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CHAPTER 16

Reduction of nocturnal slow-wave activity affects daytime vigilance lapses and memory encoding but not reaction time or implicit learning

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Abstract: Total sleep deprivation in healthy subjects has a profound effect on the performance on tasks measuring sustained attention or vigilance. We here report how a selective disruption of deep sleep only, that is, selective slow-wave activity (SWA) reduction, affects the performance of healthy well-sleeping subjects on several tasks: a "simple" and a "complex" vigilance task, a declarative learning task, and an implicit learning task despite unchanged duration of sleep.

We used automated electroencephalogram (EEG) dependent acoustic feedback aimed at selective interference with—and reduction of—SWA. In a within-subject repeated measures crossover design, performance on the tasks was assessed in 13 elderly adults without sleep complaints after either SWA-reduction or after normal sleep.

The number of vigilance lapses increased as a result of SWA reduction, irrespective of the type of vigilance task. Recognition on the declarative memory task was also affected by SWA reduction, associated with a decreased activation of the right hippocampus on encoding (measured with fMRI) suggesting a weaker memory trace. SWA reduction, however, did not affect reaction time on either of the vigilance tasks or implicit memory task performance.

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These findings suggest a specific role of slow oscillations in the subsequent daytime ability to maintain sustained attention and to encode novel declarative information but not to maintain response speed or to build implicit memories. Of particular interest is that selective SWA reduction can mimic some of the effects of total sleep deprivation, while not affecting sleep duration.

Keywords: sleep disorders; sleep deprivation; sustained attention; insomnia; PVT.

Introduction

Disruption of sleep affects daytime cognitive functioning, as borne out by a rich literature on the subject. Among those functions are vigilance and memory. Acute sleep deprivation in healthy subjects leads to reduced vigilance, as shown by a higher number of lapses, that is, late or absent responses to the stimuli (Dinges et al., 1997; Drummond et al., 2005; Van Dongen et al., 2004) and also leads to a reduced capacity for learning new declarative material (Yoo et al., 2007). These studies use total sleep deprivation to investigate the effect of sleep loss. The results do not allow to (1) judge which sleep phase or sleep parameters are most strongly involved in the effects of sleep deprivation or (2) show how different forms of memory are affected by sleep disruption.

We here aimed to investigate the effects of a specific sleep disruption, targeting deep sleep, without the confound of sleep deprivation, on different memory tasks to study their differential sensitivity.

To do so, we exposed healthy volunteers without sleep complaints to two full nights of selective slow-wave activity (SWA) reduction (Arima et al., 2001; Drewes et al., 2000; Landsness et al., 2009; Van Der Werf et al., 2009) prior to one of two cognitive testing sessions. The same volunteers were allowed two nights of normal sleep prior to the other testing session. The SWA-reduction method selectively attenuates SWA and increases alpha power. Reduced SWA and increased alpha power have both been related to the severity of subjective sleep complaints of primary insomnia patients (Krystal et al., 2002). As such, the selective SWA reduction may represent a more "ecologically valid" model of the attenuation of slow-wave sleep in primary insomnia than the frequently applied total sleep deprivation model. In spite of the fact that insomnia is the most frequent sleep disorder and a frequent complaint in psychological practice, only a few studies have quantitatively addressed the daytime behavioral, cognitive, and brain abnormalities of the condition (Altena et al., 2008a,b). Virtually, no study has evaluated the validity of experimental models for daytime complaints of insomnia, which are much needed in order to accelerate progress in our understanding of this condition.

We measured, both after normal sleep and after selective SWA interference: (a) vigilance using two adaptations of the psychomotor vigilance task (PVT), that is, a "simple" vigilance task requiring the subject to respond to an unpredictably occurring target stimulus on a computer screen (no other stimulus was presented throughout the task) and a "complex" vigilance task, requiring the subject to respond to one of two occurring stimuli; (b) declarative memory using encoding of novel pictures, followed by a recognition trial; and (c) implicit memory by requiring subjects to perform a sequence of button presses, which contained, unbeknownst to the subject, a hidden fixed sequence. Improved performance on this task is shown by a faster reaction time on the fixed sequence relative to the random sequence (Daselaar et al., 2003).

Methods

All procedures complied with the declaration of Helsinki and medical ethical approval was obtained from the medical ethical committee of the VU University Medical Center. Informed consent was obtained from all subjects.

