CHRONIC INSOMNIA: COMPARABLE TO SLOW WAVE SUPPRESSION?

Chapter 7

Suppression of nocturnal slow-wave activity selectively affects daytime vigilance lapse but not reaction time

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ABSTRACT

Insomnia is the most frequent sleep disorder and psychological disorder. Still, the quantitative behavioral, cognitive and brain abnormalities of this condition have hardly been explored. In the absence of quantitative measures of functioning in insomnia, it is not possible to determine whether sleep disruption in volunteers without sleep complaints, often implicitly regarded as a model to study insomnia-related cognitive deficits, is indeed a valid model. A recent study demonstrated that people suffering from chronic insomnia show a reversible deviant performance on vigilance tasks; while responding faster on a simple task, their reaction times are disproportionally sensitive to even a mild increase in task complexity. We here evaluated these vigilance changes in a possible model for insomnia consisting of an automated electro-encephalogram (EEG) dependent acoustic feedback method to selectively suppress slow-wave activity (SWA) and enhance alpha activity, as has been reported to be characteristic of insomnia. In a within-subject repeated measures crossover design, performance on simple and complex vigilance tasks was assessed in 13 older adults without sleep complaints after being subjected to SWA-suppression and normal control nights. Dissimilar to the effects of insomnia, SWA suppression did not affect reaction time ($p=0.77$), yet caused the percentage of vigilance lapses to increase from 3.4% to 6.5% (Odds Ratio 1.62; 95% Confidence Interval 1.04-2.52, $p=0.03$), irrespective of the type of vigilance task ($p=0.84$). The increase in lapses corroborates the findings of an increased number of lapses after total sleep deprivation in healthy subjects. Unlike previous findings applying total sleep deprivation however, selective slow-wave suppression did not affect reaction time. In conclusion, experimental sleep disturbance may not be a valid model to study cognitive sequelae of chronic insomnia. However, whereas most of the previous studies applied total or partial sleep deprivation, we here show for the first time that selective SWA suppression provides a method to selectively study vigilance lapses without confounds of changes in reaction time. The findings suggest a specific role of slow oscillations in the subsequent daytime ability to maintain sustained attention.

INTRODUCTION

One of the functions sensitive to disruption of sleep is vigilance, or sustained attention: maintaining attentiveness to unpredictably occurring stimuli. Acute sleep deprivation in healthy subjects leads to reduced vigilance, as shown by a higher number of lapses, i.e. late or absent responses to the stimuli[1-3]. These studies use total sleep deprivation to investigate the effect of sleep loss. The results therefore do not allow to 1) judge which sleep phase or sleep constituents are most strongly involved in the effects of sleep deprivation, or 2) to extrapolate the findings to insomnia-related cognitive dysfunction, as insomnia is rarely associated with total lack of sleep.

In the present study, we exposed healthy volunteers without sleep complaints to selective slow-wave activity (SWA) suppression[4,5] on one of two testing sessions, prior to vigilance testing. This method selectively attenuates SWA and increases alpha. Reduced SWA and increased alpha are both related to the severity of subjective sleep complaints of primary insomnia patients[6]. As such, the selective SWA suppression 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 psychological disorder, only a few studies quantitatively addressed the daytime behavioral, cognitive and brain abnormalities of the condition[7,8], and virtually no study 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 debilitating condition.

We hypothesized SWA suppression to be a valid model to induce daytime functional deficits typical of insomniacs in people without sleep complaints. We measured vigilance using two versions of the psychomotor vigilance task (PVT): 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.

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 older adult healthy volunteers without sleep complaints where insomnia is most prevalent (4 men, 9 women; mean age 60.1, sd 8.3) by advertisements in local and national newspapers, magazines for the elderly and through door-to-door journals. As described previously[7,8], we performed an extensive screening: in brief, sleep disorders were excluded on the basis of the Athens Insomnia Scale (AIS)[9], the Pittsburgh Sleep Quality Index (PSQI)[10] and the Sleep Disorders Questionnaire (SDQ)[11,12], a polysomnographic recording and a standard neurological examination and interview. None of the subjects scored above the cut-off of 20 points on the Geriatric Depression Scale (GDS)[13] 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)[14-16], the shortened version of the Groninger Intelligentie Test (GIT)[17], the Mini Mental State Examination (MMSE)[18] and the Boston Naming Task (BNT)[19].

