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Insomnia—perchance a dream? Results from a NREM/REM sleep awakening study in good sleepers and patients with insomnia FREE

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Abstract

Study Objectives

Insomnia disorder (ID) is a frequent sleep disorder coupled with increased risks for somatic and mental illness. Although subjective complaints are severe, polysomnography (PSG) parameters show only modest differences between groups. Rapid eye movement (REM) sleep as the most aroused sleep state may be especially vulnerable to be perceived as wake. To directly assess possible differences, we determined auditory waking thresholds and sleep perception in patients with ID and healthy control participants (good sleeper controls [GSC]) in N2 and REM sleep.

Methods

In case–control study, 27 patients with ID and 27 age- and gender-matched controls were included. Four consecutive nights were assessed in the sleep laboratory, with nights 3 and 4 each containing three awakenings either from stable N2 or REM sleep. Awakening thresholds in patients with ID did not differ from GSC, but decreased over the course of the night. Patients with ID indicated significantly more frequently than GSC having been awake when woken from REM sleep but not from N2 and were less sure when indicating they had been asleep. Additionally, participants with ID rated their REM sleep mentation as more emotionally negative compared with GSC.

Conclusions

This study presents direct evidence that the subjective experience of insomnia might be specifically coupled to the REM sleep state. Assuming chronic hyperarousal as a central pathophysiologically relevant pathway for insomnia, this might become especially evident during REM sleep, thus reflecting a hybrid sleep state in insomnia being coupled with altered sleep perception.

insomnia, dreams, awakening

Statement of Significance

Experimental awakening studies offer a unique direct approach to sleep perception. Here, we use this approach to elucidate sleep perception in insomnia disorder (ID) in comparison to good sleeper controls (27 vs 27). Although awakening thresholds were not altered, patients with ID more often reported having been awake when actually awoken from rapid eye movement (REM) sleep but not from N2 sleep. The results

show that REM sleep mentation is more wake-like and emotionally more negatively toned in ID, whereas objective measurements such as waking threshold and spectral power did not differ.

Introduction

A central unresolved enigma of insomnia research is the marked discrepancy between the subjective experience of sleep (usually measured by sleep diaries) and objective, i.e., polysomnographic (PSG) findings in insomnia disorder (ID) [1, 2]. It is a hallmark of healthy sleep (especially in younger adults) that only rarely, even if wake phases and active behavior were clearly measurable by PSG, any memory exists for the time interval between going to sleep and finally waking up. In contrast, many patients with ID report subjective nocturnal wake times much longer than determined by PSG (overview: Ref. 3). This discrepancy led to the term paradoxical insomnia for patients with a relatively normal PSG documented sleep continuity and architecture [4], in spite of drastic subjective complaints of disturbed sleep. This discrepancy is supported by a meta-analysis of PSG data [5], indicating that patients with ID on average lose 30 min of objectively measured sleep per night compared with good sleepers, whereas sleep diary data indicate a mean difference of 120 min between both groups concerning total sleep time.

Harvey and Tang [3] listed more than 10 theoretical approaches to explain this discrepancy and discuss whether increased physiological arousal, evidenced for example by increased fast frequencies in the sleep electroencephalogram (EEG) (particularly the β range [6, 7]), is coupled with increased cognitive activity during sleep and thus contributes to an altered experience or perception of sleep in insomnia.

Several studies [8–11] pointed to a pivotal role of rapid eye movement (REM) sleep and microarousals during this sleep state. As REM sleep represents the most highly aroused brain state during sleep, it seems particularly prone to arousals, especially in individuals with persistent hyperarousal [12]. Earlier work demonstrated that spontaneous arousals occurring during REM sleep, compared with arousals during NREM sleep, are more frequently experienced as changes into the wake state [13–16]. For patients with insomnia, it was demonstrated that at least 15 min of uninterrupted sleep are necessary in order to be experienced distinctly as sleep [16, 17]—thus sleep interspersed with a high density of (micro-) arousals may be perceived as wake rather than sleep by patients with insomnia. This corresponds to our finding of an increased frequency of microarousals during REM sleep in insomnia and the significant correlation between the degree of sleep misperception and the amount of REM sleep in this group [8, 9]. This line of thinking is further supported by the fact that the activated EEG of REM sleep bears strong similarities to the waking EEG. Simultaneously, event–related potential responses (ERP) to auditory stimulation during REM sleep are attenuated and morphologically different from waking ERPs, (e.g. Refs. 18 and 19), and waking thresholds are comparable to nonrapid eye movement (NREM) sleep [20–22]. It has also been noted that at least in young individuals most spontaneous awakenings occur during REM sleep, which was interpreted in the direction that REM sleep provides an optimal physiological condition for the transition from sleep to waking [23]. Klemm [24] extended this interpretation by postulating that the brain uses REM to help wake itself up after it has had a sufficient amount of sleep. Asking good sleepers whether they were awake or sleeping upon experimental awakenings during the night, Weigand et al. [25] noted that REM sleep awakenings in good sleepers have a relatively low chance of leading to awake reports (20.6 per cent compared with 38.2 per cent out of sleep stage N2).

