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Sleep deprivation disrupts the contribution of the hippocampus to the formation of novel lexical associations

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ABSTRACT

Sleep is involved in the mechanisms underlying memory consolidation and brain plasticity. Consolidation refers to a process through which labile memories are reorganized into more stable ones. An intriguing but often neglected question concerns how pre-existing knowledge is modified when new information enters memory, and whether sleep can influence this process. We investigated how nonword learning may modify the neural representations of closely-related existing words. We also tested whether sleep contributes to any such effect by comparing a group of participants who slept during the night following a first encoding session to a sleep deprived group. Thirty participants were first intensively trained at writing nonwords on Day 1 (remote nonwords) and Day 4 (recent nonwords), following which they underwent functional MRI. This session consisted of a word lexical decision task including words orthographically-close to the trained nonwords, followed by an incidental memory task on the nonwords. Participants who slept detected real words related to remote nonwords faster than those related to recent nonwords, and showed better explicit memory for the remote nonwords. Although the full interaction comparing both groups for these effects was not significant, we found that participants from the sleep-deprivation group did not display such differences between remote and recent conditions. Imaging results revealed that the functional interplay between hippocampus and frontal regions critically mediated these behavioral effects. This study demonstrates that sleep may not only strengthen memory for recently learned items but also promotes a constant reorganization of existing networks of word representations, allowing facilitated access to orthographically-close words.

1. Introduction

One central question in memory research relates to how newly encoded knowledge is incorporated into preexisting networks of memory representations. This process allowing long-term retention is called memory consolidation. Substantial experimental evidence supports that sleep may represent a privileged period for memory consolidation to occur (Maquet, 2001). In particular, sleep would favor the reactivation of information previously encoded during wakefulness (Diekelmann, Buchel, Born, & Rasch, 2011). This replay of recent memories was first observed in the hippocampus (Peigneux et al., 2004; Wilson & McNaughton, 1994). Further research then showed that the hippocampal replay may trigger coordinated reactivations across those distributed cortical and subcortical circuits initially implicated when the event was memorized, whose neural representation would ultimately be strengthened (Ji & Wilson, 2007; Lansink, Goltstein, Lankelma, McNaughton, & Pennartz, 2009). This “system consolidation” involves a temporal alignment of hippocampal ripples (during which bouts of replay occur), sleep spindles, and slow oscillations (~1 Hz). In humans, slow oscillations between the hippocampus and cortical regions, in particular frontal regions would orchestrate memory transfer from short- to long-term storage (Gais et al., 2007; Lahl, Wispel, Willigens, & Pietrowsky, 2008; Sterpenich et al., 2007; Stickgold, 2005). Over the past decade or so, research in both rodents and humans has provided strong support to this model and shown in particular that the consolidation of declarative memories is improved by some form of offline memory reprocessing and concomitant neural oscillatory activity (Maingret, Girardeau, Todorova, Goutierre, & Zugaro, 2016; Marshall,

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Helgadottir, Molle, & Born, 2006). Beyond its key role in the transfer of short-term memories across distributed specialized cortical sites and frontal brain regions for long-term storage, which would predominate during sleep, recent studies in the field of memory research also suggest that the hippocampus directly contributes to the integration of recently encoded knowledge, through associative processes and this region may thus subserve generalization processes as well as the emergence of more abstract representations (Davachi, Mitchell, & Wagner, 2003; Igloi, Doeller, Berthoz, Rondi-Reig, & Burgess, 2010). The hippocampus is necessary for recollection because of its unique ability to assign independent representations to even highly similar stimuli (Lacy, Yassa, Stark, Muftuler, & Stark, 2011; Yassa & Stark, 2011) through processes known as pattern separation and pattern completion. Our experimental design was however not meant to test for pattern separation (see Liu, Gould, Coulson, Ward, & Howard, 2016) and the resolution of our fMRI data would not allow for correlational multi-voxel pattern analyses across subfields of the hippocampus, believed to have distinct contributions to pattern separation/completion (e.g. Yassa & Stark, 2011).

