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Disruption of learning and long-term retention of prose passages in patients with focal epilepsy

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ABSTRACT

Recent investigations of accelerated long-term forgetting, a condition in which newly acquired memory is normal initially but decays rapidly over days or weeks, indicate that multiple factors might influence whether this phenomenon is seen in patients with epilepsy. Test-based differences such as learning condition or type of memory measure (e.g., recall vs recognition) as well as epilepsy variables (e.g., side, site, or frequency of epileptiform activity) may be important. The present study sought to characterize factors affecting learning and memory for prose passages in patients with focal epilepsy. We enrolled 21 patients with temporal lobe epilepsy, with and without hippocampal lesions, 11 patients with extratemporal epilepsy (ETE), and 29 healthy controls. Two matched passages were used to compare effects of initial learning condition (one exposure versus learning-to-criterion) on subsequent patterns of retention. Recall and recognition were tested at different delays (i.e., immediately, 30 min, 24 h, and 4 days). Regression analyses and one-way ANOVAs indicated that having a left-hemisphere epileptic focus had a negative impact on learning, whilst presence of a hippocampal lesion (irrespective of side) was associated with deterioration in recall for intervals up to 24 h postencoding. Learning condition affected patterns of memory decay in that the ETE group showed significant decline in recall between 24 h and 4 days only when stories were learned to criterion. In contrast with recall, no changes over time were evident in recognition memory, as patients with hippocampal lesions were impaired from 30 min onward. Epilepsy variables other than side and site of epilepsy/lesion did not influence performance. In conclusion, the left hemisphere is involved in learning of prose material, and the hippocampus is involved in the consolidation of this material mainly for the first 24 h. After this, cortical regions outside the hippocampus become important for recall.

1. Introduction

Accelerated long-term forgetting (ALF) is a newly recognized phenomenon, characterized by the rapid loss of newly acquired memories over days to weeks despite normal retention at standard (around 30 min) intervals [1–4]. It has been described in patients with temporal lobe epilepsy [TLE; e.g., 5–8] and also in patients with transient epileptic amnesia [TEA; e.g., 4].

It is well established that hippocampal lesions affect short-term retention [e.g., up to 30 min; 9,10], and recently, Lah et al. [5] reported that patients with hippocampal abnormalities showed ALF for a word list after 24 h compared with healthy controls. Wilkinson et al. [7], however, did not find any relationship between hippocampal sclerosis and retention of prose passages or a complex figure when memory was tested after a six-week delay. Together, the results seem consistent with proposals that the hippocampus plays a role in learning and memory consolidation for a limited time period [11]. In contrast, several researchers have suggested that seizures and interictal discharges (rather than hippocampal abnormalities) contribute to ALF at delays of one week or more [3,6,7,12]. However, only a few studies [e.g., 3, 13] have used concurrent EEG to investigate these proposals.

There is also some evidence that the degree of initial encoding plays a role in determining whether or not ALF occurs. Indeed, some would argue that ALF by definition is only seen in patients with intact initial recall [14]. Of the studies that have looked for ALF in patients with TLE who showed normal memory at 30 min [2,8,15–22], all but one [17] have found significant decline over longer delays compared with control subjects. Many of the studies that found normal performance at early delays followed by ALF used a learning-to-criterion approach initially [8,16,18,19], but no study to date has directly investigated the effect of learning condition (i.e., learning-to-criterion versus one exposure) on ALF.

If a material is not retained normally in the early stages (e.g., by 30-minute delay), then subsequent patterns of memory loss tend to be similar for patients and control subjects. Two studies have found that patients with TLE who were impaired at a 30-minute

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delay (on word lists, geometric designs, or prose recall, compared with healthy subjects) demonstrated no further differences in the rate of information loss over longer intervals [i.e., 24 h or 2 weeks, respectively; 23,24]. However, Mameniskiene et al. [6] and Wilkinson et al. [7] did find additional significant decline when patients who had demonstrated impairments at an early recall on similar material were retested after longer intervals (four weeks and six weeks, respectively). This suggests that ALF might take longer to become apparent when patients start with lower scores than control subjects; that is, substantial forgetting has already occurred, masking an opportunity to observe abnormally rapid forgetting *over time*. We predict that ALF will be less evident over the first several days following one-trial learning compared with learning-to-criterion.

1.1. Hemispheric specificity for the learning and retention of verbal material

When the ability to learn verbal material has been investigated in patients with TLE, several studies have shown no side-of-lesion effects [e.g., 7,8,25]. More specifically, Jones-Gotman [25] reported that both patients with right TLE and patients with left TLE showed similar performances across learning trials for lists of abstract words. Similarly, other studies found that although both groups with right TLE and groups with left TLE needed more trials to learn prose passages to criterion compared with control subjects without epilepsy, there was no ultimate difference in amount learned between the two patient groups [7,8]. In contrast, Djordjevic et al. [26] showed that patients with left TLE were more impaired at recalling a passage on the first learning trial and they needed more learning trials to reach the criterion compared with patients with right TLE and healthy subjects.