Experimental awakening studies in insomnia are scarce and the existing ones are limited by small sample size [22, 26]. Both studies did not find reduced auditory arousal thresholds in insomnia, which could be due to their low power. Johnson et al. [26] examined 12 sleep onset insomniacs and 12 good sleepers, tending to lower values in NREM sleep in the former and similar but slightly increased values in REM (their Table 2). Mendelson et al. [22], comparing 10 patients suffering from insomnia and 10 controls, reported similar auditory arousal thresholds between the groups. However, their Figure 2 shows reduced thresholds both 10 min after sleep onset and 5 min after first REM onset (somewhat stronger for the latter) in insomnia. These data indicate that a larger study could possibly find the arousal system during sleep to be more sensitive in insomnia. Regarding subjective experiences, Mercer et al. [27] reported that patients afflicted with insomnia were more likely to report wakefulness upon awakenings from both 5 min after stage 2 or REM sleep onset. More recently, Pérusse et al. [10] reported that dream content elicited by REM sleep awakenings was more negative in emotional content, which correlated with decreased sleep efficiency in patients with insomnia compared with good sleepers.

A specific role of REM sleep for insomnia might also be suggested by the bidirectional relationship between insomnia and psychopathology, especially depression. Based on the theory that sleep, especially REM sleep, serves as a process of affective brain homeostasis [28, 29], a chronic disturbance of REM sleep through microarousals or wake intrusions during the REM sleep state may explain why insomnia in the long term so frequently leads to manifest depression (see meta-analyses in Refs. 30 and 31), which is then characterized by increased REM sleep pressure as reflected by shortened REM latency and increased REM density and REM sleep amounts (overview: see Ref. 32). This frequently observed disinhibition of REM sleep in depression could thus be interpreted as a REM sleep rebound due to chronic REM sleep deprivation during insomnia. This assumption is in line with the results of our meta-analysis of PSG sleep in insomnia [5] which showed that REM sleep is slightly but significantly decreased in insomnia.

The current study aimed at elucidating the phenomenon of paradoxical insomnia (or sleep state misperception, cf. Ref. 4). Clinicians and researchers agree that this type of discrepancy between sleep time as measured by PSG and subjectively perceived sleep is observable in the majority of patients suffering from insomnia at least to some degree (ICSD-3 [33]), compared with good sleepers.

The objective of the current study was to determine the correlates of paradoxical insomnia using the method of measuring wakening thresholds together with electrophysiological analyses (spectral analysis and microarousal analysis) in good sleeper controls (GSC) and patients with ID. We investigated the sleep EEG with these methods prior to experimental awakenings (NREM vs. REM sleep) in both groups.

Our main hypotheses were as follows: (1) waking thresholds are lower in insomnia in NREM and REM sleep, (2) more awake judgments following REM sleep awakening will be observed in insomnia, (3) more emotionally negative mentation following REM sleep awakening will be reported in insomnia compared with good sleepers, and (4) the results from (1) to (3) are dependent on the EEG characteristics of sleep prior to the awakening.

Methods and Materials

Participants

Patients were recruited from our database of former inpatients with insomnia and our outpatient sleep disorder clinic. Good sleepers were recruited by word of mouth. Fourty-two GSC and 41 patients were screened with the aim of obtaining $n = 28$ participants per group (sample size calculation in Statistics). Supplementary Figure S1 shows the detailed recruitment flow.

Both patients and GSC were screened extensively prior to inclusion of the study. The screening procedure included a physical and psychiatric investigation, a routine blood sample testing, a urine sample (including drug screening), the Structured Clinical Interview for DSM-IV, Axis I (SCID-I [34]), and the sleep diaries of the "Deutsche Gesellschaft für Schlafforschung und Schlafmedizin" (DGSM, http://www.dgsm.de/) for 2 weeks.

Inclusion criteria were as follows: age 25 to 65 years (a restricted age range seemed adequate in order to avoid marked age-related confounds) and normal hearing (as determined by audiometry); signed informed consent. For the patient group, ID diagnosis (DSM-5; however, due to our exclusion criteria, the patients also conformed to a diagnosis of primary insomnia after DSM-IV) and a mismatch between subjective and objective total sleep time of at least 60 min (i.e. in the direction of a subjective underestimation of TST). Subjective TST was derived from the 14 day sleep diary and was contrasted to the PSG derived TST of the second (baseline) night. This aimed to guarantee that all patients in the ID group qualified for at least medium misperception of TST similar to the typical retrospective population of ID patients as seen, e.g., in Ref. 8.