All subjects were tested in two separate sessions, between 5 and 7 weeks apart (average 6 weeks). In each session, they performed the 'simple' and 'complex' vigilance tasks on two separate, consecutive, days. The order of task administration was similar for each subject across the two sessions, but balanced across subjects. The time of day of administration was the same for all subjects, i.e. in the late afternoon.

SWA SUPPRESSION

The 13 healthy control subjects were subjected to selective SWA suppression: on each of the two testing sessions sleep was assessed using polysomnographic recordings from thirteen 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 200Hz. On one of the two sessions we performed partial SWA supppression as described previously[5,20]. In brief, 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 slow-wave activity exceeded a threshold level that was individually tuned on the basis of a pre-experimental sleep recording, the loudspeaker of the computer emitted a beeping noise that continued to increase in amplitude in six discrete steps until it reached a maximum. The sound continued until the level of slow wave activity 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 slow wave activity into the EOG leads. Using this system, we achieved selective SWA-suppression in our healthy control subjects for two consecutive nights. In one subject sleep deprivation did not succeed due to computer failure, so that the post-SWA-suppression data were obtained for 12 healthy controls only. The two vigilance tasks were performed on consecutive days, i.e. the two days following the sleep-deprivation nights. Owing to the randomization of the two tasks over the two 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 sleep deprivation, whereas for the remaining six subjects this was the reverse.

The hypnogram was scored according to the criteria of Rechtschaffen and Kales by a trained technician[21]. This yielded 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 over all non-REM sleep periods, using fast Fourier transformation. The effect of slow wave sleep suppression 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 being recorded in each participant on two occasions. Separate analyses were run for average normalized power in the traditional EEG-bands, i.e. 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).

TASK DESIGN

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*23 centimeter LCD screen (screen resolution 640*480) against a light grey background. Subjects' eyes were approximately 40 centimeters from the screen.

For the 'simple' vigilance task, 110 asterisks would sequentially appear on the screen on the same location but with variable and random time intervals of a duration between 1-10 seconds. Prior to the task, there was a brief training session of 5 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 approximately 13 minutes 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' would appear on the screen, on the same location, with randomly changing time intervals between 0.5 and 5 seconds. This ensured that the average interval between targets, the number of targets and the duration of the task would be the same as for the 'simple' vigilance task. The target and distractor letters were so chosen because the shape and size of the letters was the same; one is a 180° rotation of the other. There was a brief training session of 10 stimuli (5 targets) preceding the task. A total of 220 stimuli was presented on the screen, of which 110 were target stimuli.

STATISTICS

We used mixed-effects model (MEM) regression analysis (MLwiN software version 2.0, Centre for Multilevel Modelling, University of Bristol, UK) to estimate the effects of SWA suppression. The regression model took into account the hierarchy of the protocol consisting of 4 levels: every subject (level 1) was tested on each of two sessions (level 2) using the two different tasks: the 'simple' vs. '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 the subjects[22].

A lapse was defined as a non-reponse or a response slower than 500 milliseconds for the 'simple' vigilance task, in accord with the literature[2]; and slower than 624 milliseconds 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 analysed using logistic MEM. Single-trial reaction times – for the complex task to the targets only – were analysed using linear MEM. In the analysis of the RT-timeseries, we ignored all responses scored as lapses. Finally, the risk of false postive responses to the nontargets of the complex reaction time task was analysed using logistic MEM.

RESULTS

EFFECTS OF SELECTIVE SWA SUPPRESSION ON SLEEP PARAMETERS

Averaged over all NREM epochs (Stages I-IV), the SWA suppression method induced a significant reduction of 4.5 ± 1.5% (mean ± s.e.m., $p=0.002$) in the 0.5-4 Hz SWA band and an increase of (18.6 ± 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[4] .

The suppression of SWA was partial and did not lead to a reduction of the time classically scored as stages II, III or IV, i.e. the SWA containing stages. The only significant change in sleep architecture was a 19.07±8.93 minute increase in the duration of the, non-SWA containing, sleep stage I, indicating a shift towards lighter sleep. Sleep stages II, III, IV and REM showed non-significant decreases in their duration. SWA suppression 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).

Variable	Normal sleep	SWA suppressed	P value
Total sleep time	6h56.7min ± 14.1min	6h38min ± 15.6min	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

Table 1: SWA suppression does not affect the primary sleep variables. Average values±standard errors of the mean for sleep variables in the undisturbed and the SWA suppressed nights. P values refer to the significance of the effect of SWA suppression as analysed using mixed effects regression analysis. The results show that selective SWA suppression does not significantly affect sleep efficiency, total sleep time or the number of sleep state transitions.

