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Memory and language impairments and their relationships to hippocampal and perirhinal cortex damage in patients with medial temporal lobe epilepsy

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Abstract

Chronic medial temporal lobe epilepsy (MTLE) is associated with memory loss due to damage in the hippocampal system. To investigate the relationship between volume of medial temporal lobe structures and performance on neuropsychological tests, we studied 39 consecutive patients with MTLE and unilateral hippocampal atrophy (HA) determined by volumetric magnetic resonance imaging (MRI). Structures of interest comprised hippocampus, amygdala, and entorhinal, perirhinal, parahippocampal, and temporopolar cortices. The findings indicated that (1) performance was significantly worse in the group with left HA as compared with the group with right HA on general memory, verbal memory, delayed recall, and verbal fluency tests and the Boston Naming Test (BNT), and (2) the volume of the left hippocampus and also the degree of asymmetry of perirhinal cortex volume were significant and independent predictors of performance on general memory, verbal memory, and verbal fluency tests and the BNT in patients with MTLE.

Keywords: Neuropsychological evaluation; Magnetic resonance imaging; Hippocampus; Amygdala; Entorhinal cortex; Perirhinal cortex; Parahippocampal cortex; Temporopolar cortex

1. Introduction

Chronic medial temporal lobe epilepsy (MTLE) is associated with progressive memory loss [1]. Earlier age at seizure onset [2–7], longer duration of epilepsy [2,8–10], higher seizure frequency [2,11], use of antiepileptic drugs (AEDs) [2], and refractoriness to drug treatment are related to more severe memory decline, whereas successful surgical treatment may stop or even reverse the memory loss [1].

Besides these factors, the etiology of epilepsy, e.g., hippocampal atrophy (HA) and other signs of medial temporal sclerosis (MTS) on magnetic resonance imaging (MRI), seems to play an important role in the memory impairment frequently seen in patients with MTLE [12–14]. The classic model of material-specific memory predicts that lesions in the left hippocampal system impair verbal memory [15–17], while those in the right hippocampal system affect visual memory [18,19]. However, more recent studies have shown that the relationship between side of hippocampal pathology and memory dysfunction is more evident in patients with left HA than in those with right HA on MRI [13,20–25].

Patients with MTLE may show atrophy not only in the hippocampus, but also in other regions anatomically and functionally linked to it, such as the parahippocampal region, composed of the entorhinal and perirhinal cortices, and the neighboring association regions of the neocortex [26–31]. Current research suggests that this whole network is involved with different aspects of memory formation and consolidation. Specifically, while the hippocampus plays a critical role from the initial formation of memories until

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their final repository in the neocortex [30], the parahippocampal region is involved in the intersection of perception and memory [32], and mediates the extended persistence of cortical representations of memory [30]. Animal studies have shown that the parahippocampal region is particularly important for recognition memory [28,30], and that selective lesions to the parahippocampal cortex severely impair memory [33]. However, the role of the parahippocampal regions in the memory deficits exhibited by patients with MTLE is not yet completely understood.

Structural MRI is a powerful tool to study in vivo the brains of patients with MTLE. Signs that are associated with MTS can be reliably detected by MRI [34], particularly by means of a careful and precise MRI morphometrical analysis [27,35].

In this study, we aimed to evaluate the relationship between the volume of not only the hippocampus but also other medial temporal lobe structures, such as amygdala, and entorhinal, perirhinal, parahippocampal, and temporopolar cortices, and performance on neuropsychological tests in patients with MTLE. This analysis allows us to test the controversial claim that lesions in the left hippocampal structure are associated with verbal memory deficits [15–17], while those in the right hippocampal structure are related to visual memory deficits [18,19].

2. Methods

2.1. Ascertainment of subjects

We studied 39 consecutive patients with chronic refractory MTLE. All patients were referred from the outpatient epilepsy clinic of our institution, where they were diagnosed based on a detailed neurological evaluation. Determination of the epileptic syndrome was based on ILAE criteria [36]. Seizures were lateralized according to the medical history, a comprehensive neurological examination, and interictal EEG and prolonged video/EEG monitoring. All patients had drug-refractory MTLE [37] and unilateral seizure onset with ipsilateral HA on routine visual analysis of MRI diagnostic protocol [38]. All of them signed a written informed consent approved by the ethics committee of our institution, in accordance with the principles stated in the 1964 Declaration of Helsinki.

