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Original Article

Sleep EEG characteristics associated with sleep onset misperception

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ABSTRACT

Study objective: To study sleep EEG characteristics associated with misperception of 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, wake after sleep onset (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 min at sleep onset were perceived as wake. The model indicated that healthy subjects are less sensitive to sleep interruptions and perceive fragments of 10 min 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.

1. Introduction

Chronic insomnia is a widespread problem, affecting about 10 percent of the adult population [1,2]. 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 [2].

People with insomnia often underestimate their amount of sleep compared to objectively scored sleep, described as sleep state misperception [3]. 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 [4–6]. However, it is not exactly known what such changes might entail. Different factors may play a role in the misperception of

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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 [7]. Signs of hyperarousal are normally observed during cognitive functions when someone is awake [8]. In the PSG, cortical hyperarousal is reflected by an increased high frequency spectral content of the EEG [9]. 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 [10,11]. It was proposed that cortical hyperarousal during the beginning of the night reduces the differentiation between sleep and wakefulness [12,13]; additionally interfering with the usual decline of memory-related functions during sleep onset [4,14]. 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 [13]. 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 [15]. Subjects from the subjective insomnia group had increased alpha, beta and sigma power and decreased delta power compared to the other two groups [15]. A third study did not find an association of sleep state misperception with high frequent EEG activity [16].

Second, sleep fragmentation might play a role in sleep onset misperception [17]. 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 [18,19]. The perception of sleep may therefore be disturbed when sleep is frequently interrupted. Notably, in 1988 a study reported that perception of awakenings during sleep seemed to be disturbed in insomnia patients [20]. 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 min prior to awakening [20]. The authors explained these findings by assuming that a sleep duration below 15 min was not long enough for the subjects with insomnia to have experienced falling asleep [20]. 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 min 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 [21]. A better agreement between subjective and objective SOL was found when the first criterion was used [21]. 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 [21]. For this reason in pharmaco-sleep studies the latency to the first consecutive 10 min of sleep is usually reported [22], although this cutoff is still somewhat arbitrary.

Indications of a fragmented sleep on a macrostructural level are an increase of 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 [23,24]. 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 [25].

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 [26]. 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 [27].

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 analysing an existing dataset comprising healthy elderly subjects with insomnia and healthy age-matched subjects [28]. We assessed the association between the amount of sleep misperception expressed as Sleep During Subjective Latency (SDSL) and several micro- and macrostructural parameters. Moreover, we modelled the perception of sleep onset, to study the influence of sleep interruptions on subjective SOL into more detail.

2. Methods

2.1. 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) [28]. In the present study, sleep data from the insomnia patients infrequently using hypnotics and the healthy subjects were re-analysed.

2.2. 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 three nights per week. The control group consisted of 21 self-defined healthy subjects [28].

As reported by Leufkens et al. [28], 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, haematology, 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 six 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 19–30 kg/m^2. Additionally, insomnia patients had to meet the following inclusion

criteria, based on DSM-IV [28]: (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 one 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 (PSQI) [29], the Sleep Wake Experience List [30], and the Groningen Sleep Quality Scale (GSQS) [31]. Moreover, subjects completed a sleep log for 14 days. Major psychopathology was screened using the Symptom Checklist 90 Revised [32], the Beck Depression Inventory (BDI) [33], the State-Trait Anxiety Inventory (STAI) [34], and the Multidimensional Fatigue Inventory (MFI) [35].

Seven patients from the insomnia group reported no history of using hypnotics [28]. The hypnotics used by the remaining 13 patients with insomnia were temazepam (n = 6), zopiclone (n = 4), lorazepam (n = 1), loprazolam (n = 1) and nitrazepam (n = 1) [28]. Their average duration of hypnotic use was 7.8 ± sd 7.9 years and their average frequency of hypnotic use was 4.1 ± 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 [36] 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. 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 h prior to arrival at the sleep laboratory. Alcohol intake was prohibited from 24 h prior to bedtime and smoking was prohibited from 1 h 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 min after awakening.

2.4. 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 [37] by experienced technicians from the sleep centre 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.

