

## Summary

### *The research project*

A sleepless night (sleep deprivation) may hamper task execution of tasks requiring concentration, attention and working memory the next day. Such problems were thus far not found unequivocally in people who reported chronic sleep problems. In this thesis we investigated if and in what way cognitive performance (memory, attention and working memory tasks) and brain activity are different between people with chronic sleep problems (chronic insomnia) and normal sleepers. We also investigated whether any deviations in behavior and brain activity as a result of insomnia normalize after sleep therapy without medication. Lastly, we tried to find a better model than total sleep deprivation in good sleepers to investigate deviations in cognitive performance and brain activity in insomnia. For this we applied a method that makes the sleep more shallow but does not change total sleep duration.

We limited our study to older adults, as insomnia mainly occurs in people over 50 years of age. Sleep disorders as a result of (other) physical or mental disorders (so-called secondary insomnia) as well as sleeping disorders resulting from respiratory problems (sleep apnea) or restless legs during nighttime were further excluded. Any results could thus be directly related to sleep problems, and confounding factors such as breathing difficulties or mental problems could be excluded.

Subjects were selected by means of sleep registration, among other methods. During nighttime, an electro-encephalogram (EEG) was administered, leg movements were measured by means of electrodes and possible breathing difficulties were detected through a flow meter and an oxygen saturation meter. In addition, questionnaires were administered. From over four-hundred candidates a group of older adults was selected who only suffered from chronic sleep problems - primary insomnia. We compared this group to a group of normal sleepers, who we also subjected to sleep measurements and questionnaires to exclude sleep disorders, mental problems and other factors that might bias the study.

Both groups underwent brain scans that measured brain activity during task performance (functional magnetic resonance imaging, fMRI). By means of double-pulse transcranial magnetic stimulation (TMS) we attempted to gain an insight in the balance between the excitatory (stimulating) and inhibitory (repressing) brain cells in the neuronal network of the cortex. The participants were also asked to perform computer tasks that measured, amongst others, the level of attention (vigilance).

A second, identical session took place after six weeks of sleep therapy (for half of the group of insomnia patients) or after a similar time interval without sleep therapy (for the other half of the group of insomnia patients). This sleep therapy consisted of a combination of methods known to be effective for treating insomnia. The time that patients could spend in bed was for instance limited (sleep restriction), patients were exposed to 30 minutes of bright light every morning and evening to regulate melatonin production (light therapy), and they took a hot bath two to three hours before going to bed alternated with fairly intensive bodily exercise (body temperature regulation). The intake of coffee and alcohol was reduced and activities allowed in bed were

restricted; e.g. they were not allowed to eat or watch TV in bed (sleep hygiene).

To find a better model than total sleep deprivation for the deviations in cognitive performance and brain activity in insomnia we applied a method that induces shallow sleep, but does not affect total sleep duration, to a group of persons without sleep complaints. We achieved this by suppressing the slow brain waves that are characteristic of sleep (slow wave suppression). During one of the two sessions, participants were exposed to beeping noises which started as they entered deep sleep and which volume increased with continuous deep sleep; the beeping noises only stopped when the subjects' EEG indicated that they entered more shallow sleep. Cognitive performance and brain activity were measured the next day to evaluate whether the effects of this intervention showed a similar profile to that of the insomnia group.

### *Summary of the individual chapters*

**Chapter 1** provides an overview of the scope of the thesis and summarizes what is known thus far about the cognitive performance and brain activity in insomnia and after sleep deprivation, and what the treatment of insomnia involves. One third of all adults, in particular older adults, complain of suffering from insomnia. Although task performance is not affected in laboratory settings, insomnia is related to an increased number of industrial accidents and absenteeism from work. Insomnia is characterized by a state of elevated "arousal" (hyperarousal), which is shown from different physiological measures and which can be detected in the brain through increased brain activity before sleep onset and during sleep. Several factors can be distinguished that (1) make someone vulnerable for insomnia, (2) could lead to insomnia and (3) maintain insomnia. An increased sensitivity to the activating function of stress hormones could play a role in the onset and maintenance of insomnia. Insomnia is also known to be related to problems with emotion regulation: emotions are internalized instead of expressed or acted upon. Non-pharmacological sleep therapy may, particularly in the long term, be more effective than sleep medication for the treatment of insomnia. **Chapter 2** further elucidates the specific research questions featured in the various chapters.

**Chapter 3** describes the performance of insomnia patients on two attention tasks. In one task, participants were required to press a button as soon as an asterisk appeared on a computer screen (the simple vigilance task). Intervals between asterisk appearances varied. Duration of the task was approximately 12 minutes. In the second, more complex task, participants were asked to press a button as soon as they saw the letter 'p' but not when the letter 'd' appeared (the complex vigilance task). Here, too, the intervals were variable and task duration was about 12 minutes. Compared to normal sleepers, insomnia patients were faster on the simple, but slower on the complex vigilance task. After sleep therapy this effect was restored; they became slower on the simple, but faster on the more complex task. This may be explained by the 'hyperarousal' effect, which influences the reaction time as long as the task involved is simple, but does not last on a more complex task which requires decision-making abilities. Sleep therapy may 'normalize' the

insomnia patients so that their performance is similar to that of normal sleepers.

