square, P = 0.48). All subjects underwent a full intelligence (FS-IQ) assessment with the Wechsler Adult Intelligence Scale (WAIS-III) (Wechsler 1997). Patients were considered to be either cognitively impaired or unimpaired based on an estimation of their premorbid IQ (Schoenberg et al. 2002). An estimate of premorbid intelligence levels was made according to the formula proposed by Schoenberg et al. (2002), which is based on the observation that the subtests Vocabulary, Information, Matrix Reasoning, and Picture Completion are relatively resistant to neurological insult (Wechsler 1997). Intelligence discrepancy scores were calculated by subtracting premorbid and full-scale IQ (FS-IQ) scores. Patients with a difference between FS-IQ and premorbid IQ lower than any differences recorded in the healthy control group were categorized as cognitively impaired. This resulted in a subgroup of n = 7 (4 males) cognitively impaired patients. This subgroup had comparable age (41 ± 10 years) to the healthy control and nonimpaired groups. Patient and epilepsy characteristics, including drug load, seizure frequency, and age at onset were collected as described in Vlooswijk et al. (2010). An overview of the study population is given in Table 1.

Image Analysis

DTI measurements were performed in all subjects on a 3-T MRI system (Philips Medical Systems, Achieva). Acquisition parameters for DTI were: 52 contiguous 2-mm thick slices, matrix size 96 × 96, pixel size 2 × 2 mm, time echo (TE) 62 ms and time repetition 6600 ms. Images were obtained along 15 noncollinear diffusion directions with a b-value of 800 s/mm²; one b = 0 s/mm² image was acquired. Anatomic reference images were acquired by a T1-weighted 3D fast gradient echo sequence (Jeukens et al. 2009). Each data set was spatially coregistered to the b = 0 image with an affine transformation to correct for head motion and eddy-current distortions utilizing CATNAP (Co-registration, Adjustment, and Tensor-solving, a Nicely Automated Program, version 1.3) software (Farrell et al. 2007). The set of gradient vectors was adjusted according to the rotation of the individual images.

Whole Brain White Matter Volume

As our network parameters are based on fiber tract volume, we also investigated group differences in white matter volume and the relation between white matter volume relative to total intracranial volume and FS-IQ. White matter volumes were obtained from a probabilistic tissue segmentation on the subjects’ T1-weighted images (Zhang et al. 2001).

Region Definition

The automatic anatomical labeling (AAL) atlas was used to define N = 90 cortical and subcortical regions (Tzourio-Mazoyer et al. 2002). The AAL volumes of interest (VOIs) were then transformed to DTI space of every individual, by first applying a nonlinear transformation between standard space and T1 space followed by an affine transformation from T1 space to DTI space (Ashburner and Friston 1999).

Tractography

Probabilistic tractography was performed in original DTI space according to previously described methods (Parker et al. 2005) using the CAMINO toolbox (Cook et al. 2006). The Probabilistic Index of Connectivity algorithm was used to apply the fiber tracking from the defined VOIs in the original space. This method models uncertainty, due to noise or crossing of fibers, in fiber orientation with probability density functions. This method is based on streamline tractography but incorporates Monte Carlo sampling methods to generate maps of connection probabilities from selected seed regions. Tracts were terminated when a curvature threshold of 60° over one voxel was encountered (Toosy et al. 2004). Tractography was performed in original DTI space.

For all subjects, an individual cerebral mask was created by applying the Brain Extraction Tool (Smith 2002) on the b = 0 diffusion image. This mask was used to limit the tractography to within the cerebrum. Only voxels on the boundary of the gray-white matter interface were used for initiating tractography. Using the T1 tissue segmentation, the gray-white matter boundary was defined by selecting voxels where the joint tissue probability (T) for gray and white matter was above a certain threshold (T > 0.2) (Vaessen et al. 2010). The results were transformed from the subjects’ T1-weighted image space to diffusion image space, using a rigid body transformation (Smith et al. 2004). One thousand tracts were initiated from each voxel, leading to an average of 23 million tracts per brain. Subsequently, for each pair of regions, the subset of tracts connecting these 2 regions were identified from the set of tracts of the whole brain tractography. As an additional noise filter, voxels that were traversed by fewer than 50 tracts were eliminated from the analysis. Exploratory analysis revealed that voxels with <50 tracts (i.e., <5% of the number of streamlines generated per seed voxel) were widespread throughout the brain and often did not seem to represent plausible anatomical connectivity and were therefore considered noise.

