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Differential effect of side of temporal lobe epilepsy on lateralization of hippocampal, temporolateral, and inferior frontal activation patterns during a verbal episodic memory task

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Abstract

The encoding of verbal stimuli elicits left-lateralized activation patterns within the medial temporal lobes in healthy adults. In our study, patients with left- and right-sided temporal lobe epilepsy (LTLE, RTLE) were investigated during the encoding and retrieval of word-pair associates using functional magnetic resonance imaging. Functional asymmetry of activation patterns in hippocampal, inferior frontal, and temporolateral neocortical areas associated with language functions was analyzed. Hippocampal activation patterns in patients with LTLE were more right-lateralized than those in patients with RTLE ($P < 0.05$). There were no group differences with respect to lateralization in frontal or temporolateral regions of interest (ROIs). For both groups, frontal cortical activation patterns were significantly more left-lateralized than hippocampal patterns ($P < 0.05$). For patients with LTLE, there was a strong trend toward a difference in functional asymmetry between the temporolateral and hippocampal ROIs ($P = 0.059$). A graded effect of epileptic activity on laterality of the different regional activation patterns is discussed.

Keywords: Functional magnetic resonance imaging; Verbal episodic memory; Lateralization; Functional asymmetry; Temporal lobe epilepsy; Medial temporal lobe; Hippocampus; Language area; Functional reorganization

1. Introduction

Functional magnetic resonance imaging (fMRI) has proven to be an attractive tool with which to assess memory functions because of its broad availability and noninvasive nature. With the use of fMRI, material-specific lateralization has been demonstrated in healthy controls: verbal material such as words elicit left-lateralized activation patterns, and visuospatial stimuli (e.g., faces) evoke right-lateralized activation patterns [1–4]. In temporal lobe epilepsy (TLE), a structural lesion and recurring seizures can lead to a decline in medial temporal lobe (MTL)-associated memory functions [5–7]. Furthermore, it has been demonstrated that patients with early-onset left TLE show reorganization of their verbal episodic memory functions [8] and a shift of language functions to the contralesional hemisphere. Reorganizational processes have been supported by fMRI studies that report deviating activation patterns within the MTL [9–11], the prefrontal cortex [12], and language areas [13,14] in patients with TLE compared with healthy control subjects. Hence, it has been assumed that an allocation of language functions to the right hemisphere is accompanied by reorganization of verbal memory functions. This assumption has influenced the

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interpretation of neuropsychological results with respect to their lateralizing value in determining the functional deficit zone prior to epileptic surgery and, thus, the counseling of patients.

Conversely, there have been reports of patients with early left temporal lobe damage who have demonstrated a shift of verbal memory skills to the right hemisphere not accompanied by a shift of language functions [15,16]. Prior to epilepsy surgery, these patients exhibited reduced nonverbal memory and relatively unimpaired verbal memory skills as a result of a crowding effect after verbal memory transfer to the right temporal lobe. With the assumption of left-lateralized language and concurrent verbal memory dominance, they would have had a high risk for postoperative amnesia. However, after temporal lobe surgery, verbal memory functions remained unchanged and nonverbal memory increased in these patients. These results support the presence of a dissociation between verbal memory and language lateralization. Otherwise, this cognitive profile would be a contraindication for temporal lobe surgery within the language-dominant hemisphere because of the risk for postoperative amnesia. Therefore, investigating a possible dissociation between verbal memory and language lateralization in patients with left-sided TLE exhibiting reduced nonverbal memory and relatively unimpaired verbal memory would substantially help in counseling them prior to temporal lobe surgery. The exact mechanisms of reorganizational and compensatory processes and the influence of recurring seizures still remain unclear.

No functional imaging study, however, has directly compared activation patterns in patients with TLE within memory- and language-relevant areas to investigate possible dissociations in lateralization of activations between them. In this study, we studied the lateralization of activation patterns within the hippocampus and language-relevant frontal and temporal neocortical areas during a verbal episodic memory task in patients with left- and right-sided TLE (LTLE and RTLE) to examine possible dissociations in functional asymmetry between memory and language regions.

2. Materials and methods

2.1. Patients

Patients with drug-resistant TLE with seizure generation within the temporal lobe and whose first language was German were included in the study. Informed written consent was obtained from each subject after the procedure had been fully explained. The study was approved by the ethics committee of the University of Freiburg according to the guidelines of the Declaration of Helsinki.

