Neurobiology of Learning and Memory 137 (2017) 77–82

Contents lists available at ScienceDirect

Neurobiology of Learning and Memory

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

Short communication

Targeted memory reactivation of newly learned words during sleep triggers REM-mediated integration of new memories and existing knowledge

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ARTICLE INFO

Article history:
Received 3 May 2016
Revised 2 November 2016
Accepted 14 November 2016
Available online 15 November 2016

Keywords:
Memory
Sleep
Memory consolidation
Targeted memory reactivation

ABSTRACT

Recent memories are spontaneously reactivated during sleep, leading to their gradual strengthening. Whether reactivation also mediates the *integration* of new memories with existing knowledge is unknown. We used targeted memory reactivation (TMR) during slow-wave sleep (SWS) to selectively cue reactivation of newly learned spoken words. While integration of new words into their phonological neighbourhood was observed in both cued and uncued words after sleep, TMR-triggered integration was predicted by the time spent in rapid eye movement (REM) sleep. These data support complementary roles for SWS and REM in memory consolidation.

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1. Introduction

Sleep may be the optimal brain state for consolidating new information in memory (Diekelmann & Born, 2010). According to the Complementary Learning Systems (CLS) account of memory (McClelland, McNaughton, & O'Reilly, 1995), representations of recent memories are initially mediated by the hippocampus and recalled independently from neocortical memories. Gradually the nature of these representations changes such that the role of the hippocampus decreases and the emerging neocortical representation becomes stronger and allows the new information to be integrated with existing knowledge. This neocortical consolidation relies on neural replay of new memories during sleep (O'Neill, Pleydell-Bouverie, Dupret, & Csicsvari, 2010). Neural populations or areas of the brain that were active during encoding become spontaneously reactivated during subsequent rest or sleep (Maquet et al., 2000; Wilson & McNaughton, 1994), and the extent of this reactivation predicts overnight improvement in performance (Peigneux et al., 2004).

Reactivation during sleep can also be cued externally. Rasch, Buchel, Gais, and Born (2007) created an association between new information and an odour during encoding. Cueing the new memories during slow-wave sleep (SWS) with the odour resulted in enhanced memory performance. While the odour was used to cue all of the new information, cueing can also be targeted to apply to selected memories. Rudoy, Voss, Westerberg, and Paller (2009) carried out targeted memory reactivation (TMR) by having participants learn picture-locations and associating each picture during learning with a unique sound. Playing a targeted set of the sounds was found to selectively benefit the memories associated with those sounds (Antony, Gobel, O'Hare, Reber, & Paller, 2012; Cairney, Durrant, Hulleman, & Lewis, 2014; van Dongen et al., 2012).

While TMR can strengthen declarative memory, little is known about the effects of TMR on other forms of learning postulated by the CLS account. For example, *integration* of new memories with existing knowledge should occur during consolidation and therefore benefit from TMR. Language learning studies have shown that the integration of new words in the mental lexicon involves a central role for sleep. Newly learned spoken words (e.g., *cathedruke*) begin to compete in a word recognition task with similar-sounding existing words (e.g., *cathedral)* after a night of sleep but not after an equivalent period of wake, suggesting that the new words became lexically integrated in their neocortical phonological neighbourhood only after sleep (Davis, Di Betta, Macdonald, & Gaskell, 2009; Dumay & Gaskell, 2007). Tamminen, Payne, Stickgold, Wamsley, and Gaskell (2010) and Tamminen, Lambon Ralph, and Lewis (2013) showed that this integration was

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http://dx.doi.org/10.1016/j.nlm.2016.11.012
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associated with sleep spindle activity. This suggests that sleep-associated neural replay may be involved in lexical integration, given that sleep spindles are temporally correlated with the occurrence of hippocampal ripples (Siapas & Wilson, 1998; Sirota, Csicsvari, Buhl, & Buzsaki, 2003), which reflect hippocampal replay of newly acquired memories (Girardeau, Benchenane, Wiener, Buzsaki, & Zugaro, 2009).

Here, we sought to establish the role of TMR on the integration of new words in the mental lexicon. If neural replay during sleep allows the integration of newly acquired information with existing knowledge, we expected TMR to facilitate lexical integration of novel words. TMR however may also enhance the contribution of different sleep stages to consolidation, including stages other than the one in which TMR was applied. Cousins, El-Deredy, Parkes, Hennies, and Lewis (2016) trained participants on two serial reaction time task sequences and cued one of them during SWS. Cueing-related changes in neural activation were modulated by time spent in SWS and by time spent in rapid eye-movement (REM) sleep, suggesting that cueing using TMR may engage multiple stages of sleep in the consolidation process. We therefore also investigated the association between different sleep stages and behavioural change when cueing was present and not present.