2.5. 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., [38].

2.5.1. 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 (Fig. 1) [17]. 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 [17]. This metric only focuses on the amount and characteristics of the sleep that is misperceived during the period of subjective sleep latency, rather than just subtracting objective and subjective sleep onsets [17]. This way, epochs of WASO will not be included in the SDSL.

2.5.2. Macrostructural parameters

Objective SOL was calculated as the time between lights off and the first epoch of any sleep stage, according to AASM criteria [39]. The percentage of 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.

2.5.3. Microstructural parameters

The microstructure of sleep was analysed using Philips Somnolyzer software [40–43].

2.5.3.1. Power spectral analysis. For each subject the power spectra of the C4-A1 lead were calculated. For one subject the C3-A2 lead

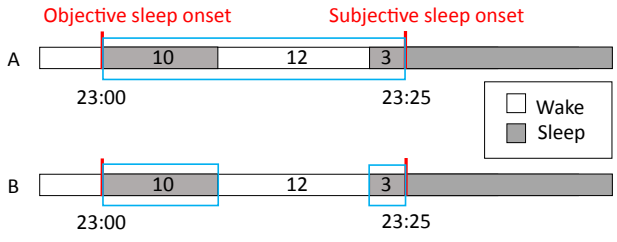

Fig. 1. Example of calculation of Sleep During Subjective Latency (SDSL). (A) The amount of sleep misperception is usually calculated as the difference between subjective and objective sleep onset, as indicated with the blue border. For this example, the amount of sleep misperception is 25 min. (B) When 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 min. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

was used because of artifacts on the C4-A2 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. Furthermore, 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 s with 2-s overlap. This way, a spectral resolution of 0.25 Hz within a frequency range of 0.25–40.0 Hz was obtained. Artifacts were automatically detected as described by Anderer et al., [44]. 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.

2.5.3.2. Arousals. Microarousals were detected by the Somnolyzer software package based on AASM criteria [39]. 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.

2.5.3.3. 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.

2.6. Statistical analysis

For all parameters, the differences between the two subject groups were assessed using unpaired t-tests when the data were normally distributed. When the data were not normally distributed, the Mann Whitney U test was used.

To determine the relation of objective sleep characteristics with misperception of sleep in patients with insomnia disorder the correlations of the variables with SDSL were assessed in the insomnia group, using Spearman's test because of nonlinearity of the data. No formal correction for testing multiple variables was applied, due to the assumed dependency of the EEG variables on each other. For example, variables indicating sleep fragmentation, such as a high WASO, multiple awakenings and a high percentage of NREM1 sleep, will most likely coincide. In the same way, spectral power during different NREM stages are likely to be correlated. Thus, we considered a Bonferroni correction as too conservative for this dataset. Instead, we used an alpha of 0.01 to correct for multiple comparisons.

2.7. 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 Fig. 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. 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.

3. Results

3.1. Subject characteristics

The insomnia group consisted of 10 males and 10 females (mean 60.8 ± sd 10.9 years old). The control group consisted of 13 males and eight females (mean 61.7 ± 5.0 years old) [28].

Both groups had a comparable objective SOL (insomnia mean 19 min ±sd 13 vs. healthy subjects mean 19 ± sd 15 min) [28]. However, the untreated insomnia patients reported a significantly longer subjective SOL than the healthy subjects (mean 68 ± sd 73 vs. mean 35 ± sd 37 min) [28]. During the measurement night, out of 20 insomnia subjects 17 subjects reported a subjective sleep onset of 30 min or more, nine subjects reported waking more than two times at night and 13 subjects reported waking up more than 30 min too early. We did not observe distinct subtypes during this night, eg, 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 (Fig. 1). Subjects with insomnia had an average SDSL of 40 ± 53 min and healthy controls had an average SDSL of 14 ± 28 min.

