Universiteit Leiden

Psychologie
Faculteit der Sociale Wetenschappen

The associations of slow wave sleep with cognition and memory.

Lindsay de Ligt

Master Thesis	Clinical Neuropsychology Faculty of Behavioural and Social Sciences – Leiden University October, 2015
Studentnumber:	s1433121
External Supervisor:	L.A. Zuurbier, Department of Epidemiology, Erasmus Medical Center, Rotterdam
Internal Supervisor:	F. Nijboer, Health, Medical and Neuropsychology, Leiden University

Abstract

Background and purpose: Changes in sleep patterns are common in elderly persons. One of these changes is the decrease of the percentage of deep sleep (stage N3), in which the more restorative slow wave sleep takes place. Previous studies consistently show that slow wave sleep is positively related to memory in the middle-aged population, but no associations are found in older elderly. Limitations of these studies are that the ecological validity is low and the samples are small. The objective of the current study was to further assess the association between slow wave sleep and other cognitive domains, including memory, in a population-based study. Furthermore we compared the associations in two different age groups; middle-aged and elderly persons. **Methods:** In this large population-based study a total of 487 participants (mean age 61.8 years) underwent polysomnography and a neuropsychological assessment. We created two age groups; younger elderly (mean age 57.6 years) and older elderly (mean age 66.1 years). To measure slow wave sleep we used the duration of N3 and the percentage of N3 of the total sleep time. By using neuropsychological tests we constructed compound scores for information processing, executive functioning and memory. **Results:** Longer durations of N3 were associated with lower performances on memory tests for the younger elderly (p= .001), for the older elderly no association between N3 and memory was found (p= .44). N3 was not associated with executive functioning (p= .27) and information processing (p= .90) in both age-groups. **Conclusion:** According to our expectation, this study has shown that in the older elderly persons slow wave sleep was not associated with memory. Against our expectations we found that in the younger elderly slow wave sleep was associated to poor memory performance. One of the explanations might be that either too much or not enough slow wave sleep is not beneficial for memory. Another explanation was that the duration of slow wave sleep differs per night, we measured slow wave sleep in only one night and the cognition tests did not take place on the same day. Further research is necessary to replicate these findings.

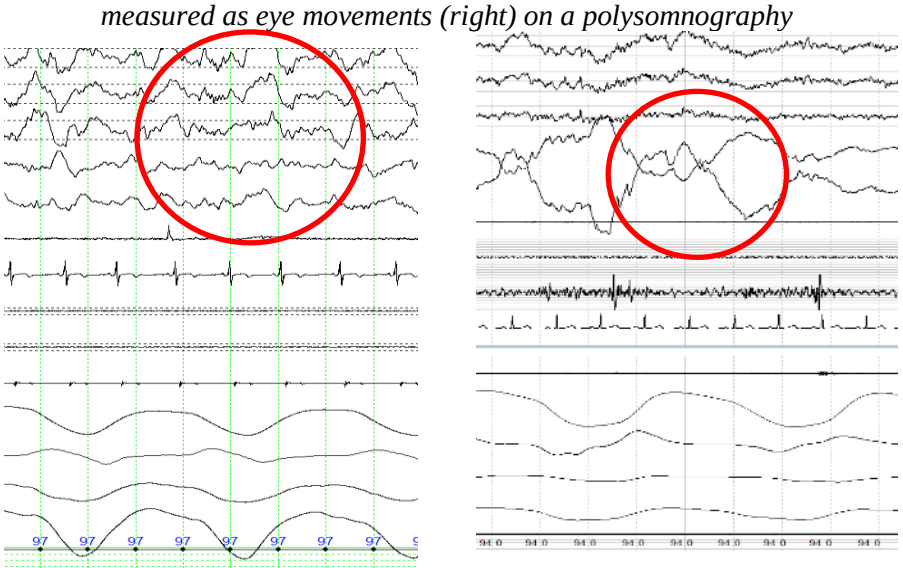
Introduction

"If sleep does not serve an absolutely vital function, then it is the biggest mistake the evolutionary process has ever made" (Rechtschaffen, 1971, p. 88).

Rechtschaffen, pioneer in the research of sleep, hereby commented on the fact that sleeps consumes about one third of our life's time. Sleep is related to several functions of the brain. For example, a good night of sleep generates positive changes on the emotional memory retrieval network (Payne & Kensinger, 2011). On the other hand, sleep deprivation can lead to impaired decision making (Killgore, Grugle, & Balkin, 2012). In the elderly there is a qualitative change in the architecture of sleep, which is linked to a decrease in cognitive abilities (Schabus et al., 2006). In the elderly we can see a decrease in total sleep time, an increase in sleep latency and an increase in wake after sleep onset (Webb & Campbell, 1980). Furthermore, the percentage of the first two sleep stages (N1 and N2) increases with age. The percentage of N3, in which the more restorative slow wave sleep (figure 1, left panel) takes place, and the percentage of rapid eye movement sleep (REM) (figure 1, right panel) both decrease with age (Espiritu, 2008; Feinberg, Koresko, & Heller, 1967; Mazzotti et al., 2014; Ohayon, Carskadon, Guilleminault, & Vitiello, 2004; Webb & Campbell, 1980).

Figure 1. Slow wave sleep measured as brain activity (left) and Rapid eye movement sleep measured as eye movements (right) on a polysomnography

.



Slow wave sleep

Studies that used polysomnography (PSG) found that during slow wave sleep a process takes places that is linked to the long term storage of hippocampal-dependent memories. During slow wave sleep the membrane potentials of all the cortical neurons slowly oscillate. The membrane is first in a hyperpolarized down-state, in which the neurons are globally silent. After this down-state it cycles into a depolarized up-state of intense firing, reaching wake-like levels. Each cycle results in a travelling wave often going to prefrontal-orbitofrontal regions that spreads to an anteroposterior direction. When sleep deepens, the occurrence of the waves increases. The pattern of waves is reproducible within subjects and is likely to be a precondition for more persisting traces. For example, during up-states of a membrane newly encoded memories are reactivated and can be redistributed from temporal hippocampal-dependent storage into long-term neocortical storage. (Born & Wilhelm, 2012; Massimini, Huber, Ferrarelli, Hill, & Tononi, 2004).

Slow wave sleep is present in stage N3. According to the American Academy of Sleep Medicine (AASM) guidelines N3 is defined by 20% of delta waves (0.5-2.0 Hz) also called slow wave sleep, in any given 30 second epoch. Slow wave sleep is often referred as deep sleep.

