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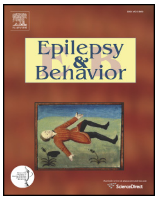

The effect of medial temporal lobe epilepsy on visual memory encoding

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ABSTRACT

Effective visual memory encoding, a function important for everyday functioning, relies on episodic and semantic memory processes. In patients with medial temporal lobe epilepsy (MTLE), memory deficits are common as the structures typically involved in seizure generation are also involved in acquisition, maintenance, and retrieval of episodic memories. In this study, we used group independent component analysis (GICA) combined with Granger causality analysis to investigate the neuronal networks involved in visual memory encoding during a complex fMRI scene-encoding task in patients with left MTLE (LMTLE; $N = 28$) and in patients with right MTLE (RMTLE; $N = 18$). Additionally, we built models of memory encoding in LMTLE and RMTLE and compared them with a model of healthy memory encoding (Nenert et al., 2014). For those with LMTLE, we identified and retained for further analyses and model generation 7 ICA task-related components that were attributed to four different networks: the frontal and posterior components of the DMN, visual network, auditory-insular network, and an "other" network. For those with RMTLE, ICA produced 9 task-related components that were attributed to the somatosensory and cerebellar networks in addition to the same networks as in patients with LMTLE. Granger causality analysis revealed group differences in causality relations within the visual memory network and MTLE-related deviations from normal network function. Our results demonstrate differences in the networks for visual memory encoding between those with LMTLE and those with RMTLE. Consistent with previous studies, the organization of memory encoding is dependent on laterality of seizure focus and may be mediated by functional reorganization in chronic epilepsy. These differences may underlie the observed differences in memory abilities between patients with LMTLE and patients with RMTLE and highlight the modulating effects of epilepsy on the network for memory encoding.

1. Introduction

The importance of effective visual memory encoding for everyday functioning is undeniable. The visual memory encoding process requires both episodic memory and semantic memory to adequately encode visual stimuli and visual sensory information for later recall [1]. In addition to the hippocampus, other temporal lobe structures such as the amygdala and entorhinal cortex are involved in visual memory encoding [2], and the function of these structures may be impaired in patients with medial temporal lobe epilepsy (MTLE). Further, visual attention mechanisms required to enhance accurate visual encoding of complex scenes involve frontal and parietal networks that form feedback loops with primary visual areas [3,4]. According to the nociferous cortex hypothesis, in patients with MTLE, extratemporal regions including the frontal and parietal attention networks are also affected [5]. These local and distributed effects may negatively influence the visual memory encoding networks in MTLE. Further, visual memory encoding involves semantic memory of visual stimuli [6] which previous studies have found to be differentially affected in patients with left MTLE and in patients with right MTLE [7,8] as the functional adequacy of the hippocampus ipsilateral to the seizure focus is often compromised and the capacity or reserve of the contralateral homologues may augment memory function [9].

Medial temporal lobe epilepsy is frequently reported to cause prominent memory deficits [10,11]. With seizures typically originating from the hippocampus and, less frequently, from other medial temporal structures, epilepsy-related damage in MTLE is thought to produce functional reorganization of memory processes [12–14], as these structures are involved in the acquisition, maintenance, and retrieval of episodic memories [15]. However, the extent of damage is confined not only to the medial temporal lobes [5]. The distributed nature of

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functional and anatomical abnormalities seen in MTLE is paralleled by widespread cognitive impairments affecting not only memory but also executive, sensorimotor, visuospatial, and language functions [16,17].

In neuroimaging studies, MTLE has been shown to differentially affect activation patterns in those whose seizures originate from the left or the right temporal lobe [6,12–14]. For example, LMTLE is usually associated with deficits in verbal functions, while patients with RMTLE typically exhibit impairments in visuospatial memory functioning [8]; both types of epilepsy are often associated with lateralization of memory encoding to the unaffected hemisphere [6,18–20]. Further, LMTLE with hippocampal sclerosis is commonly characterized by atypical language lateralization [21], and, in one study, left lateralization of a scene-encoding task was demonstrated in patients with RMTLE when compared to patients with LMTLE and healthy controls, while subject performance was similar, indicating plasticity of memory functions [6].

In line with the distributed nature of the functional damage caused by TLE, reorganization in the resting state networks has been observed in fMRI studies employing region of interest (ROI) approaches [22] as well as whole-brain network analyses including independent component analysis (ICA) [23–25]. In addition to the disruptions in the motor and sensory networks, numerous studies have demonstrated TLE-related abnormalities in the default mode [26–28] and alertness [29] networks, as well as networks subserving higher brain functions such as attention [30,31], executive control [27], and language [7]. For instance, the spatial extent of components included in the DMN was reduced in patients with MTLE, particularly in the prefrontal rather than temporoparietal cortices when compared to healthy controls [26]. Similarly, decreases in the functional connectivity of the frontal and parietal areas primarily included in the DMN and dorsal attention network (DAN) have been described in temporal lobe epilepsy (TLE) [32]. Another study reported impairments in the alertness network of patients with TLE when compared to healthy controls and demonstrated an association between the reduced overall area of activation and the patients' performance on a behavioral attention test [29]. Further, impairments in executive functions such as working memory are frequently observed in patients with TLE [16,33]. Finally, a recent fMRI study correlated decreases in working memory to lower functional connectivity between the prefrontal cortex, anterior cingulate, and inferior frontal gyrus, indicating widespread damage in focal-onset epilepsy [23].