3.2. Comparison between groups

For the parameters calculated from the whole night, no significant differences were found between the insomnia group and the

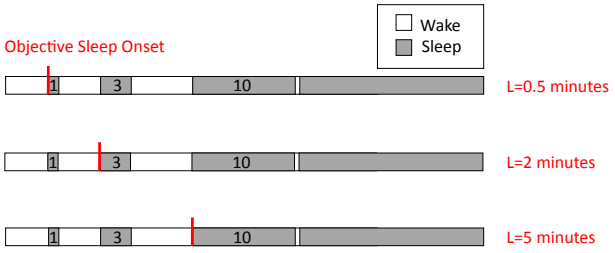

Fig. 2. Follow-up analysis: definition of sleep onset according to our model. An imaginary example of the sleep/wake pattern during a first sleep cycle is shown. (A) If we assume that sleep fragments with a length below 30 s are not perceived as sleep, the sleep onset from the model is the same as the objective sleep onset according to the AASM definition. (B) If we assume that sleep fragments with a length below 2 min 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 min 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 min and compared to the SOL perceived by the patient.

healthy subjects group at $p < 0.01$ (Table 1). However, during the first sleep cycle subjects with insomnia had a lower delta/beta power ratio during NREM2 than healthy subjects (Table 2).

3.3. Associations with sleep state misperception

We found that a higher 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 3, Fig. 3). In the healthy subjects group, the spread of the sleep onset misperception was too small to identify meaningful correlations.

When dividing the insomnia subjects into two groups based on SDSL with a cut off of 20 min in order to be able to compare our results with earlier findings [17], we found that age and sex were very comparable between the groups (short SDSL: age 60.6 ± 6.1 years, 4M 5F; long SDSL: age 60.7 ± 6.1 years; 6M 5F).

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 extend outside the SDSL (Fig. 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.

3.4. 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. Fig. 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 min 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 s. 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. Fig. 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 (MSEs) for the difference between modelled and subjective SOL for each value of L are shown in Fig. 6. For insomnia, the closest match between subjective SOL and modelled SOL was found for a length L of approximately 30 min. For the healthy subjects, an optimum was found for a length L of approximately 10 min. However, no clear improvement can be observed compared to L = 0.5. For larger values than L = 20 min, the MSEs rapidly became larger than in the initial situation.

4. Discussion

We aimed to further elucidate the mechanisms involved in misjudgement 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 study of Saline et al., who in a large retrospective dataset including subjects with and without sleep apnoea found that subjects with a SDSL of more than 20 min 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 min [17]. 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 Fig. 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

Table 1
Differences between subject groups (whole night).

Variable	Insomnia patients (N = 20)	Healthy subjects (N = 21)	t-test	Mann–Whitney U
Macrostructural parameters				
# 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	
Microstructural parameters				
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
Differences between subject groups (sleep cycle 1).

Variable	Insomnia patients (N = 20)	Healthy subjects (N = 21)	t-test	Mann–Whitney U
Macrostructural parameters				
# 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	
Microstructural parameters				
Delta/beta nREM2	43.7 ± 14.3	69.3 ± 38.7	T-2.844, p = 0.009*	
Delta/beta SWS	276.9 ± 154.5	278.8 ± 123.8		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 3
Associations of amount of sleep misperceived with PSG parameters.

Variable during sleep cycle 1	Insomnia patients
	Spearman (n = 20)
	Rho p=
Macrostructural parameters	
# awakenings	0.55 (p = 0.012)
# transitions	0.347 (p = 0.134)
WASO (minutes)	0.58* (p = 0.008)
%NREM1 sleep	0.60* (p = 0.005)
% REM sleep	0.17 (p = 0.473)
Microstructural parameters	
Delta/beta NREM2	−0.49 (p = 0.028)
Delta/beta SWS	−0.52 (p = 0.028)
Delta/beta REM	0.09 (p = 0.717)
Arousals/hour (nREM)	0.14 (p = 0.552)
Arousals/hour (REM)	0.38 (p = 0.120)
SSI (low frequent)	−0.37 (p = 0.099)
SSI (high frequent)	−0.03 (p = 0.900)

Associations of amount of sleep misperceived, expressed in Sleep During Subjective Latency (SDSL; minutes) with PSG parameters calculated during the first sleep cycle in the insomnia group. In the healthy subjects group, the spread of the sleep onset misperception was too small to identify meaningful correlations. Asterisks indicate significant correlations ($p < 0.01$).

analysis. In addition, the maximum SDSL that we found was 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 (ie, 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 physiological 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 [13,15], 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 [45].