Network Construction

Structural connection strengths between 2 regions i and j were obtained by calculating the total volume of the voxels within the fiber tracts connecting those regions and scaling these by the total intracranial volume. This scaling is necessary because total brain volume is a confounder for measures based upon tract volume. Another plausible option would be to correct for the total volume traversed by the generated fiber tracts. However, an additional analysis revealed that these 2 measures are strongly correlated (Pearson’s r = 0.99), yielding nearly equal corrections. The connection matrix A was formed by calculating the structural connection strength between all pairs of brain regions. The matrix A is a numerical representation of a graph (G), which is an abstract data structure, consisting of nodes connected by edges. In the graph, a node is related to a brain region and represents a row or column in the connection matrix. An edge in the graph is a connection between brain areas i and j (Aij).
The total number of edges (K), regardless of weight, found in each individual subject was investigated for group differences and associations with FS-IQ. We also investigated all connections of the connectivity matrices for group differences in edge-weights (tract volume) and for associations with FS-IQ.

**Graph Theoretical Analysis**

Graph theoretical network analysis was used to investigate whether the brain structural network parameters differed between epilepsy patients and the healthy control group and for possible correlations with cognition and epilepsy parameters.

Critically, as the number of edges in a network is a strong confounder for subsequent network parameters, it is best to compare networks where the number of edges is kept constant over subjects (van Wijk et al. 2010). Moreover, with tractography the presence or absence of a fiber tract might be hard to interpret, especially when the presence varies from subject to subject. Therefore, we chose the following approach: only fiber tracts that were found in every subject were allowed as edges in the final connectivity matrices. As a result all individuals had exactly the same set of edges in their networks. The use of a fixed set of edges implies that any differences in network parameters between subjects are solely due to differences in edge weights as opposed to differences in binary connectivity patterns per se.

The graph theoretical parameters weighted "characteristic path length" (L) and weighted "cluster coefficient" (C) were calculated to perform analysis on the constructed volume weighted brain graphs. The weighted characteristic path length (Rubinov and Sporns 2010) is defined as the average of the shortest paths connecting any 2 nodes in the graph:

\[
L = \frac{1}{N(N-1)} \sum_{j \in G, i \in j} w_{ij}
\]

where \( w_{ij} \) is the sum of weights (i.e., tract volume) of the shortest weighted path between nodes \( i \) and \( j \). The characteristic path length is a measure of how well connected a network is. In an unweighted graph, a small characteristic path length indicates that, on average, any 2 nodes are connected through only a few edges. In the case of a volume-weighted network, a larger tract volume will decrease the distance (i.e., the connection strength) between 2 nodes, and thus, a short path length indicates that, on average, any 2 nodes are connected by one or several large fibers bundles. The weighted cluster coefficient (Onnela et al. 2005) is defined as:

\[
C = \frac{1}{N} \sum_{j \in m} \left( \frac{A_{ij}A_{jm}A_{mj}}{k_i(k_j-1)} \right)^{1/3}
\]

The (unweighted) cluster coefficient of a network is a measure of cliqueness, that is, sets of nodes that are highly interconnected. For a volume-weighted graph, the cluster coefficient is high when the direct neighbors of a node are also interconnected and have relatively large tract volumes.

Network parameters were calculated with routines from the brain connectivity toolbox (Rubinov and Sporns 2010). The entire processing pipeline is visualized in Figure 1.