Subjects

We recruited 13 elderly adult healthy volunteers without sleep complaints (four men, nine women; mean age, 60.1; SD, 8.3) by advertisements in local and national newspapers, magazines for the elderly and through door-to-door flyers. As described previously (Van Der Werf et al., 2010), we performed an extensive screening: in brief, sleep disorders were excluded on the basis of the Athens Insomnia Scale (AIS; Soldatos et al., 2000), the Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1991), and the sleep disorders questionnaire (SDQ; Douglass et al., 1994), a polysomnographic recording and a standard neurological examination and interview. None of the subjects scored above the cutoff of 20 points on the Geriatric Depression Scale (GDS; Yesavage et al., 1982) or had a neurological or psychiatric history, chronic illnesses, a regular intake of medication known to affect sleep patterns, or an alcohol or drug dependency. All subjects obtained normal scores on the Dutch version of the Adult Reading Test (DART; Nelson, 1992; Schmand et al., 1992), the shortened version of the Groninger Intelligentie Test (GIT; Luteijn and Van Der Ploeg, 1983), the Mini Mental State Examination (MMSE; Folstein et al., 1975), and the Boston Naming Task (BNT; Kaplan et al., 1983).

Test procedures

All subjects were tested in two separate sessions, between 5 and 7 weeks apart (average 6 weeks). In each session, they performed both vigilance tasks, the declarative and the implicit memory task. The two vigilance tasks were performed on two separate, consecutive, days for each session. The order of vigilance task administration was similar for each subject across the two sessions but balanced across subjects. The time of day of administration of all tasks was the same for all subjects, that is, in the late afternoon. The declarative memory task was performed in a 1.5T Siemens Sonata MRI scanner as described before (Van Der Werf et al., 2009). In brief, we obtained 220 echoplanar images while subjects were performing the visual encoding task (see below). We also obtained a high-resolution T1-weighted scan for coregistration purposes. Subsequent event-related analysis contrasting subsequently correctly remembered items against control items was performed using FSL software (FSL 3.3, FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl).

SWA reduction

The 13 healthy control subjects were subjected to selective SWA reduction: on each of the two testing sessions sleep was assessed using polysomnographic recordings from 13 electroencephalographic (EEG) electrodes Fp1, Fpz, Fp2, F3, Fz, F4, C3, Cz, C4, P3, Pz, P4, A2; and left and right electrooculographic (EOG) electrodes, all referenced against A1. In addition, a bipolar electromyogram (EMG) was recorded from the submental muscle. The signal was sampled at 200 Hz. On one of the two sessions, we performed partial SWA reduction as described previously (Drewes et al., 2000; Van Der Werf et al., 2009). We developed a custom analysis plug-in for the Somnologica 2 software (Flaga, Reykjavik, Iceland) that performed online calculation of the relative contribution of the 0.4–4 Hz band to the frequency spectrum as a measure of the depth of sleep. When the contribution of SWA exceeded a threshold level that was individually tuned on the basis of a preexperimental sleep recording, the loudspeaker of the computer

emitted a beeping noise that continued to increase in loudness in six discrete steps until it reached a maximum. The sound continued until the level of SWA dropped below the threshold. To avoid erroneous inclusion of slow EOG signals in the 0.4–4 Hz EEG band, the sound was not emitted when the signals from the two EOG leads were negatively correlated, reflecting conjugated eye movements; a positive correlation reflects leakage of SWA into the EOG leads. Using this system, we applied selective SWA-reduction for two consecutive nights. In one subject sleep deprivation did not succeed due to computer failure, so that the post-SWA-reduction data were obtained for 12 participants only. The two vigilance tasks were performed on consecutive days, that is, the 2 days following the sleep-deprivation nights. Owing to the randomization of the two tasks over the 2 days of each session across subjects, six subjects performed the "simple" vigilance task after one night and the "complex" vigilance task after two nights of selective SWA-reduction, whereas for the remaining six subjects this was the reverse.

The hypnogram was scored according to the criteria of Rechtschaffen and Kales (1968) by a trained technician. This yielded several sleep parameters including the duration of the different sleep stages (i.e., REM sleep and non-REM sleep stages I–IV). We then calculated the average power spectral density overall non-REM sleep periods, using the fast Fourier transform. The effect of slow-wave sleep reduction on the power spectral density of the non-REM EEG was evaluated using mixed-effects regression analysis (MLwiN software version 2.0, Centre for Multilevel Modelling, Bristol, UK), accounting for the hierarchical data structure of multiple leads recorded in each participant on two occasions. Separate analyses were run for average normalized power in the traditional EEG-bands, that is, slow waves (<4 Hz), theta (4–8 Hz), alpha (8–12 Hz), sigma (12–15 Hz), beta (15–30 Hz), and gamma (30–45 Hz).