Polysomnography (PSG) is a comprehensive recording of the biophysiological changes that occur during sleep. PSG records brain waves, the blood oxygen level, heart rate and breathing, as well as eye and leg movements.

Tagney (1973) was the first to examine the relation between the degrees of enrichment of the environment and sleep stages. In his study rats showed a longer duration of slow wave sleep in an enriched environment than rats in an impoverished environment. Some previous studies investigated the association between slow wave sleep and cognition, although results are inconsistent. An epidemiological study of Prinz (1977) showed that in twelve healthy participants IQ changes over eighteen years where related, although not significantly, to the time spend in slow wave sleep, measured after those eighteen years. Negative changes in IQ were related to less time spend in slow wave sleep. Another epidemiological study found no relation between the amount of slow wave sleep and cognition in the elderly (Spiegel, Herzog,

& Koberle, 1999). Besides these contradictory results for the relation between cognition and slow wave sleep, the results for memory and slow wave sleep are much more clear.

Memory

In the study of Van Der Werf et al. (2009) slow wave sleep was manipulated in thirteen healthy seniors. When a person reached the stage of slow wave sleep a beeping noise caused the person to return to a more shallow sleep stage, without being awakened. By using this mild acoustic sleep perturbation approach, slow wave sleep was retracted from the normal sleep pattern. They found that memory performances after a night without slow wave sleep were worse than memory performances after a normal night of sleep. Furthermore, they found that the encoding-related hippocampal activity was less, but procedural memory was intact. This suggests that slow wave sleep has a role in the encoding of memory that is supported by the hippocampus (Van Der Werf, et al., 2009), which is in accordance with what we know from the process that during the up-states of a membrane in slow wave sleep hippocampal-dependent memories are stored in long-term memories. Plihal and Born (1997) were the first to find dissociation between declarative memory and procedural memory. Their 'dual stage consolidation theory' supposes that declarative memory is related to slow wave sleep, and procedural memory is related to REM sleep. These findings are supported by several other studies that found a positive relation between slow wave sleep and declarative memory. However, these studies are limited by measuring slow wave sleep during a nap (Studte, Bridger, & Mecklinger, 2015; Tucker et al., 2006), by interrupting slow wave sleep from the normal sleep pattern (Van Der Werf et al., 2009), by using small sample sizes or by performing a meta-analysis (Diekelmann & Born, 2010).

Declarative memory refers to memory that consciously can be recalled. It can be referred to as explicit memory. For this type of memory the hippocampus, entorhinal cortex and perirhinal cortex seems critical (Lezak, Howieson, Bigler & Tranel, 2012).

Procedural memory refers to unconscious memories, such as skills. Sometimes it is called implicit memory. This type of memory seems to rely on the cerebellum, putamen, caudate nucleus and the motor cortex (Lezak, Howieson, Bigler & Tranel, 2012).

Spiegel, Köberle and Allen (1986) suggested that the role of slow wave sleep changes across lifespan. They hypothesized that in early life slow wave sleep serves as a restorative function, but in elderly slow wave sleep is a 'functional meaningless remnant'. This is supported by studies that showed that the age-dependent decline of the consolidation of declarative memory was linked to a decrease in slow wave sleep (Backhaus et al., 2007; Spencer, Gouw, & Ivry, 2007). These results, combined with the fact that there is a decrease in the percentage of slow wave sleep with age and that the amplitude of delta waves during slow wave sleep reduces (Feinberg et al., 1967; Hornung, Danker-Hopfe & Heuser, 2005), suggest that the degree in which slow wave sleep contributes to cognitive functioning declines across the lifespan. However, as for the other studies on slow wave sleep small sample sizes are used.

Hypothesis

To summarize, the association of slow wave sleep with cognition is unclear, different studies found positive and negative associations. However, the association between slow wave sleep and memory seems clearer, in the relevant literature we can find that slow wave sleep is associated with better memory performances. It is suggested that newly acquired memories are repeatedly activated during slow wave sleep, thereby strengthening the synaptic connections in the neocortex, making it more persistent memory representations. This is regulated by an interaction between neocortex and hippocampus; this is under feed-forward control of the slow oscillations (Born & Wilhelm, 2012). However, the degree in which slow wave sleep contributes to cognitive functioning declines across the lifespan; in the elderly no associations are found with better memory performances. In general, the relevant studies had small sample sizes, they often disrupted the normal sleep pattern, they used naps during the day, and often persons slept in a different bed than their own.

In our study, we assessed the relation of slow wave sleep with memory and cognition in a large population-based study. We compared the association in younger and older

participants. We measured the amount of slow wave sleep with the duration of N3. The measures took place during a normal night of sleep in which the participants slept in their own bed without sleep distractions. Furthermore, we divided cognition into memory, executive functioning and information processing. Based on previous literature, the following hypotheses have been formulated: in the younger participants slow wave sleep is associated with a better performance in memory, executive functioning and information processing. We expected this association to be the strongest between slow wave sleep and memory. The hypotheses regarding older participants is that there is no association between slow wave sleep and cognition.

Methods

Study population

The present study was conducted within the Rotterdam Study, which aims to investigate the causes and determinants of chronic diseases in middle-aged and elderly persons (Hofman et al., 2013). The Rotterdam Study is a prospective cohort study in the Ommoord district in the city of Rotterdam, the Netherlands. All habitants of the Ommoord district aged 45 years and over received an invitation to participate in the Rotterdam Study. The Rotterdam study conforms to the principles outlined in the Declaration of Helsinki and has been approved by the Medical Ethics Committee of the Erasmus MC and by the Ministry of Health, Welfare and Sport of the Netherlands, implementing the "Wet Bevolkingsonderzoek: ERGO (Population Studies Act: Rotterdam Study)". All participants provided written informed consent to participate in the study and to obtain information from their treating physicians. From the 876 persons that were invited from January 2012 until June 2013 to participate in the polysomnography (PSG) study, 500 participants (57.1%) agreed to participate. Relatively more women (53.8% versus 61.2%, p=.03) declined to participate compared to men. Thirteen participants (2.6%) were excluded; for nine participants the PSG

recording was of insufficient quality, four participants (0.8%) were excluded from the analysis because they suffered from a stroke in the past. The group of 487 included participants consisted of 257 women (52.8%) and 230 men (47.2%), mean age 61. 8 years (range 52-95 years).