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**Figure 1.** Image preprocessing scheme. (I) Anatomical regions from the AAL atlas together with whole brain tractography were used to construct fiber tracts connecting different regions. (II) Fibre tracts connecting region pairs are selected for all pairs of regions (example image for part of the cingulum left and right bundle). (III) The volume of a fibre tract is calculated from the number of voxels traversed (with a tract visitation count above the threshold value, see main text), in this example, a tract visitation threshold of 3 yield a volume of 13 (green squares). (IV) A connection matrix is formed for all subjects of which the elements represent the volume of connections. (V) Based on the connectivity matrices from all subjects, only connections detected in all subjects are considered for further analysis. (VI) The group connectivity matrix showing only connections detected in all subjects. (VII) The individual connectivity matrix from (VI) is thresholded with the group matrix from (V). (VIII) Last, weighted cluster coefficients and weighted path lengths are calculated for each subject.
The weighted graph metrics are in part dependent on the average weight of the connectivity matrix. Therefore, the mean matrix weight was tested for group differences and associations with FS-IQ, and the graph metrics were tested with and without adjustment for average matrix weight.

Statistics
Group differences in parameters were tested using a Student’s t test, associations between network parameters, connections, and other subject-related variables were tested with Pearson’s correlation coefficient and partial correlation coefficients.

Results

Whole Brain White Matter Volume
The FS-IQ of the impaired patient group (mean ± standard deviation, 85.2 ± 6.0) was significantly lower compared with the healthy control group (113.2 ± 15.0, \( P < 0.001 \)) and the nonimpaired patient group (97.6 ± 15.6, \( P < 0.05 \)). The nonimpaired patient group had significantly lower FS-IQ compared with the control group (\( P < 0.001 \)), see Table 1.

White matter volumes (as a fraction of total intracranial volume) did not differ significantly between the impaired patient group (0.47 ± 0.05 L), the healthy control (0.48 ± 0.06 L, \( P = 0.73 \)) and the nonimpaired patient group (0.46 ± 0.10 L, \( P = 0.78 \)). White matter volume was significantly correlated with IQ (\( r = -0.39, P = 0.02 \)) and L (\( r = 0.46, P < 0.005 \)). No association was found between whole brain white matter volume and FS-IQ (\( P = 0.85 \)) in the entire patient group (the nonimpaired plus the impaired patient group).

Number of Connections and Fiber Bundle Volume
We found a lower number of reconstructed fiber tracts for the impaired patient group compared with the healthy control group (\( P < 0.01 \)) and the nonimpaired patient group (\( P < 0.04 \)), see Figure 2A. The number of edges (K) was found to be positively correlated with FS-IQ in the patient group (\( r = 0.41, P < 0.009 \)).

Edges showing differences in volume between the different patient groups (at \( P < 0.05 \), uncorrected) were widespread throughout the brain as shown in Figure 3. Almost all tracts volumes were smaller for the patient groups. Critically, none of these differences remained significant after false discovery rate (FDR) (\( q = 0.05 \)) correction for multiple comparisons (Benjamini and Hochberg 1995). The correlation analysis of each fiber tract with FS-IQ in the entire patient group revealed a number of significant correlations (\( P < 0.001 \), uncorrected) of edges mainly in the left hemisphere, as shown in Figure 3D. These correlations were no longer significant after FDR (\( q = 0.05 \)) correction for multiple comparisons.

The mean matrix weight was slightly lower in the nonimpaired patient group (305 ± 53) relative to the healthy control group (322 ± 39, n.s.) and even further decreased for the impaired patient group (269 ± 42, \( P = 0.01 \)). Mean matrix weight was positively correlated with FS-IQ in the entire patient group (\( r = 0.39, P < 0.02 \)).

Network Analysis
The final networks consisted of 90 cortical and subcortical regions with 1224 edges per subject. The weighted cluster coefficient was significantly lower for the impaired patient group (0.0153 ± 0.0023) compared with the healthy control group (0.0182 ± 0.0032, \( P < 0.04 \)) and the nonimpaired group (0.0180 ± 0.0029, \( P < 0.02 \)), see Figure 2B. For the path length, the impaired patient group (69.7 ± 10.1) had significantly higher values compared with the healthy control group (60.9 ± 10.0, \( P < 0.05 \)) and the nonimpaired group (63.3 ± 9.6, \( P < 0.04 \)), see Figure 2C.