2.2. MRI image acquisition

In addition to the 39 consecutive patients with chronic refractory MTLE, we also scanned 32 normal subjects (21 women) recruited in the local community, as a control group for volumetric measurements.

We acquired MRI using a standardized protocol [38]. We employed T1-weighted images with 1-mm isotropic voxels acquired on a 2-T scanner (Elscint Prestige, Haifa, Israel) using a spoiled gradient-echo sequence (TR = 22 ms, TE = 9 ms, flip angle = 5° matrix = 256 × 220, field of view = 25 × 22 cm, 1-mm sagittal slices).

2.3. Image postprocessing

The images were transferred to a Silicon Graphics O_2 workstation (Mountain View, CA, USA) and processed using a series of tools from the Montreal Neurological Institute (www.bic.mni.mcgill.ca/software/). The images were subjected to field nonhomogeneity correction using the N3 [39]. To correct for variation of total brain volume, all images were converted to a standardized Talairach space by an automated linear stereotaxic transformation using the TAL package [40].

2.4. MRI volumetric analysis

Each anatomical structure was manually identified using DISPLAY (David McDonald, www.bic.mni.mcgill.ca/software/). We assessed the volumes of the temporopolar (TPC), perirhinal (PRC), entorhinal (ERC), and parahippocampal (PHC) cortices, the amygdala (AMY), and the hippocampus (HIP). The volume for each of these regions was determined by a single observer (L.B.) according to a protocol that has been refined in our group [41]. The coefficient of repeatability ranged from 0.94 to 1.06 [41]. The asymmetry index of each structure was defined by the left/right ratio.

2.5. Neuropsychological evaluation

Neuropsychological evaluation included: vocabulary and block design subtests of the Wechsler Adult Intelligence Scale—Revised (WAIS-R) to estimate IQ; the Edinburgh Handedness Inventory and Dichotic Listening Test to determine hemispheric dominance for language and, by inference, to lateralize verbal and visual memories; the Logical Memory and Verbal Paired Associates of the Wechsler Memory Scale—Revised (WMS-R) to investigate verbal memory; and the Figural Memory, Visual Reproduction, and Visual Paired Associates of the WMS-R to investigate visual memory. To control for other cognitive functions that could influence memory tasks, we employed tests for language (Verbal Fluency Test, category: animals, and Boston Naming Test (BNT)), attention (Strub and Black Vigilance Test), and executive functions (Trail Making Test (TMT) and Wisconsin Card Sorting Test (WCST)) [42–50]. We did not use the same MRI control group for neuropsychological data. These tests were adapted for our population. The results of each test were compared with results for normal controls matched for age and educational level.

2.6. Statistical analysis

2.6.1. Morphometry of medial temporal lobe structures

Data were analyzed with Systat (9.0) and SPSS (12.0.1) software packages. Group differences for age were determined by a one-way analysis of variance (ANOVA), and gender distribution was determined using the χ^2 test. Differences in volumes among patients and control subjects were evaluated with multivariate analysis of variance (MANOVA) with two within-subject factors (side: left, right; and structures: TPC, PRC, ERC, PHC, HIP, AMY). Group differences for volumes were evaluated with MANOVA with one between-subject grouping factor (groups: controls, left MTLE, right MTLE) and one within-subject grouping factor (structures: right TPC, left TPC, right PRC, left PRC, right ERC, left ERC, right PHC, left PHC, right HIP, left HIP, right AMY, left AMY). The MANOVA was followed by Tukey HSD post hoc comparisons, to determine the structures with significant volume reduction in patients with MTLE, compared with normal controls. This procedure includes correction for multiple comparisons.

2.6.2. Neuropsychological evaluation

The results from the neuropsychological evaluation were transformed into z scores (standardized scores defined by the number of standard deviations away from the mean of the respective control group).

2.6.3. Relationships between morphometry of medial temporal lobe structures and neuropsychological tests

We used MANOVA with Tukey post hoc comparisons to determine the difference in performance on neuropsychological tests between patients with left and right HA.

We then used a simultaneous multiple regression analysis with each neuropsychological test as a dependent variable (or criterion) and the hippocampal volume and the asymmetry ratio of all other medial temporal lobe structures as predictors. The reason for using asymmetry ratios was to reduce the number of variables for the statistical analyses. We considered that, given that the neural damage to the medial temporal lobe extends beyond the hippocampus and there is possibly a strong