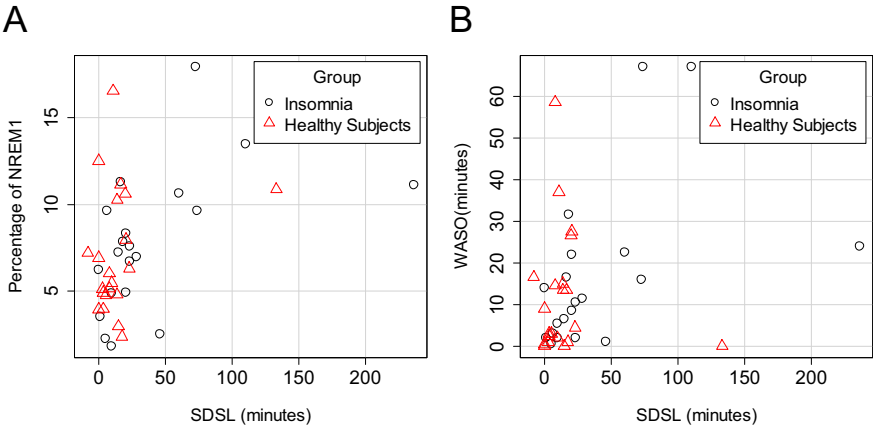

Fig. 3. The percentage of NREM1 and WASO in minutes versus the amount of sleep onset misperception expressed in SDSL. Subjects with insomnia are shown by black circles and healthy subjects are shown by red triangles. The healthy subjects show less variation in SDSL compared to the subjects with insomnia.

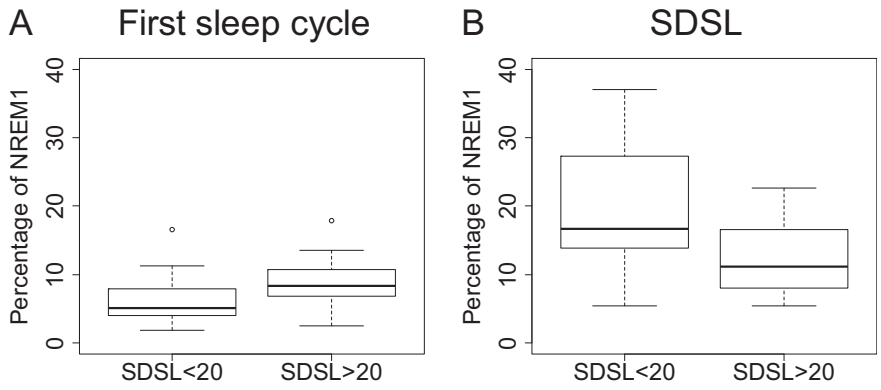

Fig. 4. Comparison of two different methods to calculate the percentage of NREM1.(A) Percentage of NREM1 during the entire first sleep cycle. (B) Percentage of NREM1 during the Sleep During Subjective Latency (SDSL) only. The subjects are divided in two groups: subjects with a SDSL of more than 20 min (N = 15) and subjects with a SDSL of less than 20 min (N = 21). Subjects with a SDSL shorter than 1 min (n = 5) are not shown. Clearly, in subjects with a short SDSL, a large part of the NREM1 epochs is concentrated within the SDSL.