Correlation analyses between C, L, IQ, premorbid IQ, and IQ discrepancy were performed in the entire patient group, with and without correction for age and gender. Figure 4 shows an overview of the tested variables. Age was found to be predictive for both C and L. An increase in age was associated with a decrease in C (\( r = -0.40, P < 0.01 \)) and an increase in L (\( r = 0.33, P < 0.04 \)).

Weighted cluster coefficient C was positively associated with FS-IQ when corrected for age and gender (\( r = 0.58, P < 0.001 \)), this was also significant without corrections (\( r = 0.39, P < 0.016 \)). Path length was significantly and negatively associated with FS-IQ when corrected for age and gender (\( r = -0.57, P < 0.001 \)) and was also significant without corrections (\( r = -0.40, P < 0.011 \)). When also correcting for...
mean matrix weight in addition to age and gender, $C$ was still correlated with FS-IQ ($r = 0.40$, $P = 0.01$) as was $L$ ($r = -0.41$, $P = 0.01$).

The IQ discrepancy score was also found to be positively associated with $C$ ($r = 0.37$, $P < 0.03$) and a trend for negative association with $L$ ($r = -0.31$, $P < 0.07$) was found, while correcting for age and gender. A positive IQ discrepancy (no intellectual decline) was associated with a higher $C$.

In the healthy control group, neither FS-IQ nor IQ discrepancy was significantly correlated with $C$ and $L$.

Drug load was negatively associated with $C$ ($r = -0.34$, $P < 0.04$) and trend for a positive association with $L$ ($r = 0.30$, $P = 0.08$) was found. We also tested for an association between $C$ and $L$ and total number of partial seizures, total number of secondarily generalized seizures, and duration of epilepsy, although none of these associations were significant when controlling for age and gender. Table 2 and Figure 5 display the correlation results.

**Figure 3.** Analysis of individual tract volumes. (A) Group differences in tract volume between the healthy control group and the impaired patient group, (B) the nonimpaired patient group and the impaired patient group, and (C) the healthy control and nonimpaired group. Blue-colored lines relate to population average volume weighted structural network. Edge thickness relates to volume of the tract (thick line represents larger tract volume). Red and green edges indicate group differences as indicated in the sub panels. Dots denote the center locations of brain regions. (D) Correlation of FS-IQ with tract volume. Blue-colored lines as in (A). Green-colored lines are edges significantly correlated with FSIQ in the entire patient group ($P < 0.01$, uncorrected). Edge thickness relates to the strength of correlation.

**Discussion**

**Main Findings**

This study was performed to find abnormalities in white matter network organization in patients with cryptogenic localization-related epilepsy that may explain the associated cognitive decline in comparison to healthy controls. A number of novel observations were obtained regarding the axonal organization of white matter in relation to cognitive impairment in chronic epilepsy. First, epilepsy patients with cognitive impairment displayed less efficient white matter network properties in the form of a lower weighted clustering and a higher weighted path length compared with healthy controls. No differences in whole brain white matter volumes were noticed. Second, in the entire patient group, a decreased weighted cluster coefficient and increased weighted path length were strongly correlated with lower FS-IQ and stronger
IQ discrepancy. Controlling for age and gender did not affect this observation. Third, whole brain white matter in itself was not correlated with FS-IQ or IQ discrepancy, although significant correlations between total white matter volume and network parameters were found.