Tasks

Vigilance

We constructed two tasks for psychomotor vigilance using E-prime 1.1 with service pack 3 (Psychology Software Tools, Pittsburgh, USA). All testing was done on an IBM-compatible laptop running Windows XP. During the tasks, stimuli (Courier New bold font size 45) appeared in the middle of a 30.5-cm $\times$ 23-cm LCD screen (screen resolution 640×480) against a light gray background. Subjects' eyes were approximately 40 cm from the screen.

For the "simple" vigilance task, 110 asterisks appeared sequentially on the screen at the same location but with variable and random time intervals lasting between 1 and 10 s. Prior to the task, there was a brief training session of five targets allowing the subjects to get acquainted with the task and the screen layout. Subjects were instructed to press the left mouse button as quickly as possible with their dominant hand whenever they saw the target. They were informed that the task had a duration of $\sim$13 min and were asked to maintain their concentration as well as they could throughout the task.

In the second task, the "complex" vigilance task, either the target letter "p" or the distractor letter "d" appeared on the screen, at the same location, with randomly changing time intervals between 0.5 and 5 s. This ensured that the average interval between targets, the number of targets, and the duration of the task were the same as for the "simple" vigilance task. The target and distractor letters were chosen such that the shape and size of the letters was the same; one is a 180° rotated version of the other. There was a brief training session of 10 stimuli (five targets) preceding the task. A total of 220 stimuli was presented on the screen, of which 110 were target stimuli.

Declarative memory

Subjects viewed 50 images of novel, unfamiliar landscapes or houses, projected on a screen outside

the MR scanner, while lying in a supine position, with the aid of a mirror positioned above their eyes attached to the head coil. We presented all images and recorded all responses using E-prime 1.1 software with service pack 3 (Psychology Software Tools). Each image was presented for 5 s, during which the subjects had to indicate whether the landscapes were, in their opinion, tropical or nontropical or whether the houses were residential or holiday houses. This served to "deepen" the encoding by requiring the subjects to attend to details in the images, enhancing hippocampal activation, and subsequent recall (Frey and Petrides, 2002). In addition, the procedure minimizes differences between subjects in their cognitive approach toward picture viewing and encoding. The images appeared in a prerandomized order, alternating with 20 control images (a previously familiarized image with a large white arrow superimposed, pointing to the left or right to which the subjects responded according to the direction of the arrow). Responses to the novel and control images were given by pressing one of two buttons (Photon Control, Burnaby, BC, Canada) with the left or right index finger. Randomized intervals of variable duration between subsequent pictures (0.6–2.4 s) were used to jitter the timing of picture presentation.

The next day we assessed memory retrieval performance by presenting a list of 100 images consisting of the 50 previously presented items and 50 novel images, randomly intermixed. Subjects were allowed to reply with "yes," "maybe," "maybe not" or "no" to each of the 100 images to indicate whether they had seen the image before and their degree of recognition certainty.

Implicit memory

We used a four-choice serial reaction time (SRT) task as a measure of implicit procedural learning, adapted from Daselaar et al. (2003). The fixed sequence consisted of six button presses, repeated six times for each block. Fixed blocks alternated with an equal number of pseudorandom button presses (never the same button press consecutively): in total, the task consisted of six blocks of six repetitions of the six-button-press fixed sequence, preceded, alternated, and followed by equally sized blocks of pseudorandom button presses. The task was divided into two halves, each starting and ending with a series of random sequences. The structure of the task was therefore: R-F-R-F-R-F-R–R-F-R-F-R-F-R (R: random, each R represents 36 random button presses; F: fixed, each F stands for six repetitions of the six-button-press fixed sequences). The task was programmed using E-prime 1.1 with service pack 3 (Psychology Software Tools). All testing was performed on an IBM-compatible laptop running Windows XP. During the tasks, four rectangles arranged on the screen appeared in the middle of a 30.5-cm $\times$ 23-cm LCD screen (screen resolution 640×480) against a light gray background. The position of the rectangles on the screen corresponded to the position of the keys "e," "d," "i," and "j" on the keyboard. Subjects' eyes were $\sim$40 cm from the screen. Subjects were required to follow the order of appearance of an asterisk appearing above one of the four rectangles for a maximum of 1 s. Corresponding to the locations of the rectangles, subjects pressed the corresponding keyboard buttons, that is, "e," "d," "i," or "j"; after which the asterisk disappeared, regardless of whether the response was correct.

