

## Sleep structure & sleep perception in insomnia

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# Sleep structure & sleep perception in insomnia

L.W.A. Hermans

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# Sleep structure & sleep perception in insomnia

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promotor:	Prof. dr. S. Overeem
1e co-promotor:	dr. M.M. van Gilst
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# List of Abbreviations

<b>AASM</b>	American Academy of Sleep Medicine
<b>AHI</b>	Apnea Hypopnea Index
<b>CBT-I</b>	Cognitive Behavioral Therapy for Insomnia
<b>DSM</b>	Diagnostic and Statistical Manual of Mental Disorders
<b>ECG</b>	Electrocardiography
<b>EEG</b>	Electroencephalography
<b>EMG</b>	Electromyography
<b>EOG</b>	Electro-oculography
<b>ICSD</b>	International Classification of Sleep Disorders
<b>IQR</b>	Inter Quartile Range
<b>ISI</b>	Insomnia Severity Index
<b>MSE</b>	Mean Square Error
<b>NREM</b>	Non Rapid Eye Movement
<b>OSA</b>	Obstructive Sleep Apnea
<b>PSAS</b>	Pre Sleep Arousal Scale
<b>PSG</b>	Polysomnography
<b>REM</b>	Rapid Eye Movement
<b>RMSE</b>	Root Mean Square Error
<b>SD</b>	Standard Deviation
<b>SDSL</b>	Sleep During Subjective Latency
<b>SFPI</b>	Sleep Fragmentation Perception Index
<b>SOL</b>	Sleep Onset Latency
<b>SSI</b>	Stanford Sleepiness Index
<b>SWS</b>	Slow Wave Sleep
<b>TST</b>	Total Sleep Time
<b>WASO</b>	Wake After Sleep Onset

# List of Symbols

- L** Input parameter of the sleep onset misperception model described in chapter 2. L depicts the minimum duration a sleep fragment should have in order to be perceived as sleep, in minutes.
- Lw** Input parameter of the sleep onset misperception model described in the appendix of chapter 3. Lw denotes the minimum length a wake fragment should have to disturb sleep. Wake fragments shorter than Lw minutes are regarded as sleep by the model.
- Ls** A more specific notation for the minimum length of a sleep fragment L, as opposed to the minimum length of a wake fragment Lw.
- $\lambda$  Scale parameter. This parameter is used for the Weibull parametrization of the survival curves described in chapter 5 and 6. The scale parameter represents the mean length of the wake and sleep fragments in case of an exponential distribution.
- k** Shape parameter. This parameter is used for the Weibull parametrization of the survival curves described in chapter 5 and 6. The shape parameter represents the type of distribution. A shape parameter of one denotes an exponential distribution.
- SEwin** Input parameter of the windowed sleep efficiency model, described in the appendix of chapter 3. Here we assumed that a minimum percentage of sleep within a certain window is required to perceive sleep. The percentage of sleep is denoted by SEwin.

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# Chapter 1

## Introduction

We spend approximately one third of our lives asleep. Sleep is a vital process, with many important functions, including energy conservation, immune system regulation and memory consolidation. [1] A substantial number of people suffer from disorders of sleep, and in our current 24-hours society these problems are likely to further increase. [2] The most common sleep disorder is insomnia, with an estimated prevalence of 6-30%, depending on the criteria used for diagnosis. [3] If the criteria of the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) are applied, stating that insomnia symptoms persist for at least 1 month and do not exclusively occur in the presence of another disorder, the prevalence is approximately 6%. [4] However, almost one third of the general population reports one or more symptoms of insomnia. [4] People with insomnia have trouble with falling asleep, maintaining sleep or awakening too early in the morning; or a combination (see text box 1). Apart from an unsatisfactory sleep pattern, insomnia additionally involves daytime complaints such as fatigue, attentional disturbances and mood disturbances. These complaints can cause serious problems for quality of life, general health and labor productivity. [4]

Insomnia has been hypothesized to be a general term for a number of subtypes consisting of different sleep complaints and having different causes (box 2). [5, 6] The effectiveness of treatment is likely to be strongly dependent of the patient's individual characteristics and the underlying mechanisms of their sleep problem. However, despite ongoing research, part of the etiology of insomnia is still unknown. As such, important characteristics of insomnia remain to be



further investigated. Insomnia has been associated with both psychological and physiological symptoms. [7] Viewing those symptoms together can help to understand the big picture of the sleep disorder. Specifically, little is known about objective sleep parameters reflecting sleep quality.

### **Box 1 : Insomnia**

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#### **Symptoms and diagnostic criteria**

People with insomnia have trouble with falling asleep or maintaining sleep, or they wake up too early in the morning. They can also experience a combination of these complaints. Many people periodically experience an incidental night of poor sleep. When sleeping poorly becomes a more chronic problem, medical attention may be required. Insomnia is usually diagnosed based on either Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [8] or International Classification of Sleep Disorders (ICSD-3) [9] criteria (Table 1.1). Both the diagnosis and treatment of insomnia are largely based on subjective complaints. [4] In clinical practice, the diagnosis is mostly based on questionnaires, sleep diaries and an interview with a sleep specialist. In part of the patients, the sleep is measured using polysomnography, for example to exclude other possible sleep disorders.

#### **Cognitive Behavioral Therapy for insomnia**

The treatment of choice for insomnia is Cognitive Behavioural Therapy for insomnia (CBT-I). [10, 11] CBT-I is a combination of different interventions, often including sleep restriction, stimulus control, sleep hygiene education and cognitive therapy. [12] People with insomnia often tend to increase their time in bed to increase the possibility of getting enough sleep. However, this strategy usually has an adverse effect, since spending a lot of time in bed without sleeping may decrease the sleep drive, as well as increasing the association of the sleep environment with wakefulness, anxiety and frustration. [10] These negative emotions further impair the sleep and can cause a vicious cycle. Sleep restriction limits the amount of time spent in bed. [10] Stimulus control in turn encourages people to only go to bed when they feel sleepy, and to leave their bed when they do not fall asleep within a specific time, for example fifteen minutes. [10] Together, these two interventions aim to increase sleep pressure and re-associate the sleeping environment with sleepiness instead of wakefulness and negative emotions. [10] Sleep hygiene focuses on eliminating bad habits that may negatively affect sleep and creating good circumstances for

sleeping. Finally, cognitive therapy can help to challenge negative thoughts about sleep. Additionally, CBT-I can involve relaxation techniques. CBT-I leads to remission of the insomnia disorder in an estimated 70-80% of the patients [13], implicating that 20-30% do not show improvement of their symptoms. [14] The success of a treatment intervention for insomnia may be partly dependent on the characteristics of the patient, and the underlying mechanisms of his or her insomnia complaints. This is further described in box 2.

### **Sleep medication**

Alternatively, patients with insomnia may be treated using prescribed medication. The drugs mostly used include benzodiazepines and benzodiazepine agonists, which have a similar mechanism of action. [15] A widely used class of benzodiazepine-agonists is formed by the so-called z-drugs (zopiclone, zolpidem and zaleplon). Benzodiazepines and benzodiazepine agonists can induce changes in sleep architecture. [15] For example, zopiclone is known to reduce the amount of time spent in REM sleep, and to delay the onset of REM sleep. [16] Additionally, benzodiazepines in general often decrease the percentage of deep sleep, and increase the number of sleep spindles. [17, 18] Sleep medication can result in a temporary relief of the sleep complaints, and an increase of perceived sleep quality. However, sleep medication is only indicated for short time use, to avoid long-term dependency. [19] Additionally, sleep medication may have negative side effects, such as drowsiness, confusion and impaired coordination. [19]

**Table 1.1:** Criteria for the diagnosis of insomnia.

DSM-V	
	A predominant complaint of dissatisfaction with sleep quantity or quality, associated with one (or more) of the following symptoms:
A	<ol style="list-style-type: none"> <li>1. Difficulty initiating sleep.</li> <li>2. Difficulty maintaining sleep, characterized by frequent awakenings or problems returning to sleep after awakenings.</li> <li>3. Early-morning awakening with inability to return to sleep.</li> </ol>
B	The sleep disturbance causes clinically significant distress or impairment in social, occupational, educational, academic, behavioral, or other important areas of functioning.
C	The sleep difficulty occurs at least three nights per week.
D	The sleep difficulty is present for at least three months.
E	The sleep difficulty occurs despite adequate opportunity for sleep.
F	The insomnia is not better explained by and does not occur exclusively during the course of another sleep-wake disorder.
G	Coexisting mental disorders and medical conditions do not adequately explain the predominant complaint of insomnia.
ICSD-3	
	The patient reports, or the patient's parent or caregiver observes, one or more of the following:
A	<ol style="list-style-type: none"> <li>1. Difficulty initiating sleep</li> <li>2. Difficulty maintaining sleep</li> <li>3. Waking up earlier than desired</li> <li>4. Resistance to going to bed on appropriate schedule</li> <li>5. Difficulty sleeping without parent or caregiver intervention</li> </ol>
B	The patient reports, or the patient's parent or caregiver observes, one or more of the following related to the nighttime sleep difficulty: Fatigue/malaise; attention, concentration or memory impairment; impaired social, family, occupational or academic performance; mood disturbance/irritability; daytime sleepiness; behavioural problems (e.g. hyperactivity, impulsivity, aggression); reduced motivation/energy/initiative; proneness for errors/accidents; concerns about or dissatisfaction with sleep
D	The sleep disturbance and associated daytime symptoms occur at least three times per week
E	The sleep disturbance and associated daytime symptoms have been present for at least three months.
C	The reported sleep/wake complaints cannot be explained purely by inadequate opportunity (i.e. enough time is allotted for sleep) or inadequate circumstances (i.e. the environment is safe, dark, quiet and comfortable) for sleep.
F	The sleep/wake difficulty is not explained more clearly by another sleep disorder.

**Box 2 : Subtypes of insomnia**

The success of a treatment intervention for insomnia may be partially dependent on the characteristics of the patient, and the underlying mechanisms of his or her insomnia complaints. We may distinguish patients with different characteristics, or even distinct subtypes.

The previously used ICSD-1 and ICSD-2 classifications distinguished nine subtypes of insomnia, which were classified based on their presumed underlying pathology. [20] Examples of subtypes were psychophysiological insomnia, i.e., the ‘classical’ type of insomnia in which worrying is an important part of the sleep problem; paradoxical insomnia, i.e., a type of insomnia in which people severely underestimate their total sleep duration; insomnia due to mental illness and insomnia with inadequate sleep hygiene. [20] Additionally, a distinction was made between primary insomnia and insomnia due to a secondary cause. [20] Nowadays, in the third version of the ICSD, less emphasis is given to these subtypes, because their clinical implications are not always exactly known. [9] The identification of characteristics of insomnia potentially relevant for treatment strategies is still subject of ongoing research. For instance, Miller et al. reported that insomnia with an objective sleep duration below six hours may be a subtype of insomnia with distinct pathophysiology [21, 22], and a worse outcome of CBT-I compared to other patients with insomnia. [22] Additionally, Blanken et al. reported five distinct subtypes based on life history and traits of affect and personality in a very large population cohort of people with insomnia complaints. [5] Because of the complex nature of insomnia, it can be expected that objective sleep characteristics, psychological characteristics and demographic characteristics are all important for characterizing subtypes of insomnia.

## 1.1 Objective parameters of insomnia

Gold-standard polysomnography (PSG; box 3-4) measurements are often performed to study sleep. When viewing insomnia as a medical problem of insufficient or non-restorative sleep, we would expect that the sleep problem could be quantified with objective measurements. Indeed, part of the patients have a reduced amount of sleep as reflected by standard PSG-derived parameters, such as total sleep time and sleep onset latency. However, in other cases, these parameters do not fully explain the complaints of the patient. [23] Sometimes a correlation between these general parameters and the symptoms of insomnia

is even almost completely lacking. Therefore, it is assumed that not only sleep quantity is important for perceiving a good night of sleep. Instead, a broader concept of sleep quality can be defined, which may be reflected by an interaction between sleep quantity and many other different objectively measurable parameters (box 5).

Here, we focus on the relation between objective and subjective sleep quality in people with insomnia. As mentioned before there is currently limited knowledge about the relation between sleep quality and objectively measured parameters other than the amount of sleep. Therefore, we especially focus on identifying objectively measurable sleep characteristics that may be important for understanding the perception of impaired sleep quality. In this introduction, first we introduce the concepts of subjective and objective sleep quality. Subsequently, we discuss possible objective parameters to reflect sleep quality, as well as approaches used in this thesis to overcome some of the current challenges within the research field. Finally, we discuss the outline of this thesis.

## 1.2 Aspects of sleep quality

In Figure 1.1, several aspects of sleep quality are illustrated. In this figure, we distinguish subjective and objective sleep quality. Arrows I-V indicate possible interactions, which are also summarized in Table 1.2. Subjective sleep quality refers to the person's impression about his or her sleep, and includes a quantitative and a non-quantitative aspect. The non-quantitative aspect of subjective sleep quality is often enquired using multiple-choice questions such as 'how would you rate the quality of your sleep?' and 'how refreshed did you feel in the morning after awakening?' The answers to these questions may be influenced by subjective sleep quantity (arrow I), since people who experienced a short night of sleep usually tend to also report a poor night of sleep. [24] Furthermore, it is thought that certain mechanisms of objective sleep may also influence having the impression of a good night of sleep and feeling refreshed (II), although this relationship is often weaker than expected. [24, 25]

Subjective sleep quantity refers to a person's experienced sleep duration. This subjective sleep duration can be measured using a sleep diary (box 6), and may be expressed using total sleep time, sleep onset latency and wake after sleep onset. As such, subjective sleep quantity can be directly compared with objective sleep quantity. A marked discrepancy between the two, which is observed in part of the people with insomnia, is called sleep state misperception or paradoxical insomnia. [26] It is assumed that sleep state misperception can

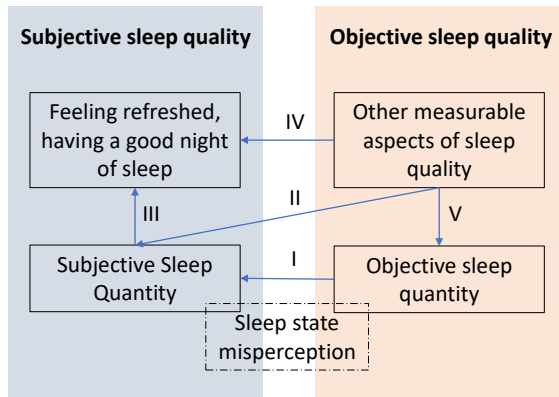


Figure 1.1: Four categories of parameters we can use to describe sleep. Arrows indicate the presumed influence of these concepts on each other.

be influenced by certain objectively measurable sleep mechanisms, causing parts of the sleep to be experienced as wake. [26] Thus, subjective sleep quantity can probably be influenced by a combination of objective sleep quantity and other, undefined objective sleep mechanisms (III and IV). For completeness, we also mention that aspects of objective sleep probably influence objective sleep quantity (V). For example, it was hypothesized that certain micro-events could act as protection mechanisms of sleep, thus reducing the number of awakenings, and potentially resulting in a longer total sleep time. [27, 28] Finally, insomnia is a sleep disorder with a major psychological component. [12] Therefore, sleep is probably influenced by a combination of psychological and objectively measurable components, which may in turn be interrelated.

### 1.3 Previous research on sleep quality

Sleep quality in relation to objective sleep parameters is directly or indirectly studied in different types of sleep research, including studies of general sleep differences between people with insomnia and healthy controls, studies of PSG-derived parameters influencing feeling refreshed and reporting a good night of sleep (Figure 1.1, arrow II), and studies of PSG-derived parameters influencing

sleep state misperception (IV). Since these studies all concern aspects of objective sleep quality, it may be useful to combine knowledge from different research protocols to learn more about objective sleep parameters reflecting impaired sleep. Relevant findings from previous research are briefly discussed in the next section.

**Table 1.2:** Summary of presumed influence of aspects of sleep quality on each other. The numbers in this table refer to numbers of arrows shown in Figure 1.1

#	Description
I	Influence of subjective sleep quantity on the experience of having a good night of sleep. People who experienced a short night of sleep tend to also report not feeling refreshed and experiencing a poor night of sleep.
II	Influence of objective sleep characteristics on the experience of a good night of sleep. It is assumed that certain objectively measured characteristics of sleep can influence its perception. The identification of such characteristics is a topic of research.
III	Influence of objective sleep quantity on sleep quantity reported by the patient. Logically, it is often assumed that people are aware of their amount of sleep. However, in some people with insomnia a marked discrepancy between the objective and subjective amount of sleep can be observed. This discrepancy is called sleep state misperception.
IV	It is assumed that certain objectively measurable sleep mechanisms can cause parts of the sleep to be experienced as wake. Thus, this may be an explanation for sleep state misperception.
V	Aspects of objective sleep could probably influence objective sleep quantity. For example, impaired sleep protection mechanisms could lead to interrupted, and therefore possibly shorter, sleep.

### 1.3.1 Differences between insomnia and healthy sleepers

A lot of effort has been devoted to identifying differences between objectively measurable sleep parameters of people with insomnia and healthy controls. Because people experience impaired sleep, this type of research can be seen as an indirect way to study effects of objective sleep mechanisms on subjective

sleep quality (III and IV). A popular hypothesis is that people with insomnia have an increased activation of the sympathetic nervous system during both the day and the night. [29] This is called hyperarousal. [29] Hyperarousal may lead to alterations of sleep architecture. [23] However, results are often not consistent across studies. [23] In a meta-analysis, Baglioni et al. showed that people with primary insomnia had an increased number of awakenings compared to healthy sleepers, and reduced percentages of slow wave sleep and REM sleep. [23] Thus, it seems that disturbed continuity of the sleep could possibly lead to complaints of impaired sleep in people with insomnia. Alternatively, it has been proposed that parameters extracted from the hypnogram do not provide sufficient detail to fully assess and understand objective sleep quality. [27] Instead of parameters that can be calculated from the hypnogram, also called macrostructural parameters, more detailed microstructural parameters can be obtained directly from the EEG signals. Parameters that were reported to differ between insomnia patients and healthy controls include spectral power within the delta and beta frequency bands, which can be an expression of hyperarousal [30]; arousals, which are disruptions of sleep too short to be scored as awakenings [31]; and k-complexes and sleep spindles, which may have a sleep-protecting function. [27, 28]

#### 1.3.2 Sleep state misperception

In addition to differences between insomnia and healthy controls, the phenomenon of sleep state misperception, i.e., a discrepancy between objectively measured and subjectively perceived sleep, has been extensively researched. Sleep state misperception can possibly be explained by worrying, memory bias, or a reduced time estimation ability. [26] Additionally, several objectively measurable sleep parameters have been studied in relation to sleep state misperception. People with sleep state misperception were reported to have increased spectral power in the beta frequency range [32], shorter sleep spindles [33], and a larger number of arousals. [34] Sleep fragmentation is another promising parameter, because the experience of being asleep seems to be dependent on the length of uninterrupted sleep fragments. [35] Sleep fragmentation may be particularly important for the perception of the sleep onset. In this thesis, we examine and quantify the relation between sleep fragmentation and sleep onset misperception.

#### 1.3.3 Correlates of subjective sleep quality

Finally, research of objective sleep parameters influencing feeling refreshed and reporting a good night of sleep can be informative. Objective TST and sleep



efficiency are often mentioned as the main PSG-derived parameters influencing perceived sleep quality. [25, 36, 37] Additionally, subjective sleep quality was reported to be negatively influenced by the number of awakenings [24, 37], the amount of wake after sleep onset, [24, 37], and the number of sleep stage transitions. [25] Subjective sleep quality was positively influenced by the percentage of slow wave sleep. [37, 38] Interestingly, microstructural parameters are mostly not among the parameters with the largest correlation with subjective sleep quality. [25, 37] Thus, subjective sleep quality seems to be mainly influenced by parameters that can be extracted from the hypnogram. Still, studies consistently report that objective sleep parameters only explain a small part of the variability of the subjective sleep quality. [24, 25]

## 1.4 Goals and considerations for this thesis

New research into objective sleep quality parameters should take into account a number of challenges that are present in the research field. First, sleep is a very complex process, in which many different psychological and physiological factors play a role. Therefore, we may expect large interindividual variability of psychological profiles, sleep deprivation during previous nights, sleep habits and comorbid disorders. This variability may also partly explain the different results across different studies. Furthermore, we still do not fully understand all the functions and mechanisms of sleep. Gold-standard PSG recordings yield approximately 8 hours of multi-channel signals, recorded with a sample frequency between 200 and 500 Hz. Therefore, the number of parameters that we can possibly extract from PSG recordings is larger than we will ever be able to evaluate. Often, different research protocols study different parameters, making it challenging to compare outcomes. For example, even a relatively simple concept such as sleep fragmentation can be described using many different parameters, including number of awakenings, number of transitions between sleep stages, and percentage of deep sleep. As a further complication, it is possible that sleep quality varies over time during the night.

Although challenging, identifying objective sleep parameters influencing sleep quality is potentially a very useful way to increase our understanding of the mechanisms underlying insomnia, and the functions of sleep in general. Furthermore, such parameters could potentially be used to identify clinically meaningful subtypes within the patient population, and possibly even aid in the choice of the best treatment options for individual patients.

**Box 3 : Polysomnography**

Polysomnography (PSG) is the gold standard diagnostic tool in sleep medicine. PSG recordings include multiple signals. One of these signals is electroencephalography (EEG); a noninvasive method to record electrical activity caused by neural oscillations from the brain. The EEG is recorded on different locations on the head, usually with six electrodes. The number of EEG electrodes may differ per sleep center. Additionally, the electrical potentials caused by movements of the eyes are measured using two electrodes. This is called electro-oculography (EOG). Electrical activity of the muscles of the chin and legs is measured using electromyography (EMG), and the activity of the heart using electrocardiography (ECG). [39] Additionally, breathing movements, respiratory airflow, and body movement are measured. [39]

To annotate sleep stages, the current method is based on periods (epochs) of 30 seconds. These epochs are individually classified by a sleep technician. [39] Nowadays, it is also possible to perform automated sleep staging. The classification of sleep and wake stages is based on standardized guidelines using three channels of EEG, two channels of EOG and two channels of chin EMG. According to the most recent scoring guidelines of the American Academy of Sleep Medicine (AASM), each 30-second epoch is scored as either wake, Rapid Eye movement (REM) sleep, or one of three Non Rapid Eye Movement (NREM) sleep stages. [40] REM sleep or 'dream sleep' refers to a stage with EEG activity similar to wake, which can be distinguished from wake by a suppression of the muscle tone. [41] During REM sleep, typical vertical and horizontal eye movements can be observed. [41] The exact function of REM sleep is unclear [42], but it possibly plays a role in memory consolidation. [43] Although the most vivid dreams occur during REM sleep, dreams are not limited to this sleep stage [41]. NREM sleep in turn is divided into three substages: NREM1, NREM2 and NREM3. [44] During NREM sleep, a gradual slowing of the EEG activity can be observed. NREM1 is observed shortly after falling asleep. During NREM2, distinct EEG patterns can be seen, such as k-complexes and sleep spindles. NREM3 is the deepest sleep stage, also called slow wave sleep (SWS). During NREM3, high amplitude EEG activity with a frequency of 0.5-2 Hz can be observed. During this sleep stage, the brain is less responsive to external stimuli and the sleep is more difficult to disturb compared to lighter sleep. [44]

The progression of sleep stages during the night can be visualized using a hypnogram (Figure 1.2). Sleep stages usually occur in ordered sleep cycles, progressing from light to deep NREM stages and ending with REM sleep. [44] A sleep cycle has a duration of approximately 90 minutes. [44] A whole night typically consists of three to five sleep cycles.

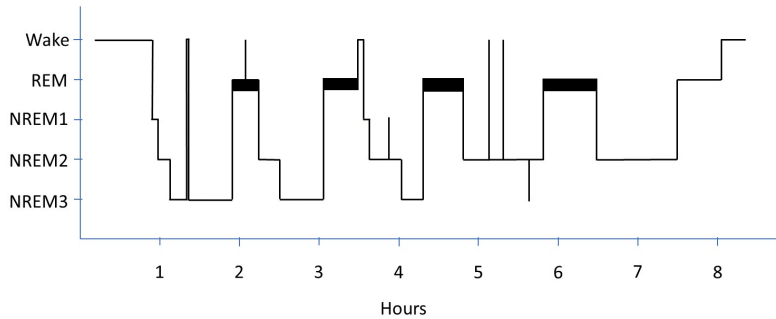


Figure 1.2: Example of a hypnogram. Occasional awakenings during the night can often be observed, and are considered normal. In general, NREM3 sleep mostly occurs during the first part of the night, and REM sleep mostly occurs during the second part of the night.

#### Box 4 : Parameters derived from PSG

We can distinguish parameters that can be derived from the hypnogram, also called ‘macrostructural parameters’, and parameters directly derived from the EEG signal, e.g. ‘microstructural parameters’.

##### Macrostructural parameters

- Sleep onset latency (SOL) – Time between the moment the participant started trying to sleep and the first instance of any epoch scored as sleep.
- Total sleep time (TST) – Total duration of all epochs scored as sleep during the night.
- Wake after sleep onset (WASO) – The total length of all epochs scored as wake after the first sleep fragment has occurred.
- Number of awakenings – The total number of awakenings during the night.

##### Microstructural parameters

- Spectral power – The magnitude of EEG waves, divided into different frequency bands. These frequency bands can be analyzed using Fourier analysis. Relevant frequency bands include delta (0.5-2 Hz), theta (4-8 Hz), alpha (8-12 Hz), sigma (12-15 Hz), and beta (15-30 Hz). Wake periods are usually dominated

by alpha and beta activity. During NREM sleep, the frequency gradually slows down to the theta and delta frequency bands.

- Sleep spindles - Sudden bursts of oscillatory brain activity with a frequency in the theta band. They mostly occur during NREM2 sleep, and are believed to protect the sleep from external stimuli<sup>19</sup>. The most-used parameter is the number of sleep spindles per minute of NREM sleep.
- Microarousals – A sudden increase of EEG frequency, which is usually associated with an internal or external disturbance of sleep.

#### **Box 5 : The sleep diary**

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The sleep diary is an important tool for both research and clinical practice. In a sleep diary, people can register their sleep and wake times over multiple days or weeks. Often used is the international ‘consensus sleep diary’, which consists of questions about the time going to bed, the time waking up, sleep onset, awakenings, total sleep time and perceived sleep quality. Alternatively a graphical sleep diary can be used, in which people can indicate their sleep and wake over the night using colored bars. Such a diary provides a more complete overview of the sleep period and enables the patients to indicate the timing of their awakenings. Examples of the two types of sleep diaries are shown in figure 1.3.

What time did you get into bed?	22:45 PM
What time did you try to go to sleep?	23:00 PM
How long did it take you to fall asleep?	30 minutes
How many times did you wake up, not counting your final awakening?	1
In total, how long did these awakenings last?	30 minutes
What time was your final awakening?	6:30 AM
After your final awakening, how long did you spend in bed trying to sleep?	30 minutes
Did you wake up earlier than you planned?	Yes
If yes, how much earlier?	30 minutes
What time did you get out of bed for the day?	7:00 AM
In total, how long did you sleep?	6 hours 30 minutes

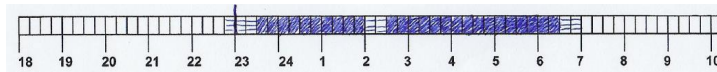


Figure 1.3: Examples of two types of sleep diaries. Top: part of the international consensus sleep diary. The international consensus sleep diary additionally consists of questions about perceived sleep quality, and about alcohol and caffeine use. Bottom: example of graphical sleep diary. In the graphical sleep diary, patients can additionally indicate the timing of their awakenings. For example, this patient woke up at 2:00 AM. Like the consensus sleep diary, graphical sleep diaries can include additional questions.

## 1.5 Outline of this thesis

The overall aim of the research described in this thesis is to identify new objectively measurable sleep parameters reflecting sleep quality in people with insomnia. We use different strategies to overcome the previously mentioned limitations of the complexity of sleep and the presumed large variations within the patient population.

In **chapter 2**, we describe an explorative analysis to identify sleep parameters measured during the first sleep cycle that may influence the perception of the sleep onset latency. We mainly focus on sleep onset misperception, because the perception of the sleep onset is localized in time, and therefore easier to study. Additionally, we propose a model to quantify the influence of the length of uninterrupted sleep fragments on the perception of the sleep onset.

In **chapter 3**, we validate the model developed in **chapter 2** on a large independent dataset, including people with insomnia and healthy controls. We compare model parameters between groups, and across insomnia subgroups with respect to sleep onset misperception, medication use, age and sex. Furthermore, we introduce the sleep fragment perception index (SFPI), a metric to quantify the relation between sleep fragmentation and sleep onset perception in individual subjects.

In **chapter 4**, we apply our knowledge of the relation between sleep fragmentation and sleep onset misperception to reduce interindividual variability caused by sleep architectural differences. To do so, we divide sleep onset misperception into a component explained by sleep fragmentation, as estimated by the model, and an unexplained component, represented by the residual error of the model. Because time estimation and pre-sleep arousal are characteristics possibly influencing sleep onset misperception, we examine the influence of time estimation and pre-sleep arousal on the unexplained component of sleep onset misperception in patients with insomnia.

In **chapter 5**, we explore potential mechanisms of sleep fragmentation that influence alterations of perceived sleep quality, using a pharmacological sleep intervention. We analyze standard in-lab polysomnography (PSG) recordings with one night of sleep medication and one night of placebo, in elderly people with complaints of insomnia and healthy controls. We apply survival curve analysis to explore potential whole-night mechanisms co-occurring with im-

proved subjective sleep quality and quantity when using the sleep medication. Co-occurring changes in sleep fragmentation and perceived sleep quality can be very informative, but do not prove that these two phenomena really influence each other. Therefore, we use the sleep length model to examine if the positive effect of sleep medication on sleep onset (mis)perception can be attributed to predictable changes of sleep fragmentation.

In **chapter 6**, the survival curve parameters identified in chapter 5 are compared between people with insomnia and healthy controls. We use Weibull distributions to represent sleep and wake survival dynamics of individual study participants. Then, we use a linear model to analyze the combined influence of participant group, age, sex and total sleep time on the Weibull parameters.

In **chapter 7**, we conclude the thesis with an integrative discussion of the findings with suggestions for future research.