White Matter Correlates of Cognitive Impairment

The weighted clustering coefficient and weighted path length were significantly different in the cognitively impaired patient group compared with both the unimpaired patient and healthy control group. A lower weighted clustering indicates that local brain regions are mutually weaker interconnected and a higher weighted path length refers to a less globally connected brain in the sense that more distal brain regions are less efficiently connected. As the clustering was lower and the path length was higher for cognitively impaired patients, the networks can be interpreted as less efficiently organized. The observation that the white matter organization rather than the white matter volume appears to be disrupted is a novel finding in epilepsy. The origin of this finding remains unknown, although different mechanisms could lead to less efficient networks, for instance subtle alterations in tract volumes due to atrophy and neuronal degeneration (Kodama et al. 2003; BeirIEWSKI et al. 2005) or compensatory mechanisms (SCHLAUG et al. 2009). Additionally, patients with cryptogenic localization-related epilepsies might have a diffuse underlying pathology such as cortical dysplasia type I or microdysgenesis (SISODIYA 2004). Although undetected at 3 T, these are real anatomical disorders and could also explain the poor connectivity and intellectual impairment as much as the epilepsy itself.

Previously, macrostructural abnormalities in gray and white matter volumes were reported in epilepsy (SEIDENBERG et al. 2005). For instance, HERMANN et al. (2010) reports abnormal white matter development in children with new onset epilepsy and Focke, THOMPSON et al. (2008) showed that gray matter volume was associated with cognitive scores in TLE patients with hippocampal sclerosis, although these changes did not reside in narrowly circumscribed brain regions. Local “macrostructural” WM lesions have been shown not to be associated with cognitive impairment in chronic epilepsy (Jansen et al. 2008). Microstructural white matter abnormalities have also been found (FOCKE, YOGARAJAH et al. 2008; MENG et al. 2010). Additionally, diffusion indices were found to be correlated with various cognitive scores (RILEY et al. 2010). The above mentioned studies were focused on finding regions in which indices of local white matter fiber integrity were abnormal. However, they have not investigated axonal connectivity per se. In POWELL et al. (2007) and YOGARAJAH et al. (2008), tractography was used to study axonal connectivity more directly. Tract volume and tract FA were used to study specific temporal and frontal lobe white matter tracts. Their results showed reduced volume and FA in the ipsilateral hemisphere (mainly in the left TLE compared with the control group), while an increase was seen in the contralateral hemisphere. In addition, YOGARAJAH et al. (2008) found an association between these white matter alterations and decreased memory scores. Both studies provide evidence for reorganization of white matter connections in TLE and support our findings that white matter connectivity alterations might underlie cognitive impairments in patients with cryptogenic localization-related epilepsy. However, our study provides a more complete picture of white matter disruption, as altered whole brain network properties were observed as opposed to disruptions in a predefined set of connections.

Cerebral network properties have previously been studied in healthy subjects with fiber tractography (HAGMANN et al. 2008; GONG et al. 2009) of which the properties have been linked to gender and brain size (YAN et al. 2010), age and development (HAGMANN et al. 2010), and intelligence (LI et al. 2009). Our finding that age, gender, and brain size are related to structural network properties is in agreement with these
studies. Furthermore, our results concur with those of Li et al. (2009), who also found a negative correlation between FS-IQ and path length. Li et al. (2009) also found a positive correlation between $C$ and FS-IQ, although this was not significant. These results support the notion that network efficiency and cognitive performance are related (Bosma et al. 2009; Li et al. 2009; van den Heuvel et al. 2009) and could imply that in vivo measurements of brain network efficiency provide a more sensitive marker for cognitive decline at an early stage.

**Clinical Perspective**

For future cognitive prognosis of patients with epilepsy, it would be clinically relevant to know whether patients are prone to developing cognitive impairment. The presented method of DTI combined with graph theoretical network analysis has the potential to discern patients with increased vulnerability for cognitive impairment on the basis of inefficient network parameters (i.e., low clustering and/or high path length). The high reproducibility (Vaessen et al. 2010; Bassett et al. 2011) of the imaging technique in combination with the calculated network parameters could make this imaging method a promising adjunctive tool in the clinical diagnosis of cognitive comorbidity in epilepsy and may influence clinical therapeutic decision making. DTI does not require any cognitive task performance during scanning and is therefore more applicable in patients with severe cognitive problems.

