Epilepsy & Behavior 42 (2015) 78–85

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Incipient preoperative reorganization processes of verbal memory functions in patients with left temporal lobe epilepsy

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ARTICLE INFO

Article history:
Received 14 October 2014
Accepted 21 November 2014
Available online 11 December 2014

Keywords:
Memory fMRI
Hippocampus
Chronic mesial temporal lobe epilepsy
Preoperative reorganization
Nonlinear correlations

ABSTRACT

We previously reported nonlinear correlations between verbal episodic memory performance and BOLD signal in memory fMRI in healthy subjects. The purpose of the present study was to examine this observation in patients with left mesial temporal lobe epilepsy (mTLE) who often experience memory decline and need reliable prediction tools before epilepsy surgery with hippocampectomy. Fifteen patients with left mTLE (18–57 years, nine females) underwent a verbal memory fMRI paradigm. Correlations between BOLD activity and neuropsychological data were calculated for the i) hippocampus (HC) as well as ii) extrahippocampal mTL structures. Memory performance was systematically associated with activations within the right HC as well as with activations within the left extrahippocampal mTL regions (amygdala and parahippocampal gyrus). As hypothesized, the analyses revealed cubic relationships, with one peak in patients with marginal memory performance and another peak in patients with very good performance. The nonlinear correlations between memory performance and activations might reflect the compensatory recruitment of neural resources to maintain memory performance in patients with ongoing memory deterioration. The present data suggest an already incipient preoperative reorganization process of verbal memory in non-amnesic patients with left mTLE by simultaneously tapping the resources of the right HC and left extrahippocampal mTL regions. Thus, in the preoperative assessment, both neuropsychological performance and memory fMRI should be considered together.

1. Introduction

Surgery within the mesial temporal lobe (mTL) bears the risk of relevant episodic memory decline, typically of verbal memory following left and of nonverbal memory following right anterior temporal lobe resection (ATLR) [1,2]. The prediction of potential postoperative memory decline is, therefore, of great importance in the clinical setting and the goal of various memory functional MRI (fMRI) studies [3–7]. There is agreement that patients with epilepsy with good memory abilities prior to surgery [2,8,9] and patients whose memory functions are lateralized to the side of surgery [10] are more likely to have memory decline.

Several fMRI paradigms have been developed with regard to the prediction of postoperative memory outcome in operated patients with mesial temporal lobe epilepsy (mTLE) [3,6,7,11]. To date, only linear correlations between preoperative fMRI activations and preoperative memory performance [3] or postoperative memory changes [11,12] were taken into account. In a recently published work, we investigated the nature of correlations between memory performance levels and fMRI activations within the mTL in healthy subjects [13]. Instead of linear correlations, we found u-shaped correlations between subjects' verbal memory performance and mTL activations. The observed hyperactivation among subjects with marginal memory performance might reflect a compensatory recruitment of neural resources to maintain memory performance, as previously reported for patients with mild cognitive impairment and Alzheimer's disease [14–16].

The purpose of the present study was to investigate the presence of nonlinear correlations in patients with left mTLE. We used a verbal memory paradigm, first published by Wagner and colleagues [17], that has been shown to produce strong left lateralized activation

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http://dx.doi.org/10.1016/j.yebeh.2014.11.026
1525-5050/

patterns in healthy subjects [17,18]. We hypothesized there would be a nonlinear correlation between neuropsychological test scores and fMRI activations in mesial temporal structures due to compensatory hyperactivation in patients with marginal memory performance.

2. Materials and methods

2.1. Subjects

We examined 15 German-speaking patients with chronic left-sided mTLE with clear mesiotemporal spikes on EEG and typical temporal lobe seizure semiology before left ATLR, 12 of them with clear signs of hippocampal sclerosis (HS) on MRI and 1 with mild and 2 without clear signs of HS. None of the patients had any extrahippocampal lesions. All patients were right-handed ($M_{\text{handedness quotient}} = 0.95$, SD = 0.08; [19]) with normal or corrected-to-normal vision (9 females, 6 males, $M_{age} = 36.3$ years, SD = 11.7 years, range = 18–57 years, $M_{education} = 12.3$ years, SD = 2.9 years) and showed left-sided language dominance as confirmed by fMRI.

The study was approved by the ethics committee of the University of Tuebingen and is in accordance with the Declaration of Helsinki. All patients gave written informed consent.

2.2. Neuropsychological tests

As memory performance level decreases with age [20,21], the use of raw scores in memory assessments appears to be, in our view, not entirely adequate when investigating a sample with a large variance of participants' age. For our analyses, we therefore considered the standardized memory performance compared to an age-matched reference population in the form of percentile ranks as determined by the manual instead of absolute values (i.e., raw scores).

