Impaired structural connectivity of language and memory networks in patients with chronic epilepsy

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Introduction

Cognitive language and memory problems are common co-morbidities in patients with chronic epilepsy, though often underestimated [1]. Previously, it was shown that patients with cryptogenic localization-related epilepsy display difficulties in language functions [2, 3], which relate to loss of functional connectivity in the language networks. Here we investigated whether structural networks were impaired in these patients using small world network analysis and fiber tractography of the whole cerebrum [4] and whether specific structural connections between regions mediating memory and language functions might be responsible for the cognitive decline.

Materials & Methods

Subjects 29 patients (age 40±12 y, mean ± SD) with cryptogenic (i.e. no MRI visible lesions at 3 T) localization-related (fronto)-temporal and frontal lobe epilepsy and 17 age-matched healthy controls (age 40±13 y) were included. All subjects underwent extensive neuropsychological testing, including tests for intelligence (WAIS-III). ***MRI*** DTI experiments were conducted in all subjects on a 3.0 Tesla MRI system. DTI acquisition parameters: voxel size 2×2×2 mm, TE 62 ms, TR 6600 ms, and parallel imaging acceleration factor 2. Images were obtained along 15 non-collinear diffusion directions with a b-value of 800 s/mm^2 and one b = 0 s/mm^2.

Small world connectivity Whole brain connectivity data was obtained by fiber tracking from an anatomical atlas containing the Brodmann areas, using probabilistic tractography (PICo [5]). A binary connection matrix was obtained from the tractography data and small world metrics average node degree (K), characteristic path length (L), and cluster coefficient (C) were computed. These parameters give a characterization of the global topology of the brain network.

Language and memory network Regions of interest (ROI) were manually drawn (*Fig.2a*) and based on regions of significant activation from several fMRI experiments related to language and memory function in the same subjects [2]. Ten regions of interest were defined: middle frontal gyrus (MFG), inferior frontal gyrus (IFG), the anterior cingulate cortex (ACC), middle temporal gyrus (MTG), posterior cingulate cortex (PCC) and hippocampus (HC). Connections between different brain areas were reconstructed from the DTI data using streamline tractography as implemented in the MRtrix software package (http://www.nitrc.org/projects/mrtrix/). Seed points for tractography were randomly placed within each ROI, the number of seeds was defined as 10 times the number of voxels in the ROI. The percentage of fibers connecting each pair of ROIs was calculated to represent the connection strength.

Statistics Using a Student's t-test the connectivity results were compared between patients and controls. The Pearson correlation coefficients were calculated for the association between connectivity values and IQ scores.

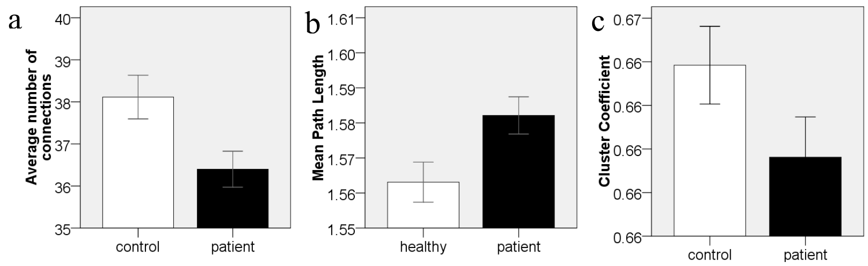

Fig. 1.(a)*Average number of connections per brain region (node degree, K) to all other regions is reduced in the patient group (p<0.02),(b) this effect is also visible through increased path length and (c) a decreased cluster coefficient. This indicates an overall loss of micro-structural neuronal network integrity.*

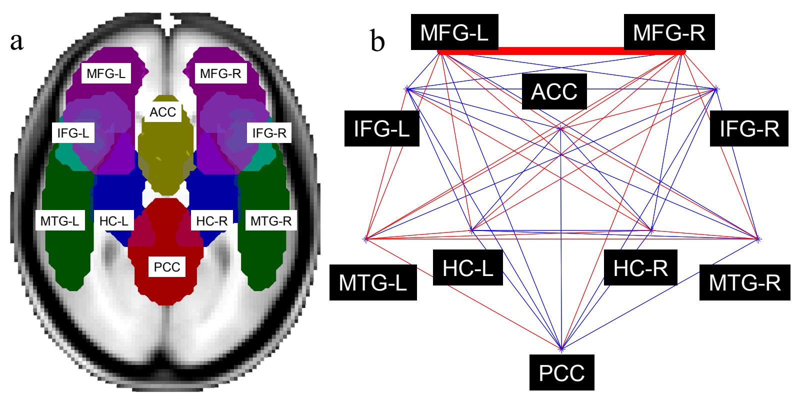

Fig. 2: *(a) Connection diagram showing an axial projection of the 3D positions of the 10 ROIs overlaid on a T1w image, diagram top is anterior. (b) Differences in mean connectivity values between the patient and control group are displayed as red and blue lines indicating lower and higher connectivity values for the patient group, respectively. The interhemispheric MFG connection reached statistical significance (bold line).*

Results

Subjects Patients with epilepsy displayed significantly lower IQ values (99±14), compared to healthy controls (115±15, p<0.001)**,** as well as reduced word fluency and reading scores [2].

Small world connectivity Patients with epilepsy showed significantly reduces node degree (K, p<0.02) and significantly increased path length (L, p<0.03) see *Fig. 1*, indicating loss of micro-structural neuronal network integrity. Furthermore, network parameters of the left-prefrontal region correlated significantly with IQ (ρ=0.44; p<0.007).

Language and memory network Patients showed significantly lower connection strength for the inter-hemispheric MFG connection (patients 0.42±0.02 %, controls 0.75±0.4 %, p<0.05), see *Fig. 2b*. Correlation of connection strengths with IQ values in the patient group revealed significant positive correlations for three connections: the HC left – MFG left connection (ρ=0.42; p<0.03), the HC left – MFG right connection (ρ=0.58; p<0.002) and the IFG left – MFG right connection (ρ=0.43; p<0.02), see *Fig. 3*.

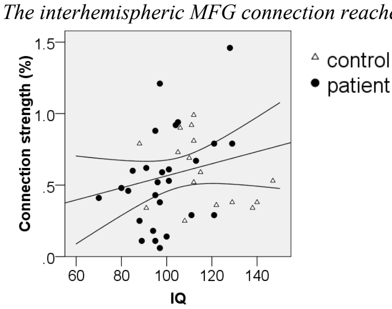

Fig. 3: *Association between IQ and connection strength of the left HC – MFG connection. Correlation between connection strength and IQ was significantly positive (connection strength increased with IQ) for the entire patient group as indicated by the regression line.*

Discussion

We found a global decline of structural connectivity for the whole brain network in patients with chronic cryptogenic epilepsy, indicating that chronic epilepsy is associated with loss of white matter fiber integrity. It was further demonstrated that these patients showed decreased structural connectivity for specific inter-hemispheric fiber connections of the frontal lobe. This means that a loss of structural connectivity was found for brain regions specifically mediating the declined cognitive performance. Furthermore, in these patients the connection strength significantly decreased for decreasing IQ in a number of connections.

References [1] Oyegbile et al, Neurology 2004 62:1736; [2] Jansen et al, Proc Int Soc Mag Reson Med 2009 17:3369; [3] Helmstaedter, Epilepsy Res 2000 41:235; [4] Bullmore, E. & Sporns, O. 2009 Nature Reviews Neuroscience, 10, 186-98; [5] Parker et al, 2003 JMRI 18-2:242-254 2003