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Declarative long-term memory and the mesial temporal lobe: Insights from a 5-year postsurgery follow-up study on refractory temporal lobe epilepsy

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ABSTRACT

It is largely recognized that the mesial temporal lobe and its substructure support declarative long-term memory (LTM). So far, different theories have been suggested, and the organization of declarative verbal LTM in the brain is still a matter of debate. In the current study, we retrospectively selected 151 right-handed patients with temporal lobe epilepsy with and without hippocampal sclerosis, with a homogeneous (seizure-free) clinical outcome. We analyzed verbal memory performance within a normalized scores context, by means of prose recall and word paired-associate learning tasks. Patients were tested at presurgical baseline, 6 months, 2 and 5 years after anteromesial temporal lobe surgery, using parallel versions of the neuropsychological tests. Our main finding revealed a key involvement of the left temporal lobe and, in particular, of the left hippocampus in prose recall rather than word paired-associate task. We also confirmed that shorter duration of epilepsy, younger age, and withdrawal of antiepileptic drugs would predict a better memory outcome. When individual memory performance was taken into account, data showed that females affected by left temporal lobe epilepsy for longer duration were more at risk of presenting a clinically pathologic LTM at 5 years after surgery. Taken together, these findings shed new light on verbal declarative memory in the mesial temporal lobe and on the behavioral signature of the functional reorganization after the surgical treatment of temporal lobe epilepsy.

1. Introduction

The mesial temporal lobe plays a pivotal role in declarative episodic long-term memory (LTM) [1–6]. In particular, studies have revealed the key involvement of the hippocampus [7–9]. This structure participates in the formation of the episodic memory encoding event sequences, associating stimulus events and their contexts, and linking them into an episodic memory trace [1,10]. Furthermore, different mesial temporal lobe subregions support the formation of these complex memories, such as the perirhinal cortex, parahippocampal gyrus, and hippocampus [11–15]. At a broader level, according to the well-known notion of material specificity [16], the left mesial temporal lobe is mainly involved in verbal aspects of memory, whereas the right mesial temporal lobe processes spatial features.

Findings from temporal lobe epilepsy (TLE) have provided contrasting evidence. Studies have shown that patients with left hemisphere TLE (LTLE) typically suffer from verbal memory deficits [17–20]. However, a significant minority of patients with right hemisphere TLE (RTLE) show verbal memory impairments after surgery as well [21–24]. Moreover, patients with LTLE have shown dissociations between different verbal memory tasks. It has been showed that patients with LTLE with hippocampal damage may show deficits in learning unrelated word paired-associates with spared prose recall. Some authors have demonstrated that left hippocampal neuronal loss impaired learning of unrelated pairs of words in the face of spared immediate recall of a short story [25–27]. However, consistent with other studies, prose recall deficits were primarily associated with hippocampal damage [28–30]. Additionally, functional magnetic resonance (fMRI) studies have revealed that word paired-associate learning activates both mesial and frontal areas [31–33]. Even if these two tasks seem to be one side of the same coin [34], a number of behavioral differences are present. The prose recall task involves learning of an episode

Abbreviations: AEDs, antiepileptic drugs; BDI, Beck Depression Inventory; fMRI, functional magnetic resonance imaging; HS, hippocampal sclerosis; LTLE, left temporal lobe epilepsy; RTLE, right temporal lobe epilepsy; TLE, temporal lobe epilepsy; LTM, long-term memory; PAL, paired-associate learning test; SS, short story test.

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(e.g., a short story), with a specific temporal context; whereas the word paired-associate test requires the subject to learn semantically related and unrelated associations between pairs of words in a list. In some cases, the retention interval could also differ between these tasks, as prose recall could have a longer delayed recall than word paired-associate learning [35]. It is also important to note that the previously observed dissociations in learning word pairs do not always have an immediate correlate in clinical practice, as in some measures, the word paired-associate learning task total score does not distinguish between related and unrelated word pairs [35].

Within this complex scenario, specific theoretical frameworks have been postulated on the role of lateral and mesial temporal lobe structures in verbal memory. Saling [36] has recently suggested a task-specificity theory, according to which dissociations between memory deficits could be related to different pathologic anatomical substrates. In particular, the observed pattern of dissociation between verbal memory tasks would depend on the integrity of two separate components: i) a mesial protosemantic component and ii) a lateral semantic component. The activity of the inferior temporal cortex supported the latter, whereas the rhinal–hippocampal cortices sustained the former. Thus, deficits in the paired-associate learning might be observed in hippocampal or MTL dysfunction, while a deficit in prose recall may emerge from lateral temporal lobe damage [25,27,36]. On the other hand, it has also been underscored that the mesial temporal lobe plays a major role in the memory recall interval. According to this view, the hippocampus would be an important mediator of declarative LTM, whereas lateral neocortical structures would play a role in short-term memory recall. Helmstaedter and colleagues [17], for instance, showed that patients with LTLE had the most pronounced deficit in acquisition and recognition compared with long-term memory consolidation after anterior temporal lobectomy. Indeed, this surgical procedure would leave intact the mesial temporal lobe structures. Allen and colleagues [37] have recently described the case of Jon, a patient affected by highly selective hippocampal damage. Jon showed a dissociation between a spared working memory and impaired long-term memory, providing evidence in favor of a major role of the hippocampus in long-term rather than short-term memory retention.