Statistical analysis

Vigilance

We used mixed-effects model (MEM) regression analysis (MLwiN software version 2.0) to estimate the effects of SWA reduction. The regression model took into account the hierarchy of the protocol consisting of four levels: every subject (level 1) was tested on each of two sessions (level 2) using the two different tasks: the "simple" versus "complex" vigilance task

(level 3), each containing 110 trials (level 4). For all the analyses, we discarded the responses to the first three target stimuli, such that all analyses were performed on 107 consecutive responses. This effectively ensured the elimination of start-up problems and associated errors and misses across subjects (Drummond et al., 2005).

A "lapse" was defined as a nonresponse or a response slower than 500 ms for the "simple" vigilance task; and slower than 624 ms for the "complex" vigilance task, as the "complex" task elicited consistently slower responses than the "simple" vigilance task. We used the same criteria for lapses as in our previous study on insomnia, to be able to compare between controls without sleep complaints and insomnia patients. The risk of lapses was analyzed using logistic MEM. Single-trial reaction times—for the complex task to the targets only—were analyzed using linear MEM. In the analysis of the RT time-series, we ignored all responses scored as lapses. Finally, the risk of false positive responses to the nontargets of the complex reaction time task was analyzed using logistic MEM.

Declarative memory

We calculated the memory score by pooling the "yes" and "maybe" on the one hand, and "maybe not" and "no" responses, on the other. This was done to obtain sufficient numbers in each response category across the group of subjects. We thus obtained four different response categories, that is, true positive (remembered), false positive (erroneously considered as seen before), false negative (forgotten), and true negative (correctly considered as not seen before). From these data we calculated *d*-prime as a measure of memory performance weighting true positive responses for the tendency to respond positively to items in general (i.e., the difference between the means of the true positive hit rate and the false positive hit rate under assumption of normal distribution). We used paired *t*-tests for statistical evaluation of the performance results (SPSS version 16.0, SPSS Inc., Chicago, IL).

Implicit memory

Performance was measured as the average reaction times for each of the 14 blocks of fixed or random sequences, for the correct responses only. The performance benefit from the fixed versus the random sequences was calculated as the reaction time difference between the fixed blocks and the subsequent random blocks, resulting in six difference scores per subject per condition. We analyzed the time-series of these reaction time differences across subsequent blocks (six levels), nested within day (days 1 and 2), session (normal sleep or SWA reduction), and subject, using MEM regression analysis (MLwiN software version 2.0).

Results

Effects of selective SWA reduction on sleep parameters

Averaged overall NREM epochs (stages I–IV), the SWA reduction method induced a significant reduction of $4.5 \pm 1.5\%$ (mean $\pm$ SEM, $p = 0.002$) in the 0.5–4 Hz SWA band and an increase of ($18.6 \pm 4.4\%$, $p < 0.001$) in the 8–12 Hz alpha band. None of the other bands were affected by the manipulation (see Van Der Werf et al., 2009, for details).

The reduction of SWA was partial and did not lead to a reduction of the duration of stages scored as II, III, or IV, that is, the SWA containing stages. The only significant change in sleep architecture was a 19.07 ± 8.93 min increase ($p = 0.03$) in the duration of the, non-SWA containing, sleep stage I, indicating a shift toward lighter sleep. Sleep stages II, III, IV, and REM each showed nonsignificant decreases in their duration. SWA reduction did not affect total sleep duration or sleep efficiency (percentage of

time spent sleeping calculated from sleep onset to final waking up) nor the number of sleep state transitions (Table 1).

Effects of selective SWA reduction on vigilance task performance

The overall percentage of vigilance lapses increased from 3.4% to 6.5% (odds ratio (OR) = 1.62; 95% confidence interval (CI) = 1.04–2.52, $p = 0.03$), irrespective of the type of vigilance task ($p = 0.84$; Fig. 1). Within the complex vigilance task, no effect of SWA reduction was found on the risk of false positive responses (OR = 1.06, CI = 0.55–2.03, $p = 0.87$). Unlike previous studies that applied total sleep deprivation, selective SWA reduction did not affect reaction times (Fig. 1). The main effect of SWA reduction over both reaction time tasks was a 6 ± 20 (mean $\pm$ SEM) ms slowing ($p = 0.77$). SWA reduction did not differentially affect simple and complex reaction times. The simple vigilance task reaction times were 353 ± 10 ms after normal sleep and 354 ± 13 ms after SWA reduction ($p = 0.85$). The complex vigilance task reaction times were 468 ± 12 ms after normal sleep and 474 ± 12 after selective SWA-reduction ($p = 0.85$).