Twenty-nine patients (14 female/15 male, mean age $\pm$ SD = 36 $\pm$ 14 years, range = 11–60) with TLE (15 left- and 14 right-sided) and a mean illness duration of 22 years (SD = 13) participated in the study during their presurgical evaluations at the University Hospital of Freiburg. Mean level of education was 13 years (SD = 3). Assessment of handedness [17] showed 26 right-handed patients (handedness quotient (HQ) > +0.3), 1 left-handed patient (HQ < −0.3), and 2 ambidextrous patients (HQ between −0.3 and +0.3) (mean handedness quotient $\pm$ SD = 0.8 $\pm$ 0.3). Structural magnetic resonance tomography revealed unilateral hippocampal sclerosis in 25 patients (15 with LTLE/10 with RTLE); one patient showed bilateral hippocampal signal abnormalities (right more than left). Two patients had a temporomesial tumor infiltrating the hippocampus, and etiology in one patient was cryptogenic. Histologic examination revealed mild hippocampal sclerosis in all three patients. The anatomical scans of four patients (two with LTLE/two with RTLE) exhibited additional extratemporal structural abnormalities. Demographic and clinical data are summarized in Table 1.

2.2. Stimuli and task design

Stimuli and task design were identical to those used in a study of test–retest reliability of fMRI activation patterns in healthy subjects [18]. Subjects were explicitly instructed to encode and later recognize concrete and highly imageable word pairs. Concrete nouns were selected from the German Version 2.5 of the CELEX Lexical Database Release 2 (http://www.kun.nl/celex), which provides information on the written and spoken frequency of about 6 million words. The overall frequency of the 144 words used ranged from 1 to 4395. The two nouns were neither semantically nor phonemically related and consisted of a maximum of three syllables.

During encoding, subjects viewed each word pair for 7 seconds and were told to memorize it. Four word pairs constituted an encoding block (32 seconds), which alternated with a block of the control condition (24 seconds), resulting in a total of 24 blocks. As a control condition, the subjects were presented names of two weekdays for 5 seconds and had to indicate by button press whether they were identical or not. In the recognition condition (32 seconds), the subjects were given three words for 7 seconds, and they had to indicate by button press which two words constituted a pair beforehand. Prior to recognition, there was a block of the control condition to clear short-term memory. Fifty percent of the distractors were phonemically related and 50% semantically related to the target. The control condition was identical for encoding and recognition. The numbers of left and right button presses were balanced throughout the whole experiment. One experimental cycle is illustrated in Fig. 1.

The stimuli were visually projected on a translucent screen at the end of the scanner table using a data projector outside the magnet. Subjects viewed the word pairs via a mirror that was positioned above the head coil. A laptop outside the scanner room using the software Presentation 0.5 (www.neurobehavioralsystems.com) was connected to the data projector. Responses were recorded by use of a button box.

2.3. Data acquisition

Magnetic resonance imaging (MRI) was performed with a Magnetom Siemens Vision 1.5 T scanner (Siemens AG, Erlangen, Germany). For high anatomical resolution, a sagittal T1-weighted 3D-MPRAGE sequence was obtained (TR/TE = 9.7/4 ms, flip angle = 12°, field of view = 256 mm, matrix = 256×256, 160 slices, voxel size = $1 \times 1 \times 1$ mm^3).

Functional magnetic resonance images were acquired using gradient-echo echo-planar imaging sequences (GE-EPI) sensitive to BOLD contrast (TR/TE = 4000/64 ms, flip angle = 90°, field of view = 256 mm, matrix = 64×64, 30 interleaved slices, voxel size = $4 \times 4 \times 3.3$ mm^3, gap = 0.3 mm). The block design included 173 acquisitions, the first 5 images of which were discarded to eliminate magnetization instability.

2.4. Image processing and data analysis

Data were analyzed in MATLAB 6.1 (http://www.mathworks.com) using the statistical parametric mapping software SPM2 (http://www.fil.ion.ucl.ac.uk/spm/). Additional calculations were accomplished with SPSS 13.0 (http://www.spss.com). Functional images were converted into Analyze format and unwarped. They were realigned, normalized onto the Montreal Neurologic Institute Atlas (MNI [19]) using the EPI template