Exclusion criteria were as follows: psychiatric disorders (acute or lifetime) in the control group (evaluated with the SCID-I); other acute and lifetime psychiatric diseases apart from insomnia in the patient group (evaluated with the SCID-I); sleep disorders according to the International Classification of Sleep Disorders (ICSD-3 [33]), in the control group (evaluated by the above mentioned clinical interview and results from the first PSG investigation in the sleep laboratory); other sleep disorders apart from insomnia according to the ICSD-3 in the patient group (evaluated by the above-mentioned clinical interview and results from the first PSG investigation in the sleep laboratory); shift work or transmeridian flights within the last 4 weeks and irregular sleep–wake rhythms (frequent shifts of bed times > 1 hr); regular intake of any psychotropic substance known to affect sleep within the 2 weeks before the investigation or during the participation in this study; or ongoing psychotherapy; pregnancy or lactation; and clinically significant, severe, or unstable medical diseases that have an impact on sleep. Furthermore, participants with an AI (Apnea Index) > 5 per hour and a PLMS (Periodic Leg Movements in Sleep) with arousal index > 5 per hour as observed during the first (adaptation) night were excluded.

All participants were informed in detail about the purpose, design, and potential risks of the current study by the physician or psychologist in charge of recruitment. All participants were informed that participation is voluntary and that the informed consent can be withdrawn without stating any reason for doing so. Study participation required a signed consent form. The study protocol was submitted to and approved by the local ethics committee of the University of Freiburg Medical Centre (Vote 399/12; October 15, 2012). The study was conducted in accordance with the Declaration of Helsinki. All participants received a reimbursement of €300 for participation.

Questionnaires

A set of questionnaires was used for an extensive psychometric characterization of all participants in addition to the diagnostic procedure of the screening investigation: Insomnia Severity Index (ISI [35]), Pittsburgh Sleep Quality Index (PSQI [36]), Epworth Sleepiness Scale (ESS [37]), Glasgow Sleep Effort Scale (GSES [38]), Ford Insomnia Response to Stress Test (FIRST [39, 40]), Dysfunctional Beliefs and Attitudes about Sleep (DBAS [41, 42]), Pre-Sleep Arousal Scale (PSAS [43]), Beck Depression Inventory (BDI [44]), and State Trait Anxiety Inventory (STAI [45]).

These questionnaires served to describe both samples and to confirm that the ID sample reflected the condition comparable to previous studies in our and other laboratories (for data see Table 1).

Table 1.

Sample characteristics

		GSC		ID		ES	*t*	*P*
		M	F	M	F			
	N	**12**	**15**	**11**	**16**			
		Mean ±*SD*		**Mean ±*SD***				
	Age	44.44 ±11.20		44.04 ±12.08		−0.03	−0.13	.898
	Duration of insomnia (yr)	0.00 ±0.00		14.47 ±16.56		1.24	4.54	**.000**
	BDI	1.41 ±2.02		9.41 ±7.36		1.48	5.45	**.000**
	STAI	27.52 ±5.09		39.42 ±9.86		1.53	5.49	**.000**
	ISI	2.11 ±1.97		16.70 ±4.30		4.36	16.02	**.000**
	ESS	4.85 ±2.88		7.78 ±4.14		0.82	3.01	**.004**
	GSES	0.59 ±0.84		6.30 ±3.46		2.26	8.32	**.000**
	FIRST	18.33 ±4.25		25.22 ±5.05		1.48	5.42	**.000**
	DBAS-16	31.15 ±17.50		79.00 ±24.88		2.22	8.17	**.000**
	PSAS-SA	8.93 ±1.49		12.56 ±3.86		1.24	4.56	**.000**
	PSAS-CA	10.59 ±2.61		19.93 ±8.43		1.50	5.50	**.000**
PSQI	SOL	11.33 ±7.10		49.56 ±42.18		1.26	4.64	**.000**
	TST	432.89 ±47.06		309.56 ±87.90		−1.75	−6.43	**.000**
	SEI	92.09 ±8.25		61.46 ±21.13		−1.91	−7.02	**.000**
	PSQI sum score	2.70 ±1.51		10.82 ±3.41		3.08	11.30	**.000**
Sleep diary	TIB	484.72 ±43.51		508.64 ±58.16		0.46	1.70	.096
	TST	439.91 ±47.33		336.63 ±89.81		−1.43	−5.26	**.000**
	SEI	90.72 ±5.13		67.23 ±18.55		−1.71	−6.34	**.000**
	SOL	10.65 ±4.96		55.88 ±79.12		0.80	2.96	**.006**
	WAKE	8.18 ±8.27		47.56 ±43.71		1.24	4.60	**.000**
	EMA	25.98 ±20.71		68.58 ±49.43		1.12	4.12	**.000**
	NAP	5.65 ±6.47		7.87 ±19.60		0.15	0.56	.581
	MOOD_EVE	4.88 ±0.93		3.72 ±0.92		−1.25	−4.54	**.000**
	WELLBEING_EVE	1.92 ±0.74		3.12 ±0.76		1.61	5.85	**.000**
	EXHAUSTION_EVE	1.59 ±0.42		2.00 ±0.51		0.88	3.23	**.002**
	RECOVERY_MOR	1.82 ±0.52		3.04 ±0.66		2.05	7.49	**.000**
	MOOD_MOR	4.98 ±0.80		3.55 ±0.80		−1.79	−6.53	**.000**

Demographic and psychometric data of both samples.