2.2.1. Verbal memory test

A verbal memory test was performed outside the scanner in which subjects had to memorize a list of 15 words (Verbaler Lern- und Merkfähigkeitstest, VLMT, [22]). We assessed three verbal memory scores: (i) 'immediate recall', i.e., the sum of words correctly reproduced during five learning trials (max. of 75); (ii) 'delayed recall', i.e., the number of correctly remembered words after a 30-minute delay (max. of 15); and (iii) 'delayed recognition' using a recognition condition after the delayed recall condition (max. of 15).

2.2.2. Nonverbal memory test

To assess the functionality of the right mesial temporal lobe regions, a nonverbal learning and memory performance test, the DCS (Diagnostikum für Cerebralschädigung [23]), was applied where subjects had to learn 9 geometrical figures. The 'immediate recall' score, i.e., the sum of correctly reproduced figures during five learning trials (max. of 45), was assessed. Scores were correlated with the VLMT to assess the ability of the nondominant mTL to maintain verbal memory functions.

2.2.3. Intelligence level

The level of verbal crystallized intelligence in each patient was assessed using the German multiple-choice vocabulary test to exclude patients with abnormal neuropsychological performance due to mental retardation (MWT-B, Mehrfachwahl-Wortschatz-Intelligenztest [24]).

2.3. Magnetic resonance data acquisition

Magnetic resonance imaging (MRI) studies were performed on a Siemens Magnetom Sonata [Maestro Class] 1.5 T scanner (Siemens AG, Erlangen, Germany). All data were acquired using an 8-channel array head coil for reception and the body coil for transmission. In order to obtain a high-resolution anatomical image of each subject's brain, a sagittal T1-weighted 3D-MPRAGE sequence was used (TR/TI/TE = 1300/660/3.19 ms, flip angle = 15°, field of view = 256 * 256 mm^2, matrix = 256 * 256, 176 slices, voxel size = 1 * 1 * 1 mm^3). Additionally, a field map was recorded for later correction of distortions in the functional images caused by magnetic field inhomogeneity. For the fMRI tasks, gradient-echo planar T2*-weighted images covering the whole brain were acquired (TR = 4000 ms, TE = 64 ms, field of view = 192 * 192 mm^2, matrix = 64 * 64, voxel size = 3 * 3 * 3 mm^3, gap = 0.3 mm, 38 interleaved slices). The task was performed in block design and consisted of 175 acquisitions. The first two images were discarded in order to reach equilibrium of magnetization.

The stimuli were visually projected on a translucent screen positioned at the end of the scanner table using a video projector outside the magnet room. Subjects saw the presentation via a mirror attached to the head coil. Outside the scanner room, a Windows laptop using the software 'Presentation 0.6' (http://www.neurobehaviouralsystems.com) was connected to the video projector. Responses were recorded by use of a fiber optic button box where patients had to press the correct one of two buttons with the thumb of the right hand.

2.4. Stimuli and fMRI task design

To investigate verbal memory, patients were presented with 24 word pairs and instructed to memorize and recognize them as described previously [17] (Fig. 1). During the blocks of the encoding condition, patients were shown four neither semantically nor phonematically related word pairs for 7 s (plus 1 s of black screen) and were asked to memorize them, e.g., "Ananas + Schraube" ("pineapple + screw"). This was alternated with a block of the control condition in which the names of two weekdays were presented [e.g., "Montag + Mittwoch" ("Monday + Wednesday")] for 5 s (plus 1 s of black screen), and patients had to indicate by button press whether they were identical or not. During the recognition condition, patients performed a two-alternative forced-choice test in which one word was presented above two alternatives (the correct associate and one distractor) for 7 s (plus 1 s of black screen) and patients were asked to select by button press the memorized associate. Both alternatives had been seen during the encoding phase, so patients were not able to distinguish between them on the basis of familiarity alone. Moreover, items were presented in randomized order, alternating with a block of the control condition. The fMRI behavioral results obtained in the recognition condition were not considered as a measure of performance, and the button presses during the recognition task were used mainly to ensure cooperation.

2.5. Image processing and fMRI data analysis

Imaging data were analyzed in MATLAB (http://www.mathworks.com) using Statistical Parametric Mapping (SPM 8) (Wellcome Trust Centre for Imaging Neuroscience; http://www.fil.ion.ucl.ac.uk/spm). Functional images were converted into NIFTI-1 format. The imaging time series of each patient underwent a slice-timing procedure, was realigned and unwarped based on the estimated field map data, and then was coregistered to the anatomical reference image and normalized to the MNI (Montreal Neurologic Institute Atlas, MNI) space [25]. The normalized data were smoothed with an isotropic Gaussian kernel (8-mm full width at half maximum) and temporally filtered with a high-pass filter with a cutoff time of 128 s.

2.6. Statistics

2.6.1. fMRI single-level statistics

For single-subject analyses, experimental task and control blocks were convolved with the hemodynamic response function (hrf) in order to evaluate individual main effects for the (i) encoding vs. control