Loss of network efficiency associated with cognitive decline in chronic epilepsy

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ABSTRACT

Objective: To study the relation between possibly altered whole brain topology and intellectual decline in chronic epilepsy, a combined study of neurocognitive assessment and graph theoretical network analysis of fMRI was performed.

Methods: Forty-one adult patients with cryptogenic localization-related epilepsy and 23 healthy controls underwent an intelligence test and fMRI with a silent-word generation paradigm. A set of undirected graphs was constructed by cross-correlating the signal time series of 893 cortical and subcortical regions. Possible changes in cerebral network efficiency were assessed by performing graph theoretical network analysis.

Results: Healthy subjects displayed efficient small world properties, characterized by high clustering and short path lengths. On the contrary, in patients with epilepsy a disruption of both local segregation and global integration was found. An association of more pronounced intellectual decline with more disturbed local segregation was observed in the patient group. The effect of antiepileptic drug use on cognitive decline was mediated by decreased clustering.

Conclusions: These findings support the hypothesis that chronic localization-related epilepsy causes cognitive deficits by inducing global cerebral network changes instead of a localized disruption only. Whether this is the result of epilepsy per se or the use of antiepileptic drugs remains to be elucidated. For application in clinical practice, future studies should address the relevance of altered cerebral network topology in prediction of cognitive deficits and monitoring of therapeutic interventions. Neurology® 2011;77:938–944

GLOSSARY

AED = antiepileptic drug; FSIQ = full-scale IQ; MTS = mesiotemporal sclerosis; TE = echo time; TR = repetition time; WAIS = Wechsler Adult Intelligence Scale.

In chronic epilepsy, patients often experience cognitive problems1 extending from memory deficits2 to language problems3 and intellectual impairment.4 Clinical factors such as antiepileptic drugs (AED)5 and high seizure frequency6 cannot always predict the individual cognitive course.

To understand the neurobiological mechanisms of cognitive dysfunction in localization-related epilepsy, fMRI research has focused on changes in activation patterns. Most fMRI studies report an association of cognitive dysfunction with either decreased activation7–9 or a shift of activation.10–12

The focus of fMRI research in epilepsy and cognition has changed to analyzing dysfunctional networks. Most studies measure functional connectivity by correlating signal time courses of different cerebral regions.13 Typically, higher functional connectivity is associated with better cognitive performance.14–16

With conventional functional connectivity methods applying a priori selection of specific networks, unexpected abnormalities outside these networks can remain undetected. With
graph theoretical analysis the organization of the whole brain network can be investigated (for a review, see reference17). A distinction can be made between a “small-world” and a random topology. Most studies18 demonstrate that brain networks are organized as small-world networks which are more efficient than random networks.19

We aimed to investigate the changes in functional networks using graph theoretical network analysis in patients with epilepsy in relation to intellectual performance and possible decline. We hypothesize that 1) patients will have lower intellectual performance; 2) patients will have a less efficient organized network than healthy controls; and 3) network abnormalities will be more pronounced in those patients with lowest IQ and distinct intellectual decline.

METHODS Participants. Inclusion criteria for the patients were localization-related epilepsy with an epileptic focus in the frontal or temporal lobe, absence of structural cerebral lesions other than mesiotemporal sclerosis (MTS), no history of status epilepticus, and no other disease that could cause cognitive decline. The final study population included 41 patients (21 women; mean age 40 years; range 22–63) and 23 healthy controls (14 women; mean age 40 years; range 18–58). See table e-1 on the Neurology® Web site at www.neurology.org for an overview of the clinical characteristics of the patients and healthy controls.

Standard protocol approvals, registrations, and patient consents. This study was approved by the Institutional Review Board of the Maastricht University Medical Center. All subjects gave written informed consent.