GSC = Good Sleeper Controls; ID = Patients with Insomnia Disorder; M = Male; F = Female; BDI = Beck Depression Inventory; STAI = State Trait Anxiety Inventory, trait version; ISI = Insomnia Severity Index; ESS = Epworth Sleepiness Scale; GSES = Glasgow Sleep

Effort Scale; FIRST = Ford Insomnia Response to Stress Test; DBAS-16 = Dysfunctional Beliefs and Attitude about Sleep-16 items; PSAS = Presleep Arousal Scale; SA = Somatic Arousal; CA = Cognitive Arousal; PSQI = Pittsburgh Sleep Quality Index; SOL = Sleep Onset Latency; TST = Total Sleep Time; SEI = Sleep Efficiency Index; TIB = Time in Bed; EMA = Early Morning Awakening; WAKE = Total time spent awake at night; NAP = Duration of daytime nap; MOOD_EVE = Mood in the evening; WELLBEING_EVE = Wellbeing in the evening; EXHAUSTION_EVE = Exhaustion in the evening; RECOVERY_MOR = Recovery at morning; MOOD_MOR = Mood in the morning.

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Design

The research protocol included four consecutive nights with PSG recordings in the sleep laboratory of our department, which has been accredited by the German Society for Sleep Research and Sleep Medicine [46]. The first night served for adaptation to the sleep laboratory and for screening of sleep apneas and periodic leg movements, whereas the second night served as a baseline night and to gain information about the amount of difference between objective (PSG) and subjective (sleep diary) measurements of total sleep time. Nights 3 and 4 were the experimental nights with awakenings from either NREM or REM sleep, in randomized order (for details, see "NREM and REM sleep awakenings" below).

Sleep recordings and EEG analyses

PSG was recorded using 24-channel Somnomedics PSG for 8 hr from 11 pm until 7 am and scored visually in 30 s epochs by experienced raters (blind to participant status) according to the criteria of Rechtschaffen and Kales [47], encompassing the modifications by the AASM [48]. During the adaptation nights, abdominal and thoracic effort, nasal airflow, oxymetry, and bilateral tibialis anterior EMG were monitored.

Sleep EEG included C3/A2 and C4/A1 derivations filtered with a time constant of 0.3 s and a low-pass at 75 Hz and then digitized at 256 Hz. Sleep continuity parameters included total sleep time (TST), sleep efficiency index (SEI; ratio of TST to time in bed), sleep onset latency (SOL; time from lights out until the first occurrence of sleep stage N2), and the number of wake periods (NWP). Sleep architecture variables included the percentages of stages Wake, N1, N2, N3, and REM within SPT (sleep period time). REM sleep variables included REM latency (interval from sleep onset to the occurrence of the first REM period) and REM density (calculated as in our previous studies, e.g. Ref. 8).

Microarousal analysis followed ASDA criteria [49] and our previous work [8]. These criteria have been used frequently in sleep research (e.g. Refs. 50 and 51); microarousals can be scored reliably [52] and with proven validity [53].

The "Schlaffragebogen-A" (SF-A [54]) was completed each morning directly after awakening for assessing subjective sleep parameters similar to the sleep diary. It allows to assess subjective SOL, TST, and SEI as well as the composite variable general sleep quality (SQ). In addition, it assesses the feeling of recovery in the morning (R_MOR), well-being in the evening (WB-EVE), exhaustion in the evening (EX-EVE), and psychosomatic symptoms during sleep (PS).

NREM and REM sleep awakenings

In nights 3 and 4, three awakenings were performed—either after 5 min of consolidated stage N2 sleep (=NREM sleep awakening night) or after 5 min of consolidated REM sleep (=REM sleep awakening night). Due to the instable nature of the first NREM–REM cycle, experimental awakenings started with the second cycle. Planned awakenings according to these rules were conducted by raters trained in online sleep EEG scoring.

In all sleep lab nights, participants were equipped with a microswitch affixed to the thumb of the dominant hand and instructed to press the button twice in quick succession upon awakening. This I'm awake double click, designed to enable discrimination between intended and inadvertent depressions of the microswitch, was rehearsed prior to lights-out every night in the sleep lab. In the adaptation and baseline nights, the presence of the switch served mainly to familiarize the participants with the equipment. In sleep lab nights 3 and 4, after the awakening stimulation was started, it indicated the experimental awakening and prompted the interview.