**Chapter 4** describes the performance of both groups on a task that involved generating as many words as possible; in a particular category, for instance animals (categorical fluency task) or generating words starting with a particular letter (letter fluency task). Insomnia patients show decreased brain activity in the frontal parts of the brain that are normally activated during this task (the lower winding of the frontal cortex -the inferior frontal gyrus) and the more centrally located frontal cortex (medial prefrontal cortex). After sleep therapy the brain activity in these regions partly recovers. Even on baseline, insomnia patients score better on both tasks than normal sleepers, possibly due to hyperarousal. Sleep therapy even improves their performance, particularly on the more complex task, the letter fluency task. It is possible that here, too, hyperarousal plays a role.

**Chapter 5** describes how insomnia patients have lower grey matter density in three brain regions, namely the orbitofrontal cortex (in the frontal part of the brain, above the eye socket), and two regions in the precuneus (located in a higher, rear and more central part of the brain). Grey matter density in the orbitofrontal cortex has a strong correlation with insomnia severity: the more a patient suffers from insomnia, the lower the density. This area is often active during decision making. The precuneus is involved in a network of areas activated when the brain is at rest, the so-called 'default network'. It may be important in future research to evaluate whether insomnia patients show less strong brain waves during wakefulness and sleep.

**Chapter 6** describes a double-pulse transcranial magnetic stimulation (TMS) experiment. With this method it is possible to measure the occurrence of inhibition or facilitation of the evoked muscle response, the so-called motor evoked potential (MEP), when a stimulus with a variable interval is preceded by a prior and weaker stimulus. Compared to normal sleepers the insomnia patients showed a strong MEP after a double pulse, but also after a single-pulse stimulus. This led to a relatively decreased facilitation effect compared to normal sleepers. Sleep therapy did not normalize this effect. The results suggest that, here too, hyperarousal may play a role.

**Chapter 7** describes how slow wave suppression of normal sleepers may influence performance on attention tasks. Slow wave suppression led to lapses, moments of total lack of attention, in which no responses are generated. These lapses occurred during the simple as well as during the complex attention tasks. The performance after slow wave suppression very much resembles the performance after total sleep deprivation, as described by others, but does not resemble the performance of insomnia patients as described in chapter 3.

**Chapter 8** discusses the influence of slow wave suppression on memory performance and brain activity. After slow wave suppression, the activity of the hippocampus, a brain area important for memory, was less strong than after a normal night of sleep. Participants could also remember less well which pictures they had or had not seen previously.

**In chapter 9** results are summarized and discussed in the context of what is known about insomnia thus far. Cognitive performance in insomnia seems particularly affected in tasks with longer duration which involve a decision-making process. Even when task performance is not affected,

brain activity of insomnia patients may be different from that of normal sleepers; sleep therapy may partly reverse this. Grey matter differences are found in different regions than the regions where functional differences are found between insomnia patients and normal sleepers. The regions where grey matter differences are found are strongly correlated to functions found to be affected in sleep deprivation and insomnia, such as decision-making. The involvement of these areas in the occurrence of spontaneous oscillations (brain waves) during rest are an indication of the importance of mapping the default network in insomnia. The irreversibility of deviant intracortical facilitation in insomnia patients further suggests a possible risk factor for developing insomnia. Studies mapping the long-term effects of sleep therapy are required to determine which structural and functional differences are reversible and which are not. We did not find support for our hypothesis that slow wave suppression in normal sleepers might offer a more valid experimental model for insomnia than total sleep deprivation.

On the basis of these results a model for the development of insomnia is proposed in which combinations of (perhaps unalterable) factors, such as genetic factors, with secondary factors, such as stressful events, might lead to insomnia and/or psychiatric complaints. An unalterable factor could be a factor that makes a person vulnerable to develop a particular condition. Such factor could be grey matter density differences or a difference in sensitivity for intracortical facilitation. Secondary factors, such as a traumatic event, would then determine whether the vulnerability factor develops into a disorder or not. Here, too, longitudinal studies can offer a better insight into the tenability of this model.

The current results give reason to detect and start treatment for insomnia earlier in the future. Improvement is possible at many levels: from a more frequent referral of the general physician to sleep clinics to availability of non-pharmacological sleep therapy and reimbursement of this treatment by health insurances. Future longitudinal research could shed more light on the reversible and non-reversible effects of insomnia. More research is also needed to investigate the relationship between insomnia, decision-making skills and emotion regulation; suggestions for questionnaires and tasks are given. Setting up a large-scale registry of people with unexplained sleep problems whose symptoms are further mapped by measuring performance and brain activity may result in a definition of the various subtypes of primary insomnia. This could lead to quicker recognition and treatment of this frequently occurring, limiting but treatable condition.