# INTRODUCTION

# Chapter 1

## Chronic insomnia and its treatment

Most of us have occasionally experienced restless nights of poor sleep. For a considerable part of us, estimated to be one out of ten, this experience is not occasional but chronic or recurrent. Poor sleep can lead to daytime complaints of concentration and memory problems and emotional instability. This chronic sleep problem known as insomnia has been studied extensively at the subjective and behavioral level, but much less so at the level of brain structure and function. This chapter discusses the diagnosis and treatment of insomnia, as well as what is known at present about behavioral and brain imaging correlates of insomnia. The overview will lead to the research questions that will be answered in this thesis. Because the prevalence of insomnia strongly increases with age, with estimates of up to four out of ten, our studies focused specifically on people older than 50 years of age.

## DIAGNOSIS OF INSOMNIA

Primary insomnia is defined by subjective problems falling asleep (sleep onset problems) or waking up too frequently or early (sleep continuation problems), while these problems cannot be explained by a medical or psychiatric condition or another sleep disorder[1]. If these problems persist for more than six months for at least three nights a week[2] we speak of chronic primary insomnia. One-third of the general adult population reports suffering from insomnia[3] with a higher prevalence at increasing age[4] and a predominant occurrence in women (estimates up to 70%)[5]. Until recently, chronic primary insomnia was diagnosed on the basis of subjective reports verified by sleep questionnaire scores and a structured interview on the basis of the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria[6]. A more precise diagnosis of insomnia, defined as psychophysiological insomnia, is given by the International Classification of Sleep Disorders (ICSD)-2[7]. Current criteria require a more elaborate diagnosis of insomnia, including polysomnography to exclude other sleep disorders[8]. Polysomnography refers to the multichannel assessment of brain activity using electroencephalography (EEG), eye movements using electrooculography (EOG), submental muscle tone using electromyography (EMG) and, if indicated, also airflow, respiratory effort and tibialis EMG to evaluate the presence of sleep disordered breathing (SDB) and periodic leg movements (PLM). Primary insomnia is then diagnosed on the basis of sleep complaints, DSM IV or ICSD-2 criteria and the absence of other sleep disorders such as restless legs, apnea and PLM syndrome (PLMS).

## UNDERLYING MECHANISMS OF INSOMNIA

The "3P-model" of Spielman[9] suggests three factors for the onset and course of insomnia: predisposing personality traits (e.g. tendency to worry); precipitating events (e.g. work-related stress); and perpetuating attitudes and practices (e.g. misconceptions about sleep). According to this model, insomnia may become independent of its cause over time[10]. Genetic factors may be involved in any of these three P's. Beaulieu-Bonneau et al.[11] showed that a family history of insomnia is a predisposing factor for the development of insomnia in later life. Twin studies support a genetic component for sleep quality[12].Predisposing factors for insomnia are depression, anxiety, excessive worrying[13] and disturbances of emotion regulation[10,14]. Internalization of emotions, instead of expressing or acting on emotions, is a typical personality trait of insomnia patients[14]. This trait has been proposed to induce physiological hyperarousal, indicated by an increased heart rate, peripheral vasoconstriction, elevated rectal temperature and increased skeletal muscle movements before and during sleep[9,15-18]. A state of hyperarousal may lead to both sleep onset problems as well as difficulties returning to sleep after nighttime awakening[15]. Evening levels of arousal furthermore predict sleep quality[19]. The chronicity of the hyperarousal condition, present 24 hours a day, may also explain why insomniacs are significantly more alert during daytime than normal sleepers[20-22].

Though showing normal circadian patterns[10,17], levels of the stress hormones adrenocorticotropic hormone (ACTH) and cortisol are increased for insomniacs compared to controls over 24 hours, with the largest difference occurring during the evening and first half of the night. Hyperarousal has been confirmed as well using a dedicated Hyperarousal Scale for insomniacs[23]. Of note, the physiological and psychological characteristics of insomnia are usually not found after experimental sleep deprivation or sleep restriction[24-26].

