Secondarily generalized seizures induce a functional reorganization of working memory, as demonstrated by fMRI

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Introduction

Cognitive impairment is the most frequent comorbid disorder in epilepsy [1]. Secondarily generalized tonic-clonic seizures (SGTCS) are thought to have a substantial effect on cognition [2]. Since cognitive problems in patients with SGTCS are often accompanied by mental slowing and impairment in executive function, the frontal lobe is proposed to be involved in this cognitive dysfunction. Secondary generalization (i.e. spreading) of seizures might explain the involvement of the frontal lobes. We investigated the effect of these seizures on cognitive deterioration using functional MRI (fMRI). Possible changes in activation patterns associated with global cognitive deficits were analyzed. When studying patients with localisation-related epilepsy and secondarily generalized seizures, one has to deal with the inherent strong variability in seizure focus and spread. Ideally one would like to probe the entire prefrontal cortex. Therefore we combined two cognitive fMRI paradigms (Sternberg and Stroop) aimed at investigating speed of mental processing and working memory, thus activating different parts of the temporal and frontal lobes.

Material and Methods

Sixteen patients with epilepsy were included (10 women and 6 men). All patients had experienced secondarily generalized seizures (range 1-200, median 18). All patients underwent extensive neuropsychological testing, including tests for IQ, handedness, attention related functions, information processing and memory function. Based on the results of these tests a composite deterioration score was derived. MRI was performed with a 1.5-Tesla unit (Philips Intera, Philips Medical Systems). 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 50 ms, flip angle 90°, voxel size 3.5×3.5×3.5 mm^3, matrix 64×64, 34 contiguous slices per volume, 96 volumes per acquisition. For anatomical reference, we acquired a 3D T1-weighted fast field-echo image, TR 11 ms, TE 3.5 ms, flip angle 90°, matrix 256×256, 150 contiguous slices and 3.5×3.5×3.5 mm^3 sized voxels. Patients performed a verbal working memory performance task (Sternberg [3]) and a color naming task (Stroop [4]). During the Sternberg paradigm, subjects were asked to memorize visually presented letters. Patients indicated by button-presses whether or not single displayed letters were in the memory set. The memory set varied from one to four letters, and was presented in a random fashion. For the Stroop paradigm, words of colour names were displayed in a different colour than the colour it actually named or in the same colour. Subjects were instructed to think of the colour in which the word was displayed. fMRI data analysis was performed in SPM2 (Wellcome Department of Cognitive Neurology, UK) and was focused on five volumes of interest (VOIs) covering the temporal and prefrontal cortex. The VOIs were the prefrontal area (i.e. superior lateral prefrontal cortex), frontotemporal area (i.e. peri-insular cortex), anterior cingulate cortex, Broca's and Wernicke's areas, thereby excluding visual, somatosensory and motor areas. For the Sternberg paradigm, activation maps were calculated for the contrast between all loads and the resting condition. The relative activation level in the VOI was expressed as the fraction of the 5,000 most active voxels (approximately 1% of the cerebrum) from the temporal and prefrontal cortex. In order to obtain a more general expression of frontal and temporal activation, the activation maps from the Sternberg and Stroop paradigms were combined using the the Z-values according to O'Brien-Lauter [5].

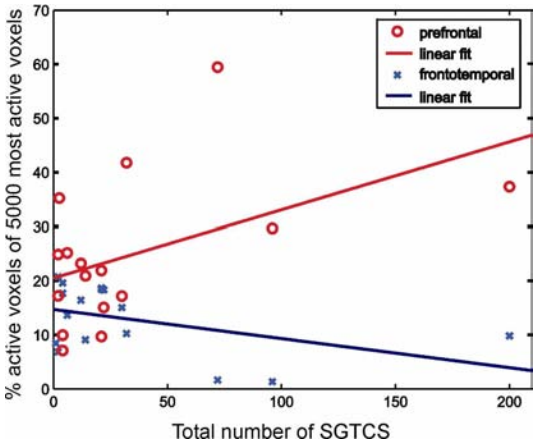

Figure 1 Relative activation of the prefrontal (red circles) and frontotemporal cortex (blue crosses) during the Sternberg fMRI task, as function of the total number of SGTCS. Solid lines indicate linear regression fit.

Results

Analysis of patients characteristics revealed that subjects with a higher number of total SGTCS had significantly lower IQ-measures (total IQ: p=0.01) than those with a lower amount of SGTCS. fMRI activation maps in VOIs were compared to the number of SGTCS experienced. In the prefrontal regions, a higher activation could be observed during the Stroop paradigm (p=0.01, r=0.60) and a trend for higher activation was observed for the Sternberg paradigm (p=0.07, r=0.46) (Figure 1,2) with increasing number of SGTCS experienced. In the frontotemporal region, a trend towards lower activation was observed for both Stroop and Sternberg paradigm (p=0.05 and p=0.10, respectively) (Figure 1,2). In the temporal regions and Broca's area, no correlation was found between activation patterns and number of SGTCS. In the cingulate cortex, higher activation was observed in the Stroop paradigm (p<0.01; r=0.72) but not in the Sternberg paradigm (p=0.33). After combining both paradigms, significantly higher activation was observed in the prefrontal region (p<0.01, r=0.65) and the cingulate region (p=0.02, r=0.57) in relation to a higher number of SGTCS. A trend towards lower activation in the frontotemporal region was observed (p=0.05; r=0.49). No correlation was found between activation patterns and IQ.

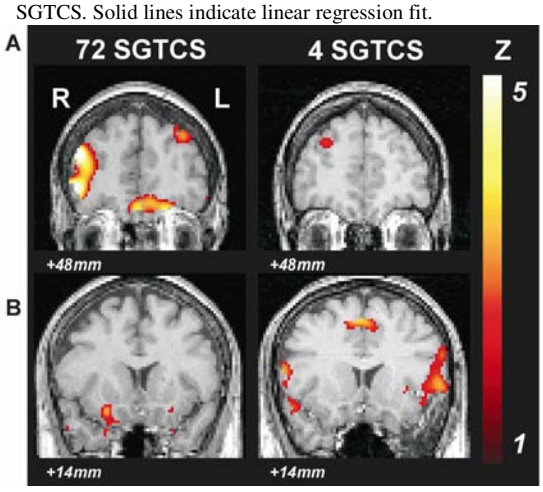

Figure 2 Coronal images of the Sternberg fMRI activation maps, with left a typical patient with many SGTCS, and right a patient with few SGTCS. **A)** Pronounced prefrontal activation corresponds to many SGTCS, **B)** whereas frontotemporal activation corresponds to few SGTCS. Slice positions are in stereotactic Talairach y-coordinates.

Discussion

We have demonstrated a relatively increased prefrontal activation related to the number of SGTCS. Furthermore, a trend towards a decreased activation in the frontotemporal areas was observed. Both fMRI paradigms used in the current study are aimed at indicating activation in the prefrontal area and temporal areas. It appears that a shift of activation has manifested from frontotemporal to prefrontal areas. This suggests that a functional reorganization of working memory has occurred in patients with a higher number of SGTCS. Whether this functional reorganization is due to a compensation mechanism to continue normal functioning, or whether the reorganization is of pathological origin underlying cognitive deterioration, could not be determined in this study. Future, prospective studies investigating progression of cognitive dysfunction related to cerebral activation changes are needed.

References

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