Effects of selective SWA reduction on declarative memory

After the sleep manipulation subjects had significantly lower scores on the true positive response category (normal sleep: mean $\pm$ SD, 36.6 ± 1.4 items; SWA reduction: 31.4 ± 1.8 items; $p = 0.008$) but no difference on the false positive response category (normal sleep: mean $\pm$ SD, 17.5 ± 2.0 items; SWA reduction: 18.6 ± 2.3 items; $p = 0.67$), leading to a significantly lower *d*-prime in the subjects after SWA reduction (normal sleep: mean $\pm$ SD, 1.07 ± 0.09; SWA reduction: 0.70 ± 0.06 items; $p = 0.007$; Fig. 2).

When we compared the brain activation data of the subjects in the SWA reduction condition with that of the normal sleep condition on the contrast correctly remembered items versus control items, a significant reduction of right hippocampal activation was observed at $z = 3.2$ (Fig. 2), as previously reported (Van Der Werf et al., 2009).

Effects of selective SWA reduction on implicit memory

Performance on the SRT improved from random to fixed sequences, as measured by reaction times on correctly responded items as shown in Fig. 3 ($p < 0.001$), that improved over time on task ($p = 0.02$). This improvement occurred regardless of condition, that is, no difference was observed for the SWA reduction condition versus the normal sleep condition ($p = 0.55$).

Discussion

Disturbances of sleep affect cognitive functioning and psychomotor vigilance. Our results indicate

Table 1. SWA reduction does not affect the primary sleep variables

Variable	Normal sleep	SWA suppressed	*p* value
Total sleep time	6 h 57 min $\pm$ 14 min	6 h 38 min $\pm$ 15 min	0.31
Sleep efficiency (%)	83.2 ± 2.5	81.2 ± 2.9	0.89
Sleep state transitions (#)	112.3 ± 7.9	131.0 ± 14.0	0.17

Average values $\pm$ standard errors of the mean for sleep variables in the undisturbed and the SWA suppressed nights. *p* values refer to the significance of the fixed effect of SWA reduction as analyzed using mixed-effects regression analysis. The results show that selective SWA reduction does not significantly affect sleep efficiency, total sleep time, or the number of sleep state transitions.

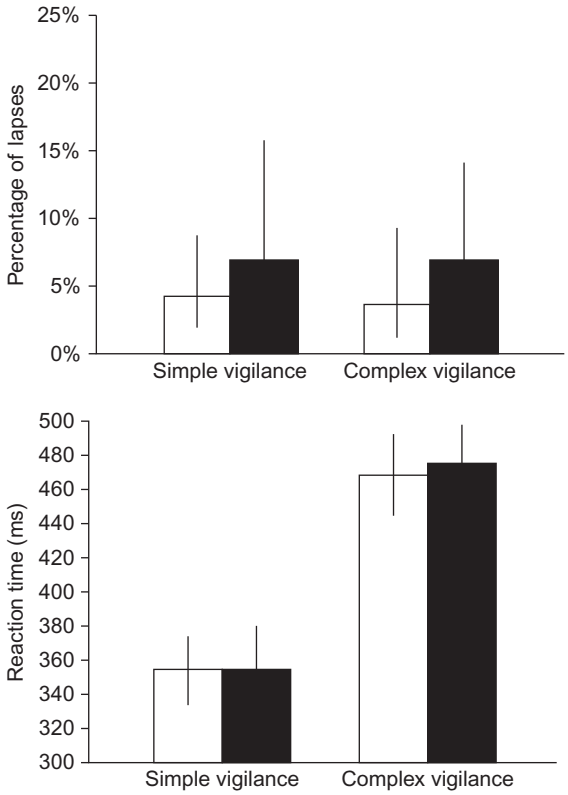

Fig. 1. SWA reduction selectively increases vigilance lapses. *Upper panel*: Relative to assessment after a normal night of sleep (open bars), a night of slow-wave sleep reduction (black bars) increases the percentage of lapses in both the simple and complex vigilance task. *Lower panel*: slow-wave reduction does not affect reaction times. Error bars show the 95% confidence interval to illustrate between-subject variance.

that the effect on performance depends, however, both on the task and on the type of sleep disruption. Selective SWA reduction in individuals without sleep complaints leads to vigilance drops, or lapses, and reduced capacity for encoding novel declarative material while leaving formation of implicit memory intact. The higher number of lapses after SWA reduction parallels the effects of total sleep deprivation: prolonged wakefulness leads to a higher number of lapses both in healthy young subjects (Urrila et al., 2007) and healthy older adult subjects, similar to our study. Our data suggest that reduction of SWA, in the absence of an effect on sleep architecture, duration or efficiency, is sufficient to induce the attenuation of vigilance performance that would be observed after total sleep deprivation. Previous research has shown that brain areas associated with decreases of vigilance in healthy subjects include the bilateral inferior parietal, bilateral ventral prefrontal, and bilateral dorsal lateral prefrontal cortices (Drummond et al., 2005; Johannsen et al., 1997; Paus, 1997, 2000; Sturm et al., 1999). It remains to be investigated whether SWA reduction affects vigilance via the same brain mechanism.