The primary aim of the present study was to investigate the neuronal networks involved in visual memory encoding during a complex fMRI scene-encoding task in patients with LMTLE and in patients with RMTLE using advanced methods of image processing — group independent component analysis (GICA) and Granger causality analysis (GCA). Based on findings from the existing literature, we hypothesized that there would be differences in the visual memory encoding network between those with LMTLE and those with RMTLE [6,7,12,13,20,34–36]. The secondary goal included the following: (1) to build a model of memory encoding in LMTLE and RMTLE and (2) to compare these results with the model of healthy visual scene encoding [36]. The hypothesis guiding this portion of the study was that LMTLE and RMTLE would have differential effects on the neural underpinnings of the visual memory encoding while not causing specific differences in memory performance (i.e., memory plasticity).

2. Methods

2.1. Participants

Sixty-eight patients with epilepsy were recruited as part of a larger study [6,35]. Of those patients, 13 were excluded from analyses because they were administered a different version of the task [34]. Additionally, patients with extratemporal or lesional epilepsy were excluded; diagnosis of LMTLE or RMTLE for all patients was determined based on video-EEG monitoring, seizure semiology, and neuroimaging results. Twenty-eight patients with LMTLE and 18 patients with RMTLE were identified and kept for subsequent analyses. The majority of subjects included in this study were previously reported in Bigras et al. [6]. Patients were 19 to 66 years of age ($M = 38$ years, $SD = 12$), 70% were male, with a mean age at seizure onset of 20 years and a mean duration of epilepsy of 19 years (Table 1). Independent samples *t*-test and chi-square test of independence revealed no significant differences between groups, both $p > 0.05$. Results of this study were compared to previously reported findings of 40 healthy controls whose demographics are reported elsewhere [6,36]. Briefly, healthy control participants were 19–59 years of age ($M = 33$), with no history of neurological disorders. This study was approved by the University of Cincinnati and University of Alabama at Birmingham Institutional Review Boards, and all participants provided written informed consent prior to enrollment.

2.2. Visual scene-encoding task

For the purpose of this study, we employed a previously well-characterized block-design fMRI scene-encoding task [13]. Briefly, during the active blocks, the participants were presented with stimuli that represented a balanced mixture of indoor (50%) and outdoor (50%) scenes including images of inanimate objects, people, and faces [13]. To assess memory encoding, we explicitly instructed participants to memorize all scenes for later (postscan) test of memory retrieval. Attention to the task was monitored by participants indicating whether the scene was indoor or outdoor via a corresponding left or right button press. The response box was held in the right hand. In the control blocks, participants viewed pairs of scrambled images presented side-by-side and were instructed to indicate (using the same response box) whether the images in each pair were the same or not (50% of pairs contained images that were the same). Scrambled pairs with different images were similar in brightness and hue. Scene encoding involves several cognitive processes with the target one being encoding of visually presented stimuli. The control condition allows for the subtraction of visuoperceptual, decision-making, and motor aspects of the task. The task was composed of 14 blocks (10 images per block). Blocks alternated between images of indoor or outdoor scenes (i.e., 7 active blocks) and images of a pair of scrambled pictures (i.e., 7 control blocks) for a total of 70 target scenes and 70 control pairs. The paradigm lasted 7 min and 15 s, and each image was presented for 2.5 s, followed by 0.5 s of a white blank screen. To ensure comprehension of the task, participants completed a practice run before entering the scanner. Practice items consisted of five indoor and outdoor scenes as well as five side-by-side scrambled image pairs. Participants were required to accurately respond to all practice items before entering the scanner. Directly after completing the in-scanner task, participants were administered a postscan recognition test that included 60 indoor and outdoor scenes, with a balanced content of target and foil pictures. Foil pictures matched the content and parameters of those presented in the scanner. Participants were instructed to indicate whether they remembered

Table 1
Demographic characteristics of the patients with left medial temporal lobe epilepsy (LMTLE) and the patients with right medial temporal lobe epilepsy (RMLTE) (AEDs — antiepileptic drugs).

	LMTLE (N = 28)	RMTLE (N = 18)
Age	36.25 (10.16)	42.00 (12.64)
Male	61%	83%
Education in years	14.14 (2.70)	13.44 (2.28)
Age at onset	18.36 (13.39)	25.39 (17.30)
Duration of epilepsy	17.89 (13.05)	16.22 (12.52)
Right-handedness	89%	89%
Total number of current AEDs	2.21 (.83)	1.89 (.68)

Note: Independent samples *t*-test an chi-square test of independence revealed no significant differences between groups, all $p > 0.05$. Demographic characteristics of the healthy controls were previously reported [36].

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