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Rimmele, Ulrike; Tambini, Arielle

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EDITORIAL

Sleep, Sleep Alterations, Stress—Combined Effects on Memory?

Commentary on Cedernaes et al. Short sleep makes declarative memories vulnerable to stress in humans. SLEEP 2015;38:1861–1868.

Ulrike Rimmele, PhD[1]; Arielle Tambini, PhD[2]

[1]*Department of Fundamental Neurosciences, University of Geneva, Geneva, Switzerland;* [2]*Helen Wills Neuroscience Institute, University of California, Berkeley, CA*

Sleep and stress interact bidirectionally: prior stress can impair sleep and alterations in sleep can change stress hormone levels.[1–4] Both stress and sleep affect cognitive functions such as memory.[5,6] Experimental research has traditionally examined the effects of either stress or sleep alone on cognitive function. For example, it has been shown that sleep or stress applied separately after learning, have a beneficial effect for retention of newly acquired memories.[7–10] However, to date there are no studies that have experimentally manipulated both sleep and stress to examine their combined effects on human memory. In this issue of *SLEEP*, Cedernaes and colleagues[11] present a novel approach by examining effects of short vs. full sleep in combination with a stress manipulation on memory.

In their study, Cedernaes and colleagues had young men learn object-location associations (similar to the game "Memory") and a finger tapping sequence in the evening, once before sleeping a normal night of sleep (23:00–07:00) and once before sleeping only half a night (03:00–07:00). In the morning their memory for both tasks was tested twice: first directly after sleep and second directly after a stress manipulation that followed the first memory test. Surprisingly, after short sleep, participants had marginally better memory for object-location associations than after full sleep in the first memory test. Memory was differentially modified by the stressor depending on prior sleep: a stronger decline in object-location memory was found when participants had slept only four hours compared to eight hours. In contrast to object-location memory, motor memory assessed with the finger-tapping task did not differ between sleep conditions at the first memory test after sleep and was not differentially modified by the stressor. One or multiple neurobiological mechanisms may be responsible for this novel pattern of behavioral results observed by Cedernaes. Are they due to sleep, to sleep deprivation, to stress or a combination of these, or other factors?

In this study, participants' physiological states clearly differed between the two conditions after learning: In the full sleep condition, participants were allowed to sleep for up to 8 hours directly after learning, whereas in the short sleep condition, participants were sleep deprived for about 4 hours and then allowed to sleep from 03:00 to 07:00. Sleep is thought to primarily support the consolidation of memories (i.e., the stabilization and reorganization of memory representations).[7] Previous studies employing similar associative memory tasks showed that the features of post-encoding NREM sleep are related to later memory performance,[12] whereas features of NREM sleep physiology as well as late nocturnal sleep appear to benefit motor memories.[13–16]

In the study by Cedernaes, participants spent significantly more time in shallow NREM and REM in the full vs. short sleep condition.[11] Given that mechanisms of reactivation are thought to stabilize and reorganize memory representations during NREM sleep,[17,18] reduced sleep could have led to weaker representations of object-location associations in the short versus the full sleep condition. It is also likely that the 4-hour wake period preceding sleep in the short sleep condition additionally contributed to differential consolidation of the learned material. Indeed, sleep deprivation itself is associated with increased sympathetic activity as well as impaired hypothalamus-pituitary adrenal (HPA) axis regulation leading to elevated basal cortisol levels.[2,3,19] These physiological changes are of particular interest given that stress-induced activation of these systems in the wake state plays a role in stress influence on memory formation,[20,21] whereas in the sleep state low circadian cortisol levels during the first half of the night help memory consolidation,[22–24] Thus, in the full sleep condition participants underwent the normal sleep-dependent circadian cortisol suppression during the first half of the night together with NREM-rich early sleep, which have been demonstrated to interactively benefit consolidation of associative memories.[22] In contrast, cortisol levels during the second half of the night likely followed the circadian rise that could have rendered the memory consolidation properties of NREM sleep in the short sleep condition less effective. Consequently, potential differences in the stability of associative memory representations as a function of short versus full sleep may make them more or less resilient to subsequent manipulations, such as a stress (perhaps analogous to literature showing sleep makes relational memories more resistant to interference[25,26]).

Another possible mechanism underlying the decline in object-location associative memory as a function of stress in the short vs. full sleep condition may be due to differential reconsolidation. Previous studies found that a stressor applied after memory reactivation alters memory reconsolidation and subsequently influences memory performance.[27–29] Since stress responses are altered after sleep deprivation,[2,19] it is possible that upon reactivation of object-location memories during the post-sleep memory test the subsequent stress manipulation altered the memory representation differentially as a function of prior sleep in the short versus full sleep condition.

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Address correspondence to: Ulrike Rimmele, Department of Fundamental Neurosciences, University of Geneva, Campus Biotech, CP 60, 1211 Geneva 20, Geneva, Switzerland; Tel: ++41223790995; Email: ulrike.rimmele@unige.ch

Of note, a recent study demonstrated that pre-learning levels of the stress hormone cortisol are related to memory performance 12 hours after learning when sleep (but not a wake interval) followed learning. These findings provide further evidence that sleep and stress systems interact to support memory formation.[30,31]

Given the intriguing findings of Cedernaes[11] and the notion that stress and sleep are regulated by shared neuronal circuitry and neuroendocrinology,[1] it may be fruitful for future memory research to take into account pre-learning physiological states such as stress or sleep alterations, as well as stress-sleep interactions during multiple memory stages (encoding, consolidation, retrieval and reconsolidation). A better understanding of stress and sleep's combined influences on memory functioning seems to be especially relevant, not only because modern lifestyles are not infrequently associated with frequent exposure to both stress and sleep alterations, but also because highly prevalent psychiatric and mood disorders, such as posttraumatic stress disorder and depression, show alterations in sleep, stress, and memory systems.[5,21,32–35] Better knowledge of stress and sleep interactions on memory functioning may thus be helpful for the development of more effective treatments for such psychiatric disorders. Lastly, a more complete understanding of sleep-stress interactions and their relevance for memory is likely to be highly relevant in educational settings.

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