Neuropsychologia 53 (2014) 64–74

Contents lists available at ScienceDirect

Neuropsychologia

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

Can temporal lobe epilepsy surgery ameliorate accelerated long-term forgetting?

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ARTICLE INFO

Article history:
Received 24 March 2013
Received in revised form
29 October 2013
Accepted 12 November 2013
Available online 20 November 2013

Keywords:
Accelerated long-term forgetting
Temporal lobe epilepsy
Seizures
Epilepsy surgery
Memory

ABSTRACT

Accelerated long-term forgetting (ALF) is a relatively newly identified phenomenon in neuropsychology which has been associated with temporal lobe epilepsy (TLE). ALF is characterised by intact acquisition and retention of memories over delays of minutes and hours, but abnormally fast forgetting over delays of 24 h or more. The causes of ALF are unknown; however disruption of "slow" consolidation processes through seizure activity in the temporal lobes is proposed as a possible explanation. We looked to establish whether seizure control following epilepsy surgery ameliorated ALF in patients with TLE. Parallel sets of verbal and visual stimuli were administered comparing seven TLE patients and 25 healthy controls, matched on key demographic characteristics. Free recall and recognition were assessed at both pre-surgery/time 1 and post-surgery/time 2 at delays of 25 or 45 s, 30 min and one week. The TLE group retained significantly less verbally and visually learned material between 30 min and one week at the pre-surgery assessment than the control group. Comparison of the groups at post-surgery assessment indicated evidence of improved retention in the TLE group for both visual and verbal material, despite reduced initial registration on the verbal sub-tests. Exploratory analysis of individuals indicated heterogeneity in the patient group with regards to the presence/absence of ALF and post-surgical improvement in ALF. The findings offer some support to the theory that ALF is associated with uncontrolled seizures and that elimination of seizures via epilepsy surgery may improve retention by providing a stable environment for "slow" consolidation to occur. However, our results suggest that this is unlikely to be the sole cause and that "slow" consolidation may normally depend also on the integrity of structures within the neocortex or medial temporal lobes. Further investigation of these apparent heterogeneous groups may be informative in further defining the nature and causes of ALF.

1. Introduction

Recent research has found that some individuals with Temporal Lobe Epilepsy (TLE) show a distinct pattern of forgetting, whereby information is acquired normally and retained over delays of minutes or hours, but is forgotten abnormally fast over delays of weeks or months (Bell & Giovagnoli, 2007; Butler & Zeman, 2008). This relatively newly described phenomenon is termed accelerated long-term forgetting (ALF) by most researchers, although it has also been called long term amnesia by some (Kapur et al., 1996). The former term will be used throughout this paper for consistency.

ALF is assumed to be caused by a disruption to the process of consolidation. Squire and Alvarez (2005) draw a distinction between the roles of "fast" and "slow" consolidation in the learning of new material. The former is thought to be reliant on medial temporal structures, including the hippocampus, to maintain representations in neocortex and accounts for memory retention over shorter intervals. The latter is thought to involve the gradual withdrawal of dependence on medial temporal lobe structures as representations become established within the neocortex over longer periods of time. One explanation for ALF is that during this period memories that have been subjected to the "fast" consolidation process are vulnerable to disruption as it is thought that stability in the neocortical environment is required for successful "slow" consolidation.

Mayes et al. (2003) postulate three explanations for ALF in TLE in the context of the consolidation model; the first two posit that pathology causes damage to either medial temporal lobe structures or the neocortex, preventing the slow consolidation process due to damage in either of these systems. Previous research has examined the role of structural pathology in ALF (see Wilkinson et al., 2012; Muhlert et al., 2011) with both papers highlighting the possibility that ALF is related to temporal damage outside medial

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http://dx.doi.org/10.1016/j.neuropsychologia.2013.11.007

temporal lobe (MTL) structures and that MTL damage may be a marker for this. The third explanation is that seizure activity disrupts the neocortical environment, thus preventing memories from becoming independently established within neocortex (Kapur et al., 1997; Squire & Alvarez, 2005).

Few studies have systematically studied the role of seizures in ALF. Mameniskiene, Jatuzis, Kaubrys and Budrys (1996) assessed verbal and non-verbal memory in patients with TLE and control participants at immediate, 30 min and 4 week delays. Results indicated that patients performed significantly worse than controls at all delays. However, comparison of subgroups of patients who either experienced or did not experience seizures during the 4 week delay indicated that the seizure group demonstrated significantly less percent retention on a test of story recall (results on list recall and complex figure recall failed to achieve significance). They noted that complex partial and secondary generalised seizures appeared to be more detrimental to memory than simple partial seizures and that a group of patients with more frequent seizures $>/=4$ showed poorer memory than those with less frequent seizures (<4). Regression analysis indicated that number of complex partial seizures was a predictor for memory at the 4 week delay. These effects, however, were not specific to ALF as participants with TLE demonstrated more general deficits in memory.