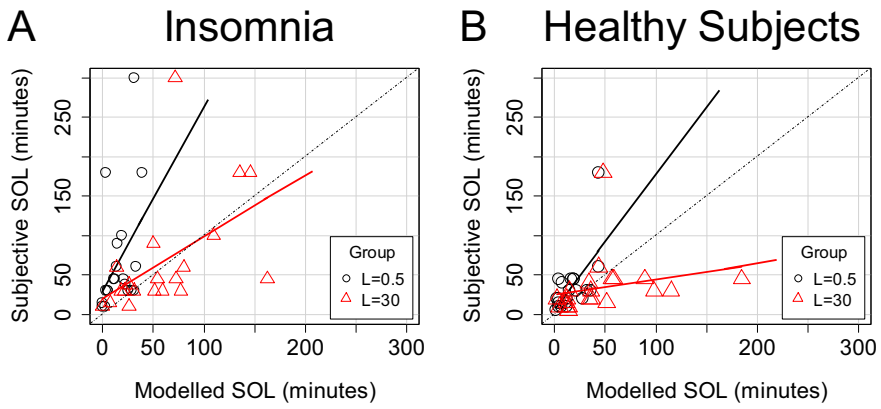

Fig. 5. Follow-up analysis: Subjective versus modelled Sleep Onset Latencies (SOLs) for each subject group. (A): Insomnia group. The SOLs calculated for L = 0.5, assuming that subjective sleep onset occurs together with the first sleep epoch, are shown by black circles. Another example of using the model, 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.

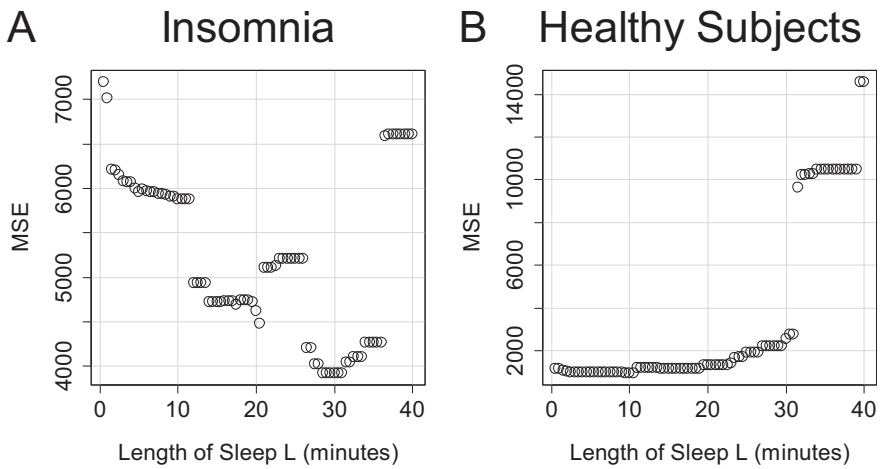

Fig. 6. Follow-up analysis: the minimum square errors (MSEs) for the difference between modelled and subjective SOLs for each value of the model parameter L. Note that the two plots have different scales on the y-axis. (A) Insomnia group. A clear minimum is shown at approximately L = 30 min. (B) Healthy subjects. The MSE shows a minimum at approximately L = 10 min, but no clear improvement is shown compared to L = 0.5.

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 [23]. 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 [23].

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 [46]. In their study two hypotheses were tested: epochs of NREM1 are perceived as wake and sleep bouts under 10 min are perceived as wake [46]. In both cases these hypotheses did not result in a match between objective and subjective sleep duration [46]. 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 min at sleep onset were not taken into account. This indicates that, in insomnia patients, interruption of sleep after less than 30 min 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 $L = 10$ min. In a study of Bonnet et al., 90% of the healthy subjects correctly estimated being asleep after 16 min of continuous sleep [19]. This finding roughly corresponds to the optimum found from our model, which was found for a sleep length of 10 min. Moreover, in the same study at 25 min of continuous sleep after sleep onset, 100% of the subjects correctly estimated being asleep [19]. This is an indication that including sleep lengths above 25 min 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. Yet, 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 ageing. For example, sleep in elderly subjects is more fragmented, the number of arousals increases and the density of sleep spindles decreases [47,48]. 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 on the correlations. 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 during 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 [49]. Intermittent and brief use of 7.5 mg temazepam did not result in rebound insomnia in eight elderly subjects with insomnia in one study [50]. Kales et al., did find moderate rebound insomnia after withdrawal from intermittently used temazepam [51]. 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" [51]. Together this suggests that it is unlikely that our results are biased by medication withdrawal effects.

We modelled 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. Conversely, 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 previously, it is possible that more subtle differences play a role which do not show when analysing conventional parameters.