**Methodological Considerations**

We used a DTI acquisition with 15 gradient directions at $b = 800 \text{s/mm}^2$. An important question is whether a different acquisition scheme with higher angular resolution and different $b$-values (Hagmann et al. 2010) will influence the results. Recent studies on the effects of different acquisition schemes on graph metrics (Vaessen et al. 2010; Zalesky et al. 2011) revealed that the effect of angular resolution and $b$-value was small, in healthy volunteers. We expect therefore no strong effects in our study population without macroscopic lesions, but future studies might address the issue of how various DWI acquisition schemes influence group differences and effects in a clinical population.

The main emphasis of this study was on connectivity of the cerebral cortex through the white matter. This requires the tracking algorithm to reach parts of the brain close to the gray matter. Therefore, we used probabilistic fiber tracking in combination with a liberal curvature threshold of 60° (calculated over the length of a voxel).

The AAL template defines regions with a variety of different sizes, which may bias certain nodal measurements such as node degree. An additional analysis was performed to check whether correcting connection weights for region size would alter the

![Figure 5. Correlation plots. (A) Plot showing correlation between full IQ (FS-IQ) and weighted clustering coefficient ($C$), for the patient group (black dots, solid regression line), and healthy controls (open dots, dashed regression line). (B) $C$ versus IQ discrepancy. (C) Path length ($L$) versus FS-IQ. (D) $L$ versus IQ discrepancy.](image-url)
results. As expected, correction for region size did not have a large effect (see Supplementary Data).

An overall lower number of fiber tracts was found in the impaired patient group compared with the healthy control and unimpaired patient group. These results cannot be interpreted unambiguously as the current state of technology does not allow to infer whether a missing fiber tract is actually anatomic nonexisting or could not be reconstructed as a result of algorithm or data features. Furthermore, the number of edges in a network is a strong confounder for subsequent network parameters (van Wijk et al. 2010). Therefore, a network was constructed with edges that could be reliably found within every subject. It is likely that relevant pathological information exist in the edges removed from the final network analysis since the number of edges was lower in the cognitively impaired patient group compared with the unimpaired and healthy control group, and this number was associated with FS-IQ in the whole patient group. That, even after such stringent data filtering, we can still observe strong and significant differences in network parameters, shows the robustness of the current approach.

Tract volume was used to weight the edges in the calculation of the connection matrix and consequently the network measures C and L. Other indices of tract integrity, such as fractional anisotropy, mean diffusivity, level of myelination, and the number of reconstructed fibers have previously been applied (Gong et al. 2009; Li et al. 2009; Hagmann et al. 2010; van den Heuvel et al. 2010). Currently, no consensus prevails which weighting method describes best the fiber tract integrity or is most sensitive to pathological effects. To test the robustness of our results, we also constructed network weighted by fractional anisotropy (FA) and mean diffusivity (MD) values. The results of those networks were comparable with those of the presented volume networks (see Supplementary Data).

The statistical tests with graph metrics were not corrected for multiple comparisons, as our 2 main study objectives were to investigate whether graph metrics would differ between the studied groups and would show a correlation with cognitive scores. Other analyses (such as a relation between graph metrics and epilepsy-related variables) were of a more explanatory nature. Future studies with a larger number of subjects and more specific hypothesis might benefit from a proper multiple comparisons correction that needs to be tailored specifically to network data (Zalesky, Fornito, and Bullmore 2010).

Conclusions

The application of graph theoretical analysis on whole brain diffusion tensor imaging data enabled the detection of loss of axonal network organization in the white matter in cognitively impaired patients with cryptogenic localization-related epilepsy. Here, deviations in network organization appear to be sensitive to cognitive decline even in patients without MRI-visible lesions. More specifically, it is not the total volume of the white matter that has changed, but the network organization of the white matter, in terms of relative volume contributions of multiple white matter fiber bundles, that is affected in cognitively impaired patients with epilepsy.

Supplementary Material

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/

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