# Chapter 2

## Sleep EEG Characteristics Associated with Sleep Onset Misperception

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## 2.1 Abstract

**Study Objective** - To study sleep EEG characteristics associated with misperception of the sleep onset latency (SOL).

**Methods** - Data analysis was based on secondary analysis of standard in-lab polysomnographic recordings in 20 elderly people with insomnia and 21 elderly good sleepers. Parameters indicating sleep fragmentation, such as number of awakenings, WASO and percentage of NREM1 were extracted from the polysomnogram, as well as spectral power, microarousals and sleep spindle index. The correlation between these parameters during the first sleep cycle and the amount of misperceived sleep was assessed in the insomnia group. Additionally, we made a model of the minimum duration that a sleep fragment at sleep onset should have in order to be perceived as sleep, and we fitted this model to subjective SOLs of both subject groups.

**Results** - Misperception of SOL was associated with increased percentage of NREM1 and more WASO during sleep cycle 1. For insomnia subjects, the best fit of modelled SOL with subjective SOL was found when assuming that sleep fragments shorter than 30 minutes at sleep onset were perceived as wake. The model indicated that healthy subjects are less sensitive to sleep interruptions and perceive fragments of 10 minutes or longer as sleep.

**Conclusions** - Our findings suggest that sleep onset misperception is related to sleep fragmentation at the beginning of the night. Moreover, we show that people with insomnia needed a longer duration of continuous sleep for the perception as such, compared to controls. Further expanding the model could provide more detailed information about the underlying mechanisms of sleep misperception.

## 2.2 Introduction

Chronic insomnia is a widespread problem, affecting about ten percent of the adult population. [3, 4] Insomnia does not only involve unsatisfactory sleep, but also daytime complaints such as fatigue, attentional disturbances and mood disturbances. These complaints can cause significant decreases in quality of life, general health and labour productivity. [4]

People with insomnia often underestimate their amount of sleep compared to objectively scored sleep, described as sleep state misperception. [45] Different types of sleep state misperception can be distinguished, for example with respect to total sleep time (TST), wake after sleep onset (WASO) or sleep onset latency (SOL).

Delays in sleep onset are among the most common complaints of insomnia, leading us to focus on the underlying mechanisms of misperception of SOL in this study. Results from multiple studies suggest that sleep is possibly interpreted as wakefulness due to physiological changes in the nature of the misperceived sleep. [26, 46, 47] However, it is not exactly known what such changes might entail. Different factors may play a role in the misperception of sleep onset, such as cortical hyperarousal, sleep fragmentation, and changes in sleep protection mechanisms such as sleep spindles.

First, sleep state misperception of the sleep onset might be related to hyperarousal, which is a key concept in the pathophysiology of insomnia. [48] Signs of hyperarousal are normally observed during cognitive functions when someone is awake. [49] In the PSG, cortical hyperarousal is reflected by an increased high frequency spectral content of the EEG. [50] Common findings in insomnia are increased high frequency spectral power over the night and a hampered decrease of beta power during sleep onset compared to healthy subjects. [29, 51] It was proposed that cortical hyperarousal during the beginning of the night reduces the differentiation between sleep and wakefulness [52] and interferes with the usual decline of memory-related functions during sleep onset. [26, 53] Indeed, in one study a correlation was found between misperception of TST and NREM beta activity within a mixed sample of subjects with primary insomnia, subjects with insomnia secondary to depression and good sleepers. [32] In another study, Krystal et al. compared spectral power during NREM sleep in three groups: healthy subjects, subjects with subjective insomnia who slept normally according to their PSG and subjects with objective insomnia who did not sleep normally according to their PSG. [54] Subjects from the subjective insomnia group had increased alpha, beta and sigma power and decreased delta power compared to the other two groups. [54] A third study did not find an association of sleep

state misperception with high frequent EEG activity. [55]

Second, sleep fragmentation might play a role in sleep onset misperception. [56] It is known that in healthy subjects the sense of having been asleep prior to awakening from NREM sleep is dependent on the length of the continuous, prior sleep time. [35, 57] The perception of sleep may therefore be disturbed when sleep is frequently interrupted. Interestingly, in 1988 a study reported that perception of awakenings during sleep seemed to be disturbed in insomnia patients. [58] The investigators asked insomnia patients and normal sleepers to press a button each time they became aware of having just awakened during the night, while their sleep was monitored using polysomnography. Results showed that subjects with insomnia only reported awakenings when PSG showed they had been sleeping continuously for at least 15 minutes prior to awakening. [58] The authors explained these findings by assuming that a sleep duration below 15 minutes was not long enough for the subjects with insomnia to have experienced falling asleep. [58] In another study, Hauri et al. compared two definitions of objective sleep onsets to subjective SOL in insomnia subjects: according to the first definition sleep onset was defined as the start of the first continuous 15 minutes of NREM2 sleep, and the second definition was according to Rechtschaffen and Kales criteria, where sleep onset has been defined by the first three consecutive sleep epochs. [59] A better agreement between subjective and objective SOL was found when the first criterion was used. [59] These findings might be particularly relevant for misperception of the sleep onset, since some insomnia patients show many awakenings at the beginning of the night, which might interrupt the process of falling asleep. [59] For this reason in pharmaco-sleep studies the latency to the first consecutive 10 minutes of sleep is usually reported [60], although this cutoff is still somewhat arbitrary.

Indications of a fragmented sleep on a macrostructural level are an increase of Wake after Sleep Onset (WASO) and an increased number of awakenings. Additionally, a higher percentage of light sleep stages and an increased number of transitions between sleep stages could indicate sleep fragmentation. However, sleep might also be disturbed by processes occurring on a too small timescale to be visible in the hypnogram, such as microarousals or Cyclic Alternating Patterns. [27, 34] For instance, when healthy sleepers wore a mask inducing microarousals, they reported a longer SOL than a control group, while the SOL calculated from the PSG was not longer than that of the control group. [61]

Finally, when looking at disturbances of sleep, studying sleep protection mechanisms such as sleep spindles might provide additional information, since it is hypothesized that these play a role in the protection of the stability of sleep. [62] Thus, subjects with sleep state misperception might have less sleep

spindles than subjects without sleep state misperception. Slow (9-12 Hz) and fast (13-15 Hz) sleep spindles seem to represent different types and functions and therefore should be examined separately. [28]

If indeed certain characteristics of sleep around sleep onset make it more prone for misperception, we expect to find more of these parameters during the first part of the night in people with sleep onset misperception. For example, if sleep fragmentation is related to sleep onset misperception, we expect to find an association between sleep fragmentation during the first sleep cycle and sleep onset misperception. Subsequently, if we take these characteristics into account, we should be able to model the influence of objective parameters on the perception of the sleep onset, by fitting the parameters of the model to subjective information about the sleep onset. Obtaining insight into the parameters influencing the perception of sleep could also provide more information about sleep in general and the factors determining its subjective quality.

Here, we further aimed to elucidate the mechanisms underlying misperception of SOL, by analyzing an existing dataset comprising healthy elderly subjects with insomnia and healthy age-matched subjects [63]. We assessed the association between the amount of sleep misperception expressed as SDSL and several micro- and macrostructural parameters. Moreover, we modeled the perception of sleep onset, to study the influence of sleep interruptions on subjective SOL in more detail.

## 2.3 Methods

### 2.3.1 Design

Data for this paper were collected as part of a study by Leufkens et al., comparing sleep macrostructure, on-the-road driving performance and driving related skills between elderly insomnia patients frequently using hypnotics (n=22), elderly insomnia patients infrequently using hypnotics (n=20), and age-matched healthy subjects (n=20). [63] In the present study, sleep data from the insomnia patients infrequently using hypnotics and the healthy subjects were re-analyzed.

### 2.3.2 Participants

Participants were recruited via newspaper advertisements and through a network of local general practitioners in the region of Maastricht. The insomnia group consisted of 20 patients with insomnia who did not use hypnotics or were using

hypnotics no more than 3 nights per week. The control group consisted of 21 self-defined healthy subjects. [63]

As reported by Leufkens et al [63] all participants had to meet the following inclusion criteria: aged between 50 and 75 years; good health based on a pre-study physical examination, medical history, vital signs, electrocardiogram, blood biochemistry, hematology, serology, and urinalysis. Exclusion criteria were history of drug or alcohol abuse; presence of a significant medical, neurological, psychiatric disorder, or sleep disorder other than insomnia; chronic use of medication that affects driving performance, except hypnotics; drinking more than 6 cups of coffee per day; drinking more than 21 units of alcohol per week; smoking more than 10 cigarettes per day; and body mass index outside the range of 19 to 30 kg/m<sup>2</sup>. Additionally, insomnia patients had to meet the following inclusion criteria, based on DSM-IV [63]: (1) subjective complaints of insomnia, defined as difficulties initiating sleep (sleep latency >30 min) and/or maintaining sleep (awakenings >30 min); (2) duration of more than 1 month; (3) the sleep disturbance causes clinically significant distress or impairment; (4) insomnia does not occur exclusively during the course of a mental disorder; and (5) insomnia is not due to another medical or sleep disorder or effects of medication or drug abuse. Volunteers were screened by a telephone interview, questionnaires, and a physical examination to confirm that participants were healthy. Sleep complaints were evaluated by a trained psychologist using Dutch versions of the Pittsburgh Sleep Quality Index [64], the Sleep Wake Experience List [65], and the Groningen Sleep Quality Scale. [66] In addition, subjects completed a sleep log for 14 days. Major psychopathology was screened using the Symptom Checklist 90 Revised [67], the Beck Depression Inventory [68], the State-Trait Anxiety Inventory [69], and the Multidimensional Fatigue Inventory. [70]

Seven patients from the insomnia group reported no history of using hypnotics. [63] The hypnotics used by the remaining 13 patients with insomnia were temazepam (n=6), zopiclone (n=4), lorazepam (n=1), loperazolam (n=1) and nitrazepam (n=1). [63] Their average duration of hypnotic use was  $7.8 \pm \text{sd } 7.9$  years and their average frequency of hypnotic use was  $4.1 \pm \text{sd } 2.9$  nights per month. Hypnotics were used irregularly. All subjects had negative blood samples the morning after the measurement night.

The study was conducted in accordance with the code of ethics on human experimentation established by the World Medical Association's Declaration of Helsinki (1964) and amended in Edinburgh (2000). The protocol was approved by the medical ethics committee of Maastricht University and University Hospital of Maastricht. Participants were explained the aims, methods, and potential hazards of the study and they signed a written informed consent prior to any

study-related assessments.

### 2.3.3 Schedule

The study protocols of all participants were completed between December 2007 and February 2009. Sleep was evaluated during two nights of polysomnography in the sleep laboratory: a habituation night and a test night. Participants arrived at the sleep laboratory at 7.00 pm. The polysomnography electrodes were attached at 9.00 pm and lights off time was at 11.30 pm. Participants were awakened the next morning at 7.30. During study participation, caffeine use was prohibited from 8 hour prior to arrival at the sleep laboratory. Alcohol intake was prohibited from 24 hour prior to bedtime and smoking was prohibited from 1 hour prior to bedtime. Use of hypnotics was prohibited from one day prior to the measurements night. This was confirmed by a blood test which was performed on the morning after the measurement night, 15-20 minutes after awakening.

### 2.3.4 Assessments

Polysomnography - A four-channel electroencephalogram (C3, C4, F4, O2), electrooculogram and electromyogram were performed. The data was recorded with a Vitaport portable EEG recorder with a common average (A1-A2) and a sample frequency of 256 Hz. Visual sleep staging was performed according to R&K criteria [71] by experienced technicians from the sleep center of Stichting Epilepsie Instellingen Nederland (Zwolle, the Netherlands). Technicians were blinded for the group affiliations of the subjects. Each polysomnogram was scored by one technician.

Subjective sleep – Subjective sleep was assessed on the morning after the PSG measurements by asking subjects to report their subjective TST, SOL, number of awakenings and time of early awakening.

### 2.3.5 Data Analysis

To determine the presence of physiological changes in sleep in patients with insomnia disorder, we compared PSG data between the insomnia and the healthy subject group, with respect to macro and microstructural parameters. We compared the parameters during the whole night and during the first sleep cycle separately. Macrostructural parameters consisted of number of awakenings, WASO, number of sleep stage transitions, percentage of NREM1 and percentage

of REM. Microstructural parameters consisted of delta/beta spectral power ratio during each sleep stage, microarousals during REM, microarousals during nREM, low-frequency sleep spindle index and high-frequency sleep spindle index.

To determine the relation of objective sleep with misperception of sleep in patients with insomnia disorder, we assessed the correlation between the aforementioned variables during sleep cycle 1 and the amount of sleep state misperception at sleep onset in the insomnia group. The hypnogram was divided into sleep cycles according to rules stated by Aesbach et al. [72]

### 2.3.6 Defining the amount of sleep misperception

The amount of sleep misperception at sleep onset was expressed in Sleep During Subjective Latency (SDSL): the amount of sleep in minutes between the first instance of any sleep stage and the subjective sleep onset (Figure 2.1). [56] This metric was based on research of Saline et al., which proposed SDSL as a new metric because large differences in the amount of sleep onset misperception can be found, depending on which definition of sleep onset is used. [56] This metric only focuses on the amount and characteristics of the sleep that has been misperceived during the period of subjective sleep latency, rather than just subtracting objective and subjective sleep onsets. [56] This way, epochs of WASO will not be included in the SDSL.

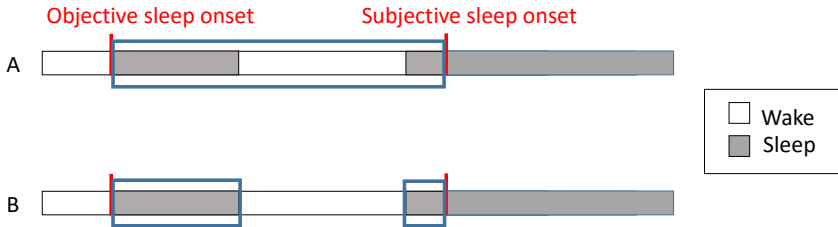


Figure 2.1: Example of calculation of Sleep During Subjective Latency (SDSL). A) Usually, the amount of sleep misperception is calculated as the difference between subjective and objective sleep onset, as indicated with the blue border. For this example, the amount of sleep misperception is 25 minutes. B) When calculating SDSL, only the sleep during the difference between subjective and objective sleep onset is taken into account. Any wake fragments are ignored. In this case, the amount of sleep misperception is  $10+3=13$  minutes.

### 2.3.7 Macrostructural parameters

Objective SOL was calculated as the time between lights off and the first epoch of any sleep stage, according to AASM criteria. [40] The percentage NREM1 sleep was calculated by dividing the number of epochs scored as NREM1 sleep by the total number of epochs scored as sleep. The percentage of REM was calculated using the same method.

### 2.3.8 Microstructural parameters

The microstructure of sleep was analyzed using Philips Somnolyzer software. [73–76]

Power spectral analysis - For each subject the power spectra of the C4-A1 lead were calculated. For one subject the C3-A2 lead was used because of artifacts on the C4-A1 lead. Spectral power was calculated separately during manually scored NREM2 sleep, Slow Wave Sleep (SWS) and REM, in order to eliminate the influence of different stage distributions across subjects. The spectral power during NREM1 sleep was not considered, because part of the subjects proceeded directly from wake to NREM2 at the start of the first sleep cycle. Additionally, the presence of movement artifacts in some other subjects lead to a very limited availability of noise-free epochs in this sleep stage. For each 30s-epoch the spectral power was an average of 15 mini-epochs of 4 seconds with 2-seconds overlap. This way, a spectral resolution of 0.25 Hz within a frequency range of 0.25 to 40.0 Hz was obtained. Artifacts were automatically detected as described by Anderer et al. [77] For each 30-s epoch, the number of artifact free mini-epochs, ranging from zero to 15, was listed. In order to improve stability of the spectral power calculations, only epochs with more than five artifact free mini-epochs were considered for calculation of the spectral power. The delta/beta spectral power ratio was calculated by dividing the activity in the delta frequency band (0.5-4 Hz) by the activity in the beta frequency band (16.25-32.0 Hz), thereby obtaining a relative index which was used as an indication of cortical hyperarousal.

Arousals - Microarousals were detected by the Somnolyzer software package based on AASM criteria. [40] In general, rather than deciding if a microstructural element is present or not, Somnolyzer provides probabilities as output. Only arousals with probabilities above 0.7 were selected. During REM sleep, arousals additionally had to co-occur with a submental EMG increase of at least 75% in order to be selected. The number of arousals during NREM sleep was divided by the total number of hours of NREM sleep during that night. The number of



arousals per hour during REM sleep was calculated using the same procedure.

Sleep spindles - Sleep spindles were only detected during the manually scored NREM2 stages, in order to decrease the probability of incorrectly detecting other events as sleep spindles. Additionally, only sleep spindles with a probability above 0.95 were considered. Sleep spindles were separated in two groups: low (<13 Hz) and high (>13 Hz) frequency sleep spindles. For both groups, the sleep spindle index (SSI) was calculated as the number of sleep spindles per minute of NREM2 sleep.

### **2.3.9 Modelling the perception of sleep onset**

As a second step in the analysis we made a model of the influence of sleep interruption on the perception of the sleep onset. In the model the following hypothesis was tested: sleep bouts with too short duration at sleep onset are perceived as wake. This assumption implies that the subject will perceive the sleep onset as the start of the first sleep fragment of sufficiently long duration, while ignoring preceding shorter sleep fragments. Because it is not known how long an uninterrupted sleep fragment at sleep onset should be in order to be perceived at sleep, this is the independent variable in the model, which we call L. The model output was sleep onset, which was defined as the start of the first continuous sleep fragment longer than L minutes, with L varying from 0.5 to 40. Any wake fragment of at least one epoch was considered as an interruption of sleep. This procedure is illustrated in Figure 2.2. We compared the sleep onset calculated from the model to the sleep onset perceived by the subject and calculated the Mean Square Error (MSE) of the difference between the two. We then selected the parameter L resulting in the smallest MSE. This was done for each subject group separately. Importantly, it should be noted that in this analysis we did not use SDSL, because for this analysis no measure of sleep onset misperception was required.

## **2.4 Results**

### **2.4.1 Subject characteristics**

The insomnia group consisted of 10 males and 10 females (mean 60.8  $\pm$  sd 10.9 years old). The control group consisted of 13 males and 8 females (mean 61.7  $\pm$  5.0 years old) [63].

Both groups had a comparable objective SOL (insomnia mean  $19 \pm \text{sd } 13$  minutes vs. healthy subjects mean  $19 \pm \text{sd } 15$  minutes) [63]. However, the untreated insomnia patients reported a significantly longer subjective SOL than the healthy subjects (mean  $68 \pm \text{sd } 73$  minutes vs. mean  $35 \pm \text{sd } 37$  minutes) [63]. During the measurement night, out of 20 insomnia subjects 17 subjects reported a subjective sleep onset of 30 minutes or more, 9 subjects reported waking more than 2 times at night and 13 subjects reported waking up more than 30 minutes too early. We did not observe distinct subtypes during this night, e.g. many patients had more than one complaint. The amount of sleep misperceived at sleep onset was expressed as SDSL: the amount of sleep in minutes between the first instance of any sleep stage and the subjective sleep onset (Figure 2.1). Subjects with insomnia had an average SDSL of  $40 \pm 53$  minutes and healthy controls had an average SDSL of  $14 \pm 28$  minutes.



Figure 2.2: Follow-up analysis: definition of sleep onset according to our model. An imaginary example of the sleep/wake pattern during a first sleep cycle is shown. A) If we assume that sleep fragments with a length below 30 seconds are not perceived as sleep, the sleep onset from the model is the same as the objective sleep onset according to the AASM definition. B) If we assume that sleep fragments with a length below 2 minutes are not perceived as sleep, the sleep onset from the model shifts to the second sleep bout. C) If we assume that sleep fragments with a length below 5 minutes are not perceived as sleep, the sleep onset shifts past the two shorter sleep bouts. Using this method, the sleep onset was defined for each value of  $L$  between 0.5 and 40 minutes and compared to the sleep onset latency perceived by the patient.

### 2.4.2 Comparison between groups

For the parameters calculated from the whole night, no significant differences were found between the insomnia group and the healthy subjects group at  $p < 0.01$  (Table 2.1). However, during the first sleep cycle subjects with insomnia had a lower delta/beta power ratio during NREM2 than healthy subjects (Table 2.2).

### 2.4.3 Associations with sleep state misperception

We found that a larger amount of sleep onset misperception expressed in SDSL was correlated with a higher percentage of NREM1 and more WASO during the first sleep cycle in the insomnia group (Table 2.3, Figure 2.3). In the healthy subjects group, the spread of the sleep onset misperception was too small to identify meaningful correlations.

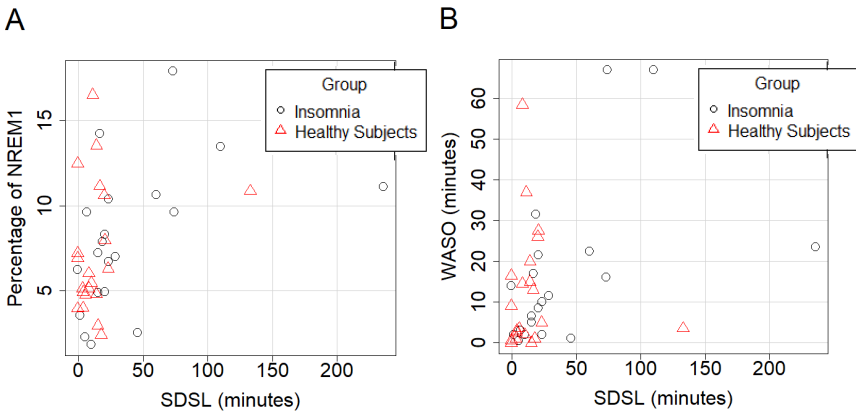


Figure 2.3: The percentage of NREM1 and WASO in minutes versus the amount of sleep onset misperception expressed in SDSL. Subjects with insomnia are shown by black circles and healthy subjects are shown by red triangles. The healthy subjects show less variation in SDSL compared to the subjects with insomnia.

When dividing all 41 subjects into two groups based on SDSL with a cut off of 20 minutes in order to be able to compare our results with earlier findings [56],

we found that age and sex were very comparable between the groups (short SDSL: age  $60.6 \pm 6.1$  years, 5F 6M; long SDSL: age  $60.7 \pm 6.1$  years; 5M 4F).

When examining the percentage of NREM1 during the first sleep cycle more closely, we noticed that the NREM1 epochs were mostly present inside the SDSL and to a lesser extent outside the SDSL (Figure 2.4). This effect was more pronounced in subjects with a shorter SDSL than in subjects with a longer SDSL. A longer duration of the SDSL was associated with a lower percentage of NREM1 during the SDSL (Spearman  $\rho = -0.60$ ,  $p < 0.001$ ). It should be noted that the direction of this correlation was opposite to the correlation between the duration of the SDSL and the percentage of NREM1 during the first sleep cycle.

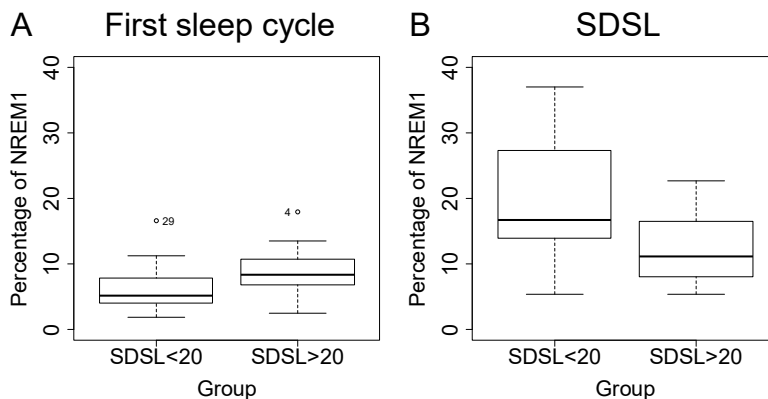


Figure 2.4: Comparison of two different methods to calculate the percentage of NREM1. A) Percentage of NREM1 during the entire first sleep cycle. B) Percentage of NREM1 during the Sleep During Subjective Latency (SDSL) only. The subjects are divided in two groups: subjects with a SDSL of more than 20 minutes ( $N=15$ ) and subjects with a SDSL of less than 20 minutes ( $N=21$ ). Subjects with a SDSL shorter than one minute are not shown. Clearly, in subjects with a short SDSL, a large part of the NREM1 epochs is concentrated within the SDSL.

#### 2.4.4 Modelling perception of sleep onset

We made a model of sleep onset perception, testing the following hypothesis: sleep bouts with length under  $L$  minutes at sleep onset are perceived as wake.

Figure 2.5a shows the relation between SOL calculated from the model and SOL perceived by the subjects of the insomnia group. The SOLs calculated for  $L=0.5$  minutes are shown in black. In this situation, the model assumes that the subjective sleep onset occurs together with the first epoch of sleep, which has a length of 30 seconds. This is equal to the objective SOL according to AASM criteria. Clearly, a considerable mismatch between subjective and modelled SOLs can be observed. The SOLs calculated for  $L=30$  are shown in red. We showed the results for  $L=30$  because this proved to be the best model parameter for the insomnia group (see next section). Applying the model with  $L=30$  greatly reduced the mismatch between modelled and subjective SOL. Figure 2.5b shows the same information for the healthy controls. The initial mismatch between subjective and modelled Sleep Onset Latencies for  $L=0.5$  was smaller than for the insomnia group. Applying the model with  $L=30$  resulted in a large mismatch between modelled SOLs and subjective SOLs, because the SOLs were overestimated by the model. The minimum square errors for the difference between modelled and subjective SOL for each value of  $L$  are shown in Figure 2.6. For insomnia, the closest match between subjective SOL and modelled SOL was found for a length  $L$  of approximately 30 minutes. For the healthy subjects, an optimum was found for a length  $L$  of approximately 10 minutes. However, no clear improvement can be observed compared to  $L=0.5$ . For larger values than  $L=20$  minutes, the MSEs rapidly became larger than in the initial situation.

## 2.5 Discussion

We aimed to further elucidate the mechanisms involved in misjudgment of sleep onset latency in patients with insomnia diagnosis according to DSM-IV criteria by assessing the correlation of sleep misperception with macro and microstructural parameters during the first sleep cycle. This approach provided additional insight in factors that could play a role in the subjective quality of sleep and the underlying mechanisms of misperception. In the insomnia group, sleep onset misperception measured as SDSL was associated with increases in WASO and a higher percentage of NREM1 sleep during the first sleep cycle. Moreover, by making a model of the influence of frequent sleep interruptions on sleep onset perception, we show that subjects with insomnia needed a longer time of uninterrupted sleep to perceive it as such compared to controls.

The positive associations of sleep onset misperception with WASO and percentage of NREM1 during the first sleep cycle in the insomnia group confirm the presence of lighter and more fragmented sleep. This is opposite to the

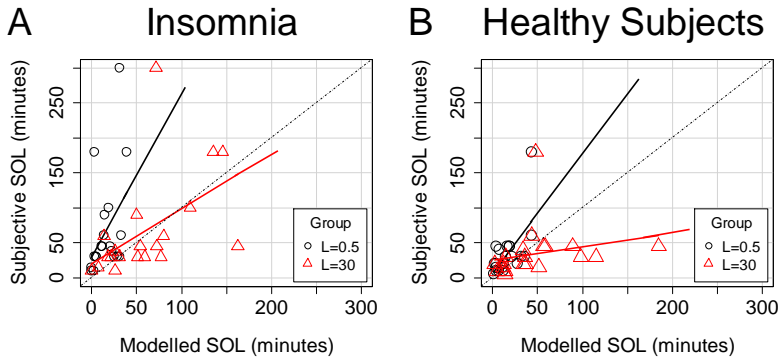


Figure 2.5: Follow-up analysis: Subjective versus modelled Sleep Onset Latencies (SOLs) for each subject group. A): Insomnia group. The Sleep Onset Latencies calculated for  $L=0.5$ , assuming that subjective sleep onset occurs together with the first sleep epoch, are shown by black circles. Another example of using the model, with parameter  $L=30$ , is shown by red triangles. The hypothetical situation with equal modelled and subjective SOLs and a MSE equal to zero is indicated with a dotted line. In the insomnia group, applying the model with parameter  $L=30$  reduces the mismatch between modelled and subjective SOLs. B) Healthy subjects. In the healthy subjects group, the mismatch for  $L=0.5$  was considerably smaller than the mismatch in the insomnia group. Applying the model with parameter  $L=30$  increased the mismatch.

study of Saline et al., who in a large retrospective dataset including subjects with and without sleep apnea found that subjects with a SDSL of more than 20 minutes showed a lower percentage of NREM1, a higher percentage of NREM3 and a lower transition frequency than subjects with a SDSL of less than 20 minutes. [56] This difference can be explained by the fact that Saline et al examined variables of sleep misperception during the SDSL, while we used the whole first sleep cycle to calculate the variables. Since a sleep cycle starts with shallow sleep which usually gets deeper as the sleep cycle progresses, subjects with a short SDSL by default will show a lot of shallow sleep during their SDSL. This effect is illustrated by our NREM1 data shown in Figure 2.4. These results show that outcomes may greatly vary depending on the part of the night from which the parameters are calculated. An advantage of calculating the parameters during the first sleep cycle is that the data of subjects with a SDSL of zero still can be included in the analysis. Additionally, the maximum SDSL that we found was

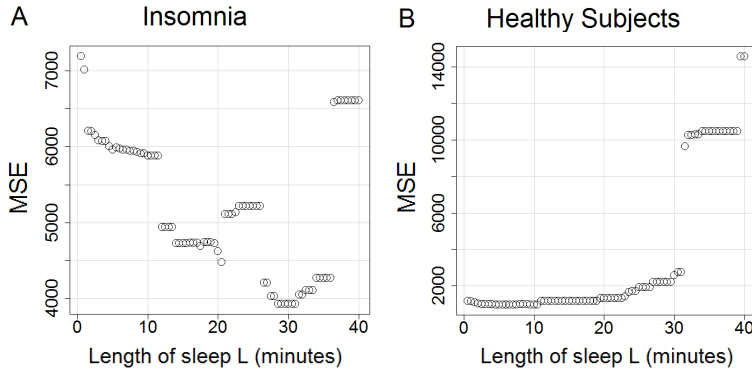


Figure 2.6: Follow-up analysis: the minimum square errors (MSEs) for the difference between modelled and subjective SOLs for each value of the model parameter  $L$ . Note that the two plots have different scales on the y-axis. A) Insomnia group. A clear minimum is shown at approximately  $L=30$  minutes. B) Healthy subjects. The MSE shows a minimum at approximately  $L=10$  minutes, but no clear improvement is shown compared to  $L=0.5$ .

approximately equal to the length of an average sleep cycle.

