Beyond acetylcholine: Next steps for sleep and memory research

Jessica D. Payne, Willoughby B. Britton, Richard R. Bootzin, and Lynn Nadel

Department of Psychology, University of Arizona, Tucson, AZ 85721.
jdpayne@u.arizona.edu **wbritton@u.arizona.edu**
bootzin@u.arizona.edu **nadel@u.arizona.edu**

Abstract: We consider Walker's thorough review in the context of thinking about future research on the relation between sleep and memory. We first address methodological issues including type of memory and sleep-stage dependency. We suggest a broader investigation of potential signaling molecules that may be critical to sleep-related consolidation. A brief review of the importance of the stress hormone cortisol illustrates this point.

Walker's impressively comprehensive review of the literature on sleep and memory consolidation is a welcome advance that renders a thorny area a bit easier to grasp. Our commentary starts with methodological suggestions and then turns to mechanisms, where we encourage a focus on neuromodulators (in addition to acetylcholine) that are critical to memory function and demonstrate substantial fluctuations across the sleep cycle. We highlight the stress hormone cortisol as an important example.

Methodological suggestions. At this early stage of investigation, we encourage a diversity of designs, as well as careful replications. More attention should be paid to different types of memory consolidation across the sleep cycle. Walker's focus is largely on procedural memory, but the story of sleep and memory consolidation is likely to be quite different for episodic and semantic memory or emotional memory, which must themselves be sharply distinguished. For example, Plihal and Born (1997; 1999a) found that episodic memory (spatial memory, list-learning) is enhanced preferentially by SWS-rich early-night sleep, whereas procedural memory (mirror tracing, priming) is enhanced by REM-rich late-night sleep. While Plihal and Born's probabilistic approach to sleep stages has its own merit, the lack of replicability of sleep stage findings (e.g., using the perceptual discrimination task of Karni et al. 1994) requires additional studies that more carefully examine the relationship between performance and sleep stage specifically. If conflicting evidence continues despite stricter stage-related methodology, the field may require a deconstruction of the traditional Rechtschaffen and Kales (1968) sleep stages into more specific electrophysiological signatures (e.g., spindles or slow-wave activity).

Mechanism issues. Walker concentrates almost exclusively on acetylcholine (ACh), which is elevated during REM sleep and is thought to be involved mainly in memory acquisition (not consolidation). However, ACh is not alone in having an impact on memory function. Just to name a few examples, serotonin, norepinephrine, immune proteins, and trophic factors, as well as the stress hormone cortisol, are also important modulators of memory.

The importance of investigating other neuromodulators can be illustrated by recent studies of cortisol, which effects memory function and shows sleep-stage specific fluctuations. Cortisol secretion is at a minimum during the early portion of nocturnal sleep (when SWS is prevalent) and achieves a diurnal maximum toward the end of the night (when REM is prevalent) (e.g., McEwen 2003). Dense concentrations of cortisol receptors are found in the hippocampus, a structure critical for spatial and episodic memory function. There is considerable evidence that high plasma cortisol concentrations impair performance on episodic memory tasks in wake (deQuervain et al. 2000; Payne et al. 2002). Therefore, one complication in the investigation of sleep and episodic memory consolidation could be the high cortisol levels associated with late-night sleep.

Plihal and Born (1997; 1999a) have argued similarly that REM sleep is an inefficient time to consolidate episodes due to the deleterious effect of elevated cortisol on memory processes. SWS, on the other hand, may be an ideal physiological environment for episodic memory consolidation, because cortisol release is inhibited during early-night periods dense in SWS. Plihal and Born (1999b) found that cortisol infusions during early sleep eradicated the typical SWS-related improvement in episodic memory, but failed to disrupt retrieval of a procedural memory task. Because episodic memory, but not procedural memory, relies on hippocampal function, they concluded that cortisol inhibition during early nocturnal sleep is necessary for episodic memory consolidation. Thus, early SWS may be optimal for the consolidation of episodic memories, while the late-night cortisol-rich REM sleep may inhibit episodic memory consolidation, and account for the episodic memory difficulties often found in REM sleep.

Given the presence of high cortisol levels during late-night sleep, it may be best to test for episodic memory gains after 4 hours of early night sleep or, possibly, with the use of early afternoon naps, as Mednick et al. (2003) did, when cortisol levels are low. Mednick et al. (2003) found that brief naps containing both SWS and REM sleep enhanced visual discrimination learning equivalent to that obtained by a full night's sleep. Naps containing only SWS failed to produce enhancement. Afternoon naps, then, may be another means of isolating SWS and dissociating REM sleep from elevated cortisol.

In addition to cortisol, a number of other neuromodulators, including both immune proteins and trophic factors, may play critical roles in sleep-related memory consolidation. For example, growth hormone, which is known to play a role in memory formation by inducing gene expression for NMDA receptors in the hippocampus (Le Greves et al. 2002), reaches its peak during SWS and drops off during REM. Similarly, SWS-related decreases in the somnogenic process S candidates adenosine and interleukin-1 may play a role in memory consolidation in SWS. Adenosine modulates synaptic plasticity (de Mendonca & Ribeiro 1997) and adenosine antagonism is beneficial to memory formation (Hauber & Bareiss 2001). Interleukin-1, like cortisol, has been implicated in hippocampus-specific memory impairments (Aubert et al. 1995; Gibertini et al. 1995) and is found in high concentrations in the hippocampus (Farrar et al. 1987). If consolidation of episodic memory primarily occurs in SWS and is inhibited in REM, the systematic sleep-stage-specific fluctuations of growth hormone, adenosine, IL-1, and cortisol may contribute to this process.

Other trophic factors that modulate synapse formation and hippocampal LTP, such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) have been found to be related to sleep, inducing changes in sleep duration (Kushikata et al. 1999) and responding to manipulations in sleep (Peyron et al. 1998; Sei et al. 2000).

Attention to these various signaling molecules which play a role in synaptic plasticity and memory formation and fluctuate systematically during sleep would be quite informative. Many of them are poorly regulated in clinical populations that suffer from memory impairment (e.g., depression, PTSD, Alzheimer's). Investigations of sleep-related memory processes in these populations could illuminate ways in which neuromodulators influence sleep and sleep-memory consolidation interactions.

In summary, Walker has provided a comprehensive review of sleep and procedural memory that will facilitate future research. We have emphasized some methodological and conceptual issues that should be attended to by such future research.

https://doi.org/10.1017/S0140525X05340027 Published online by Cambridge University Press