Prior to lights out on night 3, participants were familiarized with the awakening procedure and the interview to follow upon awakening. In the presleep sessions prior to nights 3 and 4, participants were exposed to the auditory stimulus used for nocturnal awakenings. The stimulus was a 500 ms white noise sound presented with increasing intensity every 4 s, in steps of 1 dB starting at 5 dB hearing level (HL). Computations used the dB steps from the starting level, i.e., the first presented sound was at 0 dB (=5 dB HL). After experimental awakenings, the standardized interview started with questions on sleep–wake discrimination adapted from Weigand et al. [25]: (1) judgment on the state prior to when the sound occurred (awake or asleep; 0–1); (2) certainty of judgment (not so sure, quite sure, very sure; 0–2); (3) judgment on sleep or wake stage prior to when the sound

occurred (for sleep: state between sleep and wakefulness, light sleep, deep sleep; for wake: state between sleep and wakefulness, awake but sleepy, wide awake; the two items were collapsed into a single sleep stage judgment coded 1–5 between deep sleep and wide awake); (4) following the protocol suggested by Schredl et al. [55], the question about sleep mentation (was something on your mind before you heard the tone) as well as three aspects of this mentation was rated as binary choices: clarity (vague or clear), visuality (thought- or image-like), and control (mentation just happened or was self-controlled). Two questions concerning the emotional quality of the mentation followed (strength of positive and negative emotions on a 4-level scale). During the whole procedure of awakening and interview, main room lights remained turned off; a little bedside lamp was turned on during the interview.

Offline scoring of awakenings

The raw PSG around each awakening was visually checked for indications that a spontaneous awakening might have already begun before the start of the stimulation, as this cannot be reliably determined on the basis of the 30 s epoch staging. The stage at the start of stimulation was characterized as W, N1, N2, tonic, or phasic REM sleep (no awakening was started from N3), and awakenings with a stage of W or N1 were excluded from further analysis. The distinction between tonic and phasic REM sleep was done by discriminating between phases with and without eye movements and judging into which phase the start of the stimulation fell.

Auditory waking thresholds were defined by the intensity (dB above starting level) of the last tone played before the I'm awake button response.

Additionally, EEG waking thresholds were also determined by the number of 30 s epochs from the first tone played to the first epoch scored as awake.

Statistics

Sample size calculation

In order to derive a reasonable estimate of sample size based on the previous work, we decided to focus on the auditory waking threshold, for which quantitative published data existed. Mendelson et al. [22] reported REM sleep thresholds of 56 ± 4 dB for insomniacs and 67 ± 6 dB for controls (mean ± SE; their Figure 2; note that the absolute level is arbitrary since 100 dB designated the maximum loudness the equipment could produce). With n = 10 used in that study, this resulted in a pooled SD of 16 dB and an effect size of 11 dB 16 dB=0.68. Power calculation using α=0.05 and β=0.80 resulted in necessary group sizes of 28 participants.

Auditory waking thresholds

To test our primary hypothesis, thresholds were entered into a repeated-measures ANCOVA with repeated measures variate TIME (hours since sleep onset) and between-participant factors GROUP, STAGE, and covariate AGE. This analysis was performed using log values (multiplicative model, natural log of threshold+1) for the expected asymmetric distribution with long right tail. The same transformation and analysis was performed for the number of epochs to first wake PSG, therefore constructing an EEG-based proxy to the awakening threshold.

Sleep state judgments

The main parameter was the percentage of awake judgments relative to the number of awakenings from the respective sleep stage for each participant. Furthermore, the mean certainty of the judgment was obtained separately for wake and sleep judgments.

Descriptive data are reported as means and standard deviations (SD). Reported effect sizes (ES) are Cohen's d (difference of means divided by pooled standard deviation). Parameter estimates are given as estimates ± standard error (SE). p-Values of <.05 were considered as statistically significant, and <.1 as marginally significant or tendencies. Regarding secondary end points, multiple comparisons post hoc correction was applied to avoid the inflation of type 1 statistical error. The software R (version 3.2, The R Foundation for Statistical Computing 2016, https://www.r-project.org/) was used for statistical analysis.

Results

Sample description

When applying inclusion and exclusion criteria (after the first PSG), 27 participants in each group remained, close to the targeted sample size of n = 28 for each group. Table 1 displays sample characteristics. Both groups were exactly age- and gender-matched as planned. The patient group had suffered from insomnia for 14.5 years on average and thus qualified as a group with high chronicity. With respect to the measures of depression and anxiety (BDI, STAI), the ID group revealed significantly increased values, within the subclinical range demanded by the exclusion criteria. ESS values were significantly increased in ID, though not in the range of excessive daytime sleepiness. The PSQI sum score in ID was 10.8, thus in the range of our previous work concerning insomnia samples (e.g. Ref. 8). All PSQI sleep variables were significantly impaired in ID. More specific insomnia measures (ISI, GSES, FIRST, PSAS) were all significantly enhanced in the ID sample. Sleep diary data (SD) were significantly altered in ID, apart from time in bed and naps. According to the PSQI, total sleep time (TST) was approximately 60 min shorter in ID relative to GSC; for sleep diary data, this difference was about 100 min.