Neuropsychological testing. For intelligence, the Wechsler Adult Intelligence Scale (WAIS-III) was used.20 An estimate of premorbid intelligence levels was made according to the formula proposed by Schoenberg et al.21 Intelligence discrepancy scores were calculated by subtracting premorbid full-scale IQ (FSIQ) estimates from actual FSIQ, resulting in IQ discrepancy scores (see appendix e-1 for details).

MRI protocol. All subjects underwent a clinical epilepsy protocol on a 3.0-T unit with an 8-channel head coil. fMRI data were acquired using echoplanar imaging pulse sequence (repetition time [TR] = 2 s, echo time [TE] = 5 msec, flip angle = 90°, voxel size 2 × 2 × 4 mm) and 196 volumes per acquisition. For anatomic reference, a T1-weighted 3-dimensional fast gradient echo was acquired (TR = 9.91 msec, TE = 4.6 msec, inversion time = 3 s, flip angle = 8°, voxel size 1 × 1 × 1 mm).

fMRI activation paradigm. In the word generation paradigm, subjects had to covertly generate as many words as possible starting with a visually presented letter (U-N-K-A-E-P). The paradigm consisted of 6 word-generation condition blocks (1 letter per 30-s block) alternated with baseline rest condition blocks (30 s). Afterwards, all subjects were able to sufficiently reproduce words generated during the task.

Image analysis. Image preprocessing. Analysis of the time-series data were performed in the Statistical Parametric Mapping (SPM2) software application (Wellcome Department of Cognitive Neurology, UK). Dynamic images were slice-time and realigned to correct for head movement. The corrected images were transformed into standard MNI space and spatially smoothed (6-mm kernel).

Whole brain network construction. The preprocessed and normalized fMRI images were parcellated into a high-resolution network consisting of n = 893 cortical and subcortical brain regions (see appendix e-2 for details on the parcellation scheme). Characteristic time series were calculated by averaging the signal intensities from all voxels in a region. To reduce the effect of physiologic noise and movement-related noise,22 the time series were filtered by applying standard linear regression with the movement parameters as a covariate and by applying a bandpass filter (0.01–0.1 Hz).

Network parameters. Graph theoretical parameters were used to evaluate the functional networks.17,23,24 A connection matrix was formed by calculating Pearson correlation coefficients between all pairs of brain regions. In the brain graph, a node is related to a brain region, an edge is a connection between 2 brain regions.

The brain graph of each individual was thresholded to create graphs with an equal number of nodes and edges across subjects.23 This was achieved by selecting the Tg connections with the highest correlation coefficient and removing all other connections. The threshold value Tg was expressed as a sparsity value relating the number of edges maintained in the network to the total number of edges possible (N2 – N).26 Let Tg be the number of edges maintained in the network, then the sparsity is defined as follows:

\[ \text{sparsity} = \frac{N^2 - N - T_g}{(N^2 - N)} \]

As there is no theoretical criterion for which sparsity value is the most biologically meaningful, here we explored network parameters over a range of sparsity values. To guarantee high correlation coefficients of the remaining connections, the sparsity range was chosen to be higher than 0.87, which yielded an average correlation coefficient of 0.66.

The graph theoretical metrics characteristic path length (L) and cluster coefficient (C) as well as local and global efficiency were calculated to perform analysis on the constructed brain graphs. The characteristic path length is a measure of how well-connected a network is. The cluster coefficient of a network is a measure of how many local clusters exist in the network. Parameters related to characteristic path length are global efficiency (Eglobal) and local efficiency (Elocal). Eglobal is defined as the average inverse shortest path length; Elocal is defined as the mean of the global efficiencies of subgraphs consisting of the immediate neighbors of a particular node.26 To be able to determine whether a network has small-world properties, the values of L and C must be scaled to values from generated random networks.24 Small-world networks are characterized by having L close to random: \( L = L_{\text{random}} \approx 1 \), but with C higher than random: \( C = C_{\text{random}} > 1 \). See appendix e-2 for a more elaborate description of these metrics.