Our results on declarative memory formation similarly parallel findings from total sleep deprivation studies (Yoo et al., 2007), in reducing memory encoding. In addition to the impaired memory performance, hippocampal activation for correctly remembered items is reduced, indicating that even those items that are remembered have a weaker memory trace than after undisturbed sleep in the same participants. In contrast to the vigilance and declarative memory performance, however, implicit memory seems unaffected by the SWA reduction procedure. Implicit memory acquisition does not seem to depend on the hippocampus but rather on a distributed network consisting of bilateral parietal and frontal regions, the supplementary motor area (SMA), cerebellum, and the basal ganglia (Daselaar et al., 2003). It appears that the processes that depend on hippocampal integrity, namely declarative memory, suffer more from SWA reduction than those associated with activation that seems to be less dependent on hippocampus involvement.

It might be argued that a limitation of the current study is that we did not perform a control condition with auditory stimulation not directed at SWA. However, the feasibility of an adequate control condition is questionable. We have, in fact, piloted such an approach but found several difficulties. First, if the auditory stimuli are given

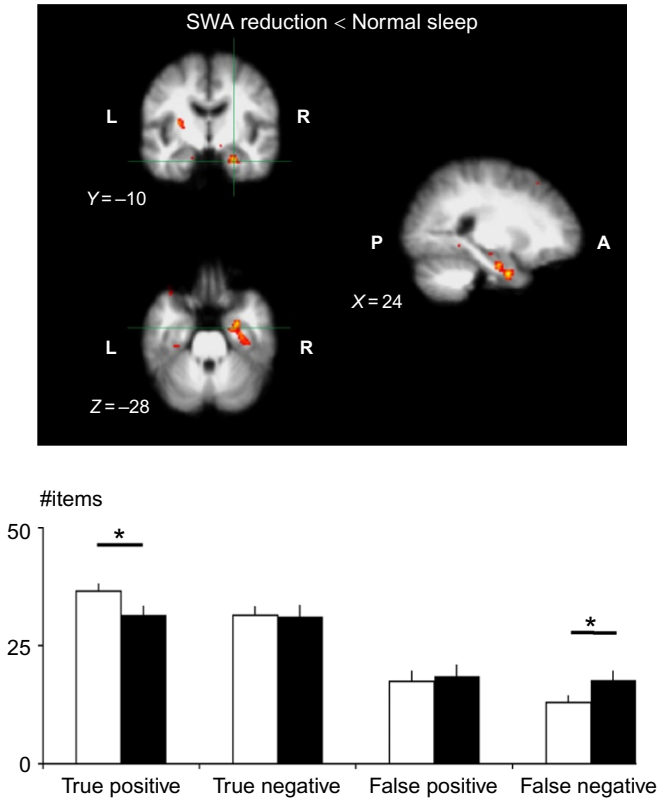

Fig. 2. SWA reduction causes a reduction in memory encoding and a reduced hippocampal activation. *Upper panel*: Relative to assessment after a normal night of sleep, a night slow-wave sleep reduction reduces the hippocampal activation for encoding of subsequently correctly remembered items. This difference was significant at $z > 3.1$, image thresholded at $z > 2.3$ to show the extent of the underlying activation difference. *Lower panel*: slow-wave reduction reduces the number of correctly remembered items (true positive) and increases the number of false negative responses, without affecting the number of false positive responses, indicative of true forgetting rather than a shift in response strategy. Open bars represent a normal night of sleep, closed bars slow-wave reduction, error bars are standard errors of the mean, asterisks denote a significant difference at $p < 0.01$.

not time-locked to SWA but randomly during sleep, they necessarily fall in the lighter phases of sleep as well; the effect of the stimulation is then to wake the subject up rather than bring him/her into a lighter sleep stage. This then introduces a qualitatively different sleep pattern, including fragmented sleep and lower sleep efficiency, which we specifically intended to prevent with our current approach. Second, targeted disruption of other sleep stages disrupts sleep architecture and causes a secondary decrease in SWA because subjects do not reach the deep stages of sleep when they are woken up before. Because such a control condition thus induces qualitatively different sleep besides disrupting SWA, we did not judge it as a suitable control.