Our results imply that, in our population, sleep onset misperception is related to fragmentation of sleep on a macrostructural level; i.e. a subgroup of the insomnia subjects showed significant sleep onset misperception and sleep fragmentation at sleep onset. However, no differences in percentages of NREM1 or WASO were found between subjects with insomnia and healthy subjects. Therefore, these variables appear to be correlated with sleep onset misperception, without being a general characteristic of insomnia. In other words, we showed that part of our insomnia subjects had biological characteristics which were associated with sleep misperception, even while their sleep seemed objectively normal on group level. This finding highlights the possibility that the same amount of sleep fragmentation has different effects in insomnia patients than in healthy sleepers.

Unlike some other studies [32, 54], we did not find any associations of sleep onset misperception with hyperarousal indicated by increased high frequency spectral power. We also did not find any indications that REM sleep related processes or disturbances on a small time scale, for example arousals, were involved in sleep onset misperception in this group. Moreover, we did not find

indications for impaired sleep protection mechanisms. However, because of a limited number of subjects our analysis was limited to sleep spindle density at the C4 electrode, although other characteristics like spindle length might play a role in sleep state misperception. [33]

The only general difference we found between the PSG of subjects with insomnia and healthy subjects was a lower delta/beta power ratio during NREM2 in the insomnia group, but only during the first sleep cycle. As mentioned before, increased high frequency spectral power is a common finding in insomnia. [27] Other differences in EEG parameters, such as microarousals and sleep spindles vary greatly between studies, possibly because of the existence of different subtypes within the insomnia population. [27]

Based on our results on the association between sleep fragmentation and sleep onset misperception we hypothesize that a sleep fragment needs to have a certain duration to be perceived as sleep, and that this duration is longer in subjects with insomnia. Nevertheless, in a study of Bianchi a similar hypothesis was not confirmed. [78] In their study two hypotheses were tested: epochs of NREM1 are perceived as wake and sleep bouts under 10 minutes are perceived as wake. [78] In both cases these hypotheses did not result in a match between objective and subjective sleep duration. [78] We tested a somewhat more flexible hypothesis: sleep bouts under L minutes at sleep onset are perceived as wake. In our model, we tested varying lengths of L. Indeed, we found that the mismatch between subjective and objective SOL in insomnia patients became smaller when we applied the model. For insomnia patients, the best agreement between modelled and subjective SOL was found when sleep epochs shorter than 30 minutes at sleep onset were not taken into account. This indicates that, in insomnia patients, interruption of sleep after less than 30 minutes can reduce the likelihood of its perception.

The healthy subjects group only showed a small discrepancy between subjective and objective sleep onset latencies. As such the model only resulted in very small improvements for approximately  $L=10$  minutes. In a study of Bonnet et al., 90 percent of the healthy subjects correctly estimated being asleep after 16 minutes of continuous sleep. [57] This finding roughly corresponds to the optimum found from our model, which was found for a sleep length of 10 minutes. Also, in the same study at 25 minutes of continuous sleep after sleep onset, 100 percent of the subjects correctly estimated being asleep. [57] This is an indication that including sleep lengths above 25 minutes most likely will not result in any improvement of our model. Indeed, for larger values than  $L=20$  the MSEs rapidly became larger than in the initial situation. As far as we know the aforementioned study protocol has not been repeated in people with insomnia



and therefore these results cannot be compared. However, the different results for the two groups suggest that, for the correct perception of sleep onset, subjects with insomnia require longer continuous sleep fragments than healthy subjects.

One limitation of this study is that the study population contained only elderly subjects. It is known that physiological changes of sleep occur with aging. For example, sleep in elderly subjects is more fragmented, the number of arousals increases and the density of sleep spindles decreases. [79, 80] Thus, elderly subjects might consist of yet another subtype of insomnia with a different type of sleep misperception and different sleep characteristics. Therefore, additional research should be done in order to find out if our results can be generalized to the whole population. Sleep changes occurring with age could also potentially effect the correlation between SDSL and EEG parameters. Due to limited statistical power we did not run a statistical analysis on the effects of age and sex. However, the result that age and sex were very similar for subjects with short and long SDSL leads us to believe that correlations were not confounded by these parameters.

A second limitation is that most insomnia subjects in this study occasionally used hypnotics at home, mostly temazepam and on average only on one night per week. Although none of them used a hypnotic drug at the recording night, it cannot be ruled out that some occasionally used a hypnotic drug at home the week before. Therefore, withdrawal effects or rebound insomnia during PSG nights might be a confounding factor. The sparse studies into the effect of intermittent use of hypnotics suggest no rebound insomnia effect during 'no-pill' nights, but these studies are often limited to Z-drugs only. [81] Intermittent and brief use of 7.5 mg Temazepam did not result in rebound insomnia in eight elderly subjects with insomnia in one study. [82] Kales et al. did find moderate rebound insomnia after withdrawal from intermittently used temazepam. [83] However, this was tested in a group of only six subjects and the authors indicate that according to their overall experience, "potential for rebound insomnia with this drug is variable and relatively moderate". [83] Together this suggests that it is unlikely that our results are biased by medication withdrawal effects.

We modeled the influence of sleep interruption on subjective SOL, taking the length of continuous sleep fragments at sleep onset into account. Indeed, we found evidence that too short sleep fragments interrupted by WASO are perceived as a single experience of wakefulness. An important observation in this regard is that the presence of short sleep fragments at sleep onset does not necessarily lead to large changes in parameters like amount of WASO and the number of awakenings. Instead, the result of the model point towards the importance of the timing of the sleep fragments. We also found additional evidence from

the model that subjects with insomnia needed a longer time of uninterrupted sleep to perceive sleep onset compared to controls. The reason for this is not clear. One explanation might be that the perception of sleep onset coincides with reaching stages of sufficiently deep sleep. This would imply that the process of falling asleep is much slower for subjects with insomnia than for healthy subjects. However, such dramatic differences in sleep architecture were not shown from our results on the differences between subjects with insomnia and healthy subjects during the first sleep cycle. As mentioned before, it is possible that more subtle differences play a role which do not show when analyzing conventional parameters

Therefore, a future analysis could be to zoom in to the dynamics of falling asleep, for example using spectral power as an index of sleep depth. Another next step could be to look at sleep stage transition dynamics. For example, it was shown that subjects with insomnia have a higher probability to move from N2 to N1 than healthy subjects. [84] However, these sleep stage dynamics might be more important for other types of sleep misperception than sleep onset misperception. Third, comparing (spectral) characteristics of epochs of sleep perceived as wake to epochs of sleep perceived as sleep over the whole night in a dataset with more detailed subjective information could be an interesting approach. This type of analysis could also aid in answering the question whether misperception of sleep onset and other types of sleep misperception, for example misperception of WASO, have the same underlying mechanisms. However, this type of analysis is difficult to perform while overcoming the problems of automatically comparing light sleep with deeper sleep, as demonstrated in this study, and would require multiple nights of the same subject with different amounts of misperceived sleep.

Our model of sleep onset misperception only considers the length of the sleep fragments. Other factors could be implemented in order to make it more realistic. For example, possibly the length of the wake fragment following the sleep fragment plays a role in sleep state misperception. In a preliminary study using actigraphy, the average length of wakefulness necessary for morning recall of nocturnal awakenings in healthy adults was approximately 4.5 minutes. [85] This might imply that shorter awakenings can in turn be misperceived in the same way as short sleep fragments. Such an assumption requires a sufficiently large dataset to be able to use different combinations of model parameters, and it might be challenging to entirely disentangle sleep and wake misperception effects.

Our results open up avenues to further study the perception and misperception of sleep in the context of insomnia. Interesting questions include for

example: why do people with insomnia need more uninterrupted sleep time for the perception of sleep onset than healthy people and does this mechanism play a role in all insomnia patients or is it only a subgroup? If yes, what are the characteristics of this subgroup and could these findings potentially have implications for their preferred treatment? Answers to these questions could bring us closer towards identifying the biological mechanisms underlying sleep state misperception and, ultimately, to tailoring the treatment of insomnia to the needs of individual patients.

**Table 2.1:** Differences between subject groups (whole night).

Variable	Insomnia patients (n=20)	Healthy subjects (n=21)	t-test	Mann-Whitney U
<b>Macrostructural parameters</b>				
# awakenings	20.4 ± 11.0	17.9 ± 11.2	t=0.719, p=0.477	
# transitions	104 ± 44	101 ± 35	t=0.292, p=0.772	
WASO (minutes)	60 ± 39	43 ± 27	t=1.70, p=0.098	
% NREM1 sleep	7.6 ± 3.7	6.2 ± 3.0		U=166, p=0.251
% REM sleep	18.5 ± 4.7	20.3 ± 6.4	t= -1.042, p=0.304	
<b>Microstructural parameters</b>				
Delta/beta nREM2	45.3 ± 19.0	65.8 ± 29.6		U=115, p=0.013
Delta/beta SWS	271 ± 144	273 ± 120		U=191, p=0.620
Delta/beta REM	15.6 ± 6.9	20.1 ± 17.4		U=200, p=0.794
Arousals/hour (nREM)	17.0 ± 7.9	12.3 ± 6.2	t=2.138, p=0.039	
Arousals/hour (REM)	9.8 ± 5.3	9.6 ± 5.8	t=0.137, p=0.892	
SSI (high frequent)	0.73 ± 0.84	0.36 ± 0.47		U=131, p=0.039
SSI (low frequent)	1.24 ± 1.20	0.71 ± 0.93		U=128, p=0.032

Differences between PSG parameters of the insomnia group and the healthy subjects group over the whole night.

Table 2.2: Differences between subject groups (sleep cycle 1).

Variable	Insomnia patients (n=20)	Healthy subjects (n=21)	t-test	Mann-Whitney U
<b>Macrostructural parameters</b>				
# awakenings	6.3 ± 5.2	4.8 ± 4.5		U=166, p=0.244
# transitions	31 ± 17	32 ± 12		U=186, p=0.531
WASO (minutes)	17 ± 19	12 ± 15		U=168, p=0.267
% NREM1 sleep	7.7 ± 4.0	7.1 ± 3.6		U=186, p=0.531
% REM sleep	14.7 ± 8.5	14.9 ± 7.4	t=-0.070, p=0.945	
<b>Microstructural parameters</b>				
Delta/beta nREM2	43.7 ± 14.3	69.3 ± 38.7	t=-2.844, p=0.009*	
Delta/beta SWS	277 ± 155	279 ± 124		U=162, p=0.460
Delta/beta REM	15.4 ± 6.5	20.4 ± 17.1		U=174, p=0.874
Arousals/hour (nREM)	12.9 ± 10.9	8.7 ± 6.8		U=162, p=0.301
Arousals/hour (REM)	8.3 ± 8.4	7.3 ± 8.4		U=151, p=0.558
SSI (high frequent)	1.4 ± 1.3	0.66 ± 0.98		U=111, p=0.0102
SSI (low frequent)	0.91 ± 0.10	0.43 ± 0.61		U=122, p=0.022

Differences between PSG parameters of the insomnia group and the healthy subjects group during the first sleep cycle. Asterisks indicate significant correlations ( $p < 0.01$ ).

**Table 2.3:** Associations of amount of sleep misperceived with PSG parameters during sleep cycle 1.

Variable during sleep cycle 1	Spearman (n=41) Rho p=
<b>Macrostructural parameters</b>	
# awakenings	0.36 (p=0.023)
# transitions	0.17 (p=0.286)
WASO (minutes)	0.34 (p=0.030)
% NREM1 sleep	0.42* (p=0.007)
% REM sleep	-0.06 (p=0.732)
<b>Microstructural parameters</b>	
Delta/beta nREM2	-0.52* (p<0.001)
Delta/beta SWS	-0.34 (p=0.028)
Delta/beta REM	0.05 (p=0.73)
Arousals/hour (nREM)	0.19 (p=0.234)
Arousals/hour (REM)	0.25 (p=0.142)
SSI (high frequent)	-0.21 (p=0.197)
SSI (low frequent)	0.02 (p=0.891)

Associations of amount of sleep misperceived, expressed in Sleep During Subjective Latency (SDSL; minutes) with PSG parameters calculated during the first sleep cycle. Asterisks indicate significant correlations (p<0.01).



# Chapter 3

## Modelling Sleep Onset Misperception in Insomnia

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### 3.1 Abstract

**Study Objective** - To extend and validate a previously suggested model of the influence of uninterrupted sleep bouts on sleep onset misperception in a large independent dataset.

**Methods** - Polysomnograms and sleep diaries of 139 insomnia patients and 92 controls were included. We modelled subjective sleep onset as the start of the first uninterrupted sleep fragment longer than  $L_s$  minutes, where parameter  $L_s$  reflects the minimum length of a sleep fragment required to be perceived as sleep. We compared the so-defined sleep onset latency (SOL) for various values of  $L_s$ . Model parameters were compared between groups, and across insomnia subgroups with respect to sleep onset misperception, medication use, age and sex. Next, we extended the model to incorporate the length of wake fragments. Model performance was assessed by calculating Root Mean Square errors (RMSEs) of the difference between estimated and perceived SOL.

**Results** - Participants with insomnia needed a median of 34 minutes of undisturbed sleep to perceive sleep onset, while healthy controls needed 22 minutes (Mann Whitney  $U=4426$ ,  $p<0.001$ ). Similar statistically significant differences were found between sleep onset misperceivers and non-misperceivers (median 40 vs 20 minutes, Mann Whitney  $U=984.5$ ,  $p<0.001$ ). Model outcomes were similar across other subgroups. Extended models including wake bout lengths resulted in only marginal improvements of model outcome.

**Conclusions** - Patients with insomnia, particularly sleep misperceivers, need larger continuous sleep bouts to perceive sleep onset. The modelling approach yields a parameter for which we coin the term Sleep Fragment Perception Index, providing a useful measure to further characterize sleep state misperception.

## 3.2 Introduction

Both the diagnosis and treatment of insomnia typically rely on self-reported data instead of objective measurements. However, if objective recordings are carried out, people with insomnia often overestimate their sleep onset latency (SOL) compared to objectively measured sleep. [26, 45] Such discrepancies between the amount of subjective sleep and the amount measured using polysomnographic recordings are described as sleep state misperception. [26, 45] Earlier results suggest that objectively measurable characteristics of sleep, such as sleep fragmentation, might play a role in sleep state misperception. [26, 45, 86]

Sleep fragmentation might be particularly relevant for misperception of the sleep onset, since some insomnia patients show many awakenings at the beginning of the night, possibly interrupting the process of falling asleep. [59] Indeed, in healthy sleepers, the sense of having been asleep prior to awakening from NREM sleep was found to depend on the length of the uninterrupted prior sleep time. [35, 57] In a study by Hauri et al., three criteria were used for scoring sleep onset in insomnia patients: the first epoch scored as stage 2 sleep, the beginning of the first 15 minutes of stage 2 sleep and the beginning of the first 30 minutes of stage 2 sleep. [59] When using the second criterion, the smallest difference between subjective SOL and objectively scored SOL was found. [59] Thus, insomnia patients seem to require a certain amount of continuous sleep to recall their sleep onset. Therefore, it is possible that assessing traditional measures solely from sleep recordings, such as objective SOL, wake after sleep onset (WASO) and number of awakenings, leads to overlooking other informative characteristics influencing the quality of sleep, such as the length and timing of individual wake and sleep bouts.

In a previous pilot study, we hypothesized that the length of uninterrupted sleep fragments at sleep onset influences the perception of the SOL, i.e. that too short sleep fragments are not perceived as sleep. [87] Based on polysomnographic data of 20 elderly participants with insomnia and 21 elderly healthy participants, we constructed a model to quantify the influence of polysomnographically monitored sleep lengths on sleep onset perception. We defined subjective sleep onset as the start of the first uninterrupted sleep fragment longer than  $L$  minutes. Sleep length parameter  $L$ , defined as the minimum length of a sleep fragment required to perceive sleep onset, was assigned a value between 0.5 and 60 minutes. We assessed the discrepancy between the objective measure and the so-modelled perception of SOL. Results showed that insomnia patients require longer uninterrupted sleep fragments to adequately perceive sleep onset than the healthy controls. Notably, the perception of sleep in insomnia

patients could even be influenced by interruptions of sleep fragments within 30 minutes. [87]

These results were found in an elderly population of limited size. Thus, it is not known whether the findings on the influence of the length of sleep fragments on sleep onset misperception are generalizable to all insomnia patients or only to this specific subgroup. In the normal aging process, changes in sleep pattern occur, which might influence sleep fragmentation at sleep onset as well as sleep state misperception. These changes include a decrease in the amount of slow wave sleep, an increase in the amount of NREM1 and NREM2 sleep, a decrease in REM latency, an increased number of spontaneous arousals and an advancement of the circadian sleep cycle. [80, 88, 89] Besides age, medication use can induce changes in sleep architecture. For instance, benzodiazepines are known to cause a reduction of the amount of slow wave sleep. [17, 90, 91] Thus, individual differences in age and medication use potentially influence the results from the sleep length model.

Another factor that may influence results from the sleep length model is the length of the awakenings. In our previous research, we only included the length of sleep fragments, and assumed that wake fragments of any length disturb sleep. It is possible that awakenings shorter than a certain threshold are misperceived in the same way as short sleep fragments. This possibility is confirmed by the finding that healthy people often underestimate their number of awakenings. [24, 92] Furthermore, in a preliminary study using actigraphy, the average length of wakefulness necessary for morning recall was approximately 4.5 minutes. [85] Taking the length of both sleep and wake fragments into account when modelling sleep onset misperception could increase our understanding of its underlying mechanisms.

Here, we aimed to validate the previously proposed model of the influence of sleep bout lengths on the perception of sleep onset in a large independent dataset containing patients with insomnia as well as healthy controls. We also tested the sleep length model in subgroups of insomnia patients, with respect to different age, gender and medication use. Additionally, to increase our understanding of the factors mediating the perception of sleep, we developed and tested extended models which include parameters reflecting the length of wake fragments.

## 3.3 Methods

### 3.3.1 Design

We validated the previously constructed sleep length model of the influence of uninterrupted sleep bout lengths on sleep onset misperception. We analyzed a retrospective dataset of polysomnography (PSG) recordings from 139 insomnia patients and 92 healthy controls from Sleep Medicine Center Kempenhaeghe Heeze, the Netherlands. The applicable protocol (20190523.3) was approved by the medical ethics committee of Sleep Medicine Center Kempenhaeghe. The data of the healthy controls was collected as part of the Healthbed study, of which the protocol (W17.128) was approved by the medical ethics committee of Maxima Medical Center, Veldhoven, the Netherlands.

### 3.3.2 Insomnia Patients

All PSGs of insomnia patients were recorded as part of usual clinical care between 2013 and 2017. The first PSG of a participant was selected when more than one recording was available. We included patients with a clinical diagnosis of “psychophysiological insomnia” or “paradoxical insomnia” according to ICSD-2 criteria [17], grouping them together in order to include a broad range of sleep onset misperception. Additional inclusion criteria for the study were: 1) age above 16, 2) complete PSG recording of at least one night available and 3) a complete subjective sleep diary of the PSG night available. Exclusion criteria were: 1) major medical comorbidities potentially influencing the PSG recording (as determined by an experienced somnologist) and 2) major sleep-related comorbidities other than insomnia that could fully explain the sleep complaints of the patient. For each participant, presence of psychiatric co-morbidities, and sleep comorbidity (mainly mild OSA and restless legs syndrome) were coded. Additionally, sleep influencing medication used was recorded and coded into four categories: benzodiazepine and z-hypnotics, sedating antidepressants, neuroleptics and melatonin or gabapentin. Medication from these four categories is further referred to as ‘sleep medication’. Other medication was not coded.

### 3.3.3 Healthy Controls

PSGs of healthy controls were recorded as part of the Healthbed study, which aimed to obtain sleep recordings in healthy people to develop new technologies for sleep assessment. Inclusion criteria were: 1) age between 18 and 65 and 2)

the ability to read and speak Dutch. Exclusion criteria were: 1) any diagnosed sleep disorders 2) a Pittsburgh Sleep Quality Index [64]  $\geq 6$  or Insomnia Severity Index [93]  $> 7$ , 3) indication of depression or anxiety disorder measured with the Hospital Anxiety and Depression Scale [94] (score  $> 8$ ) 4) pregnancy, shift work, use of any medication except for birth control medicine, and 5) presence of clinically relevant neurologic or psychiatric disorders or other somatic disorder that could influence sleep.

### 3.3.4 Assessments

Polysomnography - A clinical video-polysomnography was performed according to the AASM recommendations. Visual sleep staging was performed according to AASM criteria [40] by experienced and certified sleep technicians from Sleep Medicine Center Kempenhaeghe. Insomnia recordings were scored by various technicians (including BH) as part of usual clinical care. Healthy controls were scored by one technician (BH). In a previous institutional sleep scoring reliability check, inter-scorer reliability of BH compared to other technicians was assessed as 85.6% on average (range 83-88%). There were no systematic differences between recordings scored by different technicians for SOL, WASO or number of awakenings. Additionally, there were no systematic differences between recordings scored by BH and other technicians.

Subjective sleep – Subjective sleep was assessed on the morning after the PSG measurements by asking the participants to indicate time awake in bed, lights off time, time asleep, time awake and time outside of bed using a graphical sleep diary with a time resolution of 15 minutes.

### 3.3.5 Sleep Length Model

#### General

The goal of the sleep length model was to estimate perceived sleep onset based on sleep architecture from the hypnogram. In the model, it was assumed that sleep bouts with insufficient length at sleep onset are perceived as wake. [87] Therefore, sleep onset was defined as the start of the first sleep fragment longer than  $L_s$  minutes, where sleep length  $L_s$  was the independent parameter of the model, varying from 0.5 to 60 minutes, with an increase of 0.5 minutes. Any wake fragment of at least one 30s epoch was considered as an interruption of sleep. This procedure is illustrated in Figure 2.2. We compared the sleep onset calculated from the model to the sleep onset perceived by the participants

and calculated the root Mean Square Error (RMSE), where the error was the difference between the two values of sleep onset. We then selected the parameter  $L_s$  resulting in the smallest RMSE. RMSE could be regarded as an indicator of model performance, where a lower value indicates better model performance. Occasionally participants reported a subjective total sleep time of zero minutes, resulting in an unavailable subjective SOL. In these cases, the subjective SOL was set to the total time spent in bed according to the lights off time of the sleep recording. This methodological choice may influence the results of the model.

### Calculating Individual Model Outcomes

Since individuals with more sleep onset misperception have the highest RMSE, pooling all individuals together leads to obtaining parameter estimates that are driven by data from individuals with large sleep misperception. Therefore, as an alternative, we applied the sleep length model on each individual participant, calculating an individual estimated sleep onset for each model parameter  $L_s$ . Subsequently, we selected the individual  $L_s$  parameter resulting in the smallest absolute difference between estimated and perceived sleep onset for the individual participant, and aggregated the differences on the group level. Often, multiple values of  $L_s$  resulted in an optimal model performance for an individual, since typically not all lengths of sleep fragments are available at sleep onset. Therefore, for each participant the average of all  $L_s$  parameters with the smallest error was calculated.

### Analyzing Subgroups of Insomnia

First, the sleep length model was applied to insomnia patients and healthy controls separately. Subsequently, the model was applied to several subgroups of insomnia patients separately. We created various subgroups by dichotomizing the insomnia cohort with respect to sex, age, medication use or not, indicating subjective sleep on the sleep diary or not and amount of misperceived sleep at sleep onset. With respect to age, the dataset was divided into participants younger than 50 and participants of 50 years or older. This cutoff was chosen because architectural sleep changes are already present at middle age. [79] The amount of misperceived sleep at sleep onset was defined as the difference between the subjective sleep onset and the objective sleep onset from the PSG. The dataset was divided into participants with more than 30 minutes of misperceived sleep and participants no more than 30 minutes of misperceived sleep. Healthy controls were not divided into subgroups.

### Assessing Model Performance

Model performance was assessed by leave-one-out cross-validation to avoid over-fitting. This was done separately for the insomnia group and the healthy controls. For each participant, the model was applied to the other N-1 participants, and individual model parameters were calculated as described in the section 'Calculating Individual Model Outcomes'. Then, the median of these individual Ls parameters was used to estimate subjective SOL for the participant that was left out. Subsequently, the error committed on such individual was calculated as the difference between estimated subjective SOL and actual subjective SOL.

### Inclusion of wake parameter

The combined influence of the lengths of sleep and wake fragments on the perception of the sleep onset was assessed for all insomnia patients using two different methods. The first method was to add an independent parameter  $L_w$  to the sleep length model. This wake parameter  $L_w$  consists of the length of wake fragments at sleep onset in minutes, with  $L_w$  varying from 0.5 to 5 minutes. We assumed that awakenings shorter than  $L_w$  minutes are too short to be perceived as a disturbance of sleep and, therefore, they were not taken into account in the perception of the length of the sleep fragments. The second method was to introduce an alternative model, assuming that, instead of a minimum sleep length, a minimum percentage of sleep within a certain window is required to perceive sleep onset. The independent variable of the model was called windowed Sleep Efficiency (SEwin). Both combined sleep/wake models are explained in more detail in the supplemental section.

### Statistical Analysis

Unless stated otherwise, demographic data are presented as mean / *pm* SD (min – max) or n (%). Sleep length parameters Ls were reported using median and Inter Quartile Ranges because of non-normality of the data. Sleep length parameters were compared between insomnia patients and healthy controls and between dichotomized insomnia subgroups, using a Mann Whitney U test. Statistical analyses were done using R software. [95] A p-value below 0.05 was set to implicate statistical significance.

## 3.4 Results

### 3.4.1 Characteristics of Participants

Demographic characteristics of the included healthy subjects and insomnia patients are listed in Table 3.1, together with overall subjective and objective sleep characteristics. In total, 86 insomnia patients had a diagnosis of psychophysiological insomnia and 53 patients had a diagnosis of insomnia with sleep state misperception. All patients were grouped together as one insomnia group. Table 3.2 lists the characteristics of the insomnia patients regarding age, medication use and sleep-related and psychiatric co-morbidities. Other co-morbidities, for example cardiovascular, were not labeled. In total, 50 insomnia patients (35.9%) used medication within one of the four predefined medication categories. Of these, 11 participants used more than one type of sleep medication. A large range of SOL misperception was found in the insomnia group: the differences between subjective and objective SOL was median 37 IQR 120 minutes (-82 - 478). In total, 12 people with insomnia reported no subjective sleep at all. However, their objective SOL had a median 33.7 and an IQR of 26.3 (4 - 118) minutes and their objective TST was  $324.7 \pm 125.6$  minutes (104 - 533). For the healthy controls, the difference between subjective and objective SOL had a median of 10.5 and an IQR of 31 minutes (-67 - 209). Among the healthy controls, 18 participants overestimated their SOL by more than 30 minutes, and eight participants overestimated their SOL by more than 60 minutes.

### 3.4.2 Modelling perception of Sleep Onset

#### Insomnia versus Healthy Controls

Figure 3.1 shows the RMSEs corresponding to various values of  $L_s$ . For the insomnia patients, the best model performance i.e. the lowest RMSE was obtained for  $L_s=38$  minutes (Figure 3.1a). The RMSEs between  $L_s=33$  and  $L_s=38$  were very similar. For the healthy controls, the minimum RMSE was at  $L_s=21$ , but RMSEs were very comparable between  $L_s=0.5$  and  $L_s=21$  (Figure 3.1b). When the optimal parameters were calculated for each individual participant and then averaged on the group level, a significant difference between insomnia patients and healthy controls was found (Figure 3.1c); insomnia median 34.0, IQR 23.1 minutes; healthy controls median 21.8, IQR 35.3 minutes. Mann Whitney  $U=8234.5$ ,  $p<0.001$ ). To assess whether the difference was primarily caused by the subgroup not reporting any subjective sleep in their diary, we



**Table 3.1:** General characteristics of subjective and objective sleep.

	Healthy Participants	Insomnia Patients
N	92	139
Age (years)	36.0 ± 13.7	46.7 ± 13.7
Males (%)	38 (35 M, 57 V)	32 (45 M, 93 V)
Objective SOL (min)	Median 7 IQR 9 (0 - 67)	Median 15 IQR 25 (1 - 149)
Subjective SOL (min)	Median 17 IQR 36 (0 - 209)	Median 65 IQR 123 (0 - 480, i.e. no sleep)
Objective TST (min)	Median 438 IQR 59 (229 - 511)	Median 393 ± IQR 76 (376 - 511)
Subjective TST (min)	Median 420 IQR 60 (180 - 522)	Median 240 IQR 165 (0 - 465)

**Table 3.2:** Medication use and comorbidity in insomnia patients.

Medication	# (%)	Co-morbidities	# (%)
Hypnotics	27 (19.4)	Depression	21 (15.1)
Antidepressants	14 (10.0)	Anxiety	13 (9.3)
Melatonin or gabapentin	10 (7.2)	ADHD	7 (5.0)
Neuroleptics	10 (7.2)	Other psychiatric diagnosis	16 (11.5)
		Increased PLM index	11 (7.9)
		Mild OSA	4 (2.9)

excluded this group from the analysis, and still found a significant difference (insomnia sub selection 31.0 IQR 22.5 minutes, healthy controls median 21.8 IQR 35.3 minutes, Mann Whitney  $U=7138.5$ ,  $p=0.008$ ).

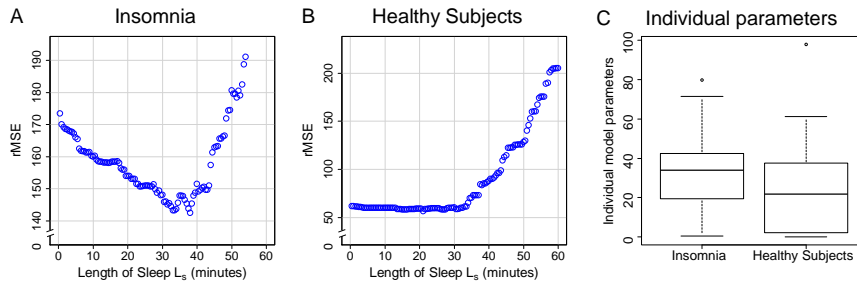


Figure 3.1: Model outcomes for all participants. A) Insomnia patients ( $n=139$ ). The optimum of the model is at  $L_s=38$  minutes. B) Healthy controls ( $n=92$ ). The optimum of the model is at  $L_s=21$  minutes, but the improvement of the RMSE compared to  $L_s=0.5$  minutes is very small. C) Individual parameters per group.

### Model Performance

When using leave-one-out cross-validation to assess the performance of the model, the error of the insomnia group had a median of 11.5 and an IQR of 77 minutes. In contrast, the difference between subjective and objective SOL using  $L_s=0.5$ , i.e. according to AASM criteria, had a median of 37 and an IQR of 120 minutes, as reported before. The improvement of the error was statistically significant (Mann Whitney  $U=12704$ ,  $p<0.001$ ). In the healthy group, the error had a median of -2 and an IQR of 32. Figure 3.2 shows histograms of individual differences between subjective SOL and objective SOL according to AASM criteria for the insomnia group and healthy controls, and histograms of individual errors resulting from the cross-validation. This figure shows that for insomnia patients, after applying the model, the errors were centered around zero. However, still a large variability between individuals is visible. In the healthy controls, applying the model did not result in a large improvement.

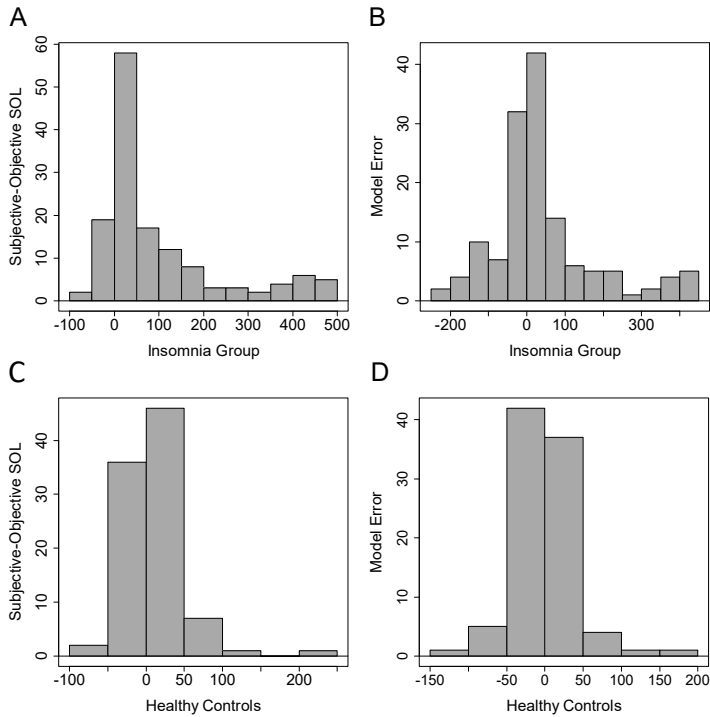


Figure 3.2: Model performance. A) Difference between individual subjective Sleep Onset Latencies (SOLs) and objective SOLs according to AASM criteria in the insomnia group. Clearly, most participants with insomnia overestimate their sleep onset compared to the objective SOL that was obtained using AASM criteria. B) Error between perceived SOL and estimated SOL, resulting from leave-one-out cross-validation in the insomnia group. The errors are now centered around zero. However, still a large variability between individuals is visible. C) Difference between individual subjective Sleep Onset Latencies (SOLs) and objective SOLs according to AASM criteria in the healthy controls. Here, the error is centered around zero, and the variability is lower than in the insomnia group. D) Error between perceived SOL and estimated SOL, resulting from leave-one-out cross-validation in the healthy controls. Applying the model to healthy controls did not greatly improve the results.

### Insomnia Subgroups

We calculated individual model parameters for different subgroups of insomnia patients, dichotomized with respect to sex, age ( $<$  or  $\geq$  50 years) and use of

sleep medication. No differences were found between any of the groups (Table 3.3).

Figures 3.3a) and 3.3b) show model outcomes for participants reporting subjective sleep in their sleep diary and participants reporting no subjective sleep at all. Clearly, the model results for participants reporting no sleep were very different from the results for the other subgroups. The optimum was shifted maximally to the right, which could be expected since these participants did not perceive any of their sleep fragments. When only applying the model to participants reporting subjective sleep (Figure 3.3a), the optimum  $L_s$  shifted to the left at approximately 23 minutes. Additionally, as expected, the baseline sleep onset misperception at group level decreased and the difference between baseline sleep onset misperception and estimated sleep onset misperception became smaller. As expected, a significant difference was found between average individual sleep parameters of participants reporting no subjective sleep and participants reporting subjective sleep (Table 3.3). It should be noted that participants reporting no subjective sleep did show an increased sleep fragmentation and lighter sleep compared to the remaining participants, indicated by increased WASO (no subjective sleep  $140.3 \pm 86.9$  minutes vs. subjective sleep  $80.3 \pm 53.2$  minutes;  $p=0.037$ ) and a higher percentage of NREM1 (no subjective sleep group  $16.4 \pm 7.5$  % vs. subjective sleep group  $11.4 \pm 5.7$  %;  $p=0.039$ ).

Figures 3.3c) and 3.3d) show model outcomes for participants with no more than 30 minutes of sleep onset misperception and participants with more than 30 minutes of sleep onset misperception. Sleep onset misperception was defined as the difference between subjective and objective SOL. The optimum of the group with less misperception was found at  $L_s=12.5$  minutes and the shape of the graph was very similar to the graph of the healthy controls in Figure 3.1b). The optimum for the group with more misperception was found at  $L_s=46$  minutes. Average individual parameters for the two groups were significantly different (Table 3.3). Histograms of individual optimal model parameters are shown in Figure 3.4 for participants with no more than 30 minutes of sleep onset misperception, participants with more than 30 minutes of sleep misperception and participants reporting no subjective sleep.

### **Adding Wake Length Parameter to the Model**

In the first combined sleep/wake lengths model, only  $L_w=1$  minute resulted in a slightly better performance of the model compared to  $L_w=0.5$ , which is equal to the initial model described in section 1.1 ( $L_w=1$ ,  $L_s=38$ ,  $RMSE=139.8$  vs.  $L_w=0.5$ ,  $L_s=45$ ,  $RMSE=142.4$ ). Other  $L_w$  parameters did not improve the

**Table 3.3:** Averaged individual model outcomes for different insomnia subgroups.

Group	Number of participants	Median parameter Ls (min)	Mann Whitney U
<b>Sex</b>			
Male	45	34.0 IQR 23.9	
Female	93	33.9 IQR 23.8	U=2263.5, p=0.505
<b>Age</b>			
< 50 years	76	34.4 IQR 23.7	
<= 50 years	63	31.0 IQR 23.1	U=2629, p=0.321
<b>Use of sleep medication</b>			
No	89	33.5 IQR 24.4	
Yes	50	33.8 IQR 22.3	U=2294.5, p=0.764
<b>Subjective TST</b>			
> 0 min	89	31.0 IQR 22.5	
= 0 min	50	67.1 IQR 10.1	U=1480.5, p<0.001
<b>Misperceived SOL</b>			
< 30.5 min	89	20.3 IQR 29.8	
> 30 min	50	39.8 IQR 26.3	U=984.5, p<0.001

performance of the model.

In the second sleep/wake model, assuming that sleep onset is perceived the first moment a threshold percentage of sleep is reached, the lowest RMSE was obtained for a SEwin of 98% and a window of 60 minutes. Again, there was an improvement, but this improvement was small compared to the initial model (RMSE SEwin model 141.8 vs. sleep length model 142.4). The results of both sleep/wake models are further discussed in the supplemental materials. On the group level, 67% of the wake fragments had a duration of one minute or shorter. Moreover, only approximately 10% of the awakenings had a duration longer than 5 minutes.

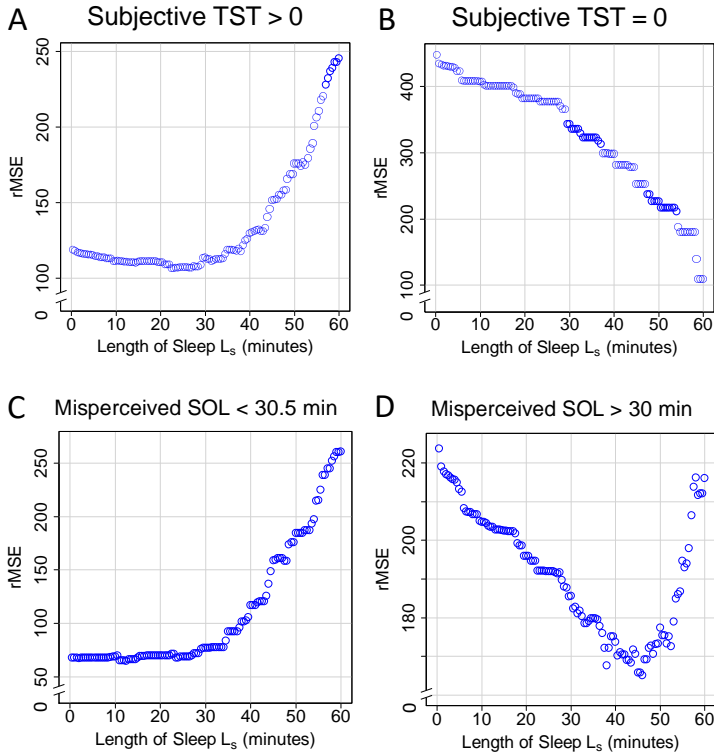


Figure 3.3: Model outcomes for insomnia subgroups with different characteristics of sleep onset misperception. A) Participants with a subjective Total Sleep Time (TST) above zero ( $n=127$ ). B) Participants with a subjective Total Sleep Time of zero, who did not indicate subjective sleep on their sleep diary ( $n=12$ ). C) Participants with a sleep onset misperception (subjective – objective SOL) of 30 minutes or less ( $n=61$ ). D) Participants with a sleep onset misperception of more than 30 minutes ( $n=78$ ). Please note that the y-axis differs across figures.

## 3.5 Discussion

In this study we aimed to increase our understanding of the underlying mechanisms of sleep state misperception by quantifying the influence of objectively measured sleep fragmentation on sleep onset perception. We validated a pre-

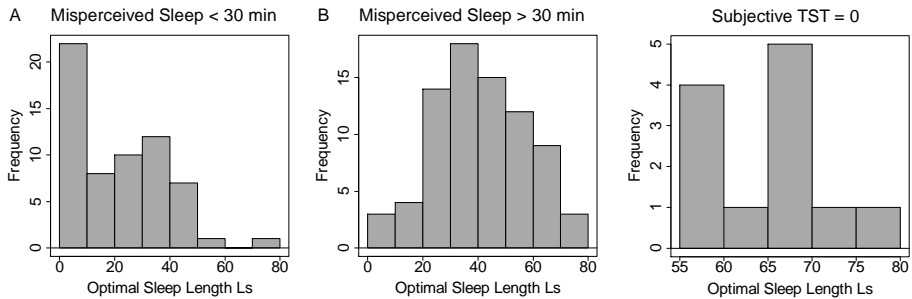


Figure 3.4: Histogram of individual model outcomes for insomnia subgroups of amount of sleep onset misperception. A) Participants with less than or equal to 30 minutes of sleep onset misperception ( $n=61$ ). B) Participants with more than 30 minutes of sleep misperception ( $n=78$ ). C) Participants reporting no subjective sleep ( $n=12$ ). This latter group is overlapping with the participants with more than 30 minutes of sleep onset misperception in B.

viously proposed model of the influence of the length of uninterrupted sleep fragments on the perception of sleep onset [87], here referred to as the sleep length model, in a large independent dataset including insomnia patients as well as healthy people. Moreover, we extended the model to also include the influence of the length of wake fragments.

Application of the sleep length model to insomnia patients and healthy controls confirmed earlier findings that the perception of sleep onset is influenced by the length of uninterrupted sleep fragments [35,57,59], and strengthened our previous hypothesis that insomnia patients require longer uninterrupted sleep fragments to adequately perceive sleep onset compared to healthy controls. [87] Patients with insomnia required a median of 34 minutes of undisturbed sleep to adequately perceive their sleep onset. Importantly, this number is approximately similar to the average time of 30 minutes that we found in the initial small study using a separate dataset. [87] Results on model outcomes show that applying the model to the insomnia group reduced the median error in the prediction of subjective SOL, compared to only using objective SOL according to the AASM criteria. For the healthy controls, there was no large reduction of the median error. After applying the model, still a large variability between individuals was present, particularly in the insomnia group. This was as expected, since

sleep misperception is most likely influenced by multiple different factors. [26] Additionally, from early research it was shown that explaining the subjective experience of sleep using objective parameters from the PSG is difficult. For example, Bianchi et al. tested three different hypothesis about the perception of sleep: N1 is perceived as wake; sleep bouts under 10 minutes are perceived as wake; or N1 and N2 are perceived in a weighted fashion. [78] None of these hypotheses resulted in a match between objective and subjective sleep duration. [78] In another study, it was found that parameters obtained from polysomnography, such as sleep stage percentages and sleep transitions, did only explain very little of the variance of subjective ratings of sleep quality. [25] In that light, the fact that misperception of the SOL could partly be explained by sleep fragmentation in our study seems quite promising.

We showed that the sleep length model is broadly applicable to insomnia patients with different characteristics, considering that there was no difference in subgroups of the insomnia group regarding age, sex and sleep medication used. Although no differences were found for age, sex and sleep medication, model outcomes did differ based on the subjective perception of sleep. In general, participants with more sleep onset misperception required longer uninterrupted sleep fragments to perceive sleep onset. In agreement with this, we observed that participants with less than 30 minutes of sleep onset misperception had model outcomes visually similar to healthy controls. This leads to the conclusion that the actual distinction should be made between sleep onset misperceivers and people with a normal perception of sleep, instead of between insomnia patients and healthy people.

A rather extreme subgroup of insomnia patients overestimating their SOL was formed by 12 participants reporting no subjective sleep at all, i.e., they did not perceive any of their sleep fragments. Although these participants constitute less than 10% of our population, they largely influenced the RMSE of the model on the group level due to the large difference between objective and subjective SOL. However, when these participants were excluded from the model calculations, still a significant difference in model parameters was found between insomnia patients and healthy controls. Besides largely influencing model results, people reporting no subjective sleep are challenging to model because subjective SOL is required as an input. However, rather than leaving them out of the analysis and reducing the applicability of the model, the subjective SOL was set to the time spent in bed. Based on the reasoning applied in the model, one could hypothesize that these participants have a whole night of fragmented sleep with only sleep fragments shorter than approximately 34 minutes, which was the median threshold for perceiving sleep onset in insomnia patients. Indeed, an



increased sleep fragmentation was found in this subgroup, but in general still sleep fragments longer than 34 minutes were present.

We explored two alternative, extended models reflecting the combined influence of the lengths of both sleep and wake fragments. Both resulted only in marginal improvements of model performance. From these results we can conclude that short and long awakenings influence sleep misperception to the same extent. In other words, the length of the sleep fragments seems to have a larger influence on the perception of sleep onset than the length of the wake fragments. Results from the second extended model, in which we assumed that a minimum windowed sleep efficiency was required to perceive sleep onset, were not considered an improvement, since most wake fragments were very short. Similar results were found by Dijk et al., who studied the regulation of frequency and duration of awakenings in older and younger healthy people. [96] They found that elderly people (>63 years old) had an increased frequency of awakenings compared to younger people (<31 years old), but the distribution of wake lengths was similar across the two groups. [96] Approximately 50% of the awakenings had a length of 0.5 minutes and only 5-10% of the awakenings was longer than 4 minutes. [96] Since this relatively infrequent occurrence of long wake fragments heavily influenced the model results and does not seem unique to our dataset, we expect that modelling the influence of wake lengths on sleep onset misperception in general will not provide better results, even if other assumptions were used or other groups of participants were studied.

This study has several limitations. First, due to the small sample sizes of the medication subgroups, it was not possible to run separate analyses for specific medication types, even though different types of medication can influence sleep architecture in different ways. [17] Furthermore, we did not have full specific information about the frequency and timing of medication intake. Second, calculating optimum parameters for individual participants presents a large uncertainty due to the limited number of sleep fragments that were available for our calculations. Nevertheless, as shown before, this approach has several advantages over immediately calculating the RMSE on the group level, such as reducing overestimation of the sleep length parameter caused by individuals with considerably large sleep misperception. Additionally, it provides the possibility to easily compare groups by using statistical analysis. To make the calculation for individuals more accurate, it might be fruitful to consider either multiple moments of falling asleep or multiple nights of sleep measurements for each individual participant. Multiple nights per individual are difficult to obtain from retrospective clinical datasets, and prospective studies are required for this purpose. In our case, repeated PSG recordings were done in only a very

small percentage of participants, and those were all recorded after a treatment intervention such as CBT-I. We did not include these recordings, because of the possibility that the interventions altered the individual's perception of sleep onset.

In future studies, calculating individual model parameters to quantify the influence of sleep fragmentation on sleep onset misperception of individuals, for example using multiple nights of sleep recordings, may yield valuable opportunities. We propose to name the optimum sleep length parameter for an individual the Sleep Fragment Perception Index (SFPI). For example, the SFPI could provide an opportunity to more precisely assess the part of sleep onset misperception not related to sleep fragmentation, by identifying whether model outcomes are dependent on factors other than the amount of sleep onset misperception. These factors could for example include time estimation, pre sleep arousal and polysomnographic characteristics other than sleep fragmentation. Another possibility could be to apply the model to assess differences between model parameters before and after treatment.

To conclude, we modelled sleep onset misperception in a large set of insomnia patients and healthy controls. We showed a robust difference between groups, with a median of 34 minutes of uninterrupted sleep required to perceive sleep onset in insomnia patients versus the 22 minutes required by healthy controls. We also show that results within the insomnia population do not depend on age, sex and sleep medication use. Additionally, we showed that our initial sleep lengths model was already reasonably complete in terms of describing the influence of sleep fragmentation on sleep onset perception, since the length of the awakenings was of limited importance compared to the length of the sleep fragments. These results confirm the existing hypothesis that objectively measurable sleep disturbances can influence the perception of sleep. [34, 48, 56, 97] Thus, we showed that, while the amount of objectively scored sleep is not always indicative of people's perception, there might be additional value in assessing the objectively measurable fragmentation of the sleep, as quantified by the Sleep Fragment Perception Index. These findings may aid in viewing sleep misperception as an actual problem of impaired sleep quality, rather than a mere erroneous perception of wakefulness.

## 3.6 Supplemental section

### 3.6.1 Combined sleep/wake lengths model

The combined influence of the length of sleep and wake fragments on the perception of the sleep onset was assessed for all insomnia patients, in two different ways. First, we added an independent parameter  $L_w$  to the sleep length model. This wake parameter  $L_w$  consists of the length of wake fragments at sleep onset in minutes, with  $L_w$  varying from 0.5 to 5 minutes (Figure 3.5). The upper boundary was set to 5 minutes because we did not expect to find many awakenings longer than 5 minutes. We assumed that awakenings shorter than  $L_w$  minutes are too short to be perceived and, therefore, are not taken into account in the perception of the length of the sleep fragments. This means that, if a wake fragment shorter than  $L_w$  minutes is found, its neighboring sleep fragments are merged together to one long sleep fragment, as illustrated in Figure 3.5. Any wake fragments longer than  $L_w$  minutes were processed as usual in the next steps of the model. The sleep length model with  $L_s$  as only independent parameter corresponds to the combined sleep/wake model with  $L_w=0.5$ , since all awakenings have a duration of at least 30 seconds.

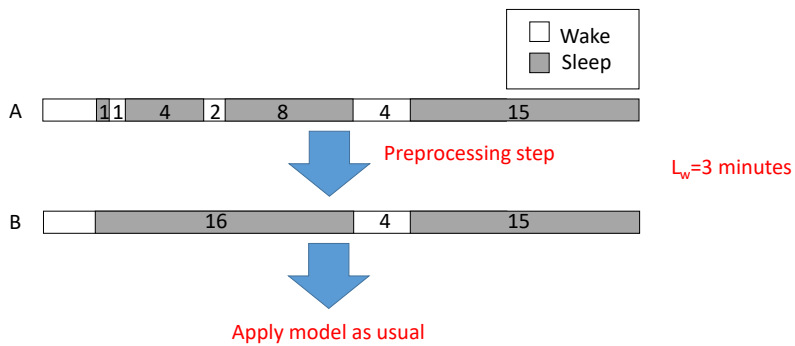


Figure 3.5: Example of adding wake length parameter  $L_w$  to the existing model of sleep onset misperception. In this case, we assume that awakenings shorter than 3 minutes are too short to be perceived. Thus, all wake fragments shorter than 3 minutes are transformed to sleep fragments, resulting in the occurrence of one long sleep fragment of 16 minutes.

Figure 3.6a shows model outcomes for different lengths of wake fragments  $L_w$  for all insomnia patients together. Only  $L_w=1$  minute resulted in a slightly better performance of the model compared to  $L_w=0.5$ , which is equivalent to not accounting for  $L_w$  ( $L_w=1$ ,  $L_s=38$ ,  $RMSE=139.8$  vs.  $L_w=0.5$ ,  $L_s=45$ ,  $RMSE=142.4$ ). Other  $L_w$  parameters did not improve the performance of the model.

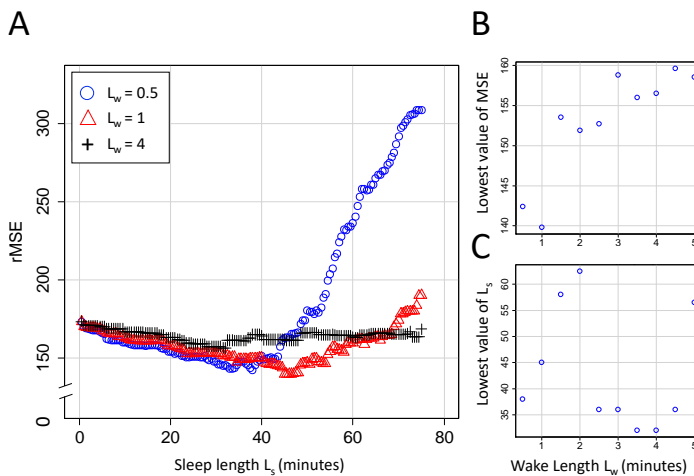


Figure 3.6: Model outcomes of combined sleep/wake model for different wake length parameters  $L_w$ . a) Model outcomes for  $L_w=0.5$ ,  $L_w=1$  and  $L_w=4$ .  $L_w=0.5$  minutes is equal to the sleep length model described in section 3.3.5., since by default no wake fragments shorter than 30 seconds are present in the hypnogram.  $L_w=1$  minute shows a slightly better performance than  $L_w=0.5$ . b) Minimum RMSE values for all  $L_w$  parameters from 0.5 to 5 minutes. Overall,  $L_w=1$  has the lowest RMSE. c) Minimum values of  $L_s$  for each  $L_w$  parameter. These values initially increase as expected, because uninterrupted sleep lengths become longer as a consequence of ignoring short awakenings. At a certain point, most of the sleep during the night is merged together into one sleep fragment, causing the minimum to shift to the left again.

### 3.6.2 Windowed sleep efficiency model

Additionally, we introduced an alternative model assuming that, instead of a minimum sleep length, a minimum percentage of sleep within a certain window

is required to perceive sleep onset (Figure 3.7). In the model described in the previous paragraph, we only considered the length of a sleep fragment and the length of the immediately following wake fragment, without taking the context of the rest of the night into account. However, including the lengths of the following sleep and wake fragments would result in an increasingly complex model with many parameters. Instead, calculating the influence of the percentage of sleep within a certain window on the perception of sleep allows for a combined assessment of the influence of multiple sleep and wake fragments. The percentage of sleep was calculated within a sliding window. Because this approach is equal to calculating a sleep efficiency within a certain time window, this independent variable was called windowed Sleep Efficiency ( $SE_{win}$ ). The length of the sliding window varied from 20 to 80 minutes and had a step size of one minute. We modelled sleep onset as the start of the first window with a sleep efficiency of more than  $SE_{win}$  % (Figure 3.7). Once again, we calculated the RMSE of the difference between estimated SOL and subjective SOL from the sleep diary. The RMSEs were used to compare the performance of different models.

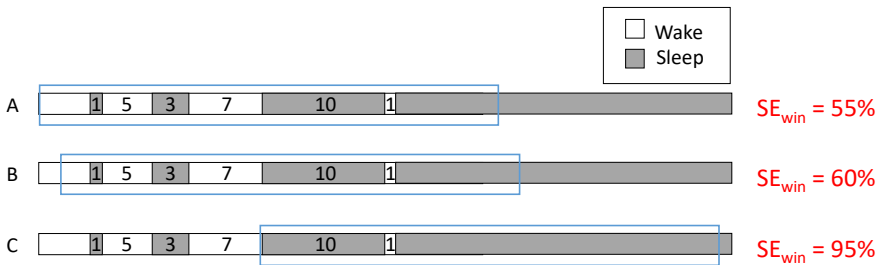


Figure 3.7: Example of alternative model using windowed sleep efficiency ( $SE_{win}$ ) as independent variable.  $SE_{win}$  is calculated each minute within a sliding window. While the sliding window moves to the right, the percentage of sleep increases. Please note that not all steps of 1 minute are shown in this figure.

As shown in Figure 3.8, the lowest RMSE was obtained for a  $SE_{win}$  of 98% and a window of 60 minutes. Again, the improvement was small compared to the initial model (RMSE  $SE_{win}$  model 141.8 vs. sleep length model 142.4).

When looking at individual sleep patterns, we observed that in the majority of the participants the windowed sleep percentage progressed towards almost 100% very quickly due to the absence of long awakenings (Figure 3.9a). We also observed that the awakenings are often regularly distributed over time, causing the  $SE_{win}$  to remain approximately constant over the course of the night. In this case, the optimum  $SE_{win}$  of approximately 100% mainly reflects the maximum windowed sleep efficiency that on average is reached during the night and does not seem to provide additional information about sleep and wake lengths. In participants who severely overestimate their sleep onset latency, the estimated SOL should be as long as possible. Thus, the lowest RMSE is achieved when sleep onset is estimated as late in the night as possible (Figure 3.9b). This again leads to estimating the maximum  $SE_{win}$  possible in these participants.

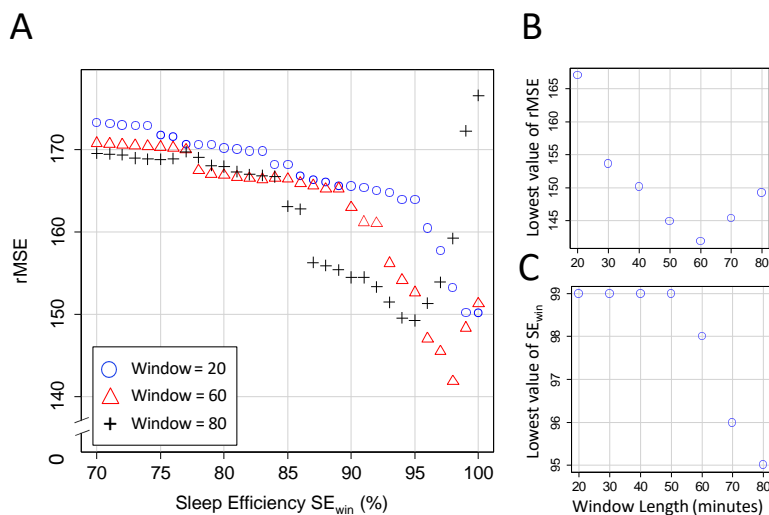


Figure 3.8: Model outcomes for alternative model of sleep onset misperception, using sleep efficiency within a time window as independent variable. We assume that sleep onset is perceived when a threshold sleep efficiency is reached. a) Model outcome for three different windows: 20 minutes, 60 minutes and 80 minutes. The best model outcomes was found for a window of 60 minutes. Within this window a windowed Sleep Efficiency of 98% was required to perceive sleep onset. b) Minimum RMSE values for each window length. c) Minimum values of  $SE_{win}$  for each window length.

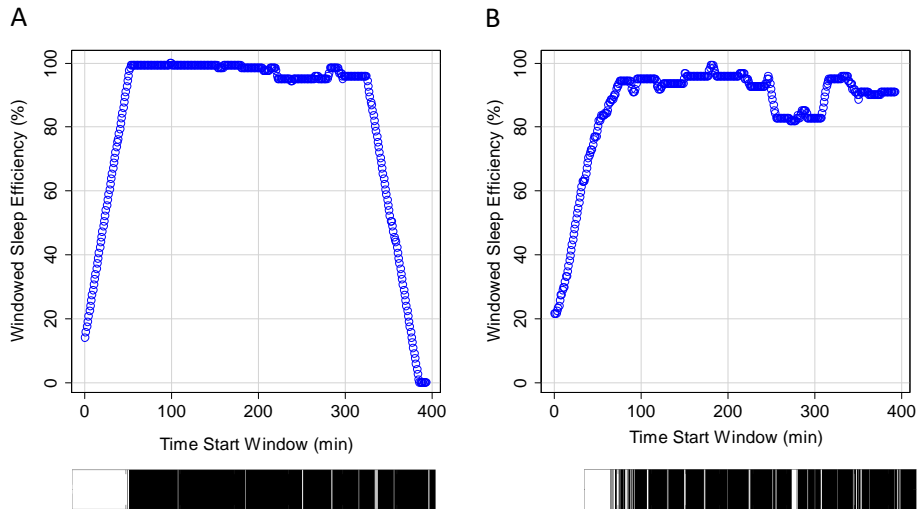


Figure 3.9: Two examples of the progress of windowed Sleep Efficiency in a window of 60 minutes over time during the night. In the bar below an overview of the sleep and wake fragments of the same participants is provided. Sleep is indicated with black and wake is indicated with white. A) Example of a participant with relatively regular short awakenings. The maximum  $SE_{win}$  of approximately 99.2% indicates an average frequency of 1 awakening of 30 seconds per hour, which does not seem to change largely during the course of the night. Since this participant overestimated sleep onset and maximum  $SE_{win}$  for this night coincides with objective sleep onset, the optimum of the model is equal to maximum  $SE_{win}$ . B) A participant who did not indicate any subjective sleep. In this recording, the frequency of awakenings clearly declines after the first part of the night. As a consequence, windowed sleep efficiency reaches its maximum later than in participant A. Since estimated sleep onset is at the end of Time in Bed in this participant, once again the maximum  $SE_{win}$  will be the optimum parameter.

# Chapter 4

## Sleep onset (mis)perception in relation to sleep fragmentation, time estimation and pre-sleep arousal

Published as:

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## 4.1 Abstract

**Study Objective** - To elucidate the contribution of time estimation and pre-sleep arousal to the component of sleep onset misperception not explained by sleep fragmentation.

**Methods** - At-home ambulatory polysomnograms of 31 people with insomnia were recorded. Participants performed a time estimation task and completed the Pre Sleep Arousal Scale (PSAS). Based on previous modelling of the relationship between objectively measured sleep fragmentation and sleep onset misperception, the subjective sleep onset was estimated for each participant as the start of the first uninterrupted sleep bout longer than 30 minutes. Subsequently, the component of misperception not explained by sleep fragmentation was calculated as the residual error between estimated sleep onset and perceived sleep onset. This residual error was correlated with individual time estimation task results and PSAS scores.

**Results** - A negative correlation between time estimation task results and the residual error of the sleep onset model was found, indicating that participants who overestimated a time interval during the day also overestimated their sleep onset latency. No correlation was found between PSAS scores and residual error.

**Conclusions** - Interindividual variations of sleep architecture possibly obscure the correlation of sleep onset misperception with time estimation and pre-sleep arousal, especially in small groups. Therefore, we used a previously proposed model to account for the influence of sleep fragmentation. Results indicate that time estimation is associated with sleep onset misperception. Since sleep onset misperception appears to be a general characteristic of insomnia, understanding the underlying mechanisms is probably important for understanding and treating insomnia.

## 4.2 Introduction

Many people with insomnia overestimate their sleep onset latency (SOL) and underestimate their total sleep time (TST) compared to objective sleep recordings. [6, 98] This is referred to as sleep state misperception. The underlying mechanisms of sleep state misperception remain to be elucidated. [26] For sleep onset misperception, multiple factors have been proposed to play a role, including sleep fragmentation, an altered time estimation ability and pre-sleep arousal. [26]

Time estimation has been hypothesized to be associated with sleep onset misperception. The underlying idea is that people who overestimate time intervals during the day, are thought to also overestimate their time awake in bed. [26, 99, 100] Time estimation in insomnia was tested in three studies, comparing patients with insomnia to healthy controls, using various time estimation paradigms. [99–101] However, in none of these studies a significant difference was found between the time estimation ability of insomnia patients and healthy controls. [99–101] In addition, Rioux et al. reported that they did not find a correlation between time estimation and the severity of insomnia. [100] These findings led Harvey and Tang to conclude in their review that the hypothesis of a time estimation deficit in insomnia has negative evidence of moderate quality. [26] However, not all patients with insomnia misperceive their sleep, and severe complaints of insomnia do not necessarily co-occur with severe sleep state misperception. Therefore, it could be argued that a better approach would be to take into account the actual discrepancy between objective and subjective sleep when assessing the influence of time estimation [100]. In other words, if time estimation is an underlying mechanism of sleep onset misperception, it is plausible that the ability of an individual to estimate time is correlated with that individual's amount of sleep misperception, rather than the seriousness of the insomnia complaints. Thus, in general, not taking the amount of sleep misperception into account as an outcome variable could result in overlooking relevant contributing factors. This probably also applies for factors other than time estimation.

Increased pre-sleep arousal is found in approximately 40% of insomnia patients. [102] It has been hypothesized that worrying before falling asleep can lead to an overestimation of the SOL. [26, 103] This hypothesis was based on the fact that psychological distress can cause a magnification of complaints in somatic and psychiatric disorders. [104] Additionally, results of early research show that people estimate elapsed time as longer when they have to process more information. [105] Indeed, a positive correlation between subjective SOL

and pre-sleep arousal assessed with an interview was found in 34 subjects, of which 13 had complaints of insomnia. [106] In the same study no correlation between pre-sleep arousal and objective SOL was found. [106] Since an increased pre-sleep arousal influenced the perception of the sleep onset without altering objective SOL [106], it seems likely that pre-sleep arousal influences the amount of sleep onset misperception. However, this hypothesis has not been confirmed.

Correlating time estimation and pre-sleep arousal with the amount of sleep state misperception is challenging, because sleep state misperception is most probably a multifactorial process, which is also influenced by objective characteristics of sleep. [26, 45, 86] Recently, we quantitatively modelled the relationship between sleep fragmentation and sleep onset misperception. [87] We identified sleep fragmentation as the most important objectively measurable characteristic influencing sleep onset misperception. [87] This conclusion fits with previous research, where the sense of being asleep prior to awakening from NREM sleep was shown to depend on the length of the preceding uninterrupted sleep fragment. [35, 57, 59] Thus, a certain minimum amount of continuous sleep seems to be required for people to recall falling asleep. It is possible that large interindividual variations of sleep architecture obscure the correlation of the amount of sleep onset misperception with time estimation and pre-sleep arousal. This could especially be important in small groups of participants.

In previous work, we modelled perceived sleep onset as a function of the minimum length that an uninterrupted sleep fragment requires to be perceived as sleep. [87] In the model, it was assumed that sleep fragments at sleep onset are not perceived as sleep if they are interrupted too soon. [87] In a follow up study, we applied this so-called sleep length model in a larger group of 139 people with insomnia with various degrees of sleep state misperception, and 93 healthy controls. [107] We also calculated optimum model parameters for individual participants. For these individual optimal parameter we proposed the name Sleep Fragment Perception Index (SFPI). [107] Comparing SFPIs on the group level showed significant differences between participants with and without sleep onset misperception. [107] Furthermore, the model did not fully predict the amount of sleep onset misperception based on sleep fragmentation only. This supports the notion that sleep misperception is multifactorial.

We hypothesize that the predictive ability of the sleep length model in individual study participants could be applied to identify other contributing factors. For example, if a participant has more sleep onset misperception than could be expected from sleep architecture alone, it is likely that other factors play a role. Thus, a correlation with the prediction error of the model could indicate such factors, including an influence of pre-sleep arousal and time estimation. In this

study, we aim to elucidate the contribution of time estimation and pre-sleep arousal to sleep onset misperception, by specifically assessing the correlation with the component of sleep onset misperception not explained by sleep fragmentation. This approach enables us to take into account interindividual variations of sleep architecture.

## 4.3 Methods

### 4.3.1 Participants

Data for this study were collected as part of a prospective study of sleep architecture in people with insomnia. We analyzed ambulatory PSG recordings of 31 participants with insomnia, who were on the waiting list of the Kempenhaeghe Center for Sleep Medicine to receive cognitive behavioral therapy for insomnia (CBT-I). Subjects were included if a complete sleep diary was available. To make sure that the objective sleep onset was recorded in all participants, PSG recordings were excluded when starting later than the lights off time reported by the participant or when recording started with an epoch scored as sleep. In order to be eligible to participate, subjects had to meet the following criteria: age older than 18, a diagnosis of insomnia according to DSM-IV criteria, and using sleep medication for less than 3 times per week. Exclusion criteria were pregnancy, conditions preventing taking part in neuropsychological tests, patients who lack the functional capacity to provide informed consent and patients who are not able to adhere to the study protocol.

The study was conducted in accordance with the code of ethics on human experimentation established by the World Medical Association's Declaration of Helsinki (1964) and amended in Edinburgh (2000). The study protocol (W17.043) was approved by the medical ethics committee of Maxima Medical Center, Veldhoven, the Netherlands. All subjects provided written informed consent.

### 4.3.2 Study design

The measurements consisted of one night of ambulatory PSG at home. Electrodes were attached between 19:30 and 21:30 in the evening of the PSG night and participants were free to choose their own bedtimes. Participants were asked to not take occasionally-used psychoactive drugs whose primary function is to induce sleep, including over-the-counter-available melatonin, from one week

preceding the sleep measurement night until the night of the measurements. Coffee and alcohol were prohibited on the day preceding the PSG recording. One week before the night of the sleep recording, an additional appointment was scheduled to perform a time estimation task and complete several questionnaires.

### 4.3.3 Measurements

PSG - A six-channel electroencephalogram (C3, C4, F3, F4, O1, O2), electrooculogram and electromyogram were performed, using a Natus Embletta MPR recorder, interfaced with a ST+ Proxy. Additionally, ECG, abdominal and thoracic respiration effort, SpO2 from finger pulse-oximetry and body position and activity were recorded. Visual sleep staging for all recordings was performed according to AASM criteria by an experienced somnotechnologist.

Electronic sleep diary – At the morning after the sleep recording, participants completed an electronic version of the consensus sleep diary [108].

Time estimation task - During the time estimation task, subjects were asked to indicate the end of a 10-minutes waiting period by pressing a key on a laptop. We chose to ask the participants to press a key, which is similar to the study design of Harrow et al. [99], rather than asking participants to estimate the length of a fixed time interval. This approach has the advantage of preventing people's tendency to call rounded numbers. [99] We chose a time interval of ten minutes, because this time interval is probably long enough to resemble the actual situation when lying in bed. Before the start of the test, patients were asked to cover all clocks in the room and to sit back and relax. The time estimation tasks were performed at the participant's home, under supervision of a researcher. Time estimation tasks were not performed on a fixed time during the day. All time estimation tasks were performed between 10:00 in the morning and 19:30 in the evening. The output of the time estimation task was the amount of seconds elapsed before pressing the key. Thus, a number of less than 600 seconds could be interpreted as an overestimation of elapsed time, e.g. the participant experiences an elapsed time of ten minutes, while in reality the elapsed time was shorter.

PSAS – Participants completed the PSAS [109] to indicate arousal prior to falling asleep. A higher score on the PSAS indicates more pre-sleep arousal. Scores for the somatic and cognitive subscales were combined into one total score. This total score was used for further analysis.

ISI – Participants completed the Insomnia Severity Index (ISI) [93] to indicate the severity of their insomnia complaints. The results of the ISI questionnaire were used to verify that all participants had at least subthreshold insomnia,

indicated by an ISI score of at least eight.

#### 4.3.4 Data analysis - sleep length model

In the sleep length model, it was assumed that sleep bouts with insufficient length at sleep onset are perceived as wake. [87] Thus, it was assumed that sleep onset was perceived as the start of the first sleep fragment longer than L minutes. Sleep length parameter L was the independent parameter of the model, i.e., the length a continuous sleep fragment should have in order to be perceived as sleep. Any wake fragment of at least one 30s epoch was considered as an interruption of sleep. This procedure is illustrated in Figure 2.2. In a previous study, we varied parameter L from 0.5 to 60 minutes in a cohort of 139 people with insomnia and 92 healthy controls to test different model assumptions. [107] We found a median optimal parameter L of approximately 30-35 minutes for participants with insomnia, with small differences depending on the exact criteria of the subgroup that was selected. [107] The optimal parameter L was referred to as SFPI. In the current study, we assigned the same reference SFPI of 30 minutes to all participants and used the model to estimate perceived sleep onset for each participant as the start of the first uninterrupted sleep fragment longer than 30 minutes. This is illustrated in Figure 4.1. Subsequently, the residual error between estimated sleep onset and actual perceived sleep onset was calculated. This residual error was referred to as 'sleep onset misperception not explained by sleep fragmentation'.

#### 4.3.5 Statistical analysis

All outcomes were reported as mean  $\pm$  standard deviation (sd) unless stated otherwise. The residual error of the sleep length model was correlated with the results of the time estimation task and the PSAS. Participants tended to round off their subjective SOL to ten or fifteen minutes. In total, 14 participants reported their subjective SOL as a multiplicity of fifteen minutes, and all but one participant reported SOL as a multiplicity of 5 minutes. Therefore, the SOLs from the consensus sleep diary were considered categorical variables. Because these subjective SOLs were used for the calculation of the residual error of the model, all correlation with this variable were assessed using Spearman's correlation test. Spearman's correlation test was also used in case of non-linearity of the other variables.

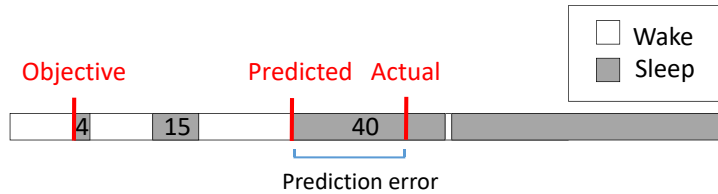


Figure 4.1: Hypothetical example of sleep onset misperception in an individual. We assigned a Sleep Fragment Perception Index (SFPI) of 30 minutes to each individual. From this assumption, the predicted sleep onset is the start of the first uninterrupted sleep fragment longer than 30 minutes. The actual perceived sleep onset is the subjective sleep onset of the participant, as obtained from the consensus sleep diary. The residual error, which can be viewed as the part of sleep onset misperception not explained by sleep fragmentation, is the difference between predicted sleep onset and actual sleep onset, indicated by a blue line. In this individual, after taking into account the presumed influence of sleep fragmentation, the Sleep Onset Latency (SOL) is still overestimated. Therefore, one could hypothesize that either poor time estimation or high pre-sleep arousal plays a role in this situation.

## 4.4 Results

### 4.4.1 Demographics and sleep characteristics

Sleep was recorded in 31 participants (14M, 17F, age  $50.8 \pm 15.1$  (range 18-71)). Participants had an ISI score of  $17.9 \pm 3.5$  (range 9-21). Time estimation task results were available in 29 participants and PSAS scores were available in 27 participants. The objective SOL was  $18.1 \pm 25.3$  (0 - 112) minutes and the subjective SOL from the consensus sleep diary was  $31.4 \pm 35.8$  (5 - 165) minutes. The amount of SOL misperception was  $13.4 \pm 31.4$  (-53 - 145). Five participants underestimated their SOL. The amount of SOL misperception was not correlated with the ISI scores (Pearson  $r = -0.01$ ,  $p = 0.97$ ).

Two participants had a very large subjective SOLs compared to the rest of the group (subjective SOL of 165 and 150 minutes; in both cases  $> \text{mean} + 3 \text{ sd}$ ) and therefore were considered outliers. These participants were males of 50 and 55 years old, who did not have any relevant comorbidities listed. We did not a priori exclude these participants from analysis.

### 4.4.2 Time estimation task

The average score on the time estimation task was  $548 \pm 139$  ([371-935]) seconds. A negative correlation was found between time estimation task results and the residual error of the sleep length model (Spearman  $\rho = -0.50$ ,  $p = 0.007$ ; Figure 4.2a). It should be noted that a time estimation task score lower than 600 seconds indicates an overestimation of elapsed time. For example, if a participant indicated that the ten minutes interval had passed after nine minutes, this indicates an overestimation of the nine-minute time interval with one minute. When assessing the same correlation again but without the two outliers with a very large subjective SOL, still a significant negative correlation was found (Spearman  $\rho = -0.45$ ,  $p = 0.020$ ). Time estimation task results were not correlated to objective SOLs (Spearman  $\rho = 0.20$ ,  $p = 0.32$ ) or to ISI scores (Pearson  $r = -0.16$ ,  $p = 0.43$ ).

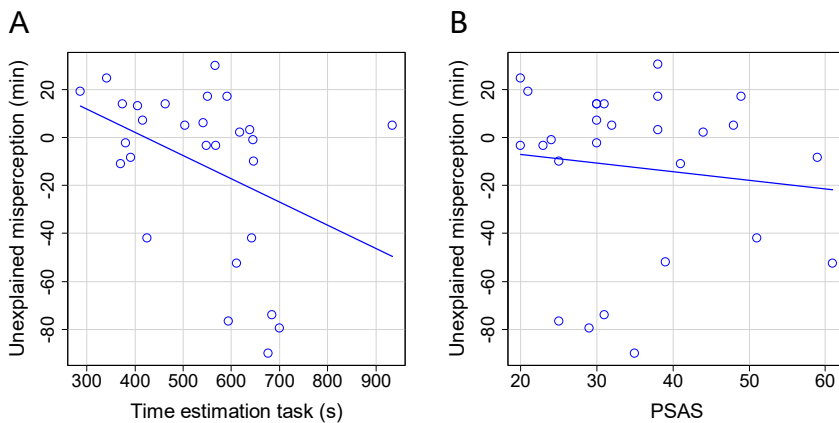


Figure 4.2: Correlations of the residual error from the sleep length model. A) Correlation of residual error with time estimation task results ( $n = 29$ ; Spearman  $\rho = -0.50$ ,  $p = 0.007$ ). B) Correlation of residual error with Pre Sleep Arousal Scale scores ( $n = 27$ ; Spearman  $\rho = -0.13$ ,  $p = 0.53$ ).



### 4.4.3 Pre Sleep Arousal Scale

The average PSAS score was  $20.44 \pm 7.85$  (8-27). No significant correlation was found between PSAS scores and the residual error of the sleep length model (Spearman  $\rho=-0.13$ ,  $p=0.53$ , Figure 4.2b). PSAS was correlated with objective SOL (Spearman  $\rho=0.41$ ,  $p=0.035$ ; Figure 4.3). The PSAS scores were not significantly correlated to the results of the time estimation task (Pearson  $r=0.39$ ,  $p=0.051$ ; Figure 4.4).

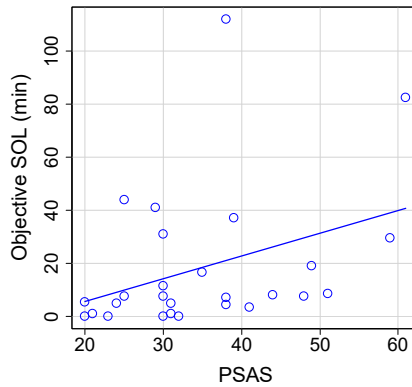


Figure 4.3: Correlation between PSAS and objective SOL ( $n=27$ ; Spearman  $\rho=0.41$ ,  $p=0.035$ ).

## 4.5 Discussion

Our goal was to obtain a clearer view of the association of time estimation and pre-sleep arousal with the amount of sleep onset misperception, while taking interindividual variation of sleep architecture into account. We estimated the perceived SOL of individual participants from the hypnogram, using model parameters obtained from a previously proposed model of the influence of sleep fragmentation on sleep onset misperception. [87] Subsequently, we calculated the residual error between estimated SOL and actually perceived SOL for each participant. This approach allowed to specifically examine the components of sleep onset misperception not explained by sleep fragmentation, i.e., the residual

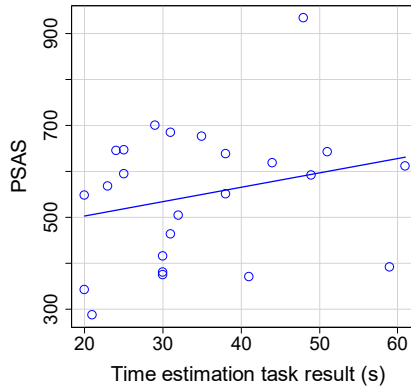


Figure 4.4: Correlation between time estimation task results and PSAS scores ( $n=26$ ; Pearson  $r=0.39$ ,  $p=0.051$ ).

error of the model. We found a correlation between the residual error of the model and the results of a time estimation task. A correlation between the residual error of the model and PSAS scores was not found.

The correlation between time estimation task results and sleep onset misperception had a negative coefficient, as was expected from the design of the task. Importantly, on average the time estimation of our participants was almost 10% too short. As opposed to this, in a similar study design, Harrow et al. found that both people with insomnia and healthy controls were very accurate on the time estimation task. [99] Although group differences were not significant, healthy people showed a tendency to estimate a longer time than insomnia patients. [99] Thus, our insomnia patients scored worse compared to both the insomnia and healthy controls reported from earlier research. This difference might be explained by the severity of the insomnia complaints, since the participants of our study were treatment-seeking people with insomnia who were referred to a tertiary sleep center. As a contrast, in most other time estimation task protocols volunteers with insomnia complaints were recruited from the general population. [99, 101] A question that arises from our results is whether time estimation and sleep architecture independently influence sleep onset misperception, or if time estimation somehow modifies the reaction of the sleep perception of an individual to the presence of short sleep fragments. This question could potentially be answered using more advanced statistical models in a larger dataset.

Although pre-sleep arousal is one of the key features of insomnia, the hypothesis that pre-sleep arousal is specifically involved in sleep onset misperception remains to be confirmed. In our study, the absence of a correlation between PSAS and sleep onset misperception not explained by sleep fragmentation, together with the presence of a correlation of PSAS with objective sleep onset, points towards pre-sleep arousal being more involved in sleep architecture than in the perception of the sleep. This finding is not in line with a previous study, which indicate that PSAS does play a role in subjective but not objective sleep onset. [106] A possible explanation for this difference is that the interview completed by van Egeren et al. is a more precise approximation of current pre-sleep arousal of the participants compared to the PSAS questionnaire, because the interview was performed on the day of the sleep recording. [106] Another intriguing possibility is that an increased level of arousal while falling asleep might contribute to sleep onset misperception by altering the architecture of the sleep at the beginning of the night, instead of altering an individual's sensitivity for the presence of short sleep fragments. This might be an interesting subject for further research.

Both the time estimation task and the PSG recordings were performed at home, giving the participants the opportunity to freely choose their bedtimes and making the data more generalizable to daily circumstances. A disadvantage of our protocol was the lack of standardization of the time of the day and the time of the year in which the time estimation task was done. Because of practical considerations, time estimation tasks were performed between 10:00 in the morning and 19:30 in the evening. Although this design does eliminate circadian effects, it could also potentially cause variation between subjects. However, Harrow et al. did not find differences between the results of the time estimation tasks performed during daytime and nighttime. [99]

In a recent study, we stated that the SFPI can be regarded as a measure of sensitivity of an individual's sleep onset perception to sleep fragmentation. [107] As such, the SFPI could be correlated with time estimation and pre-sleep arousal. However, calculating SFPIs from a single night of PSG poses two practical difficulties. First, typically not all possible lengths of sleep fragments are available at sleep onset during one night. Therefore, SFPIs cannot be calculated precisely and are sometimes rough approximations, which are more useful for comparing groups than for assessing the sleep behavior of individual patients. This problem could be solved by recording multiple nights of PSG for each patients. However, PSG is a costly and obtrusive method. As a second difficulty, because the model is based on the assumption that short sleep fragments are overlooked, and because we defined objective sleep onset as the first epoch scored as sleep, the model does not present an explanation for people who reported falling asleep before

the objective sleep onset occurs. These model assumptions imply that the SFPI is always larger than zero, resulting in an SFPI of 0.5 for all participants who underestimate their SOL. However, a difference between a small underestimation and a large underestimation of SOL might be relevant for the correlation with the time estimation task. As an alternative approach, we estimated the sleep onset for each participant as the start of the first uninterrupted sleep fragment longer than 30 minutes. The prediction error of the model was then used to express the unexplained component of sleep onset misperception. The choice of assigning an SFPI value of 30 minutes to each study participant was made because the median optimum parameter for insomnia patients was approximately 30 minutes in previous research. [87, 107]

The results of this study represent a next step towards a better understanding of the underlying mechanisms of sleep onset misperception. As far as we are aware, it is not clear whether misperception of sleep onset and of TST and WASO have the same underlying mechanisms. Since sleep onset misperception can be seen as a misperception of time awake instead of time asleep, it is possible that different mechanisms play a role. For example, we can speculate that time estimation is more important for sleep onset misperception than for TST misperception, because time estimation tasks are performed during wake. This remains to be further investigated.

From the current results, it appears that sleep onset misperception can be partly explained by a combination of objectively measurable sleep architecture and time estimation ability of the individual. Since all people have a certain degree of sleep fragmentation, which most probably differs between nights, it is plausible that the majority of people has some amount of sleep onset misperception now and then. We found a large range of time estimation abilities within the insomnia group, co-occurring with a range of sleep onset misperception. As such, it seems plausible that sleep onset misperception is a generic characteristic of insomnia. Therefore, identifying mechanisms of sleep onset misperception could be valuable for the understanding of the pathophysiology of insomnia in general. At the same time, we do not rule out the possibility that individuals with a lot of sleep onset misperception may be a subgroup with different etiology. Time estimation and sleep onset misperception were not correlated with ISI scores, indicating that the perceived severity of insomnia probably was influenced by other factors, for example misperception of TST, an objective short sleep duration, or complaints of reduced functioning during the day. It is very well possible that combinations of different psychological and physiological mechanisms result in different subtypes of insomnia, requiring different types of treatment. Thus, increased knowledge about sleep onset misperception may have important conse-

quences for the selection and tailoring of treatment, including the identification of factors that can be specifically targeted by cognitive behavioral therapy in appropriate subgroups.

# Chapter 5

## Assessing sleep-wake survival dynamics in relation to sleep quality in a placebo-controlled pharmacological intervention study with people with insomnia and healthy controls

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## 5.1 Abstract

**Rationale** - Although the experience of impaired sleep is a key feature of insomnia, objectively measurable sleep characteristics reflecting perceived sleep quality remain to be identified. Previous research suggests an important role for sleep fragmentation.

**Study Objective** - To explore potential mechanisms of sleep fragmentation that influence alterations of perceived sleep quality, using a pharmacological sleep intervention.

**Methods** - We analyzed polysomnography (PSG) recordings from a double-blind crossover study with zopiclone 7.5 mg and placebo, in healthy controls and elderly people with complaints of insomnia. We compared parametrizations of individual survival curves of NREM sleep, REM sleep and wake across group and treatment. Subsequently, we used a previously proposed model to estimate the amount of sleep onset latency (SOL) misperception from PSG-defined sleep fragmentation at the beginning of the night. Both self-reported and model-estimated amount of SOL misperception were compared across group and treatment. We also compared the unexplained component of SOL misperception, represented by the model prediction error.

**Results** - In the zopiclone night, the average segment length of NREM sleep was increased, while the average segment length of wake decreased. Self-reported and estimated amount of SOL misperception were lower during the zopiclone night. Prediction error was not altered.

**Conclusions** - Results indicate that impaired subjective sleep quality is associated with decreased NREM stability, together with increased stability of wake. Furthermore, we conclude that zopiclone-induced changes in SOL misperception can be largely attributed by predictable changes of sleep architecture, because model prediction errors were unaltered between treatment conditions. This finding further demonstrates the relation between sleep fragmentation and sleep quality.

## 5.2 Introduction

Despite ongoing research, part of the etiology of insomnia is still unknown. [27] When considering insomnia as a medical problem with insufficient sleep, it seems likely that the sleep complaints could be objectively quantified using gold standard polysomnography (PSG) recordings. However, often standard PSG-derived metrics such as total sleep time (TST), sleep onset latency (SOL) and wake after sleep onset (WASO) do not fully explain the seriousness of the complaints. [23] Specifically, in part of the patients a discrepancy can be found between the amount of sleep reported by the patient and the objectively measured quantity of the sleep. [26] Additionally, experienced sleep quality is often not reflected by standard PSG metrics as well. [37] Therefore, it is assumed that impaired sleep can possibly be reflected by other PSG-derived parameters. Identifying such parameters could be useful to increase our understanding of the mechanisms underlying insomnia. Furthermore, they could potentially be used for identifying clinically meaningful subtypes within the patient population.

One of the objectively measurable sleep characteristics reflecting sleep quality may be impaired sleep continuity as scored in the hypnogram, which we here refer to as sleep fragmentation. [26, 84, 110, 111] Interruptions of sleep at the beginning of the night may influence the perception of the SOL, since the sensation of being asleep prior to awakening from non-rapid eye movement (NREM) sleep was shown to depend on the length of the preceding bout of uninterrupted sleep. [35, 57, 59] In previous research we quantified the relationship between sleep fragmentation at the beginning of the night and sleep onset (mis)perception, and found that the perception of the sleep onset latency indeed seems particularly influenced by the length of uninterrupted sleep fragments. [107] Additionally, the objective and subjective number of awakenings have been shown to be correlated with measures of subjective sleep quality, [112, 113] providing an additional indication that sleep fragmentation may negatively influence sleep. However, it should be noted that the predictive power of objective sleep parameters for subjective sleep quality is generally low. [112]

Assessing the influence of sleep fragmentation on the experience of sleep presents two problems. First, it is likely that perceived quantity and quality of the sleep are influenced by many other factors than sleep structure, possibly including sleep habits, psychological traits [114] and time estimation ability. [101, 115] Therefore, large variability between individuals can be expected. This variability could possibly obscure the relationship between perceived sleep quality and sleep fragmentation. Although currently we do not have possibilities



to quantify and correct for these factors, they probably differ largely between people, and may have a smaller variability over consecutive nights within the same individual. We would therefore ideally study multiple nights measured from the same individual, with induced differences of sleep architecture. Hypnotics are known to alter sleep structure, and can improve the subjective experience of the sleep. [16, 116, 117] Therefore, medication studies can be useful to explore mechanisms of sleep fragmentation potentially influencing sleep quality under controlled circumstances. Secondly, currently there is no single parameter that is best suited for describing sleep fragmentation.

Survival analysis is potentially a very useful alternative for describing aspects of sleep fragmentation which may be important for perceiving a good night of sleep. Traditional parameters used to describe sleep fragmentation as scored in the hypnogram include WASO, number of awakenings and sleep stage percentages, such as NREM1 and NREM3. [118] These parameters are not very specific. As an illustration, Norman et al. showed that a large number of awakenings can be found in two entirely different types of sleep architecture. [119] For example, awakenings regularly distributed over the night would result in sleep fragments of equal lengths, while the same number of clustered awakenings could also result in one very long sleep fragment and multiple short sleep fragments. Such differences can be found using survival analysis. Considering that participants appeared to overlook short sleep fragments in previous research into sleep onset misperception [107], such differences in sleep architecture may be important to take into account. Additionally, low percentages of certain sleep stages can either reflect the presence of many interrupted sleep stage fragments, or a reduced probability to enter that sleep stage. [118] Survival analysis can be used to specifically assess the stability of a certain sleep stage or groups of sleep stages. Using survival analysis, one can analyze the expected duration of time until a certain new event occurs. In the case of sleep, the event can be the end of a sleep or wake fragment. A hazard function can be calculated to evaluate the probability of an ending sleep or wake fragment during any given time point.

In earlier research, Roth et al. showed differences in sleep survival dynamics between healthy people and people with insomnia. [120] This finding indicates that altered sleep survival dynamics may indeed be involved in impaired sleep quality in people with insomnia. However, rapid eye movement (REM) and NREM sleep were not separately modelled in this study, although research indicates that NREM and REM sleep are two different processes with different survival curve dynamics [121] and different functions [122]. Moreover, it might be useful to also study survival dynamics of wake, because earlier research suggests that patients with long WASO belong to a distinct subtype of insomnia.

[21] As a conclusion, further research is required to examine if subjectively impaired sleep co-occurs with changes of sleep and wake survival dynamics during the night, while separately assessing survival dynamics of NREM sleep, REM sleep, and wake.

Co-occurring changes in sleep fragmentation and perceived sleep quality can be very informative, but do not prove that these two phenomena really influence each other. Our earlier described modelling approach for sleep onset misperception can be used to quantify this relationship. This so-called sleep length model was based on the assumption that sleep bouts with a too short length at sleep onset are perceived as wake. [87] Using the model, perceived sleep onset can be estimated as the start of the first sleep fragment longer than  $L$  minutes. Sleep length parameter  $L$  was the independent parameter of the model, i.e., the length a continuous sleep fragment should have in order to be perceived as sleep. This concept is similar to calculating latency until persistent sleep. Applying this model yields a component of sleep onset misperception that can be predicted based on sleep fragmentation at the beginning of the night, and an unexplained component. We can use the model to test if any change in sleep onset (mis)perception as a consequence of taking sleep medication could be related to alterations in sleep fragmentation as predicted by the model.

The aim of this study was to explore potential mechanisms of sleep fragmentation that influence alterations of perceived sleep quality. We analyze data from a previously described placebo-controlled study, using a single dose of zopiclone 7.5 mg as experimental intervention. [63] In the initial paper, the authors reported that the subjective sleep quality was improved during the zopiclone night, and that participants reported longer TST and a shorter SOL. In the current study, we assessed the influence of zopiclone on survival dynamics of NREM sleep, REM sleep and wake over the whole night. This way, we can examine if the improvements of sleep quality described co-occur with alterations of sleep fragmentation. Furthermore, we aim to demonstrate a relation between sleep architecture and perceived sleep quality, using a modelling approach.

## 5.3 Methods

### 5.3.1 Design

Data were collected as part of a placebo controlled cross-over study, comparing residual effects of zopiclone 7.5 mg and placebo on highway driving performance in people with complaints of insomnia and self-defined good sleepers. [63] Study

participants included 16 individuals with insomnia complaints who frequently used hypnotics, 16 individuals with insomnia complaints who did not or infrequently used hypnotics, and 16 age-matched self-defined good sleepers.

### 5.3.2 Participants

Participants were recruited via newspaper advertisements and through a network of local general practitioners in the region of Maastricht, the Netherlands [63], and were subsequently asked to participate in the placebo controlled crossover zopiclone study. Participants had to meet the following inclusion criteria: aged between 50 and 75 years; and good health based on a pre-study physical examination, medical history, vital signs, electrocardiogram, blood biochemistry, hematology, serology, and urinalysis. Exclusion criteria were history of drug or alcohol abuse; presence of a significant medical, neurological, psychiatric disorder, or sleep disorder other than insomnia; chronic use of medication that affects driving performance, except hypnotics; drinking more than 6 cups of coffee per day; drinking more than 21 units of alcohol per week; smoking more than 10 cigarettes per day; and body mass index outside the range of 19 to 30 kg/m<sup>2</sup>.

Additionally, insomnia patients had to meet the following inclusion criteria, based on DSM-IV [8]: (1) presence of subjective complaints of insomnia, defined as difficulties initiating sleep (sleep latency >30 min) and/or maintaining sleep (awakenings >30 min); (2) complaints lasting more than 1 month; (3) clinically significant distress or impairment attributable to the sleep disturbance; (4) insomnia not occurring exclusively during the course of a mental disorder; and (5) insomnia not due to another medical or sleep disorder or to the effect of medication or drug abuse. Insomnia patients were assigned to the “frequent users” group when they used a benzodiazepine, zopiclone, or zolpidem as sleeping medication for at least four nights per week during at least 3 months preceding the study. Patients not using hypnotics or using hypnotics for less than 4 days per week were assigned to the “infrequent users” group.

Volunteers were screened by a telephone interview, questionnaires, and a physical examination to confirm that they were healthy. Sleep complaints were evaluated by a trained psychologist using Dutch versions of the Pittsburgh Sleep Quality Index, [64] the Sleep Wake Experience List, [65] and the Groningen Sleep Quality Scale. [66] In addition, subjects completed a sleep log for 14 days. Major psychopathology was screened using the Symptom Checklist 90 Revised, [67] the Beck Depression Inventory, [68] the State-Trait Anxiety Inventory, [69] and the Multidimensional Fatigue Inventory. [70]

The study was conducted in accordance with the code of ethics on human experimentation established by the World Medical Association's Declaration of Helsinki (1964) and amended in Edinburgh (2000). The protocol was approved by the medical ethics committee of Maastricht University and University Hospital of Maastricht. Participants were explained the aims, methods, and potential hazards of the study and they signed a written informed consent prior to any study-related assessments.

### 5.3.3 Schedule

The study was conducted according to a 3×2 double-blind, placebo controlled cross-over design, with three groups (insomnia frequently using hypnotics, insomnia not or infrequently using hypnotics and self-defined good sleepers) and two treatment conditions. Treatments were single oral doses of zopiclone 7.5 mg and placebo. Treatments were administered in identical looking capsules and ingested immediately before retiring to bed at 23:30 hours. All participants went to bed at the same fixed bedtime. Prior the de measurement nights, participants spent two nights in the same sleep laboratory. Treatment orders (placebo-zopiclone or vice versa) were balanced within groups. Washout periods between treatments lasted at least one week. In order to minimize withdrawal symptoms during the placebo night, patients assigned to the frequent users group were instructed to discontinue their hypnotic intake starting from three nights before each treatment period. Frequent users who expected difficulties during the three hypnotic-free nights were provided escape medication, consisting of zolpidem at a maximum of one dose of 10 mg per night, to be used only in case of intolerable withdrawal effects. Zolpidem 10 mg was selected to limit variability in hypnotic drugs used and because it is known to be free from residual effects when taken at bedtime before 8 h of sleep. [123]

### 5.3.4 Assessments

A four-channel electroencephalogram (C3, C4, F4, O2), electrooculogram and electromyogram were performed as part of the polysomnographic acquisition. The data was recorded with a Vitaport portable EEG recorder with a common average (A1-A2) and a sample frequency of 256 Hz. Visual sleep staging was performed according to R&K criteria [71] by experienced technicians from the sleep center of Stichting Epilepsie Instellingen Nederland (Zwolle, the Netherlands). Technicians were blinded for the group affiliations of the subjects. Each polysomnogram was scored by one technician.

Subjective sleep measures were assessed the morning after the PSG measurements by asking subjects to report their subjective TST, SOL, number of awakenings and time of early awakening, if applicable.

### 5.3.5 Survival analysis

We separately modelled the survival curves of NREM sleep, REM sleep and wake. This is illustrated in Figure 5.1. NREM fragments were considered terminated if followed by epochs scored as either wake or REM sleep. For the NREM analysis, we excluded NREM fragments with a length below 1 minute, to limit the influence of 30s-epoch N1 fragments occurring during wake and REM. REM fragments were terminated if they were followed by epochs either classified as wake or as NREM sleep. Again, we excluded REM fragments with a length below 1 minute. Wake fragments were terminated when followed by any epoch scored as sleep, except single N1 epochs (N1 being a subset of NREM sleep). Single N1 epochs during wake were replaced by wake, because they may give a false impression that wake is divided into many shorter fragments. Wake fragments with a length below 1 minute were not excluded from analysis.

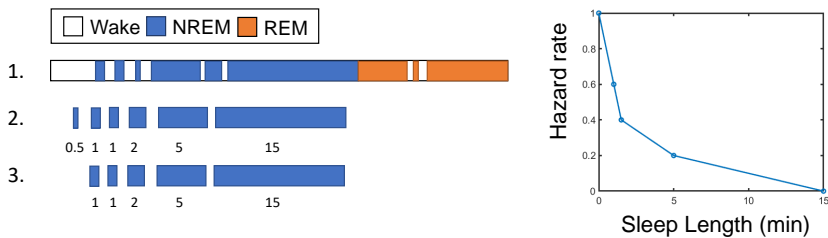


Figure 5.1: Illustration of survival curve analysis of NREM sleep. Step 1 depicts an example of sleep over time. For reasons of clarity, only one sleep cycle is depicted. During step 2, all fragments of NREM sleep are listed and sorted based on length. Fragments of NREM sleep are assumed to be terminated if they are followed by either wake or REM sleep. In step 3, NREM fragments shorter than 1 minute are excluded from analysis. On the right, the hazard rate resulting from these sleep fragments is plotted. The hazard rate represents the percentage of NREM fragments longer than a certain length, e.g. after 1 minute, three out of five (60%) of the sleep fragments is still left (i.e. 'has survived'), and after 5 minutes only one sleep fragment (20%) is left. In reality, we have four sleep cycles, and thus more sleep fragments. Survival curves of REM sleep and wake sleep were calculated using a similar approach.

In the survival analysis, we assumed that single epochs scored as N1 do not interrupt NREM sleep. We also performed an additional analysis, testing such assumption. Here, prior to calculating survival curve dynamics, we replaced single N1 epochs occurring during N2 or N3 with single epochs of wake. Subsequently, we proceeded with the analysis as described before.

Theoretically, we could combine all sleep and wake fragments together on the group level using Kaplan-Meier curves. However, this type of analysis does not take into account the clustering of sleep and wake fragments within participants, and is more difficult to use when assessing the combined influence of group and treatment. Therefore, the Kaplan-Meier plots were only used for visual comparison. Instead, we made a parametrization of the survival curves for each individual, using Weibull distributions. Weibull parameters for each of the participants were then compared across group and treatment. A Weibull distribution is characterized by two parameters: a shape parameter ( $k$ ) and a scale parameter ( $\lambda$ ). The shape parameter characterizes the shape of the distribution.  $k$  below 1 indicates that the probability of an event to occur decreases over time. This is often the case for wake fragments, because the majority of the awakenings is very short, and thus the chance to fall asleep again is largest during the first couple of minutes. When the shape parameter is equal to one, the distribution is exponential. An exponential distribution is the probability distribution when the time between events follows a Poisson process, where events occur at a constant average rate, independently of the time elapsed. An exponential distribution is described only by the scale parameter  $\lambda$ , i.e. the event rate. The expected value of an exponentially distributed random variable is  $1/\lambda$ , which in our situation would be equal to the average sleep or wake segment length. To improve the interpretability of the results, we reported the reciprocal of the estimated scale parameters ( $1/\lambda$ ) in the results section. In a distribution similar to an exponential distribution, a higher reported value of  $1/\lambda$  indicates a longer average segment length and an increased stability.

### 5.3.6 Sleep structure over the night

It is possible that sleep and wake dynamics differ over consecutive sleep cycles. This could not be evaluated in our previously described analysis. Therefore, the time course of the proportion of NREM and REM sleep was plotted per treatment condition as a function of time elapsed since sleep onset. The proportion of the sleep stages was defined for each time point as the total number of epochs scored as a certain stage at that designed time point, across all participant from each group, divided by the total number of epochs at that time point. To quantify

differences for treatment conditions, additional statistical analysis would be required. However, a detailed analysis of NREM and REM sleep over the night was not within the scope of this paper. Therefore, these graphs were used for visual reference only.

### **5.3.7 Assessing the amount of sleep misperception**

The amount of sleep onset misperception was calculated for each night as the difference between self-reported SOL from the hypnogram and objective SOL, defined as the latency from bedtime until the first epoch scored as sleep from the hypnogram. The amount of TST misperception was calculated as the difference between objective and self-reported subjective TST.

### **5.3.8 Estimating subjective sleep onset from sleep fragmentation**

We used the previously introduced model to determine whether the difference in sleep onset misperception between the zopiclone night and the placebo night could be attributed to predictable changes in sleep fragmentation, or to factors not explained by the model. [107] In the sleep length model, it was assumed that sleep bouts with a too short length at sleep onset are perceived as wake. [107] Thus, the perceived sleep onset was estimated as the start of the first sleep fragment longer than L minutes. Sleep length parameter L was the parameter of the model, i.e. the minimum length a continuous sleep fragment should have in order to be perceived as sleep. Any wake fragment with a duration of at least one 30s epoch was considered as an interruption of sleep. In a previous study, we applied the model to PSG data from people with insomnia and healthy controls, testing different model assumptions. [107] We found a median optimal parameter L of approximately 30-35 minutes for participants with insomnia, with small variations depending on subgroup characteristics. [107] The optimal parameter L for an individual was referred to as Sleep Fragment Perception Index (SFPI). In the current study, we assigned a reference SFPI of 30 minutes to all participants and used the model to estimate subjective SOL. The estimated SOL, i.e., the latency until the first uninterrupted sleep fragment longer than 30 minutes, was subtracted from the objective SOL to obtain an estimate of the amount of sleep onset misperception that can be explained by the model. This procedure is illustrated in Figure 5.2. Subsequently, we calculated the prediction error between estimated subjective sleep onset and actual perceived sleep onset based

on the sleep diary. This quantity is equal to the difference between estimated amount of SOL misperception and actual amount of SOL misperception, because objective SOL is used for both calculations. The prediction error of the model was referred to as ‘sleep onset misperception not explained by sleep fragmentation’ and was compared across groups and treatments. The estimated amount of sleep onset misperception was also compared across groups and treatment conditions.

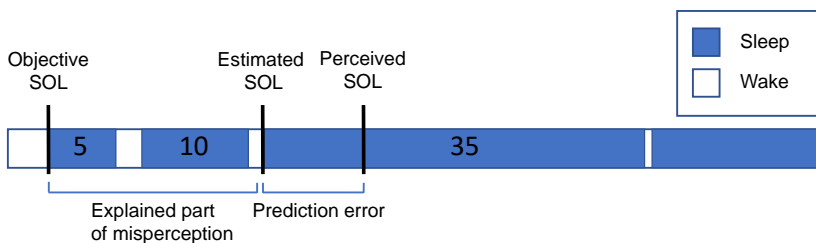


Figure 5.2: Estimation of the amount of sleep onset misperception according to the sleep length model. Subjective sleep onset was estimated from the hypnogram as the difference between lights off time and the start of the first sleep fragment longer than 30 minutes. In the figure, this estimate was labelled ‘estimated SOL’. Subsequently, the prediction error between estimated subjective sleep onset and self-reported subjective sleep onset from the sleep diary was calculated. This is referred to as ‘sleep onset misperception not explained by sleep fragmentation’. Furthermore, the difference between objective sleep onset and estimated subjective sleep onset was calculated. This was referred to as the ‘explained part of sleep onset misperception’.

### 5.3.9 Statistical analysis

Statistical analysis was done using R. [95] Multi-way ANOVA was used to compare parameters across groups and treatments. We used an alpha value of 0.0167 when comparing survival parameters, to correct for multiple testing (we are comparing survival parameters of REM, NREM and wake). For the same reason, we used an alpha value of 0.025 when assessing the effect of treatment, group and group x treatment on sleep misperception of TST and SOL. In case of a significant effect of group, we used a pair-wise posthoc test to find the differences between specific groups.



## 5.4 Results

Two participants were excluded from the analysis because of (partly) missing PSG data. One of these was from the frequent users group, while the other was from the healthy controls group. Demographic characteristics of participants and use of escape medication by participants from the frequent users group are listed in Table 5.1.

**Table 5.1:** Demographic characteristics of participants and use of escape medication.

Group	Age (years)	Sex (%M)	#Participants using escape medication under zopiclone treatment	#Participants using escape medication under placebo treatment
Frequent users (n=15)	62.1 ± 4.3	8M; 7F (53)	3	4
Infrequent users (n=16)	62.3 ± 6.2	8M; 8F (50)		
Healthy controls (n=15)	62.8 ± 4.5	7M, 8F (47)		

Frequent users who expected difficulties during the three hypnotic-free nights prior to the measurement night, were provided escape medication. The escape medication consisting of zolpidem at a maximum of one dose of 10 mg per night, to be used only in case of intolerable withdrawal effects.

### 5.4.1 Sleep survival dynamics

Table 5.2 reports the Weibull parameters of the survival curves of NREM sleep, REM sleep and wake. For REM survival curves, no significant effect of either group or treatment was found (Table 5.2). For NREM sleep, we found a significant effect of treatment for the Weibull scale parameter, i.e. the average segment length. The average segment length was smaller during the placebo night than during the zopiclone night. For wake, we found a significant effect of treatment for both Weibull parameters (Table 5.2). The average segment length of wake was larger during the placebo night compared to the zopiclone night.

The shape parameter was larger during the zopiclone night. Figure 5.3 illustrates the differences of grouped survival curves between the placebo and zopiclone nights, for all participants together. When using the alternative approach to calculate survival curve dynamics of NREM sleep, assuming that N1 sleep also disturbs NREM sleep, no significant effect was found (Group x treatment  $F=1.37$ ,  $p=0.26$ , treatment  $F=2.69$ ,  $p=0.10$ , group  $F=1.18$ ,  $p=0.31$ ).

**Table 5.2:** Parameters of sleep and wake survival analysis per group and treatment condition.

		Participant groups			Multi-way ANOVA		
		Frequent users	Infrequent users	Healthy Controls	Treatment	Group	Treatment x group
REM scale, $1/\lambda$	p	$13.5 \pm 5.3$	$15.4 \pm 8.8$	$12.7 \pm 4.5$	$F=0.99$ , $p=0.32$	$F=0.83$ , $p=0.44$	$F=0.52$ , $p=0.60$
	z	$11.0 \pm 5.3$	$13.3 \pm 7.1$	$13.3 \pm 5.2$			
REM shape, k	p	$1.5 \pm 0.57$	$2.4 \pm 1.3$	$1.5 \pm 0.40$	$F=0.34$ , $p=0.56$	$F=2.98$ , $p=0.06$	$F=0.15$ , $p=0.86$
	z	$1.8 \pm 1.43$	$2.3 \pm 2.1$	$1.8 \pm 1.1$			
NREM scale, $1/\lambda$	p	$17.3 \pm 8.1$	$15.3 \pm 3.8$	$17.8 \pm 5.0$	$F=8.89$ , <b><math>p&lt;0.01</math></b>	$F=1.16$ , $p=0.32$	$F=0.44$ , $p=0.65$
	z	$20.0 \pm 10.8$	$20.8 \pm 9.2$	$24.1 \pm 8.2$			
NREM shape, k	p	$0.98 \pm 0.19$	$0.93 \pm 0.09$	$0.89 \pm 0.13$	$F=3.32$ , $p=0.07$	$F=0.21$ , $p=0.81$	$F=1.11$ , $p=0.34$
	z	$0.85 \pm 0.17$	$0.86 \pm 0.25$	$0.89 \pm 0.19$			
Wake scale, $1/\lambda$	p	$3.6 \pm 1.8$	$2.8 \pm 1.6$	$3.3 \pm 3.1$	$F=11.49$ , <b><math>p&lt;0.01</math></b>	$F=1.48$ , $p=0.23$	$F=0.36$ , $p=0.70$
	z	$2.4 \pm 1.0$	$1.9 \pm 0.8$	$1.5 \pm 0.8$			
Wake shape, k	p	$0.87 \pm 0.23$	$0.94 \pm 0.29$	$0.93 \pm 0.43$	$F=7.22$ , <b><math>p&lt;0.01</math></b>	$F=3.08$ , $p=0.05$	$F=2.46$ , $p=0.09$
	z	$0.95 \pm 0.25$	$1.20 \pm 0.62$	$1.77 \pm 1.47$			

In case of a close-to exponential distribution, the inverse of the scale parameter  $1/\lambda$  is equivalent to the mean duration of a sleep or wake fragment. Therefore, a higher value of  $1/\lambda$  indicates a larger stability of that sleep or wake stage. Parameters were reported as  $1/\lambda$  to improve the interpretability of the results.

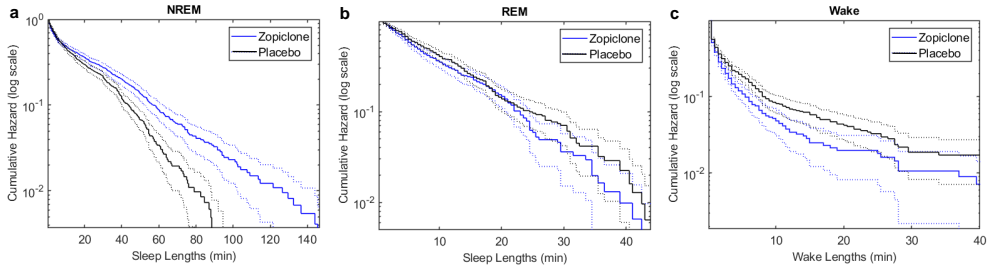


Figure 5.3: Hazard functions of NREM sleep, REM sleep and wake for all participants together. All functions are shown on a logarithmic scale. The hazard functions show the probability of the sleep or wake fragment to be terminated during any given length of that fragment. A) Survival curves of NREM sleep. B) Survival curves of REM sleep. C) Survival curves of wake.

## 5.4.2 Proportions of sleep stages over the night

Figure 5.4 shows the proportions of NREM sleep and REM sleep over the night for each of the two treatment conditions. Visually, a clear difference of the distribution of REM sleep over the night can be observed between treatment conditions. During the placebo night, a clear peak of REM sleep is visible after approximately one hour. During the zopiclone night, the first peak of REM sleep seems largely absent.

## 5.4.3 Sleep misperception

Figure 5.5 shows the actual amount of sleep onset misperception during the placebo and the zopiclone night, summarized per group and treatment condition. We found significant effects for both group and treatment, but no interaction effect (Table 5.3). Pair-wise post-hoc testing indicated a significant difference between frequent users and healthy controls (Mann Whitney  $U = 652$ ,  $p = 0.02$ ), and between infrequent users and healthy controls (Mann Whitney  $U = 587.5$ ,  $p = 0.02$ ). For misperception of TST, again a significant effect was found for group and treatment (Table 5.3). Pair-wise testing indicated a significant difference between frequent users and healthy controls (Mann Whitney  $U = 655$ ,  $p < 0.001$ ), and between infrequent users and healthy controls (Mann Whitney  $U = 638$ ,  $p = 0.03$ ).

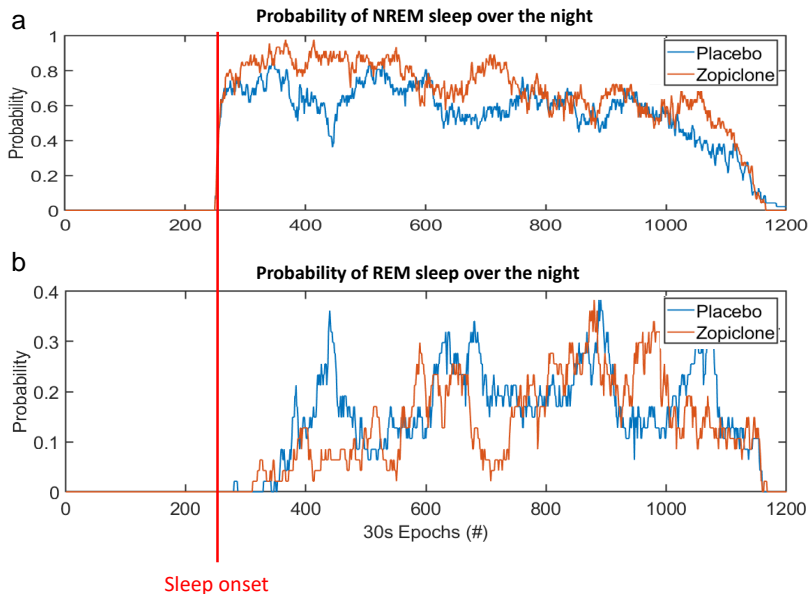


Figure 5.4: Proportions of sleep stages over the course of the night. The first epoch of sleep has been aligned between participants, to make it start at the same point in time. A) combined proportions of N2 and N3 sleep. B) proportions of REM sleep.

#### 5.4.4 Estimated SOL misperception and prediction error

Figure 5.6 shows the results of using the sleep length model to estimate the amount of SOL misperception, summarized per group and treatment condition. The estimated amount of SOL misperception showed a significant effect for treatment (Table 5.3; Figure 5.6A). The prediction error of SOL misperception did not show any significant effect of either group or treatment (Table 5.3; Figure 5.6B). However, when comparing the variance of all placebo nights to the variance of all zopiclone nights, we found that variances were significantly larger during the zopiclone nights (Levene's test, center='median',  $F=7.09$ ,  $p<0.01$ ).

**Table 5.3:** Parameters of SOL and TST misperception per group and treatment condition. Also the average and standard deviation of each value per group and treatment are reported.

		Participant groups			Multi-way ANOVA		
		Frequent users	Infrequent users	Healthy Controls	Treatment	Group	Treatment x group
SOL misp (min) <sup>a</sup>	p	75.5 ± 82.9	33.4 ± 33.2	15.2 ± 25.6	F=10.80, p<0.01	F=6.08, p<0.01	F=2.49, p=0.09
	z	19.5 ± 38.6	12.3 ± 13.3	5.5 ± 20.6			
TST misp (min) <sup>b</sup>	p	19.4 ± 42.6	11.2 ± 50.1	-7.1 ± 47.3	F=10.41, p<0.01	F=6.87, p<0.01	F=4.05, p=0.02
	z	104.4 ± 82.2	76.7 ± 113.5	3.7 ± 39.8			
Est. SOL misp <sup>c</sup>	p	18.1 ± 17.6	9.1 ± 12.9	9.4 ± 13.5	F=16.1, p<0.001	F=1.70, p=0.19	F=0.60, p=0.55
	z	57.6 ± 72.9	47.5 ± 47.8	29.2 ± 30.5			
Error SOL misp <sup>d</sup>	p	18.6 ± 73.1	-13.4 ± 61.3	-11.3 ± 20.7	F=0.20, p=0.65	F=1.62, p=0.20	F=1.01, p=0.37
	z	4.7 ± 34.2	3.9 ± 20.2	-3.1 ± 24.8			

<sup>a</sup>The difference between self-reported subjective SOL obtained from the sleep diary and objective SOL. <sup>b</sup>The difference between subjective TST obtained from the sleep diary and objective TST. <sup>c</sup>The difference between subjective SOL estimated from the hypnogram and objective SOL. <sup>d</sup>The difference between estimated amount of SOL misperception and actual amount of SOL misperception.

## 5.5 Discussion

We analyzed experimental manipulations of sleep from a pharmacological intervention protocol. The aim of the study was to explore potential mechanisms of sleep fragmentation that influence alterations of perceived sleep quality and quantity observed using a pharmacological manipulation. Results indicate an increased stability of NREM sleep and a decreased stability of wake during the zopiclone night compared to the placebo night. Additionally, we used a previously proposed model to estimate subjective sleep onset from the hypnogram based on sleep fragmentation. Both the so-obtained estimated amount of SOL misperception and the actual amount of SOL misperception were significantly lower during the zopiclone night.

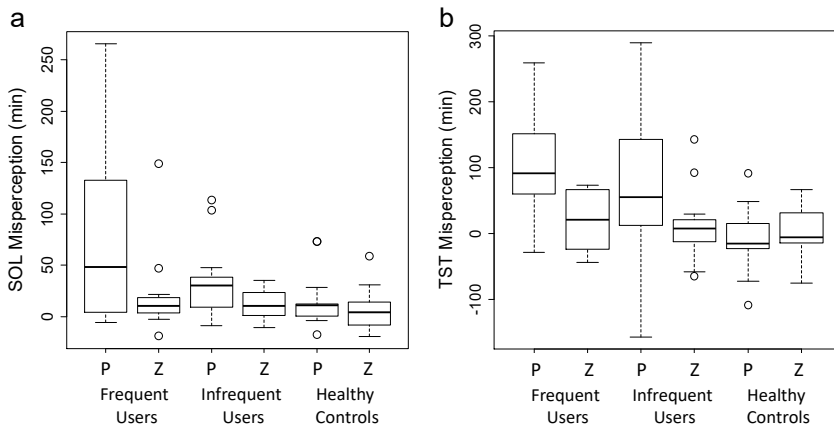


Figure 5.5: The actual amount of sleep onset misperception during the placebo and the zopiclone night, summarized per group and treatment condition. P=placebo and Z=zopiclone. The amount of sleep onset misperception was calculated as the difference between objective and self-reported (sleep diary) subjective sleep onset latency.

When fitting a Weibull distribution to the NREM sleep segments, we found that the scale parameter  $1/\lambda$  was significantly higher during the zopiclone night, while the shape parameter was unaltered. The altered scale parameter suggests that fragments of NREM sleep overall have a higher probability to ‘survive’ during the zopiclone night compared to the placebo night. Thus, NREM sleep seems more stable during the zopiclone night. This finding might be partly explained by the increased percentage of slow wave sleep that was reported during the zopiclone night [124], because from previous research it appears that the continuity of deep sleep is better protected compared to lighter sleep. [125] The unaltered Weibull shape parameter suggest that the distribution of the length of the NREM sleep fragments was not altered. Interestingly, when repeating the analysis with the alternative assumption that NREM sleep is not only disturbed by wake and REM epochs, but also by epochs scored as N1, we did not find a significant difference between treatment conditions. According to R&K guidelines, epochs of N1 are often scored when arousals during N2 sleep are observed. Therefore, our present results may indicate that the distribution and number of arousals were unaltered across treatment conditions. We may speculate that sleep disturbances by awakenings were more important for the

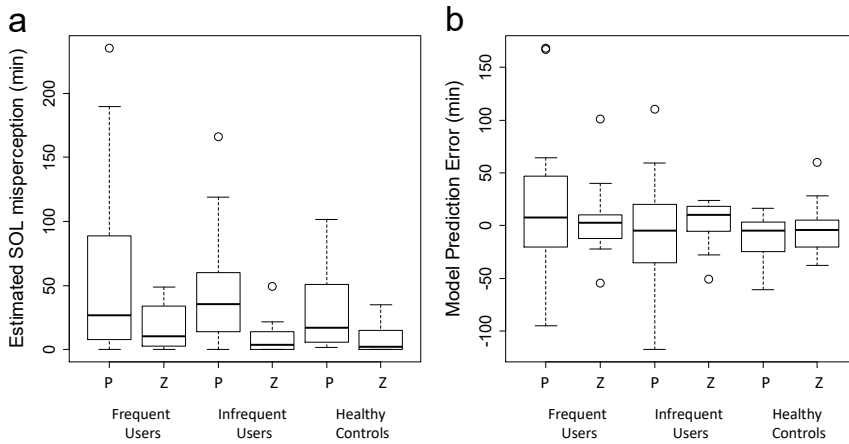


Figure 5.6: Results of using the model to estimate the subjective SOL for individual patients, summarized per group and treatment condition. P=placebo and Z=zopiclone. A) Estimated amount of SOL misperception, defined as the difference between objective and estimated subjective SOL. Subjective SOL was estimated as the latency until the start of the first uninterrupted sleep fragment longer than 30 minutes. B) Prediction error of difference between estimated sleep onset misperception and actual self-reported sleep onset misperception.

quality of the sleep than arousals. This hypothesis is supported by the fact that the model of subjective sleep onset adequately predicted a change of sleep onset misperception, without taking into account N1 sleep or arousals.

