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Sleep benefits subsequent hippocampal functioning

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Sleep before learning benefits memory encoding through unknown mechanisms. We found that even a mild sleep disruption that suppressed slow-wave activity and induced shallow sleep, but did not reduce total sleep time, was sufficient to affect subsequent successful encoding-related hippocampal activation and memory performance in healthy human subjects. Implicit learning was not affected. Our results suggest that the hippocampus is particularly sensitive to shallow, but intact, sleep.

A recent study found reduced hippocampal activation and lower memory performance after 35 h of total sleep deprivation[1]. Such findings appear to have strong face validity in view of the changing sleep habits in our society; total sleep deprivation for such an extended period, however, seldom occurs. Rather, shallow sleep has been recognized as a problem of increasing societal prevalence and relevance. Shallow sleep occurs as a result of aging, obesity-related sleep apnea, stress and environmental noise. In electroencephalographic (EEG) sleep recordings, shallow sleep is characterized by a decrease in slow-wave activity (SWA, 0.5–4 Hz) and an increase in alpha (8–12 Hz) and higher frequencies[2]. Here, we investigated whether shallow sleep, rather than sleep deprivation, would be sufficient to affect hippocampal activation and memory encoding, focusing on elderly individuals, in whom shallow sleep is most relevant, reserve capacities may be limited and variable performance on explicit memory encoding reflects variability in right hippocampal activation[3].

In 13 healthy, well-sleeping elderly individuals (nine females, average age of 60.1 ± 8.3 years), we used a mild acoustic sleep-perturbation approach[4] to induce the typical EEG profile of reduced SWA and increased higher frequencies (**Fig. 1**), while leaving sleep efficiency, total sleep duration and the number of sleep state transitions intact (**Supplementary Table 1** online). Informed consent was obtained.

Following normal and shallow sleep in a within-subject balanced design, subjects performed a visual memory encoding task while we obtained functional magnetic resonance imaging recordings (1.5 T Siemens Sonata); the task consisted of viewing 50 novel images (two parallel versions consisted of images of houses or landscapes). The scanning session was performed between 4 and 8 p.m. to avoid time-of-day effects, and the subjects did not nap during the day. Memory scores were obtained the following day by asking the subjects to respond with either a 'yes' or 'no' to 100 images (houses or landscapes), of which 50 were the original images, in response to the question of whether the image shown belonged to the set of images seen before. Subjects who received the sleep manipulation showed a significantly lower memory score, as evidenced by a reduced d-prime score (shallow sleep, 0.70 ± 0.06 (average ± s.e.m.); normal sleep, 1.07 ± 0.09; paired *t*-test, $P = 0.007$; **Supplementary Fig. 1** online).

Consistent with previous studies of declarative encoding[5,6], our analysis showed that the encoding of novel images after normal sleep activated a large region encompassing the occipital cortex, the ventral and medial temporal cortex, compatible with the 'ventral route' of information processing, and the parietal cortex, compatible with the 'dorsal route'[7]. The activation in the temporal lobe encompassed the medial temporal lobe bilaterally, including the hippocampus, the entorhinal cortex and the perirhinal and parahippocampal cortices at posterior levels, whereas more anterior activation was restricted to the hippocampus proper. In the temporal cortex, activation was stronger and more extensive on the right side (**Supplementary Table 2** online). Additional clusters of local activation were found in the left and right dorsal lateral prefrontal cortices and anterior cingulate cortex. Encoding following shallow sleep as compared with normal sleep was associated with a selectively decreased activation in the anterior part of the right hippocampal formation. Exploratory analyses revealed that the decrease in right medial temporal activation correlated positively with the induced SWA reduction ($r = 0.45$) and negatively with the induced alpha band increase ($r = -0.37$), but these correlations did not reach statistical significance ($P = 0.22$ and 0.33, respectively).

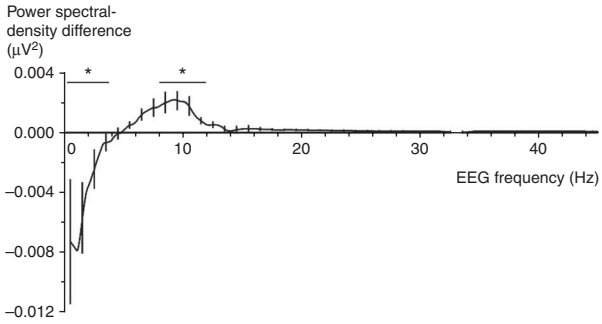

Figure 1 Changes in sleep spectral density after shallow-sleep induction. The average differences ± s.e.m. between the normalized power spectral densities of non–rapid eye movement sleep (stages I–IV) of the undisturbed versus the disturbed night are shown for electrode P4. Asterisks denote the delta (SWA, <1 Hz) and alpha (8–12 Hz) frequency bands that were significantly different ($P = 0.002$ and $P < 0.001$, respectively) irrespective of electrode location on the scalp (see **Supplementary Methods** online).

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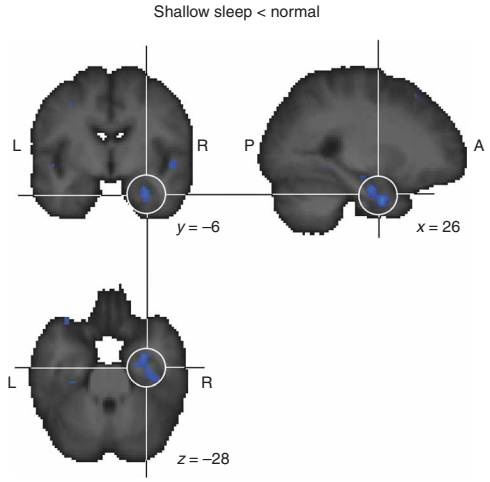

Figure 2 Shallow sleep affects hippocampal activation. We measured the difference in brain activation during encoding of subsequently successfully recalled items following normal or shallow sleep. The right anterior hippocampus showed significantly lower encoding-related activation after sleep manipulation (Zmax = 3.2, $P = 0.0007$ uncorrected; $x = 24$, $y = 0$, $z = -34$). Images were thresholded at $z = 2.3$; only the right hippocampus exceeded the significance threshold ($P = 0.001$). A, anterior; L, left; P, posterior; R, right.

To exclude the possibility that the average decrease in activation following shallow sleep was merely the result of lapses of attention during the viewing of the stimuli, we verified that the decrease of activation remained when the analysis was restricted to successfully encoded items only (**Fig. 2**). The reduction in right medial temporal activation remained significant ($Z = 3.2$, $P = 0.0007$) and was specific; we measured brain activation as percentage change in blood oxygen level–dependent activity for the contrasts remembered or forgotten versus control items from a 5 × 5 × 5 mm region of interest surrounding the voxel showing the strongest difference between successfully encoded and control items and found no significant drop in medial temporal activation as a result of shallow sleep during viewing of the subsequently forgotten items ($P = 0.66$).

To further investigate whether the effect of shallow sleep was specific to the hippocampal involvement in explicit memory encoding performance, we asked the subjects to carry out an implicit learning task that did not involve hippocampal activation. A four-choice serial reaction-time task was performed outside of the scanner, with a fixed sequence alternating with random sequences. The performance benefit for the fixed relative to the random sequences, a measure of implicit learning, did not differ between the sleep-disturbed or the control conditions ($P = 0.92$; **Supplementary Fig. 1**). On debriefing, subjects were not aware of the fixed sequence, confirming that the learning was implicit.

Our data suggest that deep sleep preceding a task optimizes the hippocampus for encoding of novel information, consistent with studies in humans and rats using total sleep deprivation[1,8]. Such a role for deep sleep in subsequent learning is complementary to the potentiating effects on consolidating previously learned material[9]. Total sleep deprivation is not necessary to induce the effects, as our intervention left sleep duration, efficiency, number of stage transitions and staging intact. Rather, only the balance between SWA and higher-frequency activity differed between the conditions. Notably, the impaired encoding of novel declarative information was a specific effect of our intervention, as performance on an implicit procedural task was unimpaired. Our manipulation led to reductions of hippocampal activation during encoding of subsequently remembered, but not forgotten, items. Our data suggest that deep sleep before learning allows for optimal hippocampal activity and benefits memory encoding. The mechanism by which deep sleep affects hippocampal function is unclear, but may involve local synaptic changes resulting from SWA[10,11]. Such hippocampal synaptic reorganization would occur in spite of the apparent absence of SWA in the hippocampus proper[12], but the synaptic changes may still be consistent with the finding that the firing rate in the hippocampus is modulated by the up and down states of the cortical SWA[13].

Note: Supplementary information is available on the Nature Neuroscience website.

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AUTHOR CONTRIBUTIONS

Y.D.v.d.W. carried out the data acquisitions, the fMRI and EEG analyses, and wrote the manuscript. E.A. performed the data acquisitions and co-wrote the manuscript. M.M.S. and E.J.S.-A. carried out the fMRI analyses. J.C.V. performed the sleep scoring. W.d.R. devised the sleep manipulation tool. E.J.W.v.S. supervised the project, performed the statistical analyses of the EEG data and co-wrote the manuscript.

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