In the current study, we sought to investigate the role of the mesial temporal lobe structures in verbal declarative memory in a large cohort of patients with TLE and HS. We also aimed to explore the specific contribution of mesial temporal lobe in prose recall and word paired-associate learning task. Finally, we aimed to shed light on the behavioral counterpart of a long-term reorganization of the verbal memory system 5 years after surgery. We retrospectively selected 151 right-handed patients with TLE with and without HS, with a homogeneous (seizure-free) clinical outcome. We analyzed verbal memory performance within a normalized scores context, by means of word paired-associate learning and a prose recall task. Patients were tested at presurgical baseline, 6 months, 2 and 5 years after surgery, using parallel versions of neuropsychological tests including Italian paired-associate learning (encoding) and prose learning tasks (encoding/recall). Our patients underwent an anteromesial temporal lobe surgery, in which typically, mesial temporal lobe structures are removed preserving the function of lateral temporal cortex. According to this type of procedure, one might hypothesize that if word paired-associate task were mainly impaired after surgery, mesial temporal structures would not play a major role in the semantic features of declarative memory. Alternatively, if after surgery we observed a memory deficit involving prose recall, the mesial temporal lobe may be more crucial for delayed retrieval of prose.

2. Materials and methods

2.1. Participants

Participants were retrospectively selected over a fourteen-year time period (from 1996 to 2010) from the surgical patients clinical database collected at the "Claudio Munari Epilepsy Surgery Centre" at the Niguarda Hospital in Milan. We selected only patients who met the following inclusion criteria: a) age range between 17 and 60 years-old (in order to exclude the consequence of memory differences due to the healthy cognitive development or memory decline observed in healthy aging); b) level of education >3 years (as the Italian normative sample only included people with more than 3 years of formal education); c) absence of psychiatric history (in order to exclude subjects with possible preexisting memory impairments due to the presence of psychiatric diseases); d) drug-resistant epilepsy involving the temporal lobe only; e) right-handedness; f) left hemisphere language dominance documented by the clinical characteristics of seizures, by means of the WADA test or fMRI for language) neuropsychological assessment available at presurgery (T0), 6 months (T1), 2 years (T2), 5 years (T3) after surgery; and h) a globally adequate abstract reasoning level.

Two hundred-twelve patients were selected. As seizures after surgery undermine memory in patients with TLE [38,39], we only studied the memory performance of seizure-free patients after surgery (Engel class I) in order to explore a more reliable cognitive profile. We found that 151 (71,2%) out of 212 patients operated on were classified in the Engel I Class one year after surgery. One hundred fifty-one right-handed patients with TLE composed the final sample. Participants were 33.95 (±11.11) years old at time of surgery (range 17–60 years), and experienced a mean of 13.5 (±17.86) seizures per month before surgery; 88 patients were male and 63 female. The seizure onset and resection site were left temporal in 75 and right temporal in 76 patients (Table 1).

The Ethical Committee of the Niguarda Hospital approved this retrospective study. As in the case of retrospective investigations, patients were not consented. All data were analyzed using an anonymized dataset. All procedures were conducted in accordance with the Declaration of Helsinki.

2.2. Neuropsychological assessment

Participants were given an extensive neuropsychological assessment providing measures of language, memory, visuo-constructive functions, attention, and abstract reasoning. In agreement with the aim of this study, we selected the memory tests for which different parallel versions have been used to monitor patients' cognitive profile over the years. Paired-associate learning and short story tests were selected and further analyzed. Importantly, as mood may have a negative impact on episodic memory [40,41], we also took into account as measured by depressive symptoms on the Beck Depression Inventory II (BDI-II) [42].

2.2.1. Verbal memory assessment

2.2.1.1. Paired-associate learning (PAL). In the paired-associate learning (PAL) test [35], the examiner pronounced a list of ten paired associated

Table 1
Characteristics of the sample. Clinical and demographic features of LTLE and RTLE patients.

	LTLE (n = 75)		RTLE (n = 76)	
	HS+ (n = 30)	HS− (n = 45)	HS+ (n = 38)	HS− (n = 38)
Mean age (at surgery)	39.53 (±9.28)	29.07 (±10.9)	38.55 (±9.89)	30.74 (±10.37)
Gender (m/f)	17/13	27/18	23/15	21/17
Mean education	11.57 (±4.26)	11.42 (±3.21)	10.25 (±4.17)	11. 82 (±2.76)
Mean epilepsy duration (years)	25.03 (±9.97)	16.29 (±11.62)	31.58 (±10.34)	13.26 (±9.39)
Mean seizure frequency (monthly)	9.77 (±7.87)	20.28 (±27.89)	10.36 (±8.58)	11.57 (±12.83)
Engel class	Ia = 24 Ic = 6	Ia = 37 Ic = 8	Ia = 31 Ic = 7	Ia = 35 Ic = 3
Antiepileptic drugs withdrawal (yes/no)	16/14	15/30	16/22	15/23