Objective and subjective sleep in nights 1 and 2

Table 2 shows PSG and subjective data measures for the first two nights in the sleep laboratory together with results from multi- and univariate repeated measures ANOVA tests for factors GROUP and NIGHT. The table shows the typical small group effects for objective but large effects for most subjective sleep parameters.

Table 2.

PSG, PSA, and SF-A in adaptation and baseline nights

		Adaptation night		Baseline night			Effects					
		GSC	ID	GSC	ID	ES	Group		Night		Group × night	
		Mean ±*SD*	Mean ±*SD*	Mean ±*SD*	Mean ±*SD*		F	*P*	F	*P*	F	*P*
PSG	Multivariate statistics (Wilk's Lambda)						0.71	.295	0.28	**.000**	0.72	.337
	SOL (min)	19 ±14	33 ±25	14 ±8	18 ±17	0.30	4.12	**.048**	20.36	**.000**	4.98	**.030**
	TST (min)	375 ±52	322 ±89	413 ±40	399 ±40	−0.36	5.28	**.026**	41.10	**.000**	3.89	.054
	SEI (%)	78 ±11	67 ±19	86 ±8	83 ±8	−0.39	5.76	**.020**	40.16	**.000**	3.91	.054
	NWP	35 ±13	28 ±16	28 ±12	27 ±12	−0.05	1.38	.246	7.42	**.009**	4.21	**.045**
	W (%SPT)	18 ±10	25 ±16	10 ±7	11 ±7	0.15	1.86	.179	43.69	**.000**	2.16	.148
	N1 (%SPT)	11 ±6	10 ±6	9 ±5	8 ±5	−0.28	0.82	.369	21.95	**.000**	0.07	.791
	N2 (%SPT)	51 ±10	46 ±10	56 ±7	56 ±10	−0.02	0.76	.387	22.59	**.000**	1.59	.213
	N3 (%SPT)	5 ±6	5 ±7	6 ±6	6 ±7	0.02	0.07	.798	2.53	.118	0.26	.610
	REM (%SPT)	15 ±5	13 ±7	19 ±5	20 ±5	0.09	0.11	.746	58.65	**.000**	2.02	.161
	REML (min)	107 ±48	118 ±46	81 ±49	82 ±32	0.01	0.30	.585	18.06	**.000**	0.62	.433
	REMD (%)	26 ±8	22±9	24 ±9	23 ±6	−0.18	1.27	.265	0.64	.428	0.30	.587
	AI/REM	17 ±9	18 ±13	18 ±7	19 ±15	0.08	0.12	.731	1.11	.297	0.01	.929
	AI/NREM	10 ±5	14 ±13	10 ±4	10 ±8	0.07	1.28	.262	3.23	.078	1.79	.187
SF-A	Multivariate statistics (Wilk's Lambda)						0.66	**.010**	0.47	**.000**	0.93	.916
	SOL	20 ±13	33 ±23	12 ±13	21 ±17	0.61	6.68	**.013**	23.51	**.000**	0.69	.411
	TST	402 ±49	329 ±126	428 ±40	384 ±70	−0.76	11.36	**.001**	9.98	**.003**	1.25	.269
	SEI	86 ±11	75 ±22	93 ±5	86 ±9	−0.91	9.43	**.003**	15.98	**.000**	0.98	.327
	SQ	2.9 ±0.8	2.3 ±0.7	3.4 ±0.6	2.8 ±0.7	−0.92	13.14	**.001**	33.16	**.000**	0.01	.928
	R_MOR	3.3 ±0.8	2.5 ±0.9	3.6 ±0.8	2.9 ±0.7	−0.96	14.45	**.000**	13.13	**.001**	0.09	.763
	WB_EVE	4.0 ±0.7	3.2 ±0.7	4.1 ±0.7	3.5 ±0.7	−0.90	16.18	**.000**	7.47	**.009**	1.80	.186
	EX_EVE	2.5 ±0.7	3.1 ±0.6	2.5 ±0.8	3.0 ±0.8	0.65	9.85	**.003**	0.22	.640	0.03	.857
	PS	1.8 ±0.4	2.0 ±0.5	1.6 ±0.4	1.7 ±0.5	0.39	2.70	.106	14.81	**.000**	0.03	.860

Objective (PSG) and subjective (SF-A) sleep data from both samples.