Age-related increased vulnerability to stress and hormonal changes could contribute to the increased prevalence of insomnia in older adults. Middle-aged men are more sensitive to the arousing effects of corticotropin-releasing hormone (CRH), a hormone with an arousing/awaking effect, than young men. This suggests that it is not the increased exposure to stressful events but rather a higher sensitivity to the resulting arousal-producing stress hormones that is involved in the development and perpetuation of insomnia, specifically in older adults[10,17]. Within a group of middle-aged women who had experienced an equal number of stressful events with equal severity, women with insomnia scored higher on a psychological distress scale (the Symptom Check List-90 Revised (SCL90-R)) than women without insomnia[27]. Insomniacs generally rate the impact of daily minor

stressors and the intensity of major negative life events higher than good sleepers and experience less control over stressful events[28]. Another contribution to the age-related increase in poor sleep may be hormonal changes; postmenopausal women without hormone replacement therapy (HRT) showed longer sleep latencies and less slow wave sleep compared to postmenopausal women with HRT[29,30].

## COGNITIVE PERFORMANCE IN INSOMNIA

Although patients with chronic insomnia complain about concentration and memory problems and a decreased ability to accomplish daily tasks as a consequence of their sleeping problems, behavioral studies generally failed to find conclusive results for cognitive correlates of this condition[31,32]. Orff et al. did not find performance differences between 32 primary insomnia patients and 17 good sleepers on tests for motor speed, attention, verbal fluency, verbal learning and memory[36]. Investigating the more complex Wisconsin Card Sorting Test, which measures working memory and set shifting functions, again no performance differences were found on any of the item scores between 18 insomniacs and 21 normal sleepers (age range 20-63) in a study by Fang et al.[37]. Varkevisser et al. did find performance differences on vigilance, working memory and motor control tasks in constant routine conditions[33]. In another study by Szelenberger et al., the number of repetitions necessary to learn a Selective Reminding Test was higher for insomniacs than for controls, and this result correlated with insomnia severity measured by the Athens Insomnia Scale[34]. Crenshaw et al. showed that reaction times of insomniacs are negatively correlated with slow wave power, occurring particularly in deep sleep (stages 3-4)[35].

Despite the lack of conclusive evidence of performance decrements on standard neuropsychological tests, impairments in daily life are evident. Insomniacs are three times more likely than non-insomniacs to have serious accidents[38]; measured over a year, 8% of insomniacs compared to 1% of non-insomniacs have an industrial accident[39]. Days spent in bed due to illness are about twice as common among insomniacs compared to non-insomniacs, even after correcting for age, gender and chronic disease[40]. Work absenteeism in days per year is estimated at 5.4 for insomniacs compared to 2.4 for good sleepers in France[41]. Combining the costs for health-care, insomnia-related work absenteeism and productivity losses, a recent Canadian study estimated the average annual costs per insomnia patient at $5.010 a year[42]. In the United States, direct (e.g. medication, consults) and indirect costs (e.g. work absenteeism) during six months were estimated to be $1253 higher

for insomniacs than non-insomniacs in young adults, and to be $1143 higher for elderly insomniacs compared to elderly non-insomniacs[43].

This discrepancy between performance on neuropsychological tasks and impairments of daily living may be due to the fact that the majority of standard neuropsychologial tests are dedicated to measure neurological deficits. They may therefore not be sensitive or specific enough to assess performance changes associated with chronic insomnia, in spite of their sensitivity to measure the effects of total sleep deprivation for one or two nights. In particular, neuropsychological tests tapping into prefrontal functions such as executive functioning[44,45], decision making[46,47], working memory[48,49] and verbal fluency[50] are affected by total sleep deprivation.