Procedure and Measures

Assessment of sleep We used the ambulant Vitaport 4 system (Temec, Kerkrade, the Netherlands) to measure a night of PSG. A trained research assistant placed all sensors during a home visit. The participants were instructed to spend the night like they normally spend the night, without any restrictions.

The PSG contained six electroencephalography (EEG) channels, F3/A2, F4/A1, C3/A2, C4/A1, O1/A2, O2/A1, bilateral electrooculography, electromyography on the chin, electrocardiography, respiratory belts on the chest and abdomen, oximetry, a nasal pressure transducer and an oronasal thermocouple.

A technician who is licensed by the American Academy of Sleep Medicine (AASM) scored all of the data. The recordings were scored manually in 30-second epochs for identification of sleep stages; the epochs were scored as Wake, N1, N2, N3, or REM. For all these sleep stages the duration and the latency was determined (Luik, Zuurbier, Whitmore, Hofman, & Tiemeier, 2015a). To measure slow wave sleep we used the duration of N3 (Carskadon & Dement, 2000) in the total sleep time. We also measured the percentage of slow wave sleep in proportion to the total sleep time, we called this the ‘occupancy N3’.

Sleep apnea was estimated with the apnea-hypopnea index (AHI). The AHI was calculated as the total number of apneas and hypopneas per hour of sleep, using Prana software (PhiToola, Strasbourg, France). Continuous reductions of airflow of at least 90% from baseline for at least 10 seconds were defined as apnea. Continuous reductions of airflow of at least 30% from baseline for at least 10 seconds, together with an oxygen desaturation of

at least 3% from pre-event baseline or an arousal were defined as hypopnea (Luik et al., 2015b).

Assessment of cognition The participants underwent a neurological test battery during a morning visit at the research center. The test battery the 15- Word Verbal Learning Test (WVLT), the Stroop Color and Word Test (Stroop), the Letter-Digit Substitution Task (LDST) and the Word Fluency Test (WFT).

The WVLT is based on the Rey Auditory Verbal Learning Test. The test measures immediate and delayed verbal memory functions (Bleecker, Bolla-Wilson, Agnew, & Meyers, 1988). Participants heard a list of 15 unrelated words repeated over 5 different trials, after each trial the participant had to repeat as many words. After the 5 trials another list of 15 unrelated words was given that the participants had to repeat, after that list the participants had to repeat the original list. 30 minutes later the participants had to repeat the original list again (Saavedra Perez et al., 2014). The Stroop measures concentration, attention and executive functioning (Golden, 1976). The Stroop consists of 3 trials. In the first trial, the participant reads the name of colors printed in black. In trial 2 the participants are asked to name the color of colored blocks. These 2 trials measure attention and concentration. Trial 3 is an interference trial and measures executive functioning. The names of colors are printed in colors that are different than the printed name, participants are asked to name the color of the ink. The outcome measure is the time needed to complete trial 3, given the time needed for trial 1 and 2 (Reeve & Schandler, 2001). The LDST was used to measure processing speed (Van der Elst, van Boxtel, van Breukelen, & Jolles, 2006). Participants have to match particular letters to other digits following an example that shows the correct combinations. They make as many letter-digit combinations as they can in 60 seconds (Lezak, Howieson, Bigler & Tranel, 2014, p. 419). The WFT was used to measure verbal fluency. Participants have to name as many animals as possible within 60 seconds (Saavedra Perez et al., 2014; Welsh et al., 1994).

For each participant a Z-score was calculated for all the tests separately. We reversed the Z-scores of the Stroop, because a high score on the Stroop indicates low cognitive functioning. To obtain robust measures we made compound scores for memory, executive functioning and information processing. The choice for these compound scores was based on a principal component analysis (Verhaaren et al., 2013). The compound score of memory consisted of the average of the Z scores for the immediate and delayed recall of the WLT. The executive functioning compound score consisted of the average of the Z-scores for the LDST, the WFT and Z-score for the Stroop trial 3. Information processing speed was constructed by averaging the Z-scores for the Stroop trial 1 and 2 and the Z-score for the LDST.

Assessment of covariates As possible covariates we selected: (1) demographic factors: sex, age, employment status, education; (2) medical status factors: body mass index, systolic blood pressure, myocardial infarction incidence, depressive symptoms; (3) lifestyle factors: alcohol use, coffee use and current smoking; and (4) sleep characteristics: sleep apnea, the use of sleep medication at night of the PSG and restless leg syndrome.

Information on employment status, educational level, smoking habits and depressive symptoms was collected during a home interview. Depressive symptoms were assessed with the Center for Epidemiologic Studies-Depression (CES-D) scale (Radloff, 1977). Scores of 16 or greater on the CES-D are traditionally interpreted as suggestive of clinically significant depression (Beekman et al., 1997). During visits to the research center we measured height and length to calculate the body mass index (kg/m^2), and we measured blood pressure. Prevalent myocardial infarction was assessed using the medical records (Leening et al., 2012). Participants were asked about alcohol and coffee usage and the use of sleep medication in a questionnaire that the participants filled in at the night of the PSG measure. Possible apnea is assessed with two questions from the Pittsburgh Sleep Quality Index (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). Sleep apnea was assessed with the AHI as described earlier. RLS was assessed with a questionnaire, based on the international restless legs syndrome

study group (IRLSSG) 2003 criteria, which are commonly used in epidemiological studies (Allen et al., 2003).

Statistical Analyses

Population characteristics are describes in number or percentage and sleep characteristics are described in mean, standard deviation and range. To analyse the population characteristics we used independent sample t-test for continuous variables and Chi-square test for categorical variables.

To test the associations of slow wave sleep with memory, executive function and information processing performances, linear regression analysis was used adjusted for body mass index, depression, restless leg syndrome, apnea-hypopnea index, smoking, myocardial infarction, systolic blood pressure and alcohol and coffee usage at night of PSG. In the linear regression analysis slow wave sleep, measured with N3, was the independent variable, memory, executive functioning and information processing performance were the dependent variables. Furthermore, to test whether there was an interaction of age and the performance on cognition test regarding the duration of slow wave sleep, we formally tested the interaction term Age*N3. Based on this significant term, we made 2 age groups based on the median (median age is 61.85), (1) younger elderly and (2) older elderly.