Rather, the approach taken here selectively targets deep sleep and importantly, causes no

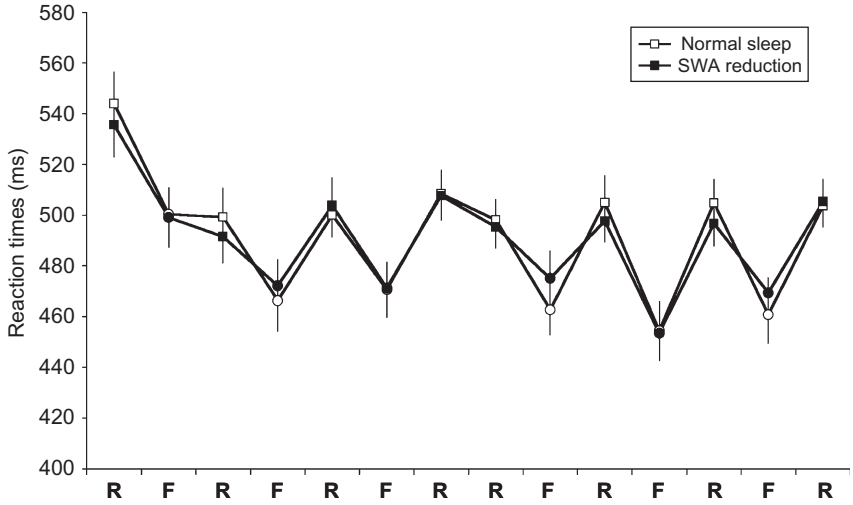

Fig. 3. SWA reduction does not lead to a difference in implicit memory formation. Mean reaction times for the random (R, square symbols) and fixed (F, circles) series of sequences. Notice the gradual development across the task of a reaction time benefit for the F relative to the R sequences, in spite of the fact that subjects did not perceive the fixed nature of the button press sequences. This performance benefit did not, however, differ between the test sessions following slow-wave reduction (filled symbols) and following a normal night (open symbols). Error bars are standard errors of the mean.

effect on sleep duration or efficiency. An important conclusion of these findings is therefore, that the performance and functional imaging changes occur in the *absence* of sleep deprivation.

In conclusion, our findings suggest that SWA reduction in healthy well-sleeping subjects may provide a more feasible and ecologically valid method than total sleep deprivation for the induction of an increase in the number of lapses and memory failure and the study of their underlying brain mechanisms. The findings offer directions for future research into regional cortical and subcortical differences in sensitivity to the effects of SWA and its disruption during the night.

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References

Altena, E., Van Der Werf, Y. D., Sanz-Arigita, E. J., Voorn, T. A., Rombouts, S. A., Kuijer, J. P., et al. (2008). Prefrontal hypoactivation and recovery in insomnia. *Sleep*, *31*, 1271–1276.

Altena, E., Van Der Werf, Y. D., Strijers, R. L., & Van Someren, E. J. (2008). Sleep loss affects vigilance: Effects of chronic insomnia and sleep therapy. *Journal of Sleep Research*, *17*, 335–343.

Arima, T., Svensson, P., Rasmussen, C., Nielsen, K. D., Drewes, A. M., & Arendt-Nielsen, L. (2001). The relationship between selective sleep deprivation, nocturnal jaw-muscle activity and pain in healthy men. *Journal of Oral Rehabilitation*, *28*, 140–148.

Buysse, D. J., Reynolds, C. F. I., Monk, T. H., Hoch, C. C., Yeager, A. L., & Kupfer, D. J. (1991). Quantification of subjective sleep quality in healthy elderly men and women using the Pittsburgh Sleep Quality Index (PSQI). *Sleep*, *14*, 331–338.

Daselaar, S. M., Rombouts, S. A., Veltman, D. J., Raaijmakers, J. G., & Jonker, C. (2003). Similar network activated by young and old adults during the acquisition of a motor sequence. *Neurobiology of Aging*, *24*, 1013–1019.

Dinges, D. F., Pack, F., Williams, K., Gillen, K. A., Powell, J. W., Ott, G. E., et al. (1997). Cumulative sleepiness, mood disturbance, and psychomotor vigilance performance decrements during a week of sleep restricted to 4–5 hours per night. *Sleep*, *20*, 267–277.

Douglass, A. B., Bornstein, R., Nino-Murcia, G., Keenan, S., Miles, L., Zarcone, V. P. Jr., et al. (1994). The sleep disorders questionnaire. I: Creation and multivariate structure of SDQ. *Sleep*, *17*, 160–167.

Drewes, A. M., Nielsen, K. D., Rasmussen, C., Arima, T., Svensson, P., Rössel, P., et al. (2000). The effects of controlled delta sleep deprivation on experimental pain in healthy subjects. *Journal of Musculoskeletal Pain*, *8*, 49–67.