When *retention* of verbal material has been investigated, the impact of a left- (as opposed to right-) sided epileptic focus seems clearer. It has been demonstrated that patients with left temporal lobectomy involving the hippocampus are impaired in prose recall after a 30- to 90-minute delay [10,27]. Even after matching for learning, Djordjevic et al. [26] found that patients with left TLE were impaired compared with those with right TLE in a 24-hour recall of prose passages. Jones-Gotman [25] found that memory for an abstract word list showed significant decline in patients with left hippocampal atrophy after a 24-hour delay compared with patients with right hippocampal atrophy. Over delays of 1 and 4 weeks, respectively, Helmstaedter et al. [28] and Blake et al. [8] both found that patients with left (but not those with right) TLE showed ALF for verbal material. In contrast, Wilkinson et al. [7] found no differences between groups with left or right TLE in memory for verbal material, with both groups impaired on prose recall compared with the healthy group after six weeks. However, in their study, the patients were divided purely on the basis of an evident hippocampal lesion and not with respect to epileptic foci; thus, it is possible that some of the patients had epileptic activity contralateral to the hippocampal sclerosis. Hence, there is some evidence that the left hemisphere is more important than the right for both learning and the retention of verbal material, though this has not been consistently found across studies.

1.2. The influence of site of epileptic focus on ALF

Both of the two main contemporary models of memory formation, the Standard Consolidation (SC) model [11] and Multiple Trace Theory [MTT; 29], concur that the hippocampus is important for memory consolidation in the short term. They differ in their proposals about how episodic memory is maintained in the longer term. According to the SC model, during memory consolidation, the hippocampal contribution gradually diminishes as the neocortex suffices to sustain a permanent memory trace and mediate its retrieval. In contrast, MTT posits that memory for a context-bound event remains dependent on the hippocampus for as long as it is available; with time, only a less integrated schematic version of that memory is supported by the neocortex.

Recently, Lah et al. [5] noted that whereas patients with TLE and hippocampal lesions forgot a word list rapidly (over a 24-hour period), a more gradual but significant memory decline was seen over days in patients with TLE with radiologically normal hippocampi. Furthermore, we found ALF for the first time in patients with epileptic foci outside the temporal lobes when we tested memory for recent autobiographical events after a four-day interval [30]. These findings offer some support to theories which state that memory consolidation over longer delays is supported by distributed cortical areas. However, further investigations should clarify if similar patterns can be seen with different types of material (e.g., stories).

1.3. Effects of type of testing (recall versus recognition) on patterns of ALF

In most cases where recognition has been assessed in addition to recall in studies of ALF, both are found to be impaired [8,19,28,31]. However, Manning et al. [15] found no impairment on verbal recognition (for a word list) in a patient with left temporal lobectomy who showed ALF on verbal recall (for prose) after a 30-hour delay. Also, Martin et al. [16] found impairments on recall but not on recognition for a word list when patients with TLE were compared with control subjects at a 24-hour delay. These findings raise the possibility that the type of testing (recall versus recognition) influences the detection of ALF. However, investigations have used different materials to contrast the two types of measures (e.g., [16]), so whether recognition is better preserved than recall remains unclear.

1.4. Aims

This study set out to examine learning, recall, and recognition memory for verbal material (prose passages) over intervals up to four days after encoding in patients with focal epilepsy. We sought to determine whether encoding condition (i.e., learning-to-criterion vs one exposure) influences ALF. We also wanted to examine the potential contributions of epilepsy variables to learning and retention of prose passages. We predicted that the presence of a hippocampal lesion would be the most significant factor with regard to memory decay over the first 24 h and that seizures and/or epileptiform discharges would account for memory loss over longer delays (i.e., by 4 days). We also expected the side of epileptic focus to affect both learning and retention, with poorer performance more likely in those with known left hemisphere involvement.

2. Method

2.1. Subjects

English-speaking patients between the ages of 20 and 65 years with a diagnosis of intractable focal epilepsy were sought for this study. Suitable candidates from the Comprehensive Epilepsy Service at Royal Prince Alfred Hospital in Sydney were contacted. Site and side of seizure focus as well as the presence/absence of a hippocampal lesion were determined by the Chief Neurologist on the service (AM) on the basis of the patient's history, seizure phenomenology, EEG, and neuroimaging (without knowledge of the patient's neuropsychological results). To determine whether patient groups were matched for epilepsy severity, the number of antiepileptic drugs (AEDs) taken and seizure frequency in the previous year were obtained from patients and their medical records.

There were 21 patients with TLE, 9 without hippocampal lesions [TLE(−)] and 12 with hippocampal lesions [TLE(+)]. Of those in the TLE(+) group, six had mesial temporal sclerosis, five had undergone temporal lobectomy, and one had a dysembryoplastic neuroepithelial tumor (DNET). In the TLE(−) group, all the subjects had normal MRI