We performed three sensitivity analyses. First, the percentage of N3 in proportion to the total sleep time, the occupancy of N3. Second, we studied N3 only in the first four hours of sleep. We performed this sensitivity analysis to test whether a better cognitive performance is not just the effect of more total sleep time instead of the effect of slow wave sleep. For the third sensitivity analysis, we used the other sleep stages (N1, N2 and REM) to measure their association with cognition. We normalized and standardized all sleep stage measurements. In all of the analyses statistical significance was set at $p= 0.05$. Analyses were performed with IBM SPSS Statistics for Windows (Version 21; IBM Corp., Armonk, NY, USA).

Results

The characteristics of the total population (n = 487), and the characteristics split by age group (younger age group (M = 57.60, SD =2.69) n = 243; older age group (M = 66.12, SD =3.85) n = 244) can be found in Table 1. The population consisted of 230 men and 257 women. There were no differences in gender and age between the two age groups. Significantly more younger elderly are employed and have a higher education than the older elderly. The older elderly have a significantly higher blood pressure and use significantly more sleep medication than the younger elderly. Table 2 describes the sleep characteristics of the total population split by age group.

In Table 3 we present the results of the associations between the duration of N3 and cognitive measures using linear regression. Longer durations of N3 were associated with lower performances on memory tests after covariate adjustment (β= -0.10, 95% confidence interval (CI): -0.20; -0.01, p= .04). In the younger elderly we found the same results, they drove this association (β= -0.24, 95% CI: -0.37; -0.09, p= .001), whereas in the older age group the duration of N3 was not associated with memory performance (β= 0.05, 95% CI: -0.08; 0.18, p= .44). We did not find an association between the duration of N3 and executive functioning (β= 0.07, 95% CI: -0.05; 0.18, p= .27), and between N3 and information processing (β= 0.01, 95% CI: -0.10; 0.11, p= .90).

Next, we performed the sensitivity analysis. First, we assessed the association between the occupancy of N3 and memory performance (Table 4). In line with duration of N3, the occupancy of N3 seems to be associated with memory. However, it did not reach statistical significance (β = -0.08, 95% CI: -0.08; -0.18, p= .09). Consistent with the previous analysis, in the younger elderly, we found that higher N3 occupancy was associated with lower performance on the memory tasks (β = -0.22, 95% CI:-0.36; -0.09, p= .002), whereas in the elderly it was not (β= 0.08. 95% CI: -0.05;0.21, p= .25).

For the second sensitivity analysis we assessed the association between the duration of N3 in the first four hours of sleep and slow wave sleep. This association between the duration of N3 in the first four hours of sleep was significant (β = 0.001, 95% CI:-0.16; 0.19, *p*= .87), no differences were found between the two age groups.

Third, we did a sensitivity analysis for the association between other sleep phases and cognition. Table 5 shows that REM sleep was also associated with memory in the age and sex adjusted model (β =-0.11, 95% CI: -0.21; -0.01, *p*= .04). However, the association between memory and REM sleep was not statistical significant anymore after covariate adjustment (β= -0.10, 95% CI: -0.21;0.01, *p*= .06). Furthermore, we found that total sleep time was associated with information processing in the age and sex adjusted model (β = 0.11, 95% CI: 0.00;0.22, *p*= .05), although this was not statistical significant anymore after covariate adjustment (β = 0.11, 95% CI: -0.01;0.22, *p*= .06).

Discussion

In this population-based polysomnography study of 486 middle-aged and elderly participants, we assessed the associations between slow wave sleep and memory, information processing and executive functioning in two age-groups. In the younger elderly an association was found between slow wave sleep and memory, but in the opposite direction as we expected. More slow wave sleep was associated with poorer memory performance. Slow wave sleep was not associated with information processing and executive functioning in the younger elderly. As we expected, we did not find an association between slow wave sleep and cognition in the older elderly. For both age-groups we found that there was no association between the duration of slow wave sleep in the first four hours of sleep and memory. Furthermore, we found that there was no association between other sleep stages and slow wave sleep.

Our results for the younger elderly are in contrast to other studies that use slow wave sleep deprivation, which measured slow wave sleep during a nap or used a small samples to measure the function of slow wave sleep (Van Der Werf, et al., 2009). In these studies, more slow wave sleep was associated with better memory performances (Studte et al., 2015; Tucker et al., 2006). However, we studied slow wave sleep during a normal night of sleep to enhance the ecological validity and we used a large sample, that was more representative of the population.

We give three possible explanations for our finding that more slow wave sleep is associated with poorer memory performance in the younger elderly. First, total sleep time has a U-shaped relation with many health and lifestyle variables (Patel, Malhotra, Gottlieb, White, & Hu, 2006). Both short and longer sleepers are more likely to have characteristics associated with poor health. So, although sleep has a restorative function, too much sleep is not beneficial. Possibly, the same is true for slow wave sleep. From previous literature we know that slow wave sleep is positively associated with memory, it could be that this association between slow wave sleep and memory is also a U-shaped association. Too much slow wave sleep may not be beneficial for the memory performance in the younger elderly. Both too much and too little slow wave sleep could indicate a poor health in which memory performance is less good than memory performance in a healthy person. This is in line with the results of our study. For the younger elderly, we did not find an association between slow wave sleep in the first four hours of sleep and memory and we found a negative association between slow wave sleep in the total sleep time and memory. It suggests that to a certain extent, slow wave sleep has no effect on memory. However in participants that sleep longer and thus have more slow wave sleep, slow wave sleep has a negative effect on memory.

Second, it is hypothesized that after a night of less slow wave sleep the next night of sleep will contain more slow wave sleep to compensate for the night before (Ferrara, De Gennaro, & Bertini, 1999; Gillberg & ÅKerstedt, 1994). This suggests that after a night

without slow wave sleep the memory performance on the test is poor, but the day after the memory performance is likely to be better, due to more slow wave sleep. In our study, the memory test did not immediately take place the day after the PSG measure. Possibly, participants performing poorly on the memory test had less slow wave sleep in their regular nights (nights other than the PSG night). However, for the PSG night they might have had planned extra sleep time, and by sleep compensation processes had more slow wave sleep compared to their normal nights. We do not have the data about the slow wave sleep duration of the night before the memory test.

Our third explanation is that for younger elderly the relation between slow wave sleep and memory is influenced by another factor. For example having more stress can influence memory performances in a negative direction (Kuhlmann, Piel & Wolf, 2005) and having a higher education can influence memory in a positive direction (Orsini et al., 1986). Possibly, in our population the percentage of employed participants was higher than the percentage other studies. Having work causes stress, which negatively influenced the relation between slow wave sleep and memory in our study.