Drummond, S. P., Bischoff-Grethe, A., Dinges, D. F., Ayalon, L., Mednick, S. C., & Meloy, M. J. (2005). The neural basis of the psychomotor vigilance task. *Sleep*, *28*, 1059–1068.

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). 'Mini-mental state': A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, *12*, 189–198.

Frey, S., & Petrides, M. (2002). Orbitofrontal cortex and memory formation. *Neuron*, *36*, 171–176.

Johannsen, P., Jakobsen, J., Bruhn, P., Hansen, S. B., Gee, A., Stodkilde-Jorgensen, H., et al. (1997). Cortical sites of sustained and divided attention in normal elderly humans. *NeuroImage*, *6*, 145–155.

Kaplan, E., Goodglass, H., & Weintraub, S. (1983). *Boston naming test.* Philadelphia: Lea & Febiger.

Krystal, A. D., Edinger, J. D., Wohlgemuth, W. K., & Marsh, G. R. (2002). NREM sleep EEG frequency spectral correlates of sleep complaints in primary insomnia subtypes. *Sleep*, *25*, 630–640.

Landsness, E. C., Crupi, D., Hulse, B. K., Peterson, M. J., Huber, R., Ansari, H., et al. (2009). Sleep-dependent improvement in visuomotor learning: A causal role for slow waves. *Sleep*, *32*, 1273–1284.

Luteijn, F., & Van Der Ploeg, F. A. E. (1983). *Groninger Intelligentie Test (GIT).* Lisse: Swets & Zeitlinger.

Nelson, H. E. (1992). *National Adult Reading Test (NART)* (2nd ed.). Windsor, UK: NFER-NELSON.

Paus, T. (1997). Time-related changes in neural systems underlying attention and arousal during the performance of an auditory vigilance task. *Journal of Cognitive Neuroscience*, *9*, 392–408.

Paus, T. (2000). Functional anatomy of arousal and attention systems in the human brain. *Progress in Brain Research*, *126*, 65–77.

Rechtschaffen, A., & Kales, A. (1968). *A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects.* Bethesda: United States Department of Health, Education and Welfare.

Schmand, B., Lindeboom, J., & Van Harskamp, F. (1992). *Nederlanse Leestest voor Volwassenen (Dutch Adult Reading Test).* Lisse, The Netherlands: Swets & Zeitlinger.

Soldatos, C. R., Dikeos, D. G., & Paparrigopoulos, T. J. (2000). Athens insomnia scale: Validation of an instrument based on ICD-10 criteria. *Journal of Psychosomatic Research*, *48*, 555–560.

Sturm, W., de Simone, A., Krause, B. J., Specht, K., Hesselmann, V., Radermacher, I., et al. (1999). Functional anatomy of intrinsic alertness: Evidence for a fronto-parietal-thalamic-brainstem network in the right hemisphere. *Neuropsychologia*, *37*, 797–805.

Urrila, A. S., Stenuit, P., Huhdankoski, O., Kerkhofs, M., & Porkka-Heiskanen, T. (2007). Psychomotor vigilance task performance during total sleep deprivation in young and postmenopausal women. *Behavioral Brain Research*, *180*, 42–47.

Van Der Werf, Y. D., Altena, E., Schoonheim, M. M., Sanz-Arigita, E. J., Vis, J. C., De Rijke, W., et al. (2009). Sleep benefits subsequent hippocampal functioning. *Nature Neuroscience*, *12*, 122–123.

Van Der Werf, Y. D., Altena, E., Van Dijk, K. D., Strijers, R. L., Rijke, W. D., Stam, C. J., et al. (2010). Is disturbed intracortical excitability a stable trait of chronic insomnia? A study using transcranial magnetic stimulation before and after multimodal sleep therapy. *Biological Psychiatry*, .

Van Dongen, H. P., Baynard, M. D., Maislin, G., & Dinges, D. F. (2004). Systematic interindividual differences in neurobehavioral impairment from sleep loss: Evidence of trait-like differential vulnerability. *Sleep*, *27*, 423–433.

Yesavage, J. A., Brink, T. L., Rose, T. L., Lum, O., Huang, V., Adey, M., et al. (1982). Development and validation of a geriatric depression screening scale: A preliminary report. *Journal of Psychiatric Research*, *17*, 37–49.

Yoo, S. S., Hu, P. T., Gujar, N., Jolesz, F. A., & Walker, M. P. (2007). A deficit in the ability to form new human memories without sleep. *Nature Neuroscience*, *10*, 385–392.