GSC = Good Sleeper Controls; ID = Patients with Insomnia Disorder; PSG = polysomnography; SF-A = Schlaffragebogen-A; min =

Minutes; SOL = Sleep Onset Latency; TST = Total Sleep Time; SEI = Sleep Efficiency Index %; NWP = Number of wake periods; SPT = Sleep period time; W = Duration of wake during the night % SPT; N1 = Duration of stage sleep NREM 1 % SPT; N2 = Duration of stage sleep NREM 2 % SPT; N3 = Duration of stage sleep NREM 3 % SPT; REM = Duration of REM sleep % SPT; REML = REM Latency (min); REMD = REM Density %; AI = Arousal Index/hr; SQ = Sleep Quality; R_MOR = Recovery in the morning; WB_EVE = Wellbeing in the evening; EX_EVE = Exhaustion in the evening; PS = Psychosomatic Symptoms.

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Mean spectral power was not significantly different between groups in any combination of night and sleep stage (N2, REM; data not shown).

Auditory and EEG waking thresholds for NREM and REM sleep awakenings

The mean awakening threshold across all awakenings was 5.2 ± 5.7 dB above the starting level, with a maximum of 38 dB, corresponding to an average time to button press of 20.8 ± 22.9 s (12 s median, 2.5 min maximum).

The repeated-measures ANCOVA on log-waking thresholds showed neither a main effect of GROUP (threshold larger by 0.087 ± 0.164 [mean ± SE] in ID, p = .599, ES = 0.074) nor of sleep stage (threshold larger by 0.092 ± 0.087 in REM than in N2, p=.291, ES = 0.065). The GROUP by STAGE interaction was also not significant (threshold lower by -0.119 ± 0.125 in ID REM sleep, p=.340, ES = -0.059). There was a significant negative TIME effect (-0.065 ± 0.016 per hour, p=.0001, ES = -0.243) and a tendency for a positive age effect (0.012 ± 0.007 per year, p=.089, ES = 0.243).

Mean thresholds in dB can be computed from this model using the intercept of 1.40, the mean age of 44.2 years, and the mean TIME of 4.67 hr: 3.98 dB in NREM and 4.46 dB in REM sleep for controls, 4.43 dB in NREM and 4.28 dB in REM sleep for ID.

Adding the distinction of phasic REM did not indicate a significant influence of this distinction on the waking thresholds within the REM sleep awakenings (-0.08 ± 0.1, p=.404, ES = -0.052).

To explore a possible influence of objective sleep quality on the waking thresholds, we also added baseline night TST to the model. The effect was not significant (0.0017 ± 0.0021, p=.413, ES = 0.117) and did not change the pattern of group differences reported above.

The repeated-measures ANCOVA results on log number of epochs until first wake PSG were as follows: a marginally significant GROUP effect (threshold larger by 0.15 ± 0.081 in ID, p=.071, ES = 0.258) and significant STAGE effect (threshold larger by 0.171 ± 0.059 in REM than in N2, p=.004, ES = 0.18). The GROUP by STAGE interaction was marginally significant (threshold lower by -0.147 ± 0.084 in ID REM sleep, p=.080, ES = -0.108). There was a significant negative TIME effect (-0.04 ± 0.011 per hour, p<.0001, ES = -0.331) and a nonsignificant positive age effect (0.003 ± 0.003 per year, p=.327, ES = 0.138).

The mean number of 30 s epochs to awakening derived from this model (intercept 0.70) was 0.75 in NREM and 1.07 in REM sleep for controls, 1.03 in NREM and 1.08 in REM sleep for ID.

Awakening reports

Table 3 shows the statistics of the awakening interviews. Sleep stage N2 was judged as awake in nearly 20 per cent of cases by both groups (4 per cent more by ID patients). However, sleep stage REM was judged as awake in significantly more (16.7 per cent) of cases by patients ID and than by GSC participants (2.6 per cent of cases). Those ID patients who did judge REM sleep as sleep were significantly less certain of this than the GSC participants were of their sleep rating. No significant difference in certainty was observed for awakenings from stage N2.

Table 3.

