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Memory Processing: The Critical Role of Neuronal Replay during Sleep

Patterns of neuronal activity present during learning in the hippocampus are replayed during sleep. A new study highlights the functional importance of this neurophysiological phenomenon by showing that neuronal replay is critical for memory processing over a night of sleep.

Jocelyn Breton and Edwin M. Robertson

As we sleep, facts, events and skills learnt during the day continue to be processed. Our memories become enhanced, stabilized and integrated with older memories, a process known as consolidation [1–3]. The biological mechanisms underlying memory consolidation remain poorly understood. Over forty years ago, David Marr [4] suggested that while we sleep, memories formed during the day may be replayed within the hippocampus, the part of our brain involved in memory formation. A new study [5] reported in this issue of *Current Biology* has sought to determine whether there is a critical connection between hippocampal replay and memory consolidation.

In a recent series of innovative studies, sensory cues were used to reactivate memories during a night of sleep [6–8]. In one such study, participants learnt to associate object-locations with the odor of rose-petals. During sleep, specifically during slow wave sleep (SWS), participants were exposed to either an odorless vehicle or to the rose-petal odor they were exposed to while awake. In the morning, participants were better able to recall object-locations if the rose-petal odor had been applied during the night compared to the odorless, control group. Furthermore, participants underwent functional brain imaging while in SWS and indeed, hippocampal activity increased during odor presentation. These findings demonstrate that the odor was able to reactivate, and thereby strengthen hippocampal-dependent memories [6].

Subsequent studies have gone on to demonstrate that memory reactivation can occur through the use of auditory cues. Various object-locations, each associated with characteristic sounds, were more accurately recalled if their associated sound was played during SWS [7]. Thus, auditory cues were able to selectively strengthen individual memories. Now, Fuentemilla and colleagues [5] have used auditory cues to reactivate memories during sleep in groups of patients, to test for a critical contribution of the hippocampus to memory reactivation and consolidation.

In this study [5], patients with chronic temporal lobe epilepsy, with damage restricted to the hippocampus, were tested in a memory reactivation task. Three groups of individuals were studied: those with unilateral hippocampal sclerosis; those with bilateral hippocampal sclerosis; and a healthy age-matched control group. On the first night, participants learned a list of 28 words, each of which was cued by an unrelated, unique sound. A sound was played and then a word would appear in one of four locations on a

computer screen (Figure 1). Participants were told it was more important to remember the word and its associated sound than the location of the word, and that the various locations were only used to increase learning. Once all of the sound-word pairs were played, the participants were given a cued recall test. All participants went through several rounds of learning until they could recall more than 50% of the words. Each group showed an equivalent amount of encoding following the learning task. Thus, the authors could attribute any subsequent changes in performance to memory consolidation over the night of sleep.

During sleep, and specifically during participants' SWS, half of the sounds from the learned sound-word pairs were played, with the sounds repeating approximately every five seconds for the entire duration of SWS. In the morning, participants were given a recall test where they heard sounds that had been played during the night and sounds that had not been played, and were then asked to recall the word associated with each sound (Figure 1). Control participants and patients with unilateral hippocampal damage recalled significantly more of the cued words (words whose sounds were played during sleep) compared to the non-cued words; however, patients with bilateral hippocampal damage did not show a significant difference in the recall of cued vs. non-cued words (Figure 1). Furthermore, the greater the volume of intact hippocampus, the greater the memory benefit from reactivation. These findings directly demonstrate the critical contribution of hippocampal reactivation to memory consolidation over a night of sleep.

Several recent studies have now used sensory cues (either auditory or olfactory) to elicit neuronal reactivation during sleep [5–8]. It is unclear, however, whether these cues are tapping into and boosting a physiological mechanism, or alternatively, if they are creating an artificial route to enhanced memory processing. In rats, auditory cues played during sleep can bias the amount of hippocampal replay towards the cued memories [9]. Thus, the auditory cues do appear to be tapping into and modifying a physiological process. Yet, they do so by making a *qualitative* rather than a *quantitative* change to neuronal replay: replay events were biased towards particular cued events but the overall amount of replay events stayed the same. By contrast, functional imaging work in humans shows that auditory cues elicit a *quantitative* increase in the reactivation of the hippocampus during sleep [6]. These differences between human and animal studies may be more apparent than real, perhaps resulting from differences in how neuronal activity is measured in human and animal studies (BOLD activation recorded by fMRI *versus* single-unit recording of neurons). Overall, converging evidence suggests sensory cues presented during sleep modify the physiological neuronal replay of memories.

Neuronal replay is envisaged to make a specific contribution to memory processing; yet, it is a widespread phenomenon present across multiple brain states, and brain areas. Originally, neuronal replay was found during rapid-eye movement (REM) sleep [10]. It was subsequently found in SWS, and has now even been found during wakefulness [11,12]. Similarly, while it was originally discovered in the hippocampus, neuronal replay has also been discovered within many other brain areas, including areas of the neocortex such as the parietal cortex [13]. With such ubiquity, neuronal replay may be more a repeating pattern of activity — a motif of the functional organization — of the resting brain than a specific aspect of memory processing. Yet, challenging such an idea are the recent human studies [5–8] showing that replay modified by external cues has a powerful effect upon memory consolidation. Such studies show that neuronal replay has an important and specific functional contribution to memory processing.