Previous studies found that slow wave sleep is related to better memory in the young/middle-aged but not in the elderly. Spiegel, Köberle and Allen (1986) hypothesized that in early life slow wave sleep serves as a restorative function, but in elderly slow wave sleep is a 'functional meaningless remnant'. We replicated the finding that there is no association between slow wave sleep and memory in the older elderly. Sleep may have a different association with memory for the younger and older adults because of the changes in sleep-architecture with age. There is a decrease of the third stage of sleep and in some elderly the whole stage is even absent (Feinberg et al., 1967; Carrier, Monk, Buysse & Kupfer, 1997). Furthermore, the amplitude of the delta waves during slow wave sleep reduces (Wolkove, Elkholy, Baltzan & Palayew, 2007). Furthermore, structural and functional changes in the hippocampus and prefrontal cortex may underlie the decrease of hippocampus-dependent

memory performance (Driscoll et al., 2003; Hedden & Gabrieli, 2004). Hornung, Danker-Hopfe & Heuser (2005) hypothesized that the changes in sleep architecture lead to impaired memory consolidation and may affect daytime memory performance; vice versa, the efficiency of memory consolidation during sleep is reduced by the structural and functional changes of brain regions.

Executive functioning and information processing were not related to slow wave sleep in both age-groups. Previous literature about this topic is inconsistent. Feinberg et al. (1967) found that slow wave sleep is negatively correlated to intelligence test measures in the elderly (mean is 77 years). Jurado, Luna-Villegas and Buela-Casal (1989) and Edinger et al. (2000) found that young adults and middle-aged adults who had more slow wave sleep performed better on a vigilance task. In contrast, the study of Crenshaw and Edinger (1999) found that in the elderly there is no association between slow wave sleep and the performance on a vigilance task. In line with the literature, we did not find an association between executive functioning and information processing with slow wave sleep in the older age group. Although, in the younger elderly an association between executive functioning and information processing with slow wave sleep is found in previous literature, we did not find this association for this group. Possibly we did not find an association because our cognitive tests were not as extensive as the tests used in the other studies. Furthermore, small effects in the association are more visible when a small sample is used, so in a population based study these small effects are not visible.

The current study had several strengths. First, we assessed cognitive performance and PSG measures within the Rotterdam Study, a prospective population based cohort study with a large sample. Generalization of our results was hereby increased, and we were able to adjust for many covariates. Second, the assessment of cognition functioning covered three cognitive domains. In contrast to other studies that assessed the association between slow wave sleep and one cognitive domain, we were able to compare associations for three cognitive domains.

Some limitations should also be considered. First, it was not possible to make any conclusion about causality since our study is cross-sectional. Second, the sleep of the participants was only measured during one night, possibly the data was affected by the 'first night effect', meaning that the first PSG measure was different from the following PSG measures (Agnew, Webb, & Williams, 1966; Browman & Cartwright, 1980). In addition, the cognition tests did not take place immediately the day after the night that slow wave sleep was measured. Possibly the duration of slow wave sleep differs between different nights, so to assess the effect of the duration of slow wave sleep on cognition it is suggested to use the memory performance immediately after the night that the PSG takes place.

In conclusion, in this population-based study of middle aged and elderly persons, slow wave sleep is specifically associated to poor memory performance, but only in the younger elderly. This suggests that in this population-based study too much slow wave sleep could be indicative of poor health. Future research in population-based studies is necessary to replicate these findings. When replicating this study in the future, some changes in the methods can be made. First, the PSG measures should take longer than one night, to prevent the 'first night effect'. Second, the cognition tests should take place on the same day as the PSG takes place, because previous studies showed that the amount of slow wave sleep can differ between nights. Furthermore, more varied age groups can be made to demonstrate the specific association in each group.

References

Agnew, H.W., Webb, W.B., & Williams, R.L. (1966). The first night effect: an EEG study of sleep. *Psychophysiology*, *2*(3), 263-266.

Allen, R.P., Picchietti, D., Hening, W.A., Trenkwalder, C., Walters, A.S., & Montplaisi, J. (2003). Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology: a report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. *Sleep Medicine, 4*(2), 101-119.

Backhaus, J., Born, J., Hoeckesfeld, R., Fokuhl, S., Hohagen, F., & Junghanns, K. (2007). Midlife decline in declarative memory consolidation is correlated with a decline in slow wave sleep. *Learning & Memory*, *14*(5), 336-341.

Beekman, A.T. F., Deeg, D.J.H., Van Limbeek, J., Braam, A.W., De Vries, M.Z., & Van Tilburg, W. (1997). Brief communication. *Psychological Medicine, 27*(01), 231-235.

Bleecker, M.L., Bolla-Wilson, K., Agnew, J., & Meyers, D.A. (1988). Age-related sex differences in verbal memory. *J Clin Psychol*, *44*(3), 403-411. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/3384968

Born, J., & Wilhelm, I. (2012). System consolidation of memory during sleep. *Psychological Research*, *76*(2), 192-203. doi:10.1007/s00426-011-0335-6

Browman, C.P., & Cartwright, R.D. (1980). The first-night effect on sleep and dreams. *Biological Psychiatry*.

Buysse, D.J., Reynolds, C.F., 3rd, Monk, T.H., Berman, S.R., & Kupfer, D.J. (1989). The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Research, 28*(2), 193-213. doi:0165-1781(89)90047-4 [pii]

Carrier, J., Monk, T. H., Buysse, D. J., & Kupfer, D. J. (1997). Sleep and morningness-eveningness in the ‘middle’years of life (20–59y). *Journal of Sleep Research, 6*(4), 230-237.

Carskadon, M.A., & Dement, W.C. (2000). Normal human sleep: an overview. *Principles and practice of sleep medicine, 2*, 16-25.

Crenshaw, M.C., & Edinger, J.D. (1999). Slow-wave sleep and waking cognitive performance among older adults with and without insomnia complaints. *Physiology & Behavior, 66*(3), 485-492.

Diekelmann, S., & Born, J. (2010). The memory function of sleep. *Nature Reviews Neuroscience, 11*(2), 114-126.