Therefore, a future analysis could be to zoom into 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 [52]. 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 min [53]. 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. Noteworthy questions include: 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.

Disclosure statement

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Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2019.01.031.

References

[1] Morin CM, LeBlanc M, Daley M, et al. Epidemiology of insomnia: Prevalence, self-help treatments, consultations, and determinants of help-seeking behaviors. Sleep Med 2006;7(2):123–30. https://doi.org/10.1016/j.sleep.2005.08.008.
[2] Roth T. Insomnia: Definition, prevalence, etiology, and consequences. J Clin Sleep Med 2007;3(5 Suppl):3–6. https://doi.org/10.1378/chest.14-0970.
[3] Bastien CH, Ceklic T, St-Hilaire P, et al. Insomnia and sleep misperception. Pathol Biol 2014;62(5):241–51. https://doi.org/10.1016/j.patbio.2014.07.003.
[4] Harvey AG, Tang N. (Mis)perception of sleep in insomnia: a puzzle and a resolution 2013;138(1):77–101. https://doi.org/10.1037/a0025730.
[5] Borkovec TD, Lane TW, VanOot PH. Phenomenology of sleep among insomniacs and good sleepers: Wakefulness experience when cortically asleep. J Abnorm Psychol 1981;90(6):607–9. https://doi.org/10.1037/0021-843X.90.6.607.
[6] Mercer JD, Bootzin RR, Lack LC. Insomniacs' perception of wake instead of sleep. Sleep 2002;25:564–71. https://doi.org/10.1093/sleep/25.5.559.
[7] Maes J, Verbraecken J, Willemen M, et al. Sleep misperception, EEG characteristics and Autonomic Nervous System activity in primary insomnia: A retrospective study on polysomnographic data. Int J Psychophysiol 2014;91(3):163–71. https://doi.org/10.1016/j.ijpsycho.2013.10.012.
[8] Riemann D, Spiegelhalder K, Feige B, et al. The hyperarousal model of insomnia: A review of the concept and its evidence. Sleep Med Rev 2010;14(1):19–31. https://doi.org/10.1016/j.smrv.2009.04.002.
[9] Perlis ML, Giles DE, Mendelson WB, et al. Psychophysiological insomnia: the behavioural model and a neurocognitive perspective. J Sleep Res 1997;6(3):179–88. https://doi.org/10.1046/j.1365-2869.1997.00045.x.
[10] Bonnet MH, Arand DL. Hyperarousal and insomnia: State of the science. Sleep Med Rev 2010;14(1):9–15. https://doi.org/10.1016/j.smrv.2009.05.002.
[11] Lamarche CH, Ogilvie RD. Electrophysiological changes during the sleep onset period of psychophysiological insomniacs, psychiatric insomniacs, and normal sleepers. Sleep 1997;20(9):724–33.
[12] Mendelson WB. Insomnia and related sleep disorders. Psychiatr Clin North Am 1993;16:841–51.
[13] Perlis ML, Smith MT, Andrews PJ, et al. Beta/Gamma EEG activity in patients with primary and secondary insomnia and good sleeper controls. Sleep 2001;1(1):110–7. 24.
[14] Wyatt JK, Bootzin RR, Anthony J, et al. Sleep onset is associated with retrograde and anterograde amnesia. Sleep 1994;17(6):502–11. https://doi.org/10.1093/sleep/17.6.502.
[15] Krystal AD, Edinger JD. Sleep EEG predictors and correlates of the response to cognitive behavioral therapy for insomnia. Sleep 2010;33(5):669–77. https://doi.org/10.1093/sleep/33.5.669.
[16] Buysse DJ, Germain A, Hall ML, et al. EEG Spectral Analysis in Primary Insomnia EEG Spectral Analysis in Primary Insomnia : NREM Period Effects and Sex Differences. Sleep 2008;31(12):1673–982. https://doi.org/10.1093/sleep/31.12.1673.
[17] Saline A, Goparaju B, Bianchi MT. Sleep fragmentation does not explain misperception of latency or total sleep time. J Clin Sleep Med 2016;12(9):1245–55. https://doi.org/10.5664/jcsm.6124.
[18] Sewitch DE. NREM sleep continuity and the sense of having slept in normal sleepers. Sleep 1984;7(2):147–54. https://doi.org/10.1093/sleep/7.2.147.
[19] Bonnet MH, Moore SE. The threshold of sleep: Perception of sleep as a function of time asleep and auditory threshold. Sleep 1982;5(3):267–76. https://doi.org/10.1093/sleep/5.3.267.
[20] Knab B, Engel RR. Perception of waking and sleeping: Possible implications for the evaluation of insomnia. Sleep 1988;11(3):265–72. https://doi.org/10.1093/sleep/11.3.265.