An earlier study by Jokeit, Daamen, Zang, Janszky, and Ebner (2001) examined ten patients with TLE using a word-position associative learning test whilst being monitored using EEG. Participants were presented with 12 words randomly positioned on a computer screen in four possible positions (left, right, down or up) and were asked to remember the positions. The process was repeated three times with each presentation followed by cued recall to establish initial learning. The participants were then retested at 30 min and 24 h delays, with ALF calculated by subtracting the 24 h delay scores from the 30 min scores. The authors found no association between seizures and retention performance in patients with right-sided TLE; however patients with left-sided TLE showed ALF on the memory task if a seizure was experienced during the 24 h delay.

Two recent studies have considered the relationship between seizures and ALF, Muhlert et al. (2011) reported no correlation between seizures and ALF in a sample of seven TLE participants on verbal and visual memory tasks tested at three delays: immediate, 30 min and 1 week. However, the number of seizures experienced by the group over the week was very small; therefore the reliability of the correlates in this study can be called into question. Wilkinson et al. (2012) provided more substantive evidence of the role of seizures in ALF, with 27 TLE patients completing tests of verbal and visual recall at three delays: immediate, one hour and six weeks. Participants' seizure frequency over the six week delay was found to be positively associated with ALF.

One of the drawbacks of the studies reported so far is that none adopted an AB experimental design to compare forgetting rates during a period of seizures (A) and then again when seizures are controlled (B). Few studies examining ALF have used this method, however the ones that have use two approaches: the first is to test for ALF pre- and again post-AED intervention, with the goal of comparing the seizure-free (post-AED) period with the pre-intervention period. This has achieved some success, with Tramoni et al. (2011) and Jansari, Davis, McGibbon, Firminger and Kapur (2010) reporting improvements post-seizure remission. The second is to study ALF pre- and post-epilepsy surgery. To our knowledge there is only one published pre- and post-surgery study in the ALF literature, a single case study by Gallassi et al. (2011), who looked at ALF pre- and post-left temporal polectomy in a patient MT. MT was a 58 year old man who experienced daily seizures and left-frontotemporal pulsating headaches before receiving surgery. He had experienced subjective memory deficits just under a year prior to the surgery, which he reported had been worsening over time. Neuropsychological examination revealed ALF at the one-week delay pre-surgery, which was calculated by averaging forgetting scores (30 min minus 1 week) across three tests of verbal and visual memory. The authors retested MT 15 months after surgery and found that ALF had improved on measures of verbal memory but not visual memory. Despite these positive findings, the study was methodologically limited due to the authors using a control group which was not IQ-matched and only using tests of recall and not recognition. They also retested the participant with identical materials pre- and post-surgery which may have confounded the results due to repeated exposure to the testing materials.

The present study is the first pre and post-surgery group study in ALF, looking to replicate the findings of Gallassi et al. (2011). The aim was to explore whether seizure reduction established through epilepsy surgery had an ameliorative effect on ALF in the TLE group. We looked to investigate one of the possible causes of ALF outlined by Mayes et al. (2003), namely that seizure activity disrupts the stable environment required for the process of "slow" consolidation, therefore preventing the retention of newly acquired memories over long-delays. Our second aim was to improve the previous methodology by using specially constructed parallel sets of stimuli with difficult-to-rehearse material.

2. Material and methods

2.1. Design overview

This study comprised a longitudinal quasi-experimental design, using a parallel battery of measures to assess ALF pre- and up to one year post-epilepsy surgery. The ALF materials comprised two parallel sets of visual and verbal testing materials. One set presented and tested pre-surgery and the other presented and tested post-surgery. Each set comprised recall and recognition paradigms which were used to test retention of visual scenes and verbal stories. The presentation of the sets of stimuli was counterbalanced between the participants and controls such that half the participants received set A first, and half the participants set B.

2.2. Setting

This study was conducted in clinics at the Royal Hallamshire Hospital (RHH) in conjunction with the Clinical Psychology Unit at the University of Sheffield. The project was ethically approved by the South Yorkshire Research Ethics Committee. Participants gave informed consent before participating in the project.

2.3. Participants

2.3.1. TLE patients

Patients who fulfilled the inclusion criteria were identified by a consultant clinical neuropsychologist. The inclusion criteria required that individuals: (a) had a formal diagnosis of TLE, (b) were due to undergo epilepsy surgery, (c) spoke English as their first language, (d) were aged between 18 and 75, (e) were assessed as having a Full Scale IQ above 80 on the Wechsler Adult Intelligence Scale-third edition (WAIS-III; Wechsler, 1997a, 1997b), and (d) were not diagnosed with co-morbid neurological conditions or severe psychiatric illness. A total of seven patients (3 males, 4 females) were recruited, (see Table 1 for demographic data). TLE participants permitted us to access additional information about seizure activity through their medical records. This information included age of onset of epilepsy, seizure frequency, MRI data and current medication use. All seven TLE patients had epilepsy surgery during the study comprising a left ($n=3$) or right ($n=4$) amygdalo-hippocampectomy, depending on the lateralisation of the patients epileptic activity (established through EEG and MRI data).

2.3.2. Control group

Control participants were recruited via email or poster, either from Sheffield Teaching Hospitals or the University of Sheffield email systems. The 25 participants most similar to the patients with TLE were selected from a pool of 60. Background measures collected from the controls at the initial testing appointment included reading derived IQ scores (Wechsler Test of Adult Reading (WTAR; Wechsler, 2001), handedness, mood measures and medical screening questions pertaining to the inclusion criteria.