Loss of functional network efficiency is associated with cognitive decline in cryptogenic epilepsy

M. Vaessen[1,2], M. Vlooswijk[2,3], J. Jansen[1,2], M. de Krom[3], M. Majoie[3,4], P. Hofman[1,2], A. Aldenkamp[3,4], and W. Backes[1,2]
[1]Radiology, Maastricht University Medical Centre, Maastricht, Netherlands, [2]School for Mental Health and Neurosciences, Maastricht University, Maastricht, Netherlands, [3]Neurology, Maastricht University Medical Centre, Maastricht, Netherlands, [4]Epilepsy Centre Kempenhaeghe, Heeze, Netherlands

Introduction

The nature of cognitive difficulties in chronic epilepsy ranges from circumscribed memory deficits to global intellectual decline [1]. With functional MRI (fMRI), abnormal activation patterns and dysfunctional cerebral networks have been linked to cognitive deficits. Previous investigations have focused on predefined cerebral networks, especially the language and default mode network. With graph theoretical network analysis, the topology of the whole cerebral network can be investigated [2]. It can then be calculated how the network is organized, and whether network organization is related to cognitive performance. To study the relation between possibly altered whole brain topology and intellectual decline in chronic epilepsy, a combined study of neurocognitive assessment and functional connectivity MRI with graph theoretical network analysis was performed.

Methods

Subjects: Forty-one adult patients with cryptogenic localization-related epilepsy and 23 healthy controls underwent an IQ test and fMRI with a silent word generation paradigm. IQ discrepancy scores were determined from a pre-morbid IQ estimate [3]. **MRI:** fMRI was acquired with an EPI sequence (TR=2s,TE=5ms, FA=90°, voxel size 2x2x4mm, 196 volumes). For anatomic reference a 3D T1 scan was made (TR=9.91ms, TE=4.6ms, TI=3s, FA=8°, voxel size 1x1x1 mm). Functional images were put through a standard SPM preprocessing pipeline (slice-time correction, movement corrections, normalization to MNI and smoothing). The pre-processed fMRI images were parcellated into N=893 cortical and sub-cortical regions, these fine grained regions were constructed by sub-dividing larger regions from the AAL atlas [4]. Next, mean time-series from all regions were bandpass filtered (0.01-0.1 Hz) and de-correlated for movement parameters. The filtered time series were cross-correlated to construct a connection matrix. **Functional connectivity:** The connectivity matrices were thresholded such that each had exactly T_k non-zero connections. T_k was varied over a range of sparsity values (sparsity=$(N^2\text{-}N\text{-}T_k)/(N^2\text{-}N)$), see Fig. 1. Network parameters normalized mean path length (λ, a measure of brain integration), normalized cluster coefficient (γ, a measure of brain segregation), local efficiency (E_l) and global efficiency (E_g) were computed from the connectivity matrices. These parameters were compared between the control and patient group (Student's t-test) and Pearson's correlation coefficient was used to study the relation between network parameters and IQ scores. Group localized abnormalities were investigated by comparing region-wise γ (normalized clustering for one region as opposed to mean clustering of the whole brain) between the control and patient group.

Results

Both patient and control networks showed a topology in the small-world regime 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 (Fig. 1). The cluster coefficient was found to be positively associated with FSIQ and IQ discrepancy over a range of sparsity values (sparsity=0.87-0.97). Several brain regions showed lower γ, however these were not significantly different after Bonferonni correction for multiple comparisons (Fig. 2).

Discussion & Conclusion

High clustering coefficients and local efficiency are parameters which reflect a high local specialization (also called segregation) of information processing, while low path length and high global efficiency express a great ability to integrate information from the whole brain. Healthy brain networks possess both features with a balanced segregation and integration of information processing. A decrease in global, local efficiency and clustering and an increase in path length is characteristic for more random networks; which can be interpreted to represent a less organized network organization. Additionally, a decrease in the clustering coefficient with a decrease in IQ and IQ discrepancy, as found in the patient population, indicates a relation between cognitive co-morbidity and altered functional network organization in epilepsy. These findings support the hypothesis that chronic localization-related epilepsy is associated with cognitive deficits by global cerebral network changes instead of a localized disruption only.

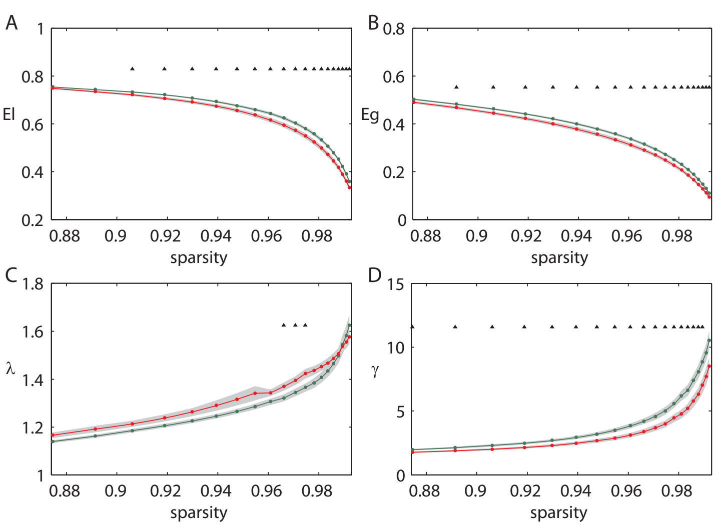

Fig.1: Network parameters for the whole brain networks of the patient group (red lines) and the control group (green lines) as function of sparsity. Black triangles indicate for which sparsity values the groups differed significantly, demonstrating consistently lower values for E_g, E_l and γ and higher values for λ in the patient group. Grey areas indicate standard error of the mean. (A) Global efficiency, (B) local efficiency, (C) normalized path length, and (D) normalized cluster coefficient.

References:
[1] Helmstaedter C, Curr Opin Neurol, 2001; [2] Bullmore, E. & Sporns, O. Nature Reviews Neuroscience 2009. [3] Schoenberg, Clin Neuropsychol, 2002. [4] Tzourio-Mazoyer, Neuroimage, 2002.

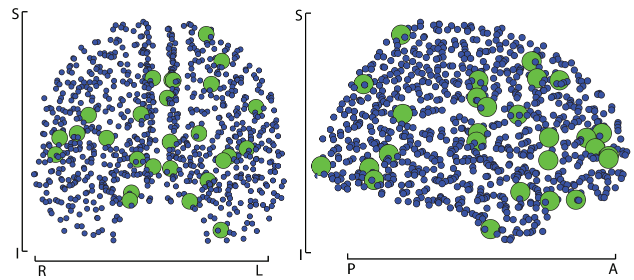

Fig.2: 3D projection of the network nodes. Green circles indicate where the nodal values of γ were significantly lower in the patient group ($p<0.005$ uncorrected). The affected nodes are distributed throughout the whole brain, not restricted to specific lobes or known functional networks. S = superior; I = inferior; L = left; R = right; A = anterior; P = posterior.