Driscoll, I., Hamilton, D. A., Petropoulos, H., Yeo, R. A., Brooks, W. M., Baumgartner, R. N., & Sutherland, R. J. (2003). The aging hippocampus: cognitive, biochemical and structural findings. *Cerebral cortex, 13*(12), 1344-1351.

Edinger, J.D., Glenn, D.M., Bastian, L.A., & Marsh, G.R. (2000). Slow-wave sleep and waking cognitive performance II: Findings among middle-aged adults with and without insomnia complaints. *Physiology & Behavior, 70*(1), 127-134.

Espiritu, J.R. (2008). Aging-related sleep changes. *Clin Geriatr Med, 24*(1), 1-14, v.

Feinberg, I., Koresko, R. L., & Heller, N. (1967). EEG sleep patterns as a function of normal and pathological aging in man. *Journal of Psychiatry Research, 5*(2), 107-144. doi:0022-3956(67)90027-1

Ferrara, M., De Gennaro, L., & Bertini, M. (1999). Selective slow-wave sleep (SWS) deprivation and SWS rebound: do we need a fixed SWS amount per night. *Sleep Research Online, 2*(1), 15-19.

Gillberg, M., & ÅKerstedt, T. (1994). Sleep restriction and SWS-suppression: effects on daytime alertness and night-time recovery. *Journal of Sleep Research, 3*(3), 144-151.

Golden, C.J. (1976). Identification of brain disorders by the Stroop Color and Word Test. *Journal Clin Psychol, 32*(3), 654-658.Retrieved from http://www.ncbi/nlm.nih.gov/pubmed/956433

Hedden, T., & Gabrieli, J. D. (2004). Insights into the ageing mind: a view from cognitive neuroscience. *Nature Reviews Neuroscience, 5*(2), 87-96.

Hofman, A., Darwish Murad, S., van Duijn, C. M., Franco, O. H., Goedegebure, A., Ikram, M.A., Klaver, C.C., Nijsten, T.E., Peeters, R.P., Stricker, B.H., Tiemeier, H.W., Uitterlinden, A.G., & Vernooij, M.W. (2013). The Rotterdam Study: 2014 objectives and design update. *European Journal of Epidemiology, 28*(11), 889-926. doi:10.1007/s10654-013-9866-z

Hornung, O. P., Danker-Hopfe, H., & Heuser, I. (2005). Age-related changes in sleep and memory: commonalities and interrelationships. *Experimental Gerontology, 40*(4), 279-285.

Jurado, J.L., Luna-Villegas, G., & Buela-Casal, G. (1989). Normal human subjects with slow reaction times and larger time estimations after waking have diminished delta sleep. *Electroencephalography and Clinical Neurophysiology, 73*(2), 124-128.

Killgore, W.D., Grugle, N.L., & Balkin, T.J. (2012). Gambling when sleep deprived: don't bet on stimulants. *Chronobiology International, 29*(1), 43-54. doi:10.3109/07420528.2011.635230

Kuhlmann, S., Piel, M., & Wolf, O. T. (2005). Impaired memory retrieval after psychosocial stress in healthy young men. *The Journal of Neuroscience, 25*(11), 2977-2982.

Leening, M.J.G., Kavousi, M., Heeringa, J., van Rooij, F.J.A., Verkroost-van Heemst, J., Deckers, J.W., Mattace-Raso, F.U.S., Ziere, G., Hofman, A., & Stricker, B.H.C. (2012). Methods of data collection and definitions of cardiac outcomes in the Rotterdam Study. *European Journal of Epidemiology, 27*(3), 173-185.

Lezak, M.D., Howieson, D.B., Bigler, E.D., Tranel, D. (2012) *Neuropsychological Assessment (fifth edition).*New York: Oxford university press.

Luik, A.I., Noteboom, J., Zuurbier, L.A., Whitmore, H., Hofman, A., & Tiemeier, H. (2015b).

Sleep apnea severity and depressive symptoms in a population-based study. *Sleep Health*.doi: 10.1016/j.pnpbp.2013.07.017

Luik, A.I., Zuurbier, L.A., Whitmore, H., Hofman, A., & Tiemeier, H. (2015a). REM sleep and depressive symptoms in a population-based study of middle-aged and elderly persons. *Journal of Sleep Research*. doi:10.1111/jsr.12273

Massimini, M., Huber, R., Ferrarelli, F., Hill, S., & Tononi, G. (2004). The sleep slow oscillation as a traveling wave. *Journal of Neuroscience, 24*(31), 6862-6870.

Mazzotti, D. R., Guindalini, C., Moraes, W. A., Andersen, M. L., Cendoroglo, M. S., Ramos, L. R., & Tufik, S. (2014). Human longevity is associated with regular sleep patterns, maintenance of slow wave sleep, and favorable lipid profile. *Front Aging Neuroscience, 6*, 134. doi:10.3389/fnagi.2014.00134

Ohayon, M. M., Carskadon, M. A., Guilleminault, C., & Vitiello, M. V. (2004). Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: developing normative sleep values across the human lifespan. *Sleep, 27*(7), 1255-1273. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/15586779

Orsini, A., Chiacchio, L., Cinque, M., Cocchiaro, C., Schiappa, O., & Grossi, D. (1986). Effects of age, education and sex on two tests of immediate memory: A study of normal subjects from 20 to 99 years of age. *Perceptual and Motor Skills, 63*(2), 727-732.

Patel, S. R., Malhotra, A., Gottlieb, D. J., White, D. P., & Hu, F. B. (2006). Correlates of long sleep duration. *Sleep, 29*(7), 881.

Payne, J. D., & Kensinger, E. A. (2011). Sleep leads to changes in the emotional memory trace: evidence from FMRI. *Journal of Cognitiv Neuroscience, 23*(6), 1285-1297. doi: 10.1162/jocn.2010.21526

Plihal, W., & Born, J. (1997). Effects of early and late nocturnal sleep on declarative and procedural memory. *Journal of Cognitive Neuroscience, 9*(4), 534-547.

Prinz, P.N. (1977). Sleep patterns in the healthy aged: relationship with intellectual function. *Journal of Gerontology 32*: 179-186

Radloff, L. S. (1977). The CES-D scale a self-report depression scale for research in the general population. *Applied Psychological Measurement, 1*(3), 385-401.

Rechtschaffen, A. (1971) "The control of sleep," in *Human Behavior and Its Control*, W. A. Hunt, Ed., p. 88, Shenkman Publishing Company, Cambridge, Mass, USA.