EFFECTS OF SELECTIVE SWA SUPPRESSION ON TASK PERFORMANCE

Unlike previous studies that applied total sleep deprivation, selective SWA suppression did not affect reaction times. The main effect of SWA suppression over both reaction time tasks was a 6 ± 20 (mean ± s.e.m.) msec slowing (p=0.77). Unlike our recent finding in insomnia, SWA suppression did not differentially affect simple and complex reaction times. The simple vigilance task reaction times were 353 ± 10 msec after normal sleep and 354 + 13 after SWA suppression (p=0.85). The complex vigilance task reaction times were 468±12 msec after normal sleep and 474 ± 12 after sleep deprivation (p=0.85). In strong contrast, 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). Within the complex vigilance task, no effect of SWA suppression was found on the risk of false positive presses (OR=1.06, CI=0.55-2.03, p=0.87).

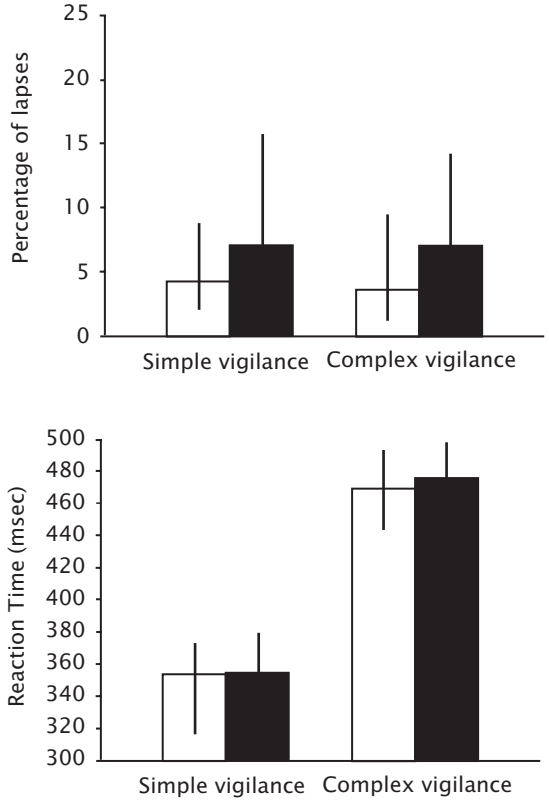

Figure 1: SWA suppression selectively increases vigilance lapses. Upper panel: Relative to assessment after a normal night of sleep (white bars), a night slow wave sleep suppression (black bars) increases the percentage of lapses in both the simple and complex vigilance task. Lower panel: slow wave suppression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

DISCUSSION

Disturbances of sleep affect psychomotor vigilance. Our results indicate that the precise effect on performance, depends, however on the type of sleep disturbance. Selective SWA suppression in individuals without sleep complaints leads to vigilance drops, or lapses. This differs markedly from patients with primary insomnia, who show a task-dependent effect on mean reaction time, but no increased lapse scores[8]. The higher number of lapses after SWA suppression parallels the effects of total sleep deprivation: prolonged wakefulness leads to a higher number of lapses

both in healthy young subjects[1,23,24] and healthy older adult subjects, similar to our study[25]. Our data indicate that suppression of SWA, in the absence of an effect on sleep architecture, duration or efficiency, is sufficient for the decrease in vigilance 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 cortex[26-30]. It remains to be investigated whether SWA suppression affects vigilance via the same brain mechanism.

Lapses induced by selective SWA suppression probably represent momentary decreases of attentiveness, resulting in reduced, absent or belated awareness of stimuli. As this effect seems to occur at the basal levels of perception, it is not surprising that it should be found regardless of the nature of the task, i.e. both in our 'simple' and 'complex' vigilance paradigm.

In conclusion, our findings suggest that SWA suppression 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 the study of their underlying brain mechanisms. Importantly, SWA suppression differs from total sleep deprivation also in leaving reaction times unchanged. It thus provides a method the study of vigilance lapses without possible confounds of altered reaction times. Unfortunately, we cannot conclude that our approach to the experimental disruption of sleep in healthy subjects without sleep complaints is a valid model for the study of daytime function in chronic insomnia.

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