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

M. Vaessen1,2, J. Jansen3, P. Hofman1, M. Vlooswijk1, H. Majoie4, M. de Krom5, A. Aldenkamp6,7, and W. Backes4

1 School for Mental Health and Neuroscience, Maastricht University Medical Centre, Maastricht, Limburg, Netherlands, 2 Kempenhaeghe Epilepsy Institute, Heeze, Netherlands, 3 Memorial Sloan-Kettering Cancer Center, New York, NY, United States, 4 Maastricht University Medical Centre, Maastricht, Limburg, Netherlands

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/mm² and one b = 0 s/mm².

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.

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 reduced 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 (p=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<0.05), 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.

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