In conclusion, insomnia evidently leads to impairments of daily living, yet performance deficits have thus far not been conclusively supported by neuropsychological tests, even if they showed sensitivity to acute short term total sleep deprivation. Hyperarousal mechanisms and a tendency towards perfectionism[51,52], which may enhance each other, may compensate for the effects of insomnia that would otherwise affect performance. The hyperarousal mechanism has so far been objectified in several physiological measures and in resting state brain activation[53] (see the next section). Brain activation during task performance has not yet been measured in insomnia. Several studies have, however, shown that the brain can compensate, at least temporarily, for the effects of degeneration[54,55], so a similar compensatory mechanism may occur in insomnia.

Brain imaging of neuronal activation patterns during task performance might therefore shed more light on the difference between the objectified effects of experimental sleep disruption and the subjective experience of difficulties with task performance in insomniacs.

## BRAIN IMAGING IN INSOMNIA AND SLEEP DEPRIVATION

Though many neuroimaging studies investigated the effects of total or partial sleep deprivation in healthy subjects, only a few focused on brain activation alterations in chronic primary insomnia. The limited number of findings thus far support the hyperarousal hypothesis previously discussed.

Measuring the resting state with Positron Emission Tomography (PET) *at the transition from wake to sleep*, insomnia patients show a relative lack of inactivation of the hypothalamus, thalamus, insular cortex, hippocampus and amygdala and of the anterior cingulate and medial prefrontal cortex[53]. Smith et al. however showed, in a single photon emission computed tomography (SPECT) pilot study, that during

initial stages of NREM sleep, insomnia patients have relative global hypoperfusion compared to normal sleepers[56] which reversed after successful behavioral therapy, in particular in the basal ganglia[57]. Additional studies should resolve this discrepancy which may be due to the difference in sleep stages measured and neuroimaging techniques applied but could also be due to variance in subtypes of insomnia, which have not been clearly defined yet. Measured with Electroencophalography (EEG) at sleep onset, insomniacs have elevated relative beta power (high frequency EEG activity) and decreased delta power (low frequency EEG activity) compared to normal-sleeping controls[58,59]. Particularly in primary insomnia patients, in comparison to good sleepers and secondary insomnia patients, high frequency EEG activity increases across NREM cycles, and occurs maximally during stage 1 and REM sleep[60].

Measuring resting state brain activation during *wake*, without performing tasks, alpha power in EEG is decreased in insomnia patients compared to normal controls[58,59]. Metabolic rate is reduced in the prefrontal cortex compared to controls without sleep complaints as measured by PET[53]. A magnetic resonance spectroscopy study suggests that the level of GABA, the most common inhibitory neurotransmitter in the central nervous system, is reduced by 30% in insomnia patients compared to controls. The average level was calculated over the basal ganglia, thalamus, temporal, parietal and occipital regions. The level of GABA was furthermore negatively related with the duration of wake after sleep onset (WASO) as measured by PSG in the same patients[61].

Functional imaging studies, measuring brain activation when participants perform a cognitive task, have thus far neglected insomnia and rather investigated the consequences of sleep restriction or total sleep deprivation in young adults without sleep complaints. Applying functional Magnetic Resonance Imaging (fMRI), Drummond et al. found an overall decrease in brain activation during a serial subtraction task after a night of total sleep deprivation compared to the activation found after a normal night of sleep. This decrease was most pronounced in the prefrontal cortex[62]. Total sleep deprivation also attenuates task-related hippocampal activation during the encoding of pictures and accordingly lowers subsequent recognition scores[63].

Several studies report *compensatory* brain activation during task performance after sleep deprivation. Compensatory activation is activation of brain regions not normally known to be task-related but known to 'take over' when task related regions are affected. Findings on compensatory activation diverge and may depend on the nature of the task. For instance, compensatory activation after sleep deprivation was found on a verbal learning[64,65], a logical reasoning[66] and one working memory task[48], but not on other working memory tasks[67-69]. Szelenberger

et al. measured high-density EEG during the Continuous Attention Test (CAT), a visual recognition task, in an insomnia population and quantified brain activation using low-resolution brain electromagnetic tomography (LORETA). They found that, in the absence of performance differences, insomnia patients showed less event-related current density in orbitofrontal, medial prefrontal, anterior cingulate, premotor and parietal cortex, but increased activation in the left dorsolateral prefrontal cortex.