Statistical analysis. Group differences of graph theoretical network parameters were assessed with the Student t test. The associations between clinical variables (age, age at onset, and drug load), cognitive variables (FS-IQ and IQ discrepancy), and network parameters were analyzed using Pearson correlation co-

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The relation between clinical seizure variables and graph theoretical parameters with intellectual decline was examined using a mediator–model approach. With this model, it is investigated whether network parameters mediate the relation between clinical and cognitive characteristics. Analyses were performed with graph theoretical network parameters and drug load (the clinical variable with the strongest link to cognition in this dataset) as independent and intellectual decline as the dependent variable. If the relation between drug load and intellectual decline becomes nonsignificant when network parameters are entered in the model, this parameter can be considered a mediator of the relation between drug load and intellectual decline.

RESULTS Neuropsychological assessment. Patients had lower FSIQ than controls (96 ± 15 vs 113 ± 15, p < 0.01). In the patient group, IQ discrepancy scores were significantly lower than in the controls, indicating intellectual decline in the patient group as a whole (mean ± SD IQ discrepancy score −8.6 ± 6.5 in patients vs −3.6 ± 8.8 in controls, p = 0.02). For the individual patients, 7 had lower IQ discrepancy scores than the minimum score in the control group; they had evident intellectual decline (impaired group).

fMRI results. Activation map results. Activation maps of the word-generation paradigm revealed significantly activated clusters in the left inferior and left middle frontal cortex (Broca region), the right middle frontal cortex, and the anterior cingulate cortex for both groups. No significant differences were found between controls and patients with epilepsy (see reference for details).

fMRI graph theoretical network parameters. Both patient and control networks showed a topology in the small-world regimen with values for λ close to 1 and values for γ higher than 1. Patients displayed significantly lower values (p < 0.05) for γ, E_global, and E_local over almost the entire sparsity range (figure 1). A trend toward higher λ values was observed in the patient group, which was significantly higher for high sparsity values (0.96–0.97). For C, patients also had lower values for the highest sparsity values. The network parameters of the impaired group revealed significant lower values for C over a broader sparsity range as compared with unimpaired patients and controls. Impaired patients displayed significantly higher values than controls for L (sparsity = 0.94–0.95) and λ (sparsity = 0.94–0.96) (figure e-1).
Summarizing, all the encountered differences point toward a disruption of network integrity characterized by a more random network topology in the patient group.

Regional analysis of network parameters. Additional analysis was carried out to investigate whether the majority of identified network abnormalities are localized in certain brain regions or networks. Results are only shown for $\gamma$, since $\gamma$ was the network parameter with the most pronounced difference between patients and controls. As can be observed from figure 2, a number of regions did show significant differences ($p < 0.005$). However, these regions were evenly distributed throughout the whole brain, without evident grouping within a specific lobe or recognizable network. When controls were compared to the impaired patients only, similar results were obtained. No associations of side of seizure focus with distribution of affected regions were observed.

fMRI graph theoretical network parameters in correlation with neuropsychological parameters. The cluster coefficient was found to be positively associated with FSIQ over a range of sparsity values (0.87–0.97). This same effect was seen for the association between $C$ and IQ discrepancy (sparsity = 0.93–0.98). Hence, a decreased amount of clustering in the activated patient brain indicates a reduced IQ, and a decreased clustering relates to a more pronounced intellectual decline. For the other network parameters, no correlation with FSIQ and IQ discrepancy was found. In the control group, there was no association between any network parameter and FSIQ.

Correlation of fMRI graph theoretical network parameters with clinical factors. From the clinical factors available, drug load was negatively associated with $C$, $\gamma$, and $E_{\text{local}}$, indicating a more random and less efficient network with higher drug load (for $C$: $p < 0.03$ for sparsity range 0.97–0.99; for $\gamma$: $p$ values range from 0.03 to 0.06 in the entire sparsity range; for $E_{\text{local}}$: $p < 0.05$ for sparsity range 0.87–0.93). For the other clinical characteristics, age and age at onset, no significant associations were found.