The findings of Fuentemilla *et al.* [5] demonstrate that neuronal replay is

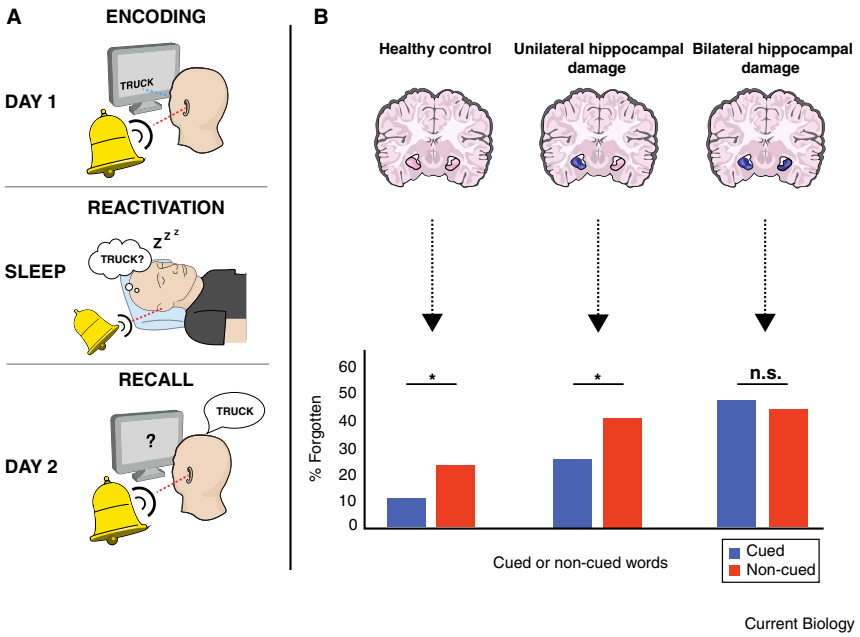

Figure 1. Schematic of experimental design and results.

(A) On day one, participants encoded sound-word pairs to a set criterion. During SWS, half of the learned sounds were played to promote memory consolidation through reactivation. On day two, participants were given a cued recall test for all of the sound-word pairs. (B) Results of the cued recall test on day two. The amount of forgetting is shown for the three groups of participants: healthy controls, unilateral hippocampal sclerosis patients and bilateral hippocampal sclerosis patients. The graph displays the percentage of words forgotten after a night of sleep, where % forgotten is defined as the number of words incorrectly recalled out of the total possible learned word pairs, multiplied by 100. One hundred percent forgetting would indicate that none were correctly recalled. The blue bars show performance on words that were cued during the night, while the red bars show performance on words that were not cued during the night. All participants demonstrated some forgetting. However, control participants and those with unilateral hippocampal damage demonstrated significantly less forgetting on words that were cued during the night, while those with bilateral damage showed a similar amount of forgetting for both the cued and the non-cued words.

critical for memory consolidation. Neuronal replay may perhaps allow for a dialogue between the hippocampus and neocortex during sleep. Yet other mechanisms, particularly within the neocortex, might also make a critical contribution to consolidation. For example, during sleep and specifically during SWS, the number of cortical synapses may be decreased [14]. Synaptic downscaling could erode certain memories, making them more easily forgotten, while, other memories are relatively strengthened [15]. During sleep there are changes in the functional organization of the neocortex that are dependent upon neuronal activity. Blocking neuronal activity within the visual cortex prevents the sleep-dependent organization of functional cortical columns [16]. Thus, several different biological mechanisms may be critical for the processing of memories over a night of sleep. An important challenge for future work is to understand the contribution of these mechanisms, and how they interact.

Changes in neuronal replay may alter the fate of a memory. For example, a reward experienced during learning can enhance subsequent neuronal replay and memory retention [17]. The effect of external cues, either olfactory or auditory, may provide a simple, robust experimental model to understand how neuronal replay can be controlled, and the destiny of a memory altered. At times, neuronal replay may be enhanced by the engagement or activation of additional neuronal processes, such as those associated with reward. Equally, at other times, neuronal replay may be subjected to an inhibitory control with the activation of neuronal processes preventing replay. So, for example, disruption of the prefrontal cortex can allow the consolidation of some memories ([18,19]; for a review see [2]). Appreciating that neuronal replay is critical for memory consolidation opens up the possibility of understanding how memory consolidation is controlled, and how the fate of a memory is determined.

In summary, the recent study by Fuentemilla *et al.* [5] demonstrates that hippocampal reactivation is critical to memory consolidation, and serves to highlight the functional relevance of neuronal reactivation to human memory processing. Understanding how neuronal reactivation is controlled and how it relates and interacts with other mechanisms of memory consolidation are important challenges that we face as we attempt to understand the biology of memory.

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Membrane Traffic: The Exocyst Meets the Cell Cycle

A new study describes a novel regulatory event that results in the inhibition of exocytic transport of a specific class of Golgi-derived vesicles during mitosis. The mechanism of inhibition is shown to involve direct phosphorylation of a subunit of the exocyst by a specific cyclin-dependent kinase complex.

Patrick Brennwald

The ability of eukaryotic cells to expand and remodel their surfaces in precise and well-orchestrated ways is central to their ability to grow, divide, and organize themselves in ways that allowed for the development of multicellular animals [1]. Appropriately timed and spatially restricted delivery of new membrane components by exocytic fusion of vesicles with the plasma membrane underlies morphogenic events, such as rapid surface growth and cytokinesis. However, in actively growing and dividing cells, different stages of the cell cycle come with distinct needs in terms of surface delivery and therefore these two events must be carefully coordinated. Recent work from the Guo lab [2] now provides new insights