In a pilot study investigating *structural* brain differences in middle aged insomnia patients in predefined prefrontal and temporal regions, Riemann et al. showed that they had a lower hippocampal volume than controls without sleep complaints[70]. Patients and controls with a current or lifetime psychiatric disorder were excluded from this study. Lower hippocampal volume could not be confirmed, however, in a considerably larger group of slightly younger male participants, 20 insomnia patients and 15 controls[71]. Hall et al.[72] did demonstrate a relation of hippocampus grey matter volume with reported sleep duration in 50 older women without sleep complaints. Since this last study however did not investigate insomnia patients per se, the exact role of the hippocampus and other structures needs to be further investigated, both by outlining selected brain regions such as with manual morphometry as by investigating whole-brain differences.

In summary, brain imaging studies during the resting state suggest that insomniacs have an increased prefrontal activation at sleep onset and a decreased prefrontal brain activation during wake, as well as a decreased level of the major inhibitory neurotransmitter GABA. Neuroimaging studies on brain activation during task performance indicate that both insomnia and total sleep deprivation are associated with attenuated activation of areas that are characteristically involved in the task. Occasionally this is accompanied by compensatory activation in other regions. Structural imaging suggests a relation of lower hippocampal volume with insomnia.

Interestingly several of those factors (decreased PFC activity, decreased PFC GABA content, temporal lobe atrophy and smaller hippocampus) will all lead to increased CRH activity.

## TREATMENT OF INSOMNIA

Although insomnia patients are often prescribed sleep medication by their general practitioner for a shorter or longer period, non-pharmacological sleep therapy has proved to be equally effective on the short term, and more effective on the long term, regardless of age[73-77]. It proved more effective than both pharmacological

sleep therapy and placebo, both on short and long term, when applied in an older primary chronic insomnia population[78].

Non-pharmacological sleep therapy for insomnia usually consists of cognitive behavioral therapy (CBT). This intervention entails cognitive therapy, sleep restriction, stimulus control, and sleep hygiene advice. Cognitive therapy challenges and redirects general ideas about sleep such as ideal total sleep time, time spent trying to fall asleep before actually falling asleep (sleep latency) and frequency and duration of awakenings (sleep continuation). In this way, associated negative thoughts to sleep and stress about sleep are treated as well.

Cognitive behavioral therapy typically lasts 4-8 weeks with sessions of one hour weekly[73,79-81]. Patients are required to keep a sleep diary for part of the treatment, which contents is discussed during the sessions. Sleep restriction limits the allowed time in bed (e.g. 6 hours) with a fixed onset and offset time (e.g. 11.30 pm to 5.30 am), after which patients are required to get up, regardless of whether they slept. In this way, sleep pressure is built up for the following night, leading to a shorter sleep latency and improved sleep continuation. When more than 95% of the time in bed is spent asleep, the patient can add half an hour to the time frame, reaching the ideal amount of sleep after a prolonged period of this intervention (e.g. 6 weeks)[82]. Stimulus control requires patients to leave the bed if they lie awake for more than 30 minutes. They are also advised to have no other activities in bed other than sleep and sex (e.g. computer use, TV, eating). The approach promotes the association of the bed with being asleep and reverses the negative association of being in bed with lying awake. Sleep hygiene advice concerns food and beverage intake (e.g. meal intake regulation, not consuming coffee after 4pm or alcohol after 6pm) as well as evening activities (no night shifts, no exercise, work, administration or other stressful activities before going to bed)[83,84].
Chronobiological interventions can also be part of the treatment for insomnia. Bright light regulates sleep and wake patterns more effectively than e.g. melatonin alone[85]. Body temperature interventions such as taking a hot bath for half an hour or exercise two hours before preferred sleep onset can optimize heat dissipation to induce sleep: a normalized core temperature in combination with the after-effect of increased skin temperature promotes sleep onset[86,87].