2. Method

2.1. Participants

We trained and tested 20 native English speaking students (4 males, mean age = 19.3 years) on novel words, followed by a nap during which half of the trained words were cued (sleep group). Another group of 20 participants (6 males, mean age = 19.7 years) remained awake and received no TMR (wake group).

2.2. Design and stimuli

The experiment was run in one continuous session consisting of several phases. Participants were first wired up for the polysomnography (PSG) recording. They were then trained on novel spoken words and their meanings. Immediately after training they carried out the first test session. This started with three tasks measuring learning of word forms: free recall, lexical competition, and old-new categorisation. Tasks measuring learning of word meanings followed. Here we focus on word forms; the meaning tasks did not show effects of sleep vs. wake or of TMR, and are reported in Supplementary materials.

At the end of the first test session, participants were told whether they were taking part in the sleep or the wake condition. Wake group watched films with no language input for 90 min. Sleep group were asked to take a nap and woken up 90 min after lights off time. This sleep/wake period started between 12.30 pm and 1.30 pm. Once the participant was in SWS, half of the trained novel words were cued by playing them once through loudspeakers located in the bedroom, integrated into unobtrusive background brown noise presented throughout the nap. If the participant woke up during cueing, they were removed from the data analysis.

68 stimulus triplets consisting of a familiar base word (e.g., *cathedral*), a fictitious novel word (e.g., *cathedruke*), and a similar-sounding nonword foil to be used in the old-new categorisation task (e.g., *cathedruce*) were selected from Tamminen and Gaskell (2008). Base words were bisyllabic or trisyllabic, 6–11 phonemes in length (M = 8.0), and with CELEX frequency in the 2–18 occurrences per million range (M = 4.3; Baayen, Piepenbrock, & van Rijn, 1995). Triplets were divided into two lists of 34, matched in number of syllables, length, and frequency. For each participant, one of the lists was used for training, and the base words from the other list remained untrained and acted as control words in the lexical competition task. This was counterbalanced. The lexical competition task also required 68 filler words which ensured that only 25% of real words encountered in the task were base words, making it unlikely that participants became aware of the relationship between base words and the phonologically overlapping novel words. The fillers were monosyllabic (N = 46), bisyllabic (N = 10), or trisyllabic (N = 10) and had slightly higher frequency to the base/control words (M = 11.0, 11.4, 11.5 respectively). 136 word-like nonwords were created by changing one phoneme of a real word (not used in the other conditions).

2.3. Procedure

2.3.1. Training session

A phoneme monitoring trial started with visual presentation of a target phoneme, followed by auditory presentation of a novel word. Participants indicated with a keypress whether the target was present in the word. In the meaning matching task a novel word was presented visually and auditorily simultaneously. Below, a candidate meaning was presented which was correct 50% of the time. Participants indicated with a keypress whether they thought the meaning was correct. Feedback was given, and the correct meaning was presented. In the cued recall task participants heard a novel word and saw it on the screen. They had to recall the meaning of the word and type it in within 30 s. The correct meaning was then presented. The meaning was always unrelated to the meaning of the base word from which the novel word was derived.

Participants first completed one block of phoneme monitoring where each word was encountered six times. One block of the meaning matching task then followed, where each word was encountered twice. Next, a block of cued recall was completed where each novel word was encountered once. This sequence of the three training tasks was then repeated twice, thus giving a total of 27 exposures to each novel word across all tasks. Participants were aware that they would be tested on memory for the novel words.

2.3.2. Test session

After training participants filled in the Stanford Sleepiness Scale and performed the first test session. There were no significant differences in sleepiness between the wake group and the sleep group at the beginning of this (p = 0.52) or the second test session (p = 0.14). In the free recall task participants were given three minutes to recall as many novel words as possible. In the lexical competition task participants were presented with a stimulus through headphones; this could be one of the base words (e.g., *cathedral*), one of the control words (e.g., *dolphin*), one of the filler words, or one of the nonwords, in random order. Participants made lexical word/nonword decisions with a keypress. In the old-new categorisation task a word was presented over the headphones, and participants indicated whether the word was a trained word ("old") or a similar-sounding foil ("new"). Stimuli were presented in a pseudorandom order such that at least four trials separated the occurrence of a novel word and its related foil.

An Embla N7000 system recorded PSG. Six scalp electrodes (F3, F4, C3, C4, O1, O2) were used with contralateral mastoid references. Two electro-oculographic channels monitored eye movements and two chin electromyographic channels monitored muscle tone. 30-s epochs of sleep data were scored into different sleep stages following the AASM scoring criteria (Iber, Ancoli-Israel, Chesson, & Quan, 2007). Number of sleep spindles was detected during Stage 2 sleep and SWS using the algorithm developed by Ferrarelli et al. (2007).

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