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Research report

Sleep-dependent memory consolidation and accelerated forgetting

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ABSTRACT

Accelerated long-term forgetting (ALF) is a form of memory impairment in which learning and initial retention of information appear normal but subsequent forgetting is excessively rapid. ALF is most commonly associated with epilepsy and, in particular, a form of late-onset epilepsy called transient epileptic amnesia (TEA). ALF provides a novel opportunity to investigate post-encoding memory processes, such as consolidation. Sleep is implicated in the consolidation of memory in healthy people and a deficit in sleep-dependent memory consolidation has been proposed as an explanation for ALF. If this proposal were correct, then sleep would not benefit memory retention in people with ALF as much as in healthy people, and ALF might only be apparent when the retention interval contains sleep. To test this theory, we compared performance on a sleep-sensitive memory task over a night of sleep and a day of wakefulness. We found, contrary to the hypothesis, that sleep benefits memory retention in TEA patients with ALF and that this benefit is no smaller in magnitude than that seen in healthy controls. Indeed, the patients performed significantly more poorly than the controls only in the wake condition and not the sleep condition. Patients were matched to controls on learning rate, initial retention, and the effect of time of day on cognitive performance. These results indicate that ALF is not caused by a disruption of sleep-dependent memory consolidation. Instead, ALF may be due to an encoding abnormality that goes undetected on behavioural assessments of learning, or by a deficit in memory consolidation processes that are not sleep-dependent.

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1. Introduction

Memories are not static entities. Processes that occur after encoding alter memory traces and the likelihood that they will subsequently be successfully retrieved. Memory consolidation is a set of, as yet, poorly understood processes that transform initially labile memories into a more stable form (Stickgold & Walker, 2007). Neuropsychological models play a central role in the scientific study of human memory, but models of a pure consolidation deficit have thus far been conspicuously absent. This may be because the brain structures involved in memory consolidation overlap with those involved in memory encoding (Battaglia, Benchenane, Sirota, Pennartz, & Wiener, 2011; Mednick, Cai, Shuman, Anagnostaras, & Wixted, 2011). Patients with brain lesions affecting the long term retention of episodic memory therefore tend to have prominent learning deficits which confound the investigation of consolidation. Instead, a deficit in consolidation has been inferred from the 'temporal gradient' often seen in retrograde amnesia, whereby memories acquired shortly before brain injury are more vulnerable than those acquired remotely (e.g., Alvarez & Squire, 1994). However, studies of retrograde amnesia inherently suffer from a lack of experimental control over the memories under investigation. Moreover, the existence of a temporal gradient in episodic memory is disputed (Nadel & Moscovitch, 1997). Ideally, therefore, a neuropsychological model of memory consolidation would exhibit normal learning performance but excessively rapid forgetting. In this paper, we sought to investigate the cause of rapid forgetting in such a model, focussing particularly upon the role of sleep in the memory impairment.

1.1. *Accelerated long-term forgetting (ALF)*

ALF is a recently described memory impairment in which new information appears to be learnt and initially retained normally but then forgotten at an accelerated rate over subsequent days (Bell & Giovagnoli, 2007; Butler & Zeman, 2008a). There is some evidence to suggest that ALF may be restricted to declarative memory, which is dependent on the medial temporal lobes (MTLs) (Deak, Stickgold, Pietras, Nelson, & Bubrick, 2011; Muhlert, Milton, Butler, & Zeman, 2010). It has been proposed that ALF reflects a deficit in memory consolidation (e.g., Kapur et al., 1997).

ALF is particularly common amongst patients with transient epileptic amnesia (TEA), a form of late-onset epilepsy (mean onset 62 years, Butler et al., 2007). In TEA, seizures manifest as brief (30–60 min), recurrent episodes of memory loss (Butler et al., 2007; Kapur, 1990; Zeman, Boniface, & Hodges, 1998) which are sometimes associated with other features of epilepsy, most often olfactory hallucinations. While TEA patients typically perform within the normal range on interictal (between seizure) neuropsychological tests (Butler et al., 2007), approximately 50% complain of ALF (Zeman & Butler, 2010). The amnesic attacks in TEA usually cease with the initiation of anti-epilepsy medication, but the memory complaints often persist (Zeman & Butler, 2010).

Several lines of evidence point to the seizure focus in TEA lying in the MTLs (Zeman & Butler, 2010): (i) The memory loss experienced during attacks is similar to that occurring in other MTL disorders, including lesions (Squire & Zola-Morgan, 1991) and transient global amnesia (Bartsch & Butler, 2013); (ii) electroencephalography (EEG) evidence, when available, suggests a temporal lobe focus (Butler et al., 2007; Zeman et al., 1998); (iii) The common seizure-related symptom of olfactory hallucinations most likely reflects epileptic activity spreading out from the MTL to the nearby piriform cortex (Zeman & Butler, 2010); (iv) While brain scans in individuals with TEA are usually clinically normal, there is focal MTL atrophy at the group level (Butler et al., 2009, 2013); (v) A patient scanned during a flurry of attacks was found to have high signal in the left hippocampus on a T2-weighted magnetic resonance (MR) scan and hypermetabolism in the same region on a positron emission tomography (PET) scan, both of which had resolved once the seizures had been successfully treated (Butler & Zeman, 2008b).

The neural basis of ALF is unknown. Structural brain abnormalities have been identified in patients with ALF (e.g., Butler et al., 2009, 2013; Malmgren & Thom, 2012), but these have not been found to correlate with ALF severity. TEA patients have subtle atrophy in the hippocampus, but while this correlates with performance on standard tests of anterograde memory (which typically test memory at only 30 min after encoding), it does not correlate with ALF (Butler et al., 2009).

1.2. *Possible link between ALF and sleep*

A number of observations suggest a relationship between ALF and sleep.

There is a widely documented reciprocal relationship between sleep and epilepsy. Sleep modulates epileptic activity; slow wave sleep, in particular, has often been shown to increase it (Bazil, 2000; Bazil & Walczak, 1997; Goncharova, Zaveri, Duckrow, Novotny, & Spencer, 2009; Kotagal, 2001; Mayanagi, 1977; Nazer & Dickson, 2009; Romcy-Pereira, Leite, & Garcia-Cairasco, 2009; Rossi, Colicchio, & Pola, 1984; Sammaritano, Gigli, & Gotman, 1991). In turn, epilepsy often disrupts sleep, both in terms of subjective sleep quality and objectively measured sleep architecture (Bazil, 2000; Derrt & Duncan, 2013; Kotagal, 2001; Matos, Andersen, do Valle, & Tufik, 2010).

The amnesic attacks of TEA often occur upon waking (approximately 70% of patients have attacks in this context, Zeman & Butler, 2010), indicating that seizure activity may preferentially occur during sleep or at the transition from sleep to wakefulness (Butler et al., 2007). Further, TEA patients are more likely to show epileptiform abnormalities on sleep or sleep-deprived EEGs than wake EEGs (Butler et al., 2007; Zeman et al., 1998). And finally, ALF has been reported at delays as short as 24 h (i.e., after the first post-learning night of sleep) in groups of patients who have been shown to learn and initially retain new information normally (Fitzgerald, Thayer, Mohemed, & Miller, 2013; Martin et al., 1991; Muhlert et al., 2010).

1.3. *Sleep and memory consolidation*

There is now a large body of literature supporting the notion that sleep plays a major role in memory consolidation. The most prominent theory regarding the mechanism is that