Reeve, W. V., & Schandler, S. L. (2001). Frontal lobe functioning in adolescents with attention deficit hyperactivity disorder. *Adolescence, 36*(144), 749.

Saavedra Perez, H. C., Ikram, M. A., Direk, N., Prigerson, H. G., Freak-Poli, R., Verhaaren, B. F., Hofman, A., Vernooij, M., & Tiemeier, H. (2014). Cognition, structural brain changes and complicated grief. A population-based study. *Psychological Medicine*, 1-11. doi:S0033291714002499

Schabus, M., Hodlmoser, K., Gruber, G., Sauter, C., Anderer, P., Klosch, G., Parapatics, S., Saletu, B., Klimesch, W., & Zeitlhofer, J. (2006). Sleep spindle-related activity in the human EEG and its relation to general cognitive and learning abilities. *European Journal of Neuroscience, 23*(7), 1738-1746.

Spencer, R. M., Gouw, A. M., & Ivry, R. B. (2007). Age-related decline of sleep-dependent consolidation. *Learning & Memory, 14*(7), 480-484.

Spiegel, R., Herzog, A., & Köberle, S. (1999). Polygraphic sleep criteria as predictors of successful aging: an exploratory longitudinal study. *Biological Psychiatry, 45*(4), 435-442. doi:S0006322398000420

Spiegel, R., Köberle, S., & Allen, S. R. (1985). Significance of slow wave sleep: considerations from a clinical viewpoint. *Sleep*, 9(1), 66-79.

Studte, S., Bridger, E., & Mecklinger, A. (2015). Nap sleep preserves associative but not item memory performance. *Neurobiological of Learning and Memory, 120*, 84-93. doi:S1074-7427(15)00036-2

Tagney, J. (1973). Sleep patterns related to rearing rats in enriched and impoverished environments. *Brain Research, 53*(2), 353-361.

Tucker, M. A., Hirota, Y., Wamsley, E. J., Lau, H., Chaklader, A., & Fishbein, W. (2006). A daytime nap containing solely non-REM sleep enhances declarative but not procedural memory. *Neurobiology of Learning and Memory, 86*(2), 241-247.

Van der Elst, W., van Boxtel, M. P. J., van Breukelen, G. J. P., & Jolles, J. (2006). The Letter Digit Substitution Test: normative data for 1,858 healthy participants aged 24–81 from the Maastricht Aging Study (MAAS): influence of age, education, and sex. *Journal of Clinical and Experimental Neuropsychology, 28*(6), 998-1009.

Van Der Werf, Y. D., Altena, E., Schoonheim, M. M., Sanz-Arigita, E. J., Vis, J. C., De Rijke, W., & Van Someren, E. J. (2009). Sleep benefits subsequent hippocampal functioning. *Nature reviews Neuroscience, 12*(2), 122-123.

Verhaaren, B. F. J., Vernooij, M. W., Koudstaal, P. J., Uitterlinden, A. G., van Duijn, C. M., Hofman, A., Breteler, M. M. B., & Ikram, M. A. (2013). Alzheimer's disease genes and cognition in the nondemented general population. *Biological psychiatry, 73*(5), 429-434.

Webb, W. B., & Campbell, S. S. (1980). Awakenings and the return to sleep in an older population. *Sleep, 3*(1), 41-46. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed /7466125

Welsh, K. A., Butters, N., Mohs, R. C., Beekly, D., Edland, S., Fillenbaum, G., & Heyman, A. (1994). The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part V. A normative study of the neuropsychological battery. *Neurology, 44*(4), 609-614. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8164812

Wolkove, N., Elkholy, O., Baltzan, M., & Palayew, M. (2007). Sleep and aging: 1. Sleep disorders commonly found in older people. *Canadian Medical Association Journal, 176*(9), 1299-1304.

Tables

Table 1. Population characteristics

	Total sample N = 487	Younger elderly [a] N = 243	Older elderly [b] N = 244
Demographic factors			
Gender (%)			
Women	52.8	49.8	55.7
Men	47.2	50.2	44.3
Age (years)	61.8 ± 5.4	57.6 ± 2.7	66.0 ± 3.8
Employed (%) *	50.4	79.8	20.9
Education (%) *			
Low	8.5	3.3	13.6
Intermediate	59.0	56.2	61.7
High	32.5	40.5	24.7
Medical Status factors			
Body mass index (kg/m²)	27.8 ± 4.7	27.7 ± 4.8	27.9 ± 4.7
Mean systolic blood pressure (mm Hg) *	133.7 ± 18.0	130.1 ± 16.1	137.2 ± 19.2
Myocardinal infarction incidence (%)	3.1	2.5	3.8
Depressive symptoms (%)	7.4	7.0	7.8
Lifestyle factors			
Alcohol use at night PSG (units)	0.51 ± 1.00	0.59 ± 1.10	0.44 ± 0.89
Coffee use at night PSG (cups)	0.91 ± 0.93	0.85 ± 1.02	0.95 ± 0.83
Smoking (%)			
No	27.4	27.6	27.2
Before	54.5	52.3	56.8
Current	18.1	20.2	16.0
Sleep characteristics			
Apnea-hypopnea index	14.1 ± 13.3	13.5 ± 13.2	14.7 ± 13.5
Use of sleepmedication at night PSG (%) *	7.0	3.7	10.2
Restless legs syndrome (%)	12.3	11.8	13.2

Values given as mean ± standard deviation, unless stated otherwise, * indicates significant difference between the younger elderly and older elderly at $P < 0.05$ analyzed with a Chi-square test for qualitative variables or a one-way analysis for quantitative variables.

[a] Younger elderly, age < 61.85; [b] Older elderly age ≥ 61.85

Table 2. Polysomnography data

	Mean ± SD	Minimum	Maximum
Sleepstage 1 (N1), min			
All [a]	49.10 ± 24.40	11.50	188.50
Younger elderly [b]	47.40 ± 22.16	11.50	188.50
Older elderly [c]	50.76 ± 26.40	11.50	178.00
Sleepstage 2 (N2), min			
All	215.30 ± 50.50	86.50	376.50
Younger elderly	214.67 ± 51.96	86.50	376.50
Older elderly	216.00 ± 49.12	88.00	373.50
Sleepstage 3 (N3), min			
All	38.50 ± 32.00	0.00	153.50
Younger elderly	39.24 ± 33.13	0.00	153.50
Older elderly	37.75 ± 30.45	0.00	135.50
Rapid Eye Movement (REM), min			
All	80.00 ± 25.10	10.50	160.00
Younger elderly	81.21 ± 26.67	10.50	160.00
Older elderly	78.76 ± 23.35	16.00	138.00
Sleep latency, min			
All	21.41 ± 26.20	1.00	228.00
Younger elderly	19.97 ± 26.69	1.00	228.00
Older elderly	22.84 ± 25.68	1.50	173.00
Total sleep time, min			
All	382.90 ± 62.60	156.50	597.50
Younger elderly	382.53 ± 67.48	156.50	597.50
Older elderly	383.27 ± 57.38	208.00	537.00

SD. Standard Deviation

***** indicates significant difference between the younger elderly and older elderly at $P < 0.05$ analyzed with a one-way analysis.