Model for the relation between clinical characteristics, network parameters, and intellectual decline. The relation of clinical epilepsy variables and graph theoretical network parameters to intellectual decline was examined using the mediator analysis. Since drug load had the strongest correlation with intellectual decline ($p = 0.03$), this factor was entered in the mediator analysis. The other clinical characteristics did not meet the criteria to be entered in a mediator analysis. Drug load was no longer a significant predictor of intellectual decline when the clustering coefficient $C$ was included in the model (figure e-2). On the contrary, $C$ was the mediating factor between drug load and intellectual decline, indicating that abnormalities in graph theoretical network parameters, particularly the clustering coefficient $C$, mediated the impact of drug load on cognition (sparsity = 0.96–0.98).

DISCUSSION In the present study, fMRI time series data from a language paradigm were used to evaluate functional brain networks in patients with chronic epilepsy and healthy controls. Graph theoretical network parameters were compared between patients and controls and compared with cognitive performance. First, the patients with epilepsy displayed disturbed network parameters, such as a lower normalized clustering coefficient ($\gamma$), and lower local and global efficiencies. Second, for the subgroup of
patients with most pronounced cognitive decline, lower absolute clustering coefficient and higher absolute and normalized path length were observed. Third, cognitive status (IQ) and the degree of intellectual decline (IQ discrepancy score) were correlated with graph theoretical network parameters, which revealed that poorer cognitive status and more pronounced intellectual decline were associated with lower absolute clustering coefficients. Fourth, as expected, the topologic parameters were consistent with a small-world organization of the cerebral networks in the control group.

Lower clustering coefficients and an increased path length have been demonstrated in neuropsychiatric disorders such as AD and schizophrenia. These disorders are accompanied by pronounced cognitive deficits, although graph theoretical network parameters have not previously been linked directly with cognitive measures.

Previously, in patients with bilateral mesial temporal lobe epilepsy, whole-brain graph network analysis with fMRI demonstrated lower absolute and normalized path lengths together with a decrease in absolute clustering coefficients. This was interpreted as a disruption of the whole brain network with a more random topology. The apparent contradictory results concerning path length are difficult to explain due to differences in study population and methodology. For example, patients in the latter study were on average much younger, which might have influenced the results. One might hypothesize that brain networks of younger patients respond differently to disease. For instance, young patients might be able to compensate better by acquiring alternate brain regions for cognitive processing, while older patients might have lost this ability. This could lead to a different expression of network parameters between control and patient groups in different age categories.

Cognitive functioning depends on several cerebral networks instead of isolated brain regions. It is reasonable to assume that in patients with epilepsy a disruption of whole brain networks is involved in the development of cognitive deficits, instead of a localized disruption at the site of seizure focus only. This is supported by magnetic resonance studies demonstrating volumetric loss, microstructural white matter abnormalities, cortical thinning, and functional abnormalities outside the epileptic focus. The application of methods sensitive to overlapping localized abnormalities seems to be limited in patient populations with heterogeneous seizure foci and cognitive deficits over multiple domains. Graph theoretical network analysis allows for analysis of whole brain networks rather than at a local level. Hence, it might be better capable of detecting patient-specific abnormalities in functional brain organization and reorganization than more conventional (single connection) analysis methods. Indeed, the disruption of small-world characteristics in our patient group could not be localized within one or more specialized brain regions, which could represent diffuse disruptions throughout the whole brain. No global technical differences between patients and controls, such as the motion correction parameters, could be identified in this study. The possibility that differences in the location of epileptogenic zone or the use of antiepileptic drugs contribute to the nonlocalized abnormalities cannot be ruled out. Furthermore, the silent word-generation task does not allow for objective assessment of task performance. Theoretically, differences in task performance could affect the network parameters. Nevertheless, based on post-task performance assessment and careful inspection of individual activation maps it is unlikely that salient differences in task performance have influenced the fMRI data.