Additionally to alterations in NREM dynamics, we found differences of both the wake scale and shape parameters between treatment conditions. The increased scale parameter during the zopiclone night indicates a decreased stability of wake fragments, i.e., participants fell asleep sooner after awakening. This finding explains the shorter WASO and longer TST during the zopiclone night, as previously reported. [124] The decreased scale parameter during the zopiclone night probably resulted from a decreased percentage of long awakenings. For the current dataset lower percentages of REM sleep were reported during the zopiclone night. [124] Indeed, effects on REM sleep density are commonly reported for zopiclone. [16, 126, 127] Survival curve analysis did not indicate a decreased stability of REM sleep, leading to the conclusion that only the probability of entering REM sleep was reduced. Indeed, plotting the probability of REM sleep

over the night indicated an absence of the first peak of REM sleep during the zopiclone night.

Since using hypnotics can result in large changes of many aspects of sleep architecture, it is difficult to actually indicate which of these changes are associated with sleep quality. Therefore, we used a modelling approach to demonstrate the relationship between sleep fragmentation and sleep onset misperception, which may be an expression of impaired objective sleep quality at the beginning of the night. We found a lower amount of predicted sleep onset misperception during the zopiclone night, as well as a lower amount of actual sleep onset misperception. In contrast, the prediction error of the model did not differ between treatment conditions. These results suggest that a considerable part of the difference of sleep onset misperception between treatment conditions can be explained by predictable alterations of sleep fragmentation at the beginning of the night. Importantly, the model to estimate subjective sleep onset was developed from another night of measurement, partly with the same study participants. [87] This may explain why the parameter of 30 minutes seemed to fit so well in the current study. However, the model was independently validated in a larger study sample with younger participants from a different sleep laboratory. Also in that case the parameter of 30 minutes was proven to be applicable outside the initial study population. [107] Although the prediction error of the model, i.e. the unexplained component of sleep onset misperception, did not differ significantly between treatment conditions, its variation was larger during the placebo night. Therefore, it is possible that zopiclone also influences components of sleep onset misperception not explained by the model, but to a lesser extent. Other mechanisms of influence could include anterograde amnesia, which is a side effect reported for zopiclone. [128, 129]

The current finding that decreased stability of NREM sleep may be associated with impaired sleep quality is consistent with previous modelling results, which indicate that the length of sleep fragments at the beginning of the night is important for the perception of the sleep onset. [107] Furthermore, in the current study a decreased stability of wake was indicated as a possible parameter reflecting impaired sleep quality. However, in previous research we found that the length of wake fragments interrupting sleep was not of great importance for the perception of the sleep onset, mainly because the majority of the awakenings was very short. [107] Additionally, in earlier research, the subtype of insomnia with short objective sleep duration was not associated with sleep state misperception. [130] Considering that long awakenings often co-occur with a short sleep duration, it is possible that the current findings of altered wake survival parameters are not connected with sleep (onset) misperception. However, it is possible that



the length of the wake fragments is associated with other components of sleep quality. Next to altered parameters of NREM sleep and wake, a third finding of sleep architectural changes during the zopiclone night was a delayed latency until REM sleep. REM sleep latency is not incorporated in our model of sleep onset misperception, and therefore is not part of the explained part of sleep onset misperception. However, we cannot exclude the possibility that the delay of REM sleep during the zopiclone night influenced sleep onset misperception as part of the altered variance of the unexplained part of the sleep onset model.

A limitation of this research is that we used the 30 minutes parameter to estimate subjective sleep onset in all participants, because estimating optimal parameters for individuals would require multiple nights of data per subject and per treatment condition. Previous research yielded an optimal parameter of approximately 20 minutes for healthy controls. [107] Thus, by estimating subjective sleep onset as the first sleep fragment longer than 30 minutes, we probably exaggerated the influence of sleep fragmentation in this group. However, the number of sleep fragments with a length between 20 and 30 minutes at sleep onset was very limited, and thus, the exact choice of the parameter would probably not heavily influence the results. As another limitation, the current survival analysis was based on R&K scoring rules. Therefore, results may slightly differ from PSGs scored according to AASM guidelines. However, based on research by Moser et al. comparing AASM and R&K guidelines, we expect that the percentage of epochs scored as N1 during NREM sleep may be influenced by the scoring rules used, while differences for wake epochs after sleep onset may be very limited. [131] Therefore, we expect that the scoring guidelines used will only influence the results of the approach in which we assumed that N1 stages interrupt NREM sleep, while the analysis in which we only considered awakenings seems most promising for further research. A third limitation was that patients had a fixed bed time in this study. It is possible that misalignments between the participant's usual bed time and the fixed bed time influenced the results for sleep onset misperception. However, since both measurement nights had the same fixed bed time, we do not expect that the conclusions on the effect of treatment will be affected. Still, it is possible that a confounding effect was present for the group comparisons. This highlights the additional need to study survival parameters in larger study samples.

In this study, improvements of subjective sleep quality and quantity co-occurred with decreased stability of NREM sleep and increased stability of wake over the entire night, while no alterations of REM stability were observed. In a similar protocol with multiple nights of zolpidem and multiple nights of placebo, similar improvements of perceived sleep quantity and quality were found during

the zolpidem nights. [117] During the zolpidem nights, the latency to persistent sleep became shorter [117], pointing towards the possibility that our model would also have estimated a lower amount of sleep onset misperception in this case. However, whole-night differences of number of awakenings and WASO were not found. [117] This finding could possibly be related to the shorter half-life time of zolpidem compared to zopiclone, as well as to the possibility that survival parameters are better suitable to express relevant aspects of sleep fragmentation.

From the present data, we cannot conclude whether the altered sleep dynamics we found are specific for the influence of zopiclone in elderly people, or if they also play a role in younger people not using hypnotics. Larger datasets are required to examine if differences of NREM and wake dynamics can be found between people with insomnia and healthy participants. Such differences were not found in our study. However, based on the results of a simplified sample size calculation, comparing two independent means [67] and assuming means and standard deviations similar to the ones found in this study, we conclude that a difference between a NREM scale parameter of 20 and 15 minutes with a standard deviation of 8 minutes would require a sample size of 41 participants with insomnia and 41 healthy controls. If the survival curve of NREM is close to mono-exponential, this would correspond to a difference between three and four awakenings per hour, which in our opinion could already be a clinically significant difference. Therefore, we conclude that, at least for the NREM scale parameter, our sample size was probably not large enough to detect clinically meaningful differences between groups. Previous research does indicate that differences of sleep dynamics may exist between people with insomnia and healthy controls. [120] Furthermore, it has been shown that insomnia patients have a higher probability of transitioning from stage N2 to N1 or wakefulness compared to healthy controls, and a decreased stability of N2. [84] In the light of the current results, we can speculate that these differences may indeed represent differences of sleep quality between insomnia patients and controls.

In this study, we treated impaired subjective sleep quality, sleep onset misperception and misperception of TST as different expression of the same objectively measurable sleep quality. However, there might be different aspects of sleep quality that are influenced by different parameters. For example, currently we do not know if sleep onset misperception and misperception of TST share the same mechanisms. It is difficult to separately assess misperception of SOL and TST, because TST misperception is influenced by SOL misperception. Therefore, we would like to stress the importance of specifically asking study participants for their subjective WASO. When studying larger groups of insomnia patients,

it would be interesting to use interindividual differences between components of sleep quality to disentangle different mechanisms. For example, it is possible that part of the insomnia patients predominantly experience sleep onset misperception, while other patients mainly have complaints of misperception of WASO, or impaired subjective sleep quality without marked sleep state misperception. Within the patient population, such different subtypes could be compared regarding survival parameters. As such, the survival parameters identified in this study could be possibly used as a tool for understanding mechanisms of impaired sleep quality in specific subtypes of sleep problems. Additionally, dividing sleep onset misperception into a component explained by sleep fragmentation and an unexplained component can also present valuable opportunities for research into treatment interventions.

# Chapter 6

## Sleep-wake survival dynamics in people with insomnia

Submitted as:

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## 6.1 Abstract

Assessing objective measures of sleep fragmentation could yield important features reflecting impaired sleep quality in people with insomnia. Survival analysis allows the specific examination of the stability of NREM sleep, REM sleep and wake. The objective of this study was to assess the differences between survival dynamics of NREM sleep, REM sleep and wake between people with insomnia and healthy controls. We analyzed polysomnography (PSG) recordings from 88 people with insomnia and 92 healthy controls. For each participant, survival dynamics of REM sleep, NREM sleep and wake were represented using Weibull distributions. We used lasso penalized linear regression to analyze the difference between participant groups with respect to the Weibull parameters, while correcting for age, sex, total sleep time (TST) and relevant interaction effects. Significant group effects were found for the NREM scale parameter, and for the scale and shape parameters of wake. Results indicated that people with insomnia had less stable NREM sleep and more stable wake after sleep onset compared to healthy controls. Additionally, the altered distribution of wake segment lengths indicated an increased difficulty to fall asleep after longer awakenings in the insomnia group. However, these differences were mainly observed in younger participants. The current findings suggest that people with insomnia have an increased fragmentation of NREM sleep, but not necessarily of REM sleep. Additional research into the underlying mechanisms of NREM sleep fragmentation could possibly lead to a better understanding of impaired sleep quality in people with insomnia.

## 6.2 Introduction

Worldwide, insomnia is the most common sleep disorder. [4] Insomnia greatly affects general health, work productivity and quality of life [4], and is probably caused by a combination of psychological and physiological mechanisms. [7] Gold-standard polysomnography (PSG) measurements are often performed to objectively study sleep. When performing PSG in the clinical setting, sleep is typically quantified using standard overall parameters, such as total sleep time (TST), sleep onset latency (SOL) and wake after sleep onset (WASO). Part of the people with insomnia have a reduced amount of sleep as reflected by these parameters, but often, these general indicators do not fully explain the seriousness of the sleep complaints. [26, 27, 97] Apparently, sleep quantity is not necessarily always sufficient to define a good night of sleep. Instead, a broader concept of sleep quality could be defined, which may be reflected by other PSG-derived features.

Sleep fragmentation, i.e., disturbed sleep continuity as represented in the hypnogram, has been proposed as a measure of impaired sleep quality. [26, 84, 110, 111] For instance, a meta-analysis showed that people with primary insomnia have an increased number of awakenings compared to healthy sleepers. [23] Additionally, both PSG-defined and subjectively reported number of awakenings were correlated with measures of subjective sleep quality in healthy sleepers. [24, 112, 113] Furthermore, interruptions of sleep at the beginning of the night have been proven to play a role in the misperception of the sleep onset in people with insomnia. [35, 57] This is a relevant finding for the topic of sleep quality, because it has been assumed that sleep onset misperception can be caused by a reduced sleep quality at the beginning of the night. [26] Identifying objective parameters reflecting sleep quality is potentially useful to increase our understanding of the characteristics that are important for perceiving a good night of sleep.

We previously identified two main challenges that may complicate research into the influence of sleep fragmentation on sleep quality. [132] First, because sleep is influenced by many different psychological and physiological factors, a large variability between people may be expected. Interindividual variability may be reduced by assessing differences between multiple nights within the same individual. [132] Second, sleep fragmentation can be assessed using many different parameters, making it difficult to compare results across studies. Currently, there is not a standard set of parameters to adequately describe sleep fragmentation.

Traditionally, sleep macrostructure is mainly described using parameters such

as WASO, sleep efficiency, number of awakenings and sleep stage percentages. [133] However, more sophisticated methods to analyze the sleep architecture have been proposed, including survival analysis. [119] Survival analysis can be used to analyze the expected amount of time until the end of a sleep or wake fragment. [119] Subsequently, a hazard function can be calculated to evaluate the probability of a sleep or wake fragment to end at any given time point. Or similarly, to evaluate the probability of a fragment to survive. This survival function not only provides information about the average duration of the fragment concerned, but also about its probability distribution. For example, sleep is often modelled as an exponential distribution [134], implying that awakenings occur at a constant average rate, independently of the occurrence of previous awakenings. In contrast, the survival dynamics of wake fragments are usually modelled using power law transition dynamics, because the probability of falling asleep becomes lower if the length of the wake fragment increases. [134] A power law distribution indicates that the rate of occurrence of events of falling asleep is dependent on the wake time. [134] This is important information that cannot be obtained using traditional PSG-derived parameters. Another benefit of survival analysis over other parameters such as sleep stage percentages, is that survival analysis is more specific. Survival curve analysis can be used to assess if low percentages of certain sleep stages reflect the presence of many interrupted fragments of that sleep stage, or a reduced probability to enter that specific sleep stage.

In previous research, we examined sleep and wake survival parameters in a sleep medication intervention study. [132] We found that elderly people with insomnia complaints, as well as healthy controls, had an improved self-reported sleep quality when using zopiclone for one night compared to using placebo. These improvements of self-reported sleep quality co-occurred with an increased stability of NREM sleep and a decreased stability of wake. [132] No alterations of REM sleep were found. We concluded that survival parameters of wake and NREM sleep may be useful for further studying impaired sleep quality in people with insomnia. [132] However, this conclusion was based on the specific circumstances of a medication study in a small, elderly sample. The question of whether similar changes of sleep architecture could be found in a larger and younger population of both medication-free people with insomnia and healthy individuals remains unanswered. If survival parameters of wake and NREM indeed reflect sleep quality, it is possible that differences between insomnia and healthy controls will be detected. Roth et al. indeed showed differences of sleep survival dynamics between healthy people and people with insomnia, but distinctions between NREM and REM sleep were not made. [120] In the

present study, we further study the presence of altered sleep survival dynamics in people with insomnia and controls, including differences between NREM and REM sleep.

## 6.3 Methods

### 6.3.1 Study design

We analyzed polysomnography (PSG) recordings from 88 insomnia patients and 92 healthy controls. The insomnia data were recorded as part of usual clinical care at Sleep Medicine Center Kempenhaeghe, Heeze, the Netherlands. The data of the healthy controls were collected as part of the Healthbed study, performed to obtain sleep recordings in healthy people to develop new technologies for sleep assessment. The applicable protocol (W17.128) was approved by the medical ethics committee of Maxima Medical Center, Veldhoven, the Netherlands. The current data analysis protocol (20190523.3) was approved by the medical ethics committee of Sleep Medicine Center Kempenhaeghe.

### 6.3.2 Insomnia patients

All PSGs of insomnia patients were recorded between 2013 and 2017. In case more than one recording was available, the first PSG of a participant was selected. We included patients with a clinical diagnosis of “psychophysiological insomnia” or “paradoxical insomnia” according to ICSD-2 criteria [20], and grouped these diagnoses together. Additional inclusion criteria for the study were: 1) age above 16, 2) complete PSG recording of at least one night available and 3) a complete subjective sleep diary of the PSG night available. Exclusion criteria were: 1) major medical comorbidities potentially influencing the PSG recording (as determined by an experienced somnologist), such as  $AHI > 15$  2) major sleep-related co-morbidities other than insomnia that could fully explain the sleep complaints of the patient and 3) using prescribed medication that could impact sleep.

### 6.3.3 Healthy controls

Inclusion criteria of healthy controls were: 1) age between 18 and 65 and 2) the ability to read and speak Dutch. Exclusion criteria were: 1) any diagnosed sleep disorders 2) a Pittsburgh Sleep Quality Index [64]  $\leq 6$  or Insomnia Severity



Index [93] > 7, 3) indication of depression or anxiety disorder measured with the Hospital Anxiety and Depression Scale [94] (score >8) 4) pregnancy, shift work, use of any medication except for birth control medication, and 5) presence of clinically relevant neurologic or psychiatric disorders or other somatic disorder that could influence sleep.

### 6.3.4 Assessments

Polysomnography - A clinical video-polysomnography was performed according to the AASM recommendations. Visual sleep staging was performed according to AASM criteria. [40] All recordings were (re)scored by one single experienced technician from the team of authors (BH). The hypnograms obtained with this rescoring were processed for further analysis.

Subjective sleep – Subjective sleep was assessed the morning after the PSG measurements by asking the participants to indicate time awake in bed, lights off time, time asleep and time outside of bed using a graphical sleep diary with a time resolution of 15 minutes.

### 6.3.5 Survival analysis

Survival dynamics of NREM sleep, REM sleep and wake were modelled separately. For NREM sleep, REM sleep and wake, all fragments were listed and sorted based on length (Figure 5.1). A NREM fragment was considered terminated if it was followed by either wake or REM sleep. When fitting the Weibull distributions to the NREM sleep lengths, we excluded fragments shorter than one minute. This was done to limit the influence of isolated 30s-epoch N1 fragments occurring during wake and REM (N1 being a subset of NREM sleep). REM fragments were terminated if they were followed by wake or NREM sleep epochs. We excluded REM fragments shorter than one minute, again to limit the influence of short fragments. Wake fragments were terminated when followed by any epoch scored as sleep, except single N1 epochs. Single N1 epochs during wake were replaced by wake, because they may give a false impression of wake being divided into many shorter fragments. Wake fragments shorter than one minute were *not* excluded from analysis, because they generally constitute a large part of the total number of awakenings.

### 6.3.6 Parametrization

We parametrized the survival dynamics of each participant using the Weibull distribution. Individual Weibull parameters were compared across group and treatment. A Weibull distribution is characterized by two parameters: a shape parameter ( $k$ ) and a scale parameter ( $\lambda$ ). The shape parameter characterizes the shape of the distribution. A shape parameter  $k$  below one indicates that the probability of an event, i.e., the end of a wake or sleep fragment, decreases over time. This is often the case for wake fragments, because most awakenings are very short, and the chance of falling asleep again is largest during the first couple of minutes. A shape parameter above one indicates an opposite trend. When the shape parameter is equal to one, the distribution is exponential. An exponential distribution is the probability distribution of the time between events in a Poisson process, where events occur continuously at a constant average rate, independently of the time elapsed. In case of an exponential distribution, the scale parameter is equal to the rate of an event. Thus, in a near-to-exponential distribution,  $\lambda$  can be interpreted as the inverse of the mean duration of the sleep or wake length segment. In this case, a lower scale parameter, and thus longer segments on average, indicates an increased stability.

### 6.3.7 Modelling

Modelling and statistical analysis were performed in R, version 3.6.2. [95] For NREM and REM sleep, we used a lasso penalized linear regression model [135] to assess the difference between groups (insomnia/healthy controls) on the survival curve parameters, while accounting for the possibly confounding effects of age, sex (0 male/ 1 female), TST, and all possible second-order interactions between these variables. Age and TST were centered and normalized. The lasso algorithm was used in combination with bootstrapping with 100 replications to estimate the regularization parameter. For this, we used the HDCI package. [136]

We expect that TST may be a possible confounding parameter for sleep survival parameters, because the degree of sleep fragmentation may vary over the night. From experimental sleep studies, we can learn that the arousal threshold is at its maximum near the middle of the night. [137] Therefore, we may expect a higher number of awakenings at the end and the beginning of the night, and less awakenings in the middle of the night. However, for wake, the relation between TST and the survival parameters is more complicated. Research shows that the average length of the awakenings somewhat increases over the night [96], which could imply that people with a shorter TST on average have

shorter awakenings. However, people with insomnia often have excessively long awakenings at any moment of the night. In a sleep center, where the opportunity to spend time in bed is limited, these long awakenings will most likely result in a reduction of TST. Therefore, TST and wake survival parameters mutually influence each other, and assessing the confounding influence of TST would not provide any meaningful results for the wake parameters. For this reason, for wake survival parameters, we did not incorporate PSG-derived quantities in the analysis. Instead, we only incorporated group, age, sex and all interactions in the lasso algorithm.

Note that in previous research [132], we reported the results about the scale parameter in terms of the mean fragment length  $1/\lambda$  instead of the mean hazard rate  $\lambda$  itself, to facilitate the interpretation. In this study, we used  $\lambda$ , because performing an inverse transformation would alter the distribution of the parameters, and make it more difficult to apply a linear model.

### 6.3.8 Statistical analysis

Because comparisons were done for REM sleep, NREM sleep and wake, a Bonferroni correction was applied, resulting in an alpha value of 0.0167. Group statistics were expressed as mean  $\pm$  standard deviation (sd) in case of a normal distribution, and as median  $\pm$  inter quartile range (IQR) in case of a non-normal distribution. Prior to analysis, we used the rule of thumb proposed by Tabachnick and Fidell [138] to assess if the dataset contained a sufficient number of observations for the intended analysis. The rule of thumb states that the sample size for a multiple linear regression model should be at least  $50+8*m$ , where  $m$  is the number of factors evaluated in the model. Counting the four basic variables and their second-order interaction effects, the lasso regression model would yield a maximum of ten factors. This would result in a sample size of 130, which is less than the sample size used in this study.

## 6.4 Results

### 6.4.1 Demographics

The age of the participants with insomnia (58 females, 30 males) had a median of  $47.0 \pm$  IQR 19.5 years. The healthy controls (57 females, 35 males) had a median age of  $33.0 \pm$  IQR 27.0 years. The median of total sleep time was  $383 \pm$  IQR 73 minutes for the people with insomnia and median  $438 \pm$  IQR 59 minutes

for the healthy controls. In Table 6.1, co-morbidities within the insomnia group are listed.

**Table 6.1:** Frequency (percentage) of co-morbidities within the insomnia group.

<b>Co-morbidities</b>	<b># (%)</b>
Depression and/or anxiety	13 (14.8)
ADHD	2 (2.3)
Other psychiatric diagnosis	9 (10.2)
PLM index >15	4 (4.5)
Mild OSA: $4 < \text{AHI} < 15$	2 (2.3)

### 6.4.2 Missing data

For two participants with insomnia, the REM shape parameter could not be calculated, because all REM sleep bouts had the same length. These participants both had a TST of less than 2.5 hours, and only a few very short fragments of REM sleep. In these participants, both the REM shape and scale parameters were omitted from the analysis. Furthermore, in one healthy participant the wake shape parameter could not be calculated due to the same cause. One healthy participant had only one REM fragment. In this case, again both the REM shape and the REM scale parameters were omitted from analysis.

### 6.4.3 Survival parameters in patients versus controls

Results of the statistical analysis on the sleep and wake survival parameters are shown in Table 6.2. The two groups differed significantly in the NREM scale parameter, the wake scale parameter and the wake shape parameter, after correcting for possible confounders. For ease of interpretation, we report the scale parameter  $\lambda$ : a larger  $\lambda$  indicates a higher hazard rate (which in turn is equal to a shorter average segment length). Results indicate that people with insomnia had a higher hazard rate for NREM sleep, and a lower hazard rate for wake compared to healthy controls. Additionally, people with insomnia had a smaller wake shape parameter, which was further away from one. Thus, the

distribution was further away from an exponential distribution in people with insomnia. This can be interpreted as a larger effect of elapsed time awake on falling asleep again, i.e., it takes longer to fall asleep after longer awakenings.

#### **6.4.4 The effect of age, sex and TST on survival parameters**

Age was a statistically significant confounder for none of the survival parameters (Table 6.2). Sex was a statistically significant confounder for both the NREM and REM scale parameters (Table 6.2). Males had higher NREM and REM hazard rates compared to females. TST was a statistically significant confounder for the REM scale parameter. People with a longer TST had a lower hazard rate of REM sleep. We did not find any significant interaction effects.

#### **6.4.5 Model evaluation and sensitivity analysis**

Residual diagnostics for the models for NREM and REM sleep survival dynamics did not indicate any violation of the model assumptions. Evaluating the model for the wake shape parameter indicated the presence of large studentized residuals, which were not normally distributed. These large residuals were found only in young people between 18 and 28 years old from the control group, who seemed to have shorter awakenings than expected based on their age and sex. We performed a sensitivity analysis, including only participants older than 29. This approach yielded a sample size of 76 people with insomnia and 51 healthy controls. In this sensitivity analysis (Table 6.3), no significant effects were found. The effect of group and age on the wake shape parameter and the effect of age on the wake scale parameter were near-to significant. The signs of the coefficients were the same as those reported in Table 6.2.

#### **6.4.6 Correlations between survival parameters**

Within the insomnia group, we did not find a significant correlation between the NREM scale parameter and the wake scale parameter (Spearman  $\rho = -0.02$ ,  $p = 0.83$ ). We also did not find a significant correlation between the NREM scale parameter and the wake shape parameter (Spearman  $\rho = -0.07$ ,  $p = 0.53$ ).

## 6.5 Discussion

Sleep fragmentation is a potential mechanism underlying impaired sleep quality in people with insomnia, with multiple dimensions. To study sleep fragmentation in more detail, we assessed both sleep and wake survival dynamics in patients with insomnia and healthy controls. We found that people with insomnia had a decreased stability of NREM sleep compared to controls. Additionally, altered wake dynamics indicated that wake was more stable in the insomnia group, and that it took longer for people with insomnia to fall asleep after long awakenings. In contrast, dynamics of REM sleep did not differ between groups.

In our statistical analysis, we corrected for the effects of age, sex, TST and interaction effects. Taking the influence of TST into account for sleep survival parameters is important, because the number and length of the awakenings may vary over the night. [96, 139] Additionally, correcting for age was of particular importance for this study, since the participants were not age-matched. The limited amount of information available about sleep and wake fragmentation made it difficult to select relevant interaction effects based on prior knowledge. Therefore, we used lasso penalized regression to make a first selection of relevant parameters that can possibly explain the sleep and wake survival parameters. The intention of using the lasso algorithm was exploratory, to choose the variables that could explain the survival parameters, and not to build a model that adequately predicts those parameters.

Evaluating the model diagnostics showed that our approach of using a linear regression model was valid for sleep survival parameters. For the wake survival parameters, sensitivity analysis indicated the possibility that the effect of group was largely driven by a small number of participants within the age range of 18 to 28 years. We observed that several young people in the healthy control group had very large wake scale and shape parameters, indicating a short average wake length and a relatively small percentage of longer awakenings. It is possible that these participants were college students, who may have been sleep deprived because of different sleep habits compared to the other people in the study sample. However, we did not find signs of rebound sleep, such as high percentages of slow wave sleep, in the PSG recordings of these participants. Therefore, we do not expect that these results were caused by prior sleep deprivation. Another possibility is that the effect of age on the survival dynamics of wake was non-linear. Therefore, the results of the wake parameters should be interpreted with caution. At the same time, when only analyzing participants older than 29, the predicting effect of group on the wake shape parameter was still near-to significant, despite a sample size reduction of 50% in the healthy

control group. This indicates that a group effect may still be present in older people, but this would need to be confirmed with a larger sample size of this age range.

We did not find confounding effects of age on any of the survival parameters. Earlier research reported that older participants have higher hazard rates of NREM sleep compared to younger participants. [121] Therefore, we expected an effect of age for NREM sleep. It is possible that the two interaction effects age\*sex and age\*TST partly account for the effect of age. Alternatively, it is possible that we did not find an effect because the groups were unbalanced for age, or because of the relatively low percentage of elderly people in the dataset. For example, only nine participants were older than 65. Additionally, our model results indicated that men had less stable NREM and REM sleep compared to women. Although women have an increased risk of developing insomnia and report more sleep problems [140, 141], the finding that women objectively sleep better than men is commonly described in the literature. [141] Women were reported to have a lower sleep efficiency [142], less WASO [142], a lower percentage of SWS [143, 144], and a lower arousal index. [143] Finally, in our study, participants with a shorter TST had less stable REM sleep. This result intuitively seems plausible, because the total amount of REM sleep during a sleep cycle usually increases over the night. We can hypothesize that this increase of REM sleep density co-occurs with an increased stability of REM sleep. This hypothesis would illustrate the importance of correcting for TST when assessing sleep fragmentation. However, the association between TST and sleep fragmentation should be further examined. For example, in one study, people with a short TST had shorter sleep bout lengths during the first three hours of the night, compared to people with a long TST. [145] Thus, it is possible that sleep fragmentation can also lead to a shorter total sleep duration. In that case, we should be careful not to overcompensate when correcting for TST. In this analysis, we chose to incorporate age, sex, TST and interaction effects as confounding factors in a lasso penalized linear model. For age and sex, matching would present an alternative solution. However, age-matching would probably result in predominantly evaluating sleep in older people, since the number of young people seeking medical attention for insomnia is relatively small. Younger people with insomnia may have different profiles compared to older people with insomnia [146].

Survival analysis has important advantages and disadvantages. As an important caveat, this type of analysis is very sensitive to sleep staging differences between experts. We sometimes observe differences between scorers regarding the number of awakenings, possibly because scorers have different sensitivity to

events during sleep that may lead to scoring an epoch as wake, such as alpha activity and eye movements. Such a difference can even be observed in the presence of a very high general agreement between scorers. A small difference in the number of 30s-awakenings scored during sleep can already greatly affect the average segment length. Therefore, in this study all PSGs were scored or rescored by one and the same expert. In research into survival dynamics with multiple scorers, we would recommend specifically assessing the number of awakenings as a parameter for inter-scorer reliability. The same would apply for assessing the reliability of automated scoring.

Different methods exist to compare survival curves between groups of participants. We chose to use the Weibull distribution to represent survival dynamics for each participant rather than pooling the sleep and wake fragments of all participants together, because the latter approach would not take into account the effect of clustering within participants. Additionally, when pooling all fragments together, participants with many short fragments would influence the pooled survival dynamics more than participants with few longer fragments. However, this approach may introduce additional uncertainty in the results due to the estimation of the parameters. Moreover, in a few participants, we were not able to calculate the Weibull parameters due to a limited amount of either REM sleep or wake segments. Nonetheless, in our opinion the advantage of not pooling the data outweighs the limitations of this approach. Furthermore, parameterization of the survival curves allows for the use of a linear model to correct for possible confounders, which is an important additional advantage. We chose to use the Weibull distribution instead of calculating only the average, because by calculating the average we would assume an exponential distribution. By allowing different types of shape parameters, we took possible dependencies into account between the time slept and the probability to wake up/fall asleep again.

As illustrated by our results, survival analysis can be very useful for disentangling different types of sleep and wake fragmentation. For instance, the current findings suggest that people with insomnia have fragmented NREM sleep, but not necessarily fragmented REM sleep. This finding is relevant, because research indicates that NREM and REM sleep have different functions. [122] Our results on REM sleep are not consistent with earlier research, where people with insomnia scored higher on a combined index of awakenings and arousals compared to good sleepers. [86] In the current study, we limited our analysis to awakenings and sleep stage transitions, while we did not incorporate arousals. This can possibly explain the differences between the study results.

We also confirmed our hypothesis that people with insomnia have an in-



creased stability of wake after sleep onset, although this finding should be interpreted with caution, since it seemed to be particularly relevant for the younger participants. Nevertheless, assessing wake survival dynamics could also be relevant in older people, because long awakenings could be an important characteristic of people with an objective short sleep duration, a subtype of insomnia discovered by Vgontzas et al. [22] A short sleep duration often co-occurs with a long WASO, and WASO is in turn heavily influenced by the length of the awakenings. The absence of a correlation between NREM sleep and wake survival parameters in our insomnia group suggests that people with short NREM fragments, and thus probably many awakenings during NREM sleep, do not necessarily have long awakenings. Therefore, it is important to separately assess sleep and wake survival mechanisms.

Our current findings show that NREM sleep fragmentation is an important phenomenon in people with insomnia, requiring additional examination. For example, the exact causes of sleep fragmentation are unknown. Furthermore, it is not known if sleep fragmentation is present in all patients or only in a subgroup, how much it varies over different nights of sleep, and if improvement can be observed after cognitive behavioral therapy for insomnia (CBT-I). Learning more about fragmentation of NREM sleep can possibly lead to a better understanding of impaired sleep quality in people with insomnia, and consequently to improved treatment.

Table 6.2: Results of sleep and wake survival analysis.

	Group (health/ins)	Age (years)	Sex (m/f)	TST (hours)	Group *Age	Group *Sex	Age *Sex	Group *TST	Age*TST	Sex*TST
NREM scale, $\lambda$	B=-0.80	B=0.14	B=-1.2	B=-0.16			B=0.23	B=-0.67	B=-0.23	
	t=-3.0	t=0.63	t=-4.8	t=-0.89	X	X	t=0.85	t=-2.1	t=-1.79	X
	<b>p&lt;0.01</b>	p=0.53	<b>p&lt;0.001</b>	p=0.38			p=0.40	p=0.041	p=0.075	
NREM shape, k	B=-0.029		B=0.017			B=0.049				
	t=-0.95	X	t=0.62	X	X	t=-1.3	X	X	X	X
	p=0.34		p=0.54			p=0.20				
REM scale, $\lambda$	B=-1.3	B=-0.33	B=-1.4	B=-1.1					B=-0.32	
	t=-2.4	t=-1.3	t=-2.7	t=-3.6	X	X	X	X	t=-1.4	X
	p=0.019	p=0.21	<b>p&lt;0.01</b>	<b>p&lt;0.001</b>					p=0.17	
NREM shape, k	B=0.084		X	X	X	X	X	X	X	X
	t=0.77	X								
	p=0.44									
Wake scale, $\lambda$	B=7.1	B=-3.6								
	t=2.6	t=-1.9	X		B=-5.9	X	X			
	p=0.010	p=0.062			t=-2.2					
Wake shape, k	B=0.20	B=-0.064	B=-0.062							
	t=2.8	t=-1.2	t=-0.87		B=-0.15	X	X			
	<b>p&lt;0.01</b>	p=0.21	p=0.39		t=-2.1					
										p=0.041

B=unstandardized model coefficient. X=parameter for which the lasso algorithm determined a coefficient of zero.

Table 6.3: Results of sensitivity analysis for wake parameters, including only participants older than 29.

	Group (health/ins)	Age (years)	Sex (m/f)	TST (hours)	Group *Age	Group *Sex	Age *Sex	Group *TST	Age*TST	Sex*TST
Wake scale, $\lambda$	B=4.2 t=1.4 p=0.17	B=-4.3 t=-2.1 p=0.039	X		B=-1.7 t=-0.43 p=0.67	X	X			
Wake shape, k	B=0.12 t=1.9 p=0.059	B=-0.079 t=-1.9 p=0.058	B=-0.0001 t=-0.003 p=0.99		B=-0.004 t=-0.05 p=0.96	X	X			

B=unstandardized model coefficient. X=parameter for which the lasso algorithm determined a coefficient of zero.

# Chapter 7

## Summary, discussion and future perspectives

### 7.1 General summary and discussion

The aim of the research described in this thesis was to identify objectively measurable sleep parameters reflecting impaired sleep quality in people with insomnia. The first part of the thesis focused on sleep onset misperception, i.e., the phenomenon that people with insomnia often overestimate their sleep latency compared to objective recordings. Sleep onset misperception can probably be considered as an expression of impaired sleep quality at the beginning of the night, and therefore may be associated with certain objective sleep parameters. In the second part of this thesis, we shifted our focus from sleep onset towards whole night sleep/wake dynamics using survival analyses.

#### 7.1.1 Modelling sleep onset misperception

In **chapter 2**, we assessed the correlation of sleep misperception with macro- and microstructural parameters during the first sleep cycle of people with insomnia. The amount of sleep onset misperception was associated with increases in wake after sleep onset, and with a higher percentage of NREM1 sleep during the first sleep cycle. These results imply that sleep onset misperception is related to fragmentation of the sleep macrostructure. Based on this information, we proposed a model to quantify the influence of sleep fragmentation at the beginning of the

night on sleep onset misperception. In the model, we assumed that the subjective moment of falling asleep co-occurs with the start of the first uninterrupted sleep bout of sufficient length. In other words, we assumed that people do not perceive sleep fragments shorter than a certain length at the beginning of the night are not perceived as sleep. Results indicated that people with insomnia needed an uninterrupted sleep fragment with a minimum length of approximately 30 minutes for an adequate perception of the sleep onset. In contrast, healthy people needed an uninterrupted sleep fragment of only approximately ten minutes. Thus, the results suggested that people with insomnia need a longer time of uninterrupted sleep to perceive their sleep onset compared to healthy sleepers.

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*Patients with insomnia require longer continuous sleep fragments to adequately perceive their sleep onset when compared to healthy sleepers.*

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The sleep onset misperception model was validated and extended in **chapter 3**. Again, patients with insomnia, those who misperceived their sleep in particular, needed longer continuous sleep fragments to adequately perceive their sleep onset compared to controls. Comparing various model types and assumptions additionally lead to the conclusion that the length of the uninterrupted sleep fragments was of more influence for the perception of the sleep onset than the length of the awakenings. The modelling approach resulted in a parameter for which we coined the term Sleep Fragment Perception Index (SFPI), providing a useful measure to characterize sleep onset misperception in individuals. Using the SFPI, we can quantify the influence of objectively measurable sleep fragmentation on sleep onset misperception. Thus, we can express the sensitivity of the sleep perception of a person to fragmented sleep. This is useful for clinical research, such as identifying other factors that can contribute to sleep onset misperception.

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*The SFPI is a valuable tool to model sleep onset misperception in individuals.*

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In this part of the thesis, we showed that objective sleep characteristics can indeed influence the perception of the sleep. These findings may aid in viewing sleep

misperception as an actual problem of impaired sleep quality, rather than a mere erroneous perception of wakefulness. In general, occasional short awakenings during the night are considered normal for healthy sleepers. However, based on our research results, it seems that in part of the people with insomnia, these short awakenings can greatly influence the perception of the sleep onset depending on their timing. Therefore, monitoring the number and distribution of awakenings during the night may be of clinical significance for people with sleep disorders. Furthermore, the finding that short sleep fragments are often not perceived as sleep, suggests that there is a time-dependent component to perceiving sleep. It is possible that this is related to the propagation to deeper sleep, and that lighter sleep is more easily overlooked compared to deep sleep. This hypothesis remains to be further investigated. Further research could specifically assess the behavior of sleep after awakenings: how long does it take to return to deep sleep, and is this the same for all awakenings and for all people? For this type of research, one could consider using an index of sleep depth based on spectral power, for example the odds ratio product proposed by Younes et al. [147], or the bispectral index proposed by Sleight et al. [148]

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*Monitoring the number and distribution of awakenings during the night may be of clinical significance for people with sleep disorders.*

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Apart from providing insights into the relation between sleep fragmentation and sleep onset misperception, our model also provides an approach to divide sleep onset misperception in two components: a component predicted by the model and a component not explained by sleep fragmentation. The latter component was used to assess the influence of pre-sleep arousal and time estimation on sleep onset misperception (**chapter 4**). We concluded that people who overestimated a time interval during the day also overestimated their sleep onset latency. An influence of pre-sleep arousal was not found. However, this finding does not exclude the possibility that pre-sleep arousal influences sleep onset misperception by means of altering the sleep structure. The influence of pre-sleep arousal on sleep structure remains to be further investigated.

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*Sleep onset misperception is influenced by the ability to estimate time.*

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### 7.1.2 Sleep and wake survival analysis

As a next step, we extended our research to whole-night sleep parameters. Based on the results of the sleep onset misperception model, we expected that not only the number of awakenings would be important to capture in a whole-night parameter, but also their timing. For example, according to the assumptions made in the model, someone who regularly awakes every ten to fifteen minutes would overestimate his or her sleep onset more than someone with many clustered awakenings in the first few minutes of the night. We identified survival analysis as a valuable tool to describe whole-night sleep fragmentation, because it can be used to describe both the average duration of the sleep bouts and their distribution. In **chapter 5**, we assessed the influence of sleep medication on sleep misperception, subjective sleep quality and survival dynamics in people with insomnia and healthy controls. All participants used a placebo for one night, and zopiclone, a frequently used sleep drug, for another night. Participants from both groups on average had less sleep onset misperception during the zopiclone night compared to the placebo night. Using the SFPI, we concluded that the zopiclone-induced changes in sleep onset misperception could be largely attributed to predictable changes of sleep architecture. During the zopiclone night, the participants did not only have less sleep onset misperception, but also less misperception of their total sleep time. They also experienced a better whole-night sleep quality. When using survival analysis, we observed that the participants had more stable NREM sleep during the zopiclone night, as well as less stable wake after sleep onset. Thus, we identified a reduced stability of NREM sleep and an increased stability of wake as possible contributors to impaired whole-night sleep quality.

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*Zopiclone-induced changes in sleep onset misperception can be largely attributed to predictable changes in sleep architecture.*

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In **chapter 6**, we assessed differences between survival parameters of sleep

and wake between people with insomnia and healthy controls. We used a linear model to analyze the difference between patients and healthy controls, while correcting for age, sex and total sleep time. Results indicated that the people with insomnia indeed had less stable NREM sleep and more stable wake after sleep onset compared to the healthy controls. The altered wake dynamics seemed particularly applicable in younger participants.

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*People with insomnia have less stable NREM sleep and more stable wake compared to healthy sleepers.*

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Survival analysis can be used to obtain valuable information about mechanisms of sleep and wake fragmentation. For instance, the distribution of the sleep and wake bout lengths can be studied. [149] Bout length distributions are often fitted with either an exponential or a power-law distribution. An exponential distribution indicates that the probability of an event to happen is not dependent on the time since the previous event. [150] An example of an exponential distribution is the amount of time until an earthquake occurs. A power-law distribution indicates that the majority of the bout lengths is short, while longer bout lengths are rare. [150] This distribution is also applicable in for example cities, where the majority of the cities are small, and a small percentage is very large. Wake bout lengths are assumed to follow a power law distribution, because short awakenings are much more common than long awakenings. For sleep bout lengths, the appropriate type of distribution is still under debate. [134] The type of the distribution is of interest, because it provides information about whether or not deeper sleep is better protected from disturbances than lighter sleep. For example, research of Klerman et al. indicated that the hazard rate of NREM sleep abruptly drops after ten minutes. [121] In other words, the chance of passing to wake or REM sleep is largest during the first ten minutes of NREM sleep. This could be of interest for sleep disorders, because a reduced NREM sleep stability in an individual could hypothetically lead to an increased number of awakenings and a smaller proportion of stable sleep (i.e., sleep not within the first ten minutes after awakening), in turn leading to more awakenings and potentially resulting in an unfortunate vicious cycle. We should note that the differences in sleep dynamics that we found in chapter 6 between insomnia and healthy controls only concerned the average sleep length, and not the type of the distribution. However, we do not intend to provide detailed conclusions



about the types of sleep bout distributions involved. To be able to draw such conclusions, one would preferably have access to multiple nights of data for each participant. [149]

When performing survival analysis, several limitations should be taken into account. Perhaps the most important limitation is the need to reliably detect short awakenings and sleep stage transitions. In general, manually scored sleep stages show subtle or less subtle differences, depending on the person who evaluated the hypnogram. For instance, the interrater reliability for all sleep stages together using AASM criteria is approximately 82%. [151] Survival analysis may be particularly sensitive to differences between sleep scorers, because differences of short bouts of scored sleep stages can have a large effect on the outcome of the analysis. For example, if one would want to calculate the amount of wake after sleep onset for an individual, scoring one 30s-epoch of wake as sleep would not largely influence that calculation. In contrast, when analyzing the dynamics of sleep bouts during the night, that same awakening could result in counting two distinct sleep fragments instead of one. This may in turn largely affect the average length of the sleep bouts. A further complicating factor is that the number of awakenings is not a routinely used parameter for the evaluation of the agreement between sleep scorers. Therefore, it is possible that this metric may show more variation between sleep scorers than routinely evaluated parameters, such as sleep onset latency and wake after sleep onset. In research into survival dynamics with multiple scorers, we would recommend specifically assessing the number of awakenings as a parameter for inter-scorer reliability. The same would apply for assessing the reliability of automated scoring. Probably, currently the best option is to compare survival parameters of PSGs which were evaluated by the same scorer.

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*Survival analysis can be used to obtain valuable information about mechanisms of sleep and wake fragmentation, as long as the need to reliably detect short awakenings is taken into account.*

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Additionally, for sleep and wake survival analysis, we would recommend to carefully consider the assumptions made in the model. It may be useful to exclude certain events. For example, as we did in **chapter 5** and **chapter 6**, it can make sense to exclude the influence of single epochs of NREM1 sleep during long awakenings, because they give a misleading impression of highly

fragmented wake after sleep onset. However, following the same procedure for one-epoch wake fragments during sleep would not make sense, based on our previous conclusions that short awakenings greatly influence sleep onset misperception. Such decisions should ideally be based on knowledge about the implications and importance of certain elements of sleep architecture, as well as the sensitiveness of such elements to inter-scorer differences. Unfortunately, this knowledge is not always available.

Finally, it is important to keep in mind that survival curve analysis is a simplified analysis, because of the inherent assumption that the stability of sleep and wake fragments does not change over the night. From experimental sleep studies, we can learn that the arousal threshold is at its maximum near the middle of the night. [137] Therefore, we may expect a higher number of awakenings at the end and the beginning of the night, and less awakenings during the middle of the night. Thus, total sleep time could be a confounding factor in survival curve analysis. Recently, Bizzotto et al. described an approach to model the bout lengths of distinct sleep stages, while taking into account the time of the night. [139] Bout lengths were compared at one quarter and three quarters of sleep time. [139] A similar approach could be followed for survival curve analysis of NREM sleep, REM sleep and wake bouts. Another possible approach is to adjust for total sleep time during the statistical analysis, as we did in chapter 6. However, we do not yet understand the exact nature of the possible correlation between total sleep time and sleep survival dynamics. It has been shown that people with a short total sleep time have shorter sleep bout lengths during the first three hours of the night, compared to people with a long total sleep time. [145] Thus, it is possible that sleep fragmentation can also lead to a shorter total sleep duration. In that case, we should be careful not to overcompensate when correcting for total sleep time.

## 7.2 Future perspectives

### 7.2.1 Assessing sleep macrostructure: The importance of the hypnogram

From a practical point of view, it is important to emphasize that we only used macrostructural parameters for both the sleep onset misperception model and the survival curve analysis. These parameters are easy to calculate from routine clinical PSG measurements, and do not require additional scoring of micro-events.

Although PSG and sleep staging have already been performed in the sleep clinic for a long time, we can state that a large part of the information contained in the recorded signal is not used in clinical practice. Apart from visual evaluation of the hypnogram, the only information routinely obtained from the sleep staging consists of a small number of standard parameters, such as total sleep time, sleep onset latency, wake after sleep onset, and percentages of the sleep stages. Although it is known that a normal night of healthy sleep usually consists of alternating stages of NREM and REM sleep, there are many things we do not know. For example, we do not have reference values for normal numbers of awakenings, numbers of sleep stage transitions and timing of events. Research into sleep macro-architecture is highly relevant, because it can help clinicians to take advantage of information that is already easily accessible in the sleep clinic.

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*Research into new macro-architectural sleep parameters is highly relevant, because it can help clinicians to take advantage of information that is already easily accessible in the sleep clinic.*

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Survival analysis may be one way to help reveal important information from the sleep macrostructure, but there are many other approaches. For example, Markovian modelling is often used to model sleep transition dynamics, of people with obstructive sleep apnea (OSA) in particular. [119] The simplest form of a Markov model can be used to model randomly changing systems, in which future states depend only on the current state and not on the previous events. The output of such a model would be the probability of entering a certain sleep stage, given the identity of the current sleep stage. [84] For example, one could report that 5% of the epochs scored as NREM3 are followed by a NREM2 epoch. In some cases, Markov models are combined with fitting distributions to individual sleep stages or combinations of sleep stages [133], making this approach rather similar to the survival analysis approach described in this thesis. Survival analysis and Markov models are both forms of probabilistic sleep architecture modelling. The probabilistic sleep models described above do only consider the length of the current sleep or wake fragment, and therefore it is implicitly assumed that the sleep structure does not change over the course of the night. Thus, these models are suitable to compare relevant aspects of sleep architecture between groups of participants, but they do not contain sufficient information to realistically model a whole night of sleep. This is probably also the reason that, for automated sleep

staging based on cardiac signals, Markovian models have been outperformed by more recent approaches using recurrent neural networks, which are able to take into account information from earlier in the night. [152] Unfortunately, deep learning approaches are less suitable for clinical interpretation, because they do not output any clinically meaningful parameters. For clinically oriented research, we have to find a balance between simpler models that may not be able to capture all characteristics of sleep macrostructure, and more complex models which are difficult to interpret.

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*Studying sleep architecture requires finding a balance between model complexity and ease of interpretation.*

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### 7.2.2 Unobtrusive sleep recordings and automated sleep staging

An important advantage of analyzing parameters derived from the sleep macrostructure, is that they can be obtained using unobtrusive measurement techniques. PSG is a burdensome and costly diagnostic method, which is not suitable for multiple-night measurements. Therefore, alternative methods are being developed. Roughly, two different strategies can be distinguished. The first strategy involves simplification of the current standard PSG recording systems, usually by a combination of reducing the number of required electrodes and making the electrodes easier to apply. As part of the second strategy, automated sleep staging is being developed based on other physiological signals, for example actigraphy and heart rate variability. While sleep staging based on actigraphy has important limitations, such as the fact that it can only distinguish sleep and wake, sleep staging based on heart rate variability has shown promising results. [152, 153] Both strategies for unobtrusive sleep measurements are mainly being developed with the aim of obtaining sleep stages and macrostructural sleep parameters. In contrast, microstructural parameters are often not readily available. Sleep measurements based on heart rate variability understandably do not provide any opportunity to assess standard EEG-based microstructural parameters. For simplified PSG recording systems, assessment of microstructural parameters may be an option, depending on the quality of the signal and the number of EEG electrodes.

Multiple-night recordings are probably very important for sleep research, because statistical comparisons of sleep macro-architecture between groups of people can become more accurate and more informative if intraindividual variation is taken into account. Additionally, the variation of sleep architecture between nights may be important characteristics of certain sleep disorders. For example, recent research indicates that night-to-night variability of combined objective and subjective sleep metrics can be important for distinguishing subtypes of sleep state misperception. [154] Because good-quality unobtrusive sleep recordings in combination with automated sleep staging have only been available for a relatively short time, the amount of research in this field is currently limited.

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# Summary

## Sleep structure and sleep perception in people with insomnia

Chronic insomnia is a widespread problem, affecting about ten percent of the adult population. People with insomnia have chronic problems with falling asleep, maintaining sleep or waking up too early. Insomnia additionally involves daytime complaints such as fatigue, attentional disturbances and mood disturbances, impairing quality of life, general health and labor productivity.

Polysomnography (PSG) is the gold standard measurement for sleep. Often, standard PSG-derived metrics reflecting sleep quantity, such as total sleep time (TST) and sleep onset latency (SOL), do not fully explain the complaints of the patient. Therefore, it is assumed that not only sleep quantity is important for perceiving a good night of sleep. Instead, a broader concept of sleep quality can be defined, which may be reflected by other PSG-defined parameters. Identifying such parameters is potentially a very useful way to increase our understanding of the mechanisms underlying insomnia. Furthermore, these parameters may be useful to identify clinically meaningful subtypes within the patient population, and possibly even aid in the choice of the best treatment options for individuals. The aim of the research described in this thesis was to identify objectively measurable sleep parameters possibly reflecting impaired sleep quality in people with insomnia.

The first part of the thesis focuses on sleep onset misperception, i.e., the phenomenon that people with insomnia often overestimate their SOL compared to objective recordings. Sleep onset misperception can probably be considered as an expression of impaired sleep quality at the beginning of the night, and therefore may be associated with certain objective sleep parameters. In **chapter 2**, we performed an explorative analysis to identify correlates of sleep onset



misperception. Misperception of SOL was associated with increased percentage of NREM1 and more WASO during the first sleep cycle, suggesting that sleep onset misperception is mainly related to sleep fragmentation at the hypnogram level. Based on these results, we proposed a model to quantify the influence of the length of uninterrupted sleep fragments on the perception of the sleep onset. This model was validated and extended in a larger, independent population in **chapter 3**. The modelling approach yielded a parameter for which we coined the term Sleep Fragment Perception Index (SFPI), providing a useful measure to characterize sleep onset misperception of individuals.

In **chapter 4** we demonstrated that modelling the relation between sleep fragmentation and sleep onset misperception can aid in identifying the influence of other mechanisms not related to sleep architecture. Using the SFPI, we divided sleep onset misperception in a component that is explained by the model, and an unexplained component, which was calculated as the residual error of the model. This approach was used to reduce the variability caused by sleep architectural differences in 31 patients with insomnia. Results indicate that time estimation ability influences sleep onset misperception.

In the remainder of this thesis, we broadened our scope to studying whole-night sleep quality. Based on knowledge obtained from our modelling approach, we chose sleep and wake survival parameters as a suitable way to express whole-night sleep fragmentation. **Chapter 5** describes survival parameters of NREM sleep, REM sleep and wake in recordings from a double-blind crossover design with zopiclone 7.5 mg and placebo. Results indicated that decreased stability of NREM sleep and increased stability of wake may be important parameters reflecting sleep quality. Differences between people with insomnia and healthy controls with respect to these parameters will be assessed in **chapter 6**. Results indicated that the people with insomnia indeed had less stable NREM sleep and more stable wake after sleep onset compared to the healthy controls. The altered wake dynamics seemed particularly applicable in younger participants. Additional research into the underlying mechanisms of NREM sleep fragmentation could possibly lead to a better understanding of impaired sleep quality in people with insomnia.

# Samenvatting

## Slaapstructuur en -perceptie bij mensen met slapeloosheid

Slapeloosheid is een veelvoorkomend probleem. Ongeveer tien procent van de volwassenen heeft last van chronische problemen met in slaap vallen, doorslapen, en/of ochtends te vroeg wakker worden. Daarnaast hebben mensen met slapeloosheid vaak ook overdag klachten, zoals vermoeidheid, concentratieproblemen en stemmingsstoornissen. Deze klachten kunnen een grote impact hebben op het dagelijks leven.

De standaardmethode om de slaap te meten is polysomnografie (PSG). Door middel van PSG kan de totale hoeveelheid slaap worden berekend. Het komt echter vaak dat de slapeloosheidsklachten ernstiger zijn dan men op grond van alleen de hoeveelheid slaap zou verwachten. Daarom wordt algemeen aangenomen dat niet alleen de hoeveelheid slaap belangrijk is, maar ook de kwaliteit van de slaap. Mogelijk zijn er meetbare slaapkenmerken die de slaapkwaliteit kunnen beïnvloeden. Het identificeren van zulke parameters zou kunnen helpen om slapeloosheid beter te begrijpen. Ook bieden deze parameters mogelijk de kans om subcategoriën binnen de patiëntenpopulatie te vinden, en zouden ze zelfs een rol kunnen spelen bij het vinden van de beste behandelstrategie voor individuele patiënten. Het doel van het onderzoek in dit proefschrift was dan ook het vinden van objectief meetbare slaapparameters die een uiting kunnen zijn van een slechte slaapkwaliteit bij mensen met slapeloosheid.

In het eerste deel van het proefschrift concentreren we ons op misperceptie van de inslaaplatentie. Mensen die last hebben van slapeloosheid overschatten vaak de tijd die het kost om in slaap te vallen, vergeleken met objectieve slaapmetingen. We kunnen deze vorm van misperceptie waarschijnlijk beschouwen als een specifiek geval van verminderde slaapkwaliteit aan het begin van de

nacht. In **hoofdstuk 2** beschrijven we een exploratieve analyse, waarbij we op zoek gingen naar correlaties tussen slaapmisperceptie en parameters gemeten tijdens de eerste slaapcyclus. Bij mensen met veel misperceptie vonden we een verhoogd percentage lichte slaap. Ook waren deze mensen vaker wakker dan mensen zonder misperceptie. Deze resultaten suggereren dat slaapfragmentatie een belangrijk mechanisme kan zijn voor misperceptie. Met behulp van deze informatie hebben we een model geïntroduceerd, dat de relatie tussen misperceptie en de duur van onverstoorde slaapfragmenten kan beschrijven. Dit model is gevalideerd en uitgebreid in **hoofdstuk 3**. Het model leverde ons een maat op die kan worden gebruikt om de slaapmisperceptie van individuen te beschrijven. Deze maat noemden we de Sleep Fragment Perception Index (SFPI).

In **hoofdstuk 4** hebben we het model gebruikt om andere factoren te vinden die kunnen bijdragen aan misperceptie. Met behulp van de SFPI konden we twee aparte componenten van misperceptie onderscheiden: een 'slaapfragmentatie'-component die voorspeld kan worden door het model, en een onverklaarde component. De onverklaarde component kan worden berekend als de predictiefout van het model. Door alleen naar het niet-voorspelde deel van slaapmisperceptie te kijken, verminderden we de natuurlijke variatie tussen de onderzoeksdeelnemers als gevolg van slaapstructuur, en konden we nauwkeurigere analyses doen. In een groep van 31 mensen met slapeloosheid bleek dat een verkeerde inschatting van tijd een bijdrage kan leveren aan misperceptie.

In het vervolg van de thesis zijn we breder gaan kijken naar slaapkwaliteit tijdens de hele nacht. We gebruikten survivalanalyse om de overlevingstijd van slaap- en waakfragmenten tijdens de nacht te bestuderen. In **hoofdstuk 5** beschrijven we een survivalanalyse van de slaap van mensen die meededen aan een studie naar het effect van 7.5 mg zopiclone, een veelgebruikt slaapmiddel. Aan de hand van de resultaten van deze analyse concludeerden we dat een verlaagde stabiliteit van NREM-slaap en een verhoogde stabiliteit van wakkere periodes een rol kunnen spelen bij een verminderde slaapkwaliteit. In **hoofdstuk 6** beschrijven we opnieuw een survivalanalyse. Dit keer vergeleken we de slaap van een grote groep mensen met slapeloosheid met de slaap van gezonde proefpersonen. In deze studie lieten mensen met slapeloosheid een verlaagde stabiliteit van NREM-slaap zien, en een verhoogde stabiliteit van wakkere periodes. De verhoogde stabiliteit van waak leek vooral van toepassing te zijn op jongere patiënten. Om meer te weten over NREM-fragmentatie is verder onderzoek nodig.

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# Curriculum Vitae

*Lieke Hermans was born in 1992 in Alphen a/d Rijn, the Netherlands. In 2016, she received her M.Sc. degree at the University of Twente in Technical Medicine, with the specialization Medical Sensing and Stimulation. During her master thesis she was involved in a project at the UMC Utrecht about EEG network analysis as a tool for detecting postoperative cognitive impairment in the elderly. In September 2016 she started a PhD project at the Eindhoven University of Technology, of which the results are presented in this dissertation.*



# List of Publications

## Journal Papers

- Hermans, L.W.A, Leufkens, T., van Gilst, M., Weysen, T., Ross, M., Anderer, P., Overeem, S. and Vermeeren, A. Sleep EEG characteristics associated with sleep onset misperception. *Sleep Medicine*. vol. 57, May 2019.
- Hermans, L. W. A., van Gilst, M. M., Regis, M., van den Heuvel, L. C. E., Langen, H., van Mierlo, P., Krijn, R., Hoondert, B., Maass, H., van Dijk, J. P., Leufkens, T. R. M. and Overeem, S. Modelling Sleep Onset Misperception in Insomnia. *Sleep*. vol. 43 no. 8, 2020.;
- Hermans LWA, Nano MM Van, Leufkens TR, van Gilst MM and Overeem S. Sleep fragmentation, time estimation and pre sleep arousal as factors related to sleep onset (mis)perception. *Sleep Medicine: X*. vol. 2, December 2020.;
- Hermans LWA, Regis M, Fonseca P, Overeem S, Leufkens TRM, Vermeeren A and van Gilst MM. Assessing sleep-wake survival dynamics in relation to sleep quality in a placebo-controlled pharmacological intervention study with people with insomnia and healthy controls. *Psychopharmacology*. 2020
- Hermans LWA, Regis M, Fonseca P, Hoondert B, Leufkens TRM, Overeem S, van Gilst MM. Sleep-wake survival dynamics in people with insomnia. (submitted).

## Conference abstracts

- Hermans, L., Leufkens, T., van Gilst, M., Weysen, T., Ross, M., Anderer, P., Overeem, S. and Vermeeren, A. Modelling sleep state misperception at

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# The TU/e Sleep Series

1. Maaïke Goelema. Perceived Sleep Quality in a Personal Health Monitoring Context.
2. Pedro Fonseca. Home Sleep Monitoring.
3. Mark van Gastel. Remote photoplethysmography in infrared – Towards contactless sleep monitoring.
4. Lieke Hermans. Sleep structure & sleep perception in people with insomnia.