Awakening reports

		GSC	ID	ES	*t*	*P*
		Mean ±*SD*	**Mean ±*SD***			
N2	n_reports	2.48 ±0.80	2.56 ±0.75	0.10	0.35	.728
	awake_percent	18.59 ±27.21	22.84 ±33.38	0.14	0.51	.613
	certainty_awake	0.90 ±0.74	1.00 ±0.24	0.18	0.41	.691
	certainty_asleep	1.59 ±0.46	1.37 ±0.62	−0.40	−1.42	.162
	stage_judgment	1.99 ±0.66	2.15 ±0.85	0.22	0.79	.434
	mentation	0.29 ±0.29	0.25 ±0.32	−0.12	−0.42	.675
	mentation_awake	0.40 ±0.52	0.40 ±0.46	0.00	0.00	1.000
	mentation_asleep	0.29 ±0.32	0.25 ±0.36	−0.12	−0.41	.680
	clarity	0.43 ±0.47	0.55 ±0.48	0.26	0.67	.510
	visuality	0.54 ±0.46	0.29 ±0.45	−0.54	−1.37	.185
	control	0.14 ±0.36	0.46 ±0.52	0.72	1.84	.080
	pos_feelings	0.46 ±0.78	0.51 ±0.64	0.08	0.28	.784
	neg_feelings	0.05 ±0.18	0.24 ±0.49	0.51	1.87	.071
REM	n_reports	2.63 ±0.74	2.67 ±0.78	0.05	0.18	.859
	awake_percent	2.56 ±9.06	16.67 ±30.18	0.63	2.28	**.030**
	certainty_awake	1.50 ±0.71	1.14 ±0.38			
	certainty_asleep	1.63 ±0.38	1.27 ±0.64	−0.68	−2.40	**.021**
	stage_judgment	1.61 ±0.53	1.97 ±0.79	0.54	1.96	.056
	mentation	0.64 ±0.35	0.63 ±0.38	−0.02	−0.06	.950
	mentation_awake	0.50 ±0.71	0.62 ±0.39			
	mentation_asleep	0.65 ±0.36	0.59 ±0.43	−0.15	−0.55	.588
	clarity	0.79 ±0.35	0.70 ±0.40	−0.25	−0.81	.423
	visuality	0.71 ±0.38	0.69 ±0.41	−0.07	−0.24	.815
	control	0.16 ±0.31	0.27 ±0.39	0.31	1.01	.316
	pos_feelings	0.69 ±0.92	0.78 ±0.64	0.12	0.44	.666
	neg_feelings	0.13 ±0.34	0.53 ±0.63	0.80	2.88	**.006**
	phasic_percent	66.67 ±34.96	59.62 ±29.13	−0.22	−0.79	.433

Awakening interview statistics: n_reports = Number of valid awakening reports per participant and sleep stage; awake_percent = Percentage of reports with ”awake” judgments; certainty_awake = Certainty of ”awake” judgments (0-2); certainty_asleep = Certainty of ”asleep” judgments (0-2); stage_judgment = Deep sleep to wide awake (1-5); mentation = no-yes (0-1); mentation_awake = mentation within ”awake” judgments; mentation_asleep = mentation within ”asleep” judgments; clarity, visuality, control = no-yes (0-1); pos_feelings, neg_feelings = None to strong (0–3).

Note that the group *t*-test cannot be computed for certainty_awake and mentation_awake in REM because only two GSC participants reported having been awake after REM awakenings.

View Large

Regarding sleep mentation, 29 per cent (GSC) and 25 per cent (ID) of awakenings from N2 and 64/63 per cent of awakenings from REM sleep were rated as associated with something was on my mind. There were no significant group differences, also when further discriminating awake and asleep judgments.

Patients with ID rated their sleep mentation as more negatively toned than controls when mentation occurred in REM sleep. With respect to stage N2 sleep mentation, no significant group difference for negative feelings was observed.

When adding the individual percentage of awakenings from phasic REM sleep as covariate in the REM sleep analyses, the influence was significant only for awake_percent, which was smaller when a higher percentage of awakenings was from phasic REM sleep (coefficient -0.22 ± 0.09, p=.023, ES = -0.335).

Discussion

This is the first study to simultaneously investigate auditory waking thresholds, the perception of being awake versus asleep upon experimental awakening and sleep mentation in GSC and patients with ID with a certain degree of sleep state misperception.

The main hypotheses of our study were that arousal thresholds are lowered in ID compared with GSC, especially in REM sleep, and that the perception of being awake or asleep is altered differentially between both groups in NREM and REM sleep.

Waking thresholds

Our first main hypothesis of reduced waking thresholds in ID was not supported in either N2 or REM sleep. We did find a significant decrease of waking thresholds over the course of the night regardless of sleep stage or group, indicating that the measurement of waking thresholds *per se* was sensitive.

To the best of our knowledge, only two prior studies actually measured waking or arousal thresholds in patients with insomnia [22, 26]. Both were limited by small sample size (12 and 10 per group, respectively) and failed to find significantly reduced arousal thresholds in ID. Several other studies [27, 56–58] employed continuous waking sounds which were stopped after participants awoke, thus allowing to measure the reaction time but not an awakening threshold. Sewitch [58] reported a reduced reaction time of the single ID patient relative to 11 controls in both N2 and REM sleep awakenings.

The current study found nonsignificantly increased waking thresholds in ID (marginally significant when using the EEG waking threshold instead of key press). Thus, the nonsignificant result is unlikely to be caused by low power of the current study and we must conclude, in accordance with the previous studies, that auditory awakening thresholds are not reduced in ID. A small reduction in REM sleep awakening thresholds in ID became marginally significant for EEG waking thresholds but cannot be interpreted further.

Forget et al. [59] found no differences of evoked K complexes in ID, whereas Bastien et al. [60] found an enlarged P2 component of the auditory evoked potential in REM sleep specifically in paradoxical insