Disrupted functional connectivity networks in patients with localization-related cryptogenic epilepsy

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Introduction

Decline of cognitive function is the most frequent co-morbid disorder in epilepsy, particularly in patients with localization-related (partial) epilepsy with a temporal or frontal lobe origin [1]. Expressions of cognitive decline may vary from memory impairment or slowing of information processing speed to even cognitive deterioration with IQ-decline. Currently, no clear evidence is available which factors contribute to cognitive impairment in localization-related epilepsy. Characteristics that describe the chronicity of epilepsy, such as duration and number of seizures, are most likely related to the deterioration of the mental status. Even less is known about the brain-behavior relationships, i.e. what neuronal mechanisms underlie the cognitive and behavioral changes. Possible changes in fMRI silent word generation activation patterns associated with global cognitive deficits were analyzed. Additionally, lateralization index and functional connectivity analyses were performed.

Material and Methods

Patients The study population included 40 patients with localization-related, cryptogenic epilepsy (22F, 18 M, age 43±12) with or without secondarily generalized seizures, and 20 healthy volunteers (12F, 8 M, age 40±13). IQ was tested using WAIS-III, and a cognitive discrepancy score was derived, comparing the actual level with the expected level, based on premorbid educational level. ***MRI*** Imaging 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 mm^3, 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 mm^3, matrix 128×128, 32 contiguous slices per volume, 196 volumes per acquisition. During fMRI, subjects performed a standard expressive language task (covert word generation). The paradigm was tested extensively outside the scanner with each subject, to make sure the test was performed correctly. This was checked individually afterwards.

Analysis fMRI data analysis of the language activation data was performed in SPM2 (Wellcome Department of Cognitive Neurology, UK). 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). Additionally, a lateralization index (LI) was calculated for each subject using the formula LI = (VL −VR)/(VL + VR), where VL and VR represent the extent (i.e. number of voxels) of brain activation above the statistical threshold in the left and right hemispheres, respectively. 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 the left middle frontal gyrus (MFG), the left inferior frontal gyrus (IFG), the dorsal part of anterior cingulate cortex (ACC) and posterior cingulated cortex (PCC), according to Waites et al. [2]. Within these regions, the 200 most activated (MFG, IFG, and ACC) or deactivated (PCC) 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. Finally, the correlation coefficients of all signal intensities vectors for all regions were calculated, and subsequently transformed using the Fisher-Z transformation. The obtained connectivity values were compared with IQ, and cognitive discrepancy score, all using Pearson correlation. Additionally differences between patients with epilepsy and healthy volunteers were assessed using a Student's t-test. Results are mean ± standard error of the mean.

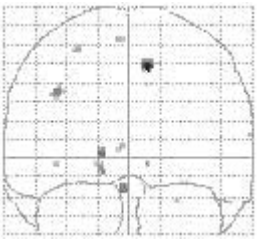

Figure 1. Random effect analysis of differences between controls and patients with epilepsy. $p < 0.05$, corrected.

	ACC	IFG	MFG	PCC
ACC		0.95 (0.04)*	1.21 (0.04)*	-0.15 (0.04)*
IFG	1.12 (0.04)		0.99 (0.04)	-0.09 (0.03)*
MFG	1.40 (0.04)	1.13 (0.05)		-0.24 (0.04)*
PCC	-0.30 (0.06)	-0.24 (0.05)	-0.37 (0.06)	

Table 1. Fisher-Z transformed connectivity values for patients with epilepsy (grey) and healthy controls (white). * $p < 0.05$ controls vs patients.

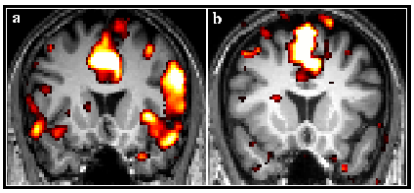

Figure 2. Functional connectivity maps obtained by regression of ACC time course against all brain voxels (**A**) healthy control (IQ = 115), (**B**) epilepsy patient (IQ = 85).

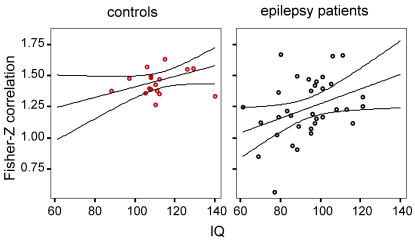

Figure 3. Fisher-Z transformed connectivity values (ACC-IFG) as function of IQ. Lines indicate the 95% confidence interval.

Results

Patients with epilepsy had significantly lower IQ values (-22, $p < 0.001$) and cognitive discrepancy scores (-12, $p < 0.001$), compared to healthy controls. The random-effects analysis did not reveal any differences between the word generation activation maps between controls and patients with epilepsy (Fig 1). The lateralization indices were 0.48±0.09 and 0.44±0.07 for the controls and patients, respectively, and did not differ between the groups ($p > 0.8$). Patients with epilepsy had significantly deviating connectivity values for most connections of the four regions (Table 1). Figure 2A shows a functional connectivity map of a healthy control, with clear activation in both ACC and MFG, whereas 2B from a patient only shows ACC. Furthermore, for the patients, the connections (ACC – IFG, $\rho = 0.41$, $p < 0.02$) and (ACC – MFG, $\rho = 0.36$, $p < 0.04$) significantly correlated with IQ (Fig 3). Also the connection (ACC – IFG, $\rho = 0.48$, $p < 0.01$) correlated with the cognitive discrepancy score. No such relationship was seen for the controls ($p > 0.09$) (Fig 3).

Discussion

Although the random-effects analysis did not reveal any substantial differences in word generation activation maps between healthy controls and patients with epilepsy, functional connectivity analysis proved to be able to observe subtle differences in activation patterns between the two groups. As both groups were able to perform the covert word generation task correctly, it is not unlikely to assume that the location of the activated regions for both groups is the same. Though, especially the functional connectivity properties seem to be indicative of cognitive performance. This is strengthened by the high correlation of functional connectivity values and cognitive scores.

Conclusion

Our observations demonstrate that functional connectivity can measure subtle disturbances in a higher cognitive function. We observed a reduction in the functional connectivity in the language system in patients with localization-related, cryptogenic epilepsy, when compared with controls. Further studies are required to assess the individual conditions leading to altered connectivity in patients. Functional connectivity is an elegant method to assess the language system in a different way.

References

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