Associative processes were studied in a paradigm in which participants had to learn novel made-up words (e.g., BANARA) that were visually close (one letter change) or ‘‘neighbors” of familiar so-called ‘‘hermit words”, i.e., words initially without any such neighbors (e.g., BANANA, Bowers, Davis, & Hanley, 2005). When tested on a semantic categorization task (word referring to artefact vs. natural objects) on the next day, participants were slowed for those words which had acquired one novel neighbor. These results were interpreted as reflecting lexical competition effects, whereby a newly learned word transiently interferes with the categorization of a related word. In a study using a similar task with spoken familiar and novel words, Dumay and Gaskell (2007) demonstrated that sleep contributes to the emergence of these interference effects 12–24 h after learning, plausibly by strengthening the representation of newly learned lexical information. Moreover, the quantity of spindles during the night was also related to the degree of lexicalization (Tamminen, Payne, Stickgold, Wamsley, & Gaskell, 2010). While the results of these studies are consistent, it is however important to highlight that the delay between encoding and test was comprised between 12 and 24 h. While this rather short time interval is apparently prone to competing or interfering effects, we expect that a longer time interval (i.e. several days), allowing for the stabilization of the lexical and/or semantic changes, may eventually lead to facilitating effects. In fact, in these paradigms, lexical competition between memory elements could reflect an intermediate and possibly unstable state of memory representations, while a more integrated and better structured state of these networks of representations later in time would rather facilitate lexical access to closely related memory elements. This point is of high importance for the understanding of the impact of novel material encoding and motivated the design of our study. Additionally, facilitation could also occur due to higher perceptual priming for words when semantically and/or lexically associated with other words or nonwords (McDermott, 1997).

To account for such memory integration effects, Shohamy and Wagner (2008) developed the concept of *integrative encoding*, according to which the presence of a common feature (e.g., ***B***) between two separately encoded elements (e.g., A***B*** and ***B***C) would strengthen their association in memory and elicit a higher probability of remembering one element (A) whenever the other is presented (C). The authors further emphasized the role of the hippocampus in such generalization processes during learning and memory consolidation, also consistent with the observation that the hippocampus contributes to the integration of overlapping visual stimuli (Heckers, Zalesak, Weiss, Ditman, & Titone, 2004). It therefore appears that encoding new information in memory can both interfere with previously stored knowledge through competition (presumably at an early stage, 12–24 h after encoding) and, at some later stage of memory consolidation, facilitate the access to closely related-material through integrative memory processes (at least 2–3 days after encoding, according to our hypothesis). It is thus still not clear whether facilitating or competing behavioral effects can coexist, and/or follow a distinct deployment in time. Moreover, how sleep may influence memory integration processes underlying such behavioral effects is not yet well understood.

Extending previous studies looking at the effects of sleep on lexicalization (e.g. Dumay & Gaskell, 2007; Tamminen et al., 2010), here we addressed these issues by using a simple lexical (word/nonword) decision task involving familiar written words related to recently learned nonwords. Specifically, to investigate the impact of time and sleep on memory, we tested one group of participants (N = 15), who slept normally the night immediately following an initial learning session, and one group of participants (N = 15) who did not sleep during that night. All participants performed a second learning session 72 h after the first learning session, i.e., after the sleep-deprived had two recovery nights. To assess whether facilitating/competing effects on real words in the lexical decision task would implicate better consolidation of the associated nonwords, we also tested recognition memory for the nonwords. Using this experimental design, we tested (i) whether learned nonwords either facilitate or interfere with the processing of related words during the lexical decision task; (ii) how the memory for the learned nonwords and their impact on related words may vary in a time-dependent and/or sleep-dependent manner; and (iii) whether the integration of novel nonwords relies on a functionally-connected network of brain regions involving the hippocampus.

2. Material and method

2.1. Participants

Thirty normally-sighted, right-handed, healthy volunteers (20 women, 10 men, mean age 23.3 ± 4.5 years old) gave their written informed consent to take part in this fMRI study, which was approved by the Ethics Committee of the Faculty of Medicine of the University of Geneva. None of the participants had a history of neurological, psychiatric or sleep disorder. Their scores on the Beck depression scale (Steer, Ball, Ranieri, & Beck, 1997) and Beck anxiety scale (Beck, Epstein, Brown, & Steer, 1988) were within normal range. Participants with extreme morning and evening types, as assessed by the Horne-Ostberg Questionnaire (Horne & Ostberg, 1976), were not included in the study. No participant complained of excessive daytime sleepiness as assessed by the Epworth Sleepiness Scale (Johns, 1991) or of sleep disturbances as determined by the Pittsburgh Sleep Quality Index Questionnaire (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). During 7 days prior to the first visit, participants were asked to follow a regular sleep schedule (aligned to their own sleep rhythm ± 2 h), which they also kept during the next 3 days until their second visit to the laboratory. Compliance to the schedule was assessed using sleep diaries and wrist actigraphy (Actiwatch, Cambridge Neuroscience; Daqtometer by Daqtix GbR, Oetzen, Germany).

2.2. Experimental material

Nonwords were created using 144 real French words. These words were selected from a meta-analysis from Bonin et al. (2003) who investigated the concreteness, imageability, subjective frequency, and emotional valence of 866 French words, assessed by 97 native French speakers. All 144 selected words were