[21] Hauri P, Olmstead E. What is the moment of sleep onset for insomniacs? Sleep 1983;6(1):10–5.
[22] Jobert M, Wilson FJ, Roth T, et al. Guidelines for the recording and evaluation of pharmaco-sleep studies in Man: The international pharmaco-EEG society (IPEG). Neuropsychobiology 2013;67(3):127–67. https://doi.org/10.1159/000343449.
[23] Feige B, Baglioni C, Spiegelhalder K, et al. The microstructure of sleep in primary insomnia: An overview and extension. Int J Psychophysiol 2013;89(2):171–80. https://doi.org/10.1016/j.ijpsycho.2013.04.002.
[24] Parrino L, Milioli G, De Paolis F, et al. Paradoxical insomnia: The role of CAP and arousals in sleep misperception. Sleep Med 2009;10(10):1139–45. https://doi.org/10.1016/j.sleep.2008.12.014.
[25] Smith S, Trinder J. The effect of arousals during sleep onset on estimates of sleep onset latency. J Sleep Res 2000;9(2):129–35. https://doi.org/10.1046/j.1365-2869.2000.00194.x.
[26] Weiner OM, Dang-Vu TT. Spindle oscillations in sleep disorders: A systematic review. Neural Plast 2016;2016. https://doi.org/10.1155/2016/7328725.
[27] Lüthi A. Sleep spindles: Where they come from, what they do. Neuroscientist 2014. https://doi.org/10.1177/1073858413500854.
[28] Leufkens TR, Ramakers JG, de Weerd AW, et al. On-the-road driving performance and driving-related skills in older untreated insomnia patients and chronic users of hypnotics. Psychopharmacology (Berl) 2014;231(14):2851–65. https://doi.org/10.1007/s00213-014-3455-z.
[29] Buysse DJ, Reynolds 3rd CF, Monk TH, et al. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatr Res 1989. https://doi.org/10.1016/0165-1781(89)90047-4.
[30] Van Diest R, Milius H, Markusse RSJ. The sleep-wake experience list. Tijdsch Soc gezondheidsz 1989;67:343–7.
[31] Van Der Meulen Mulder-Hajonides. Measurement of Subjective Sleep Quality. Amsterdam: WREH; 1981.
[32] Derogatis L. The SCL-90-R: Administration, Scoring and Procedures Manual II. Baltimore: Baltimore Clinical Psychometric Research; 1983.
[33] Beck AT, Ward CH, Mendelson M, et al. An inventory for measuring depression. Arch Gen Psychiatr 1961. https://doi.org/10.1001/archpsyc.1961.01710120031004.
[34] Spielberger C, Gorsuch R, Lushene R, et al. Manual for the State-Trait Anxiety Inventory (Form Y). Palo Alto: Consulting Psychologists Press Inc.; 1983.
[35] Smets EMA, Garssen B, Bonke B, et al. The multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. J Psychosom Res 1995. https://doi.org/10.1016/0022-3999(94)00125-O.
[36] World Medical Association. World medical association declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013;310(20):2191–4. https://doi.org/10.1001/jama.2013.281053.
[37] Rechtschaffen A, Kales A. A manual of standardized techniques and scoring system for sleep stages of human subjects, vol. 12. Washington: DC US Gov Print Off; NIH Public; 1968. https://doi.org/10.1016/0013-4694(69)90021-2.
[38] Aeschbach D, Dijk DJ, Trachsel L, et al. Dynamics of slow-wave activity and spindle frequency activity in the human sleep EEG: effect of midazolam and zopiclone. Neuropsychopharmacology 1994;11:237–44. https://doi.org/10.1038/sj.npp.1380110.
[39] Iber C, Ancoli-Israel S, Chesson AL, et al. The AASM Manual for the Scoring of Sleep and Associated Events: Rules. Terminology and Technical Specifications; 2007.
[40] Schimicek P, Zeitlhofer J, Anderer P, et al. Automatic sleep-spindle detection procedure: aspects of reliability and validity. Clin EEG Neurosci 1994;25(1):26–9. https://doi.org/10.1177/155005949402500108.
[41] Anderer P, Saletu B, Saletu-Zyhlarz GM, et al. Recent advances in the electrophysiological evaluation of sleep. In: Drinkenburg W, Ruigt G, Jobert M, editors. Essentials and Applications of EEG Research in Preclinical and Clinical Pharmacology, vol. 1. Berlin: Unipublish Verlag Für Studium&Praxis OHG; 2004. p. 307–39. https://doi.org/10.1146/annurev.ecolsys.34.011802.132351.
[42] Anderer P, Gruber G, Parapatics S, et al. An E-Health solution for automatic sleep classification according to Rechtschaffen and Kales: Validation study of the somnolyzer 24 x 7 utilizing the siesta database. Neuropsychobiology 2005;51(3):115–33. https://doi.org/10.1159/000085205.