[a] All n=491; μ= 61.87

[b] Age < 61.85; n=243

[c] Age ≥ 61.85; n=244

Table 3. Duration N3 in association with information processing, executive functioning and memory

		Information processing (SD)				Executive functioning (SD)				Memory (SD)			
		β	95% CI		p	β	95% CI		p	β	95% CI		p
Duration N3 (SD)													
All [a]	model I [d]	< 0.00	-0.09	0.08	.91	0.04	-0.04	0.11	.32	-0.10	-0.20	-0.01	**.03**
	model II [e]	0.01	-0.10	0.11	.90	0.07	-0.05	0.18	.27	-0.10	-0.20	-0.01	**.04**
Younger elderly [b]	model I	0.01	-0.1	0.11	.92	0.05	-0.04	0.15	.30	-0.21	-0.33	0.09	**.001**
	model II	0.02	-0.14	0.18	.78	0.10	-0.08	0.28	.29	-0.24	-0.37	-0.09	**.001**
Older elderly [c]	model I	-0.01	-0.14	0.12	.88	0.04	-0.07	0.16	.47	0.05	-0.10	0.19	.51
	model II	-0.11	-0.15	0.12	.87	0.05	-0.10	0.20	.50	0.05	-0.08	0.18	.44

CI. Confidence Interval ; N. Sleep stage; SD. Standard Deviation

[a] All n=487 μ= 61.87;Information processing n=478 ; Executive functioning n=477; Memory n=464

[b] Age < 61.85; n=243; Information processing n=240 ; Executive functioning n=240; Memory n=234

[c] Age ≥ 61.85; n=244; Information processing n=238 ; Executive functioning n=237; Memory n=230

[d] model I: linear regression analysis adjusted for age and sex

[e] model II: lineair regression analysis adjusted for body mass index, depressive symptoms, restless leg syndrome, apnea-hypopnea index, smoking, myocardial infarction, systolic blood pressure and alcohol and coffee usage at night of PSG

All cognitive tests have been standardized. Duration N3 has been normalized and standardized.

Appendix

Table 4. Occupancy N3 in total sleep time and N3 in first four hours in association with memory

		Memory (SD)			
		β	95% CI		p
Occupancy N3 (SD)					
All [a]	model I [d]	-0.08	-0.18	0.01	0.07
	model II [e]	-0.08	-0.18	0.01	0.09
Younger elderly [b]	model I	-0.20	-0.32	-0.07	**0.002**
	model II	-0.22	-0.36	-0.09	**0.002**
Older elderly [c]	model I	0.07	-0.07	0.21	0.29
	model II	0.08	-0.05	0.21	0.25
N3 in first four hours of sleep (SD)					
All	model I	0.03	-0.13	0.19	0.75
	model II	0.02	-0.14	0.19	0.77
Younger elderly	model I	-0.02	-0.22	0.19	0.86
	model II	-0.02	-0.22	0.19	0.89
Older elderly	model I	0.09	-0.17	0.35	0.5
	model II	0.07	-0.22	0.37	0.63

CI. Confidence interval ; N. sleepstage; SD. Standard deviation

[a] All n=487; Memory n=464

[b] Age < 61.85; Memory n=234

[c] Age ≥ 61.85; Memory n=230

[d] model I: linear regression analysis is adjusted for age and sex

[e] model II: lineair regression analysis is adjusted for body mass index, depression, smoking, myocardinal infarction, systolic blood pressure and alcohol and coffee usage at night of PSG.

All cognitive tests have been standardized.

Occupancy N3 and N3 in first four hours of sleep have been normalized and standardized.

Table 5. N1, N2, REM and Total sleep time in association with information processing, executive functioning and memory

		Information processing (SD)				Executive functioning (SD)				Memory (SD)			
		β	95% CI		p	β	95% CI		p	β	95% CI		p
Duration N1, min													
All[a]	model I[b]	0.00	-0.10	0.11	0.95	0.01	-0.11	0.13	0.87	0.05	-0.05	0.14	0.34
	model II[c]	-0.01	-0.10	0.09	0.92	-0.02	-0.12	0.09	0.78	0.06	-0.03	0.15	0.21
Duration N2, min													
All	model I	0.11	-0.002	0.22	0.06	0.03	-0.10	0.16	0.66	-0.02	-0.12	0.08	0.67
	model II	0.11	-0.002	0.23	0.05	0.05	-0.08	0.18	0.41	-0.03	-0.14	0.08	0.57
Duration REM, min													
All	model I	0.09	-0.02	0.21	0.11	0.03	-0.10	0.16	0.65	-0.11	-0.21	-0.01	**0.04**
	model II	0.08	-0.04	0.19	0.18	0.01	-0.12	0.15	0.85	-0.10	-0.21	0.01	0.06
Total sleep time, min													
All	model I	0.11	0.00	0.22	**0.05**	0.06	-0.07	0.18	0.36	-0.10	-0.20	0.01	0.06
	model II	0.11	-0.01	0.22	0.06	0.06	-0.07	0.19	0.38	-0.10	-0.21	0.01	0.07

CI. Confidence Interval ; N. Sleep stage; SD. Standard Deviation

[a] All n=487 μ= 61.87;Information processing n=478 ; Executive functioning n=477; Memory n=464

[b] model I: linear regression analysis adjusted for age and sex

[c] model II: lineair regression analysis adjusted for body mass index, depressive symptoms, restless leg syndrome, apnea-hypopnea index, smoking, myocardial infarction, systolic blood pressure and alcohol and coffee usage at night of PSG

All cognitive tests have been standardized. Duration N1, N2, REM and Total sleep time have been normalized and standardized.