Impaired functional connectivity and language in non-symptomatic localization-related epilepsy

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Introduction

Cognitive language problems are a common comorbid disorder in patients with epilepsy, though often underestimated [1]. The relationship between language dysfunction and memory deficits was previously confirmed in patients with temporal lobe epilepsy [2]. However, it is difficult to relate cognitive impairment to specific epileptic parameters, especially on an individual patient level. This research was devised to explore a neurobiological explanation for language deficits in patients with non-symptomatic epilepsy. The main objectives were (i) to investigate language performance by assessing word fluency and text reading performance in patients with epilepsy compared with healthy controls, (ii) to explore the relation with cerebral activation and connectivity in the language circuits with fMRI, and (iii) to relate word fluency and text reading performance to functional connectivity in prefrontal and temporal language areas.

Materials and Methods

Subjects The study population included 34 patients with non-symptomatic epilepsy (18F, 16M, age 40±13y), and 20 healthy volunteers (11F 9M, age 40±11y). All subjects underwent extensive neuropsychological testing, including tests for intelligence (WAIS-III), word fluency (SAN), and text reading (SAN) abilities. **MRI** MRI was performed with a 3.0-Tesla whole-body unit (Philips Achieva [software release 1.5.4.0], Philips Medical Systems, Best, The Netherlands). For anatomic reference, first T1-weigthed three-dimensional (3D) turbo field echo (TFE) images were acquired with the following parameters: repetition time (TR) 9.91 ms, echo time (TE) 4.6 ms, inversion time (TI) 3 s, flip angle 8°, matrix 256x256x160, field of view (FOV) 256x256x160 mm3, 1 mm adjacent coronal slices. Functional MRI data were acquired using a whole-cerebrum single-shot multi-slice 3D blood-oxygen-level dependent echo-planar imaging sequence, with TR 2 s, TE 35 ms, flip angle 90°, voxel size 2×2×3.5 mm3, matrix 128×128, 32 contiguous slices per volume, 196 volumes per acquisition. During fMRI, subjects performed the covert word generation and a reading task). The paradigms were tested extensively outside the scanner with each subject, to make sure the test was performed correctly. **Analysis** fMRI data analysis of the language activation data was performed in Matlab and SPM2. A standard random-effects analysis was performed to assess differences between the epilepsy and control groups. Results were thresholded at the $p < 0.05$ level (corrected for multiple comparisons). Also connectivity analysis was performed using SPM2. Per subject, for 4 regions a vector was obtained with the course of signal intensity over the 196 acquisitions. These regions included for word generation the left and right middle frontal gyrus (MFG), the left inferior frontal gyrus (IFG), the dorsal part of anterior cingulate cortex (ACC), according to Waites et al. [3], and for reading the left and right middle temporal gyrus (MTG), left IFG and ACC. Within these regions, the 200 most activated voxels were selected, for which the signal intensity was subsequently averaged. Each vector was low-pass-filtered using a finite impulse response filter to remove the effect of high-frequency noise ($f \leq 8.3$ mHz). Also, the six motion correction parameters were included in the design matrix as confounds. The correlation coefficients between all regions of interest were calculated, and subsequently transformed using the Fisher-Z transformation to facilitate statistical testing. Finally, for the resulting six possible interregional connections, a mean functional connectivity value was calculated per subject. For each language task the functional connectivity values were compared with neuropsychological test results and epilepsy parameters.

Results

Patients with epilepsy displayed significantly lower IQ values (97±16), compared to healthy controls (115±15, $p<0.01$). The performance on the word fluency test was also worse than controls (32±8 and 43±9, respectively; $p<0.01$). Patients read less words than controls in one minute (179±44 and 207±34, respectively; $p=0.02$). No significant differences were found for the activation maps of the word generation or the text reading paradigm between controls and patients with epilepsy. Functional connectivity values of word generation for patients were significantly lower than healthy controls for three connections between the four selected regions (ACC-left IFG, ACC-left MFG and left IFG-left MFG) (figure 1). Correlation of functional connectivity with neuropsychological language performance demonstrated a statistically significant correlation between mean functional connectivity and word fluency performance in patients (figure 2). Functional connectivity values for the text reading paradigm were lower in patients for the connections left IFG-left MTG and left IFG-right MTG (figure 1). The mean functional connectivity values for both the word fluency and the text reading paradigm in patients were significantly lower than controls ($p=0.01$).

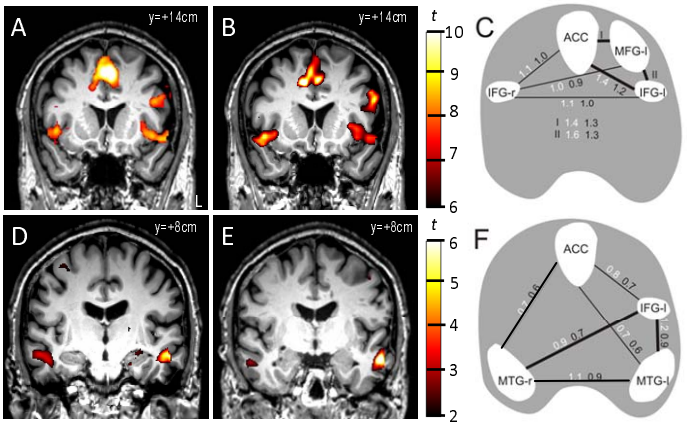

Figure 1: Coronal images of group averaged fMRI activation maps for the word generation (A-C) and text reading (D-F) paradigm. Mean activation patterns for patients are shown in (A, D), and for healthy controls in (B, E). The color bar indicates the t-value of the color-coded activation level. The selected regions of interest with the functional connectivity values for patients (black) and controls (white) for all the connections between these regions are schematically illustrated on C and F, for word generation and text reading, respectively. A thick line in C and F indicates a statistically significant difference between patients and controls.

Discussion and conclusion

In this study, it was demonstrated that patients with non-symptomatic localization-related epilepsy display difficulties in language functions, which relate to loss of functional connectivity in the language networks. Brain activation patterns between patients with epilepsy and healthy controls were similar, but functional connectivity values were significantly lower for patients during fMRI of word generation and text reading when compared with controls. Furthermore, neuropsychologically assessed word fluency and text reading performance positively correlated with functional connectivity in the language regions of the prefrontal and temporal cortex in patients with epilepsy. Our observations demonstrate that language deficits in patients with non-symptomatic, localization-related epilepsy are attributable to reduced functional connectivity of the different regions involved in the language networks and not to altered activation in these regions. Reduced functional connectivity in the language networks may be one of the neuronal correlates for cognitive dysfunction and possibly even cognitive decline. Further studies are required to assess the individual conditions leading to altered functional connectivity in patients, which would ideally lead to the identification of patients at risk for developing cognitive impairment and improve therapeutic decisions.

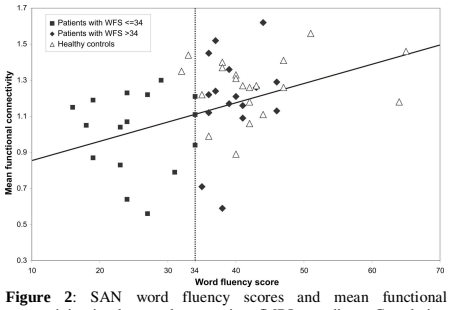

Figure 2: SAN word fluency scores and mean functional connectivity in the word generation fMRI paradigm. Correlation between word fluency scores and mean functional connectivity was significantly positive for the entire patient group as indicated by the (solid) regression line. The (dotted) vertical line represents the discrimination level between normal and abnormal performance on word fluency. WFS = word fluency score.

References [1] Oyegbile, Neurology 2004 62:1736; [2] Helmstaedter, Epilepsy Res 2000 41:235; [3] Waites, Ann Neurol 2006 59:335.