In normal brain networks, high clustering coefficients (C and y) and local efficiency (Elocal) are parameters which reflect a high local specialization (segregation) of information processing. Contrarily, low path length (L and ) and high global efficiency (Eglobal) express a great ability to integrate information from the whole brain. Optimal brain networks possess both features with a balanced segregation and integration of information processing. In contrast, a decrease in clustering coefficient with a decrease in IQ, as found in the patient population, is characteristic for more random networks and can be interpreted as a loss in network organization.

In healthy controls, graph theoretical network parameters are related with level of intelligence, supporting the theory that cognitive processes depend on an optimal organization of segregation and integration. To our knowledge, this relation has not been investigated before in patients with epilepsy, who are prone to have a range of cognitive deficits. It is an interesting observation that network topology changes in the presence of epilepsy, and that this alteration is associated with a decline in intelligence.

Of the clinical factors studied, only drug load was associated with network parameters. AEDs inhibit the spread of abnormal neuronal firing to distant sites, thereby suppressing the occurrence of clinical seizures. As AEDs might also have a more generalized suppressive effect, an alteration of neuroexcitability may affect local and global efficiency parameters such as found in the present study. There is too much overlap in AEDs used (table e-1) to pro-
vide any information on the effect of specific AEDs on network topologic parameters, which would be of high interest for future studies. In an epilepsy population, it is complicated to disentangle the effects of AED use and epilepsy per se on network parameters. It would therefore be interesting to investigate whether AED use in other patient populations than those with epilepsy (e.g., in patients with migraine or neuropathic pain) is also associated with change of network parameters.

Although no other clinical factor could be identified to influence the network characteristics, this does not imply that no relation exists. For example, decreased local clustering and small-worldness within the epileptogenic temporal lobe has been associated with longer duration of temporal lobe epilepsy.16 Moreover, clinical epilepsy factors cannot be viewed as totally independent factors. For example, drug load is likely to increase when patients do not achieve seizure control. In that case, higher drug load can be a marker for a more severe form of epilepsy. Maybe it is not the seizures as such that disturb the cerebral networks, but simply the epilepsy itself. This could imply that there is a shared mechanism leading to both epilepsy and a disruption of cerebral networks that is associated with cognitive decline.

Network parameters may obtain a role in identifying patients at risk for developing cognitive problems. If clinical factors can be identified, this can be beneficial in decision-making: for example, patients with advantageous network organization may need less stringent seizure control than patients with disadvantageous network organization. Additionally, network topology might be a more sensitive marker for disease progression: if network parameters change before intellectual decline can be measured (normally clinically relevant decline can be observed only after intervals of several years), this may also call for more strict treatment of seizures, or earlier referral for epilepsy surgery. Finally, network topologic characteristics might be of value in predicting cognitive outcome after epilepsy surgery.

AUTHOR CONTRIBUTIONS

Dr. Vlooswijk: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, statistical analysis.
M.J. Vaessen: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, statistical analysis.
Dr. de Krom: drafting/revising the manuscript, study concept or design, acquisition of data, study supervision, obtaining funding.
Dr. Hofman: drafting/revising the manuscript, study concept or design. Prof. Aldenkamp: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, contribution of vital reagents/tools/patients, statistical analysis, study supervision, obtaining funding.
Dr. Backes: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, contribution of vital reagents/tools/patients, acquisition of data, statistical analysis, study supervision, obtaining funding.

ACKNOWLEDGMENT

The authors thank Leonie Diepman and colleagues for neuropsychological assessments.

DISCLOSURE

Dr. Vlooswijk, M.J. Vaessen, Dr. Jansen, Dr. Majoe, Dr. Hofman, and Dr. de Krom report no disclosures. Prof. Aldenkamp served as Editor-in-Chief of Seizure and serves on the editorial boards of Epilepsy & Behavior, Acta Neurologica Scandinavica, and Clinical Neurology & Neurosurgery. Dr. Backes reports no disclosures.

REFERENCES


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