[43] Punjabi NM, Shifa N, Dorffner G, et al. Computer-assisted automated scoring of polysomnograms using the somnolyzer system. Sleep 2015;38(10):1555–66. https://doi.org/10.5665/sleep.5046.
[44] Anderer P, Saletu B, Saletu-zyhlarz GM, et al. Textbook for the Training Course of the. International Pharmaco-EEG Society; 2006.
[45] Normand MP, St-Hilaire P, Bastien CH. Sleep spindles characteristics in insomnia sufferers and their relationship with sleep misperception. Neural Plast 2016;2016. https://doi.org/10.1155/2016/6413473.
[46] Bianchi MT, Williams KL, Mckinney S, et al. The subjective-objective mismatch in sleep perception among those with insomnia and sleep apnea. J Sleep Res 2013;22(5):557–68. https://doi.org/10.1111/jsr.12046.
[47] Carrier J, Viens I, Poirier G, et al. Sleep slow wave changes during the middle years of life. Eur J Neurosci 2011;33(4):758–66. https://doi.org/10.1111/j.1460-9568.2010.07543.x.
[48] Edwards BA, O'Driscoll DM, Ali A, et al. Aging and sleep: physiology and pathophysiology. Semin Respir Crit Care Med 2010;31(5):618–33. https://doi.org/10.1055/s-0030-1265902.
[49] Perlis M, Gehrman P, Riemann D. Intermittent and long-term use of sedative hypnotics. Curr Pharm Des 2008;14(32):3456–65. https://doi.org/10.2174/138161208786549290.
[50] Vgontzas AN, Kales A, Bixler EO, et al. Temazepam 7.5 mg: effects on sleep in elderly insomniacs. Eur J Clin Pharmacol 1994;46(3):209–13. https://doi.org/10.1007/BF00192550.
[51] Kales A, Manfredi RL, Vgontzas AN, et al. Rebound insomnia after only brief and intermittent use of rapidly eliminated benzodiazepines. Clin Pharmacol Ther 1991;49(4):468–76. https://doi.org/10.1038/clpt.1991.55.
[52] Wei Y, Colombo MA, Ramautar JR, et al. Sleep stage transition dynamics reveal specific stage 2 vulnerability in insomnia. Sleep 2017;40(9). https://doi.org/10.1093/sleep/zsx117.
[53] Winser MA, McBean AL, Montgomery-Downs HE. Minimum duration of actigraphy-defined nocturnal awakenings necessary for morning recall. Sleep Med 2013;14(7):688–91. https://doi.org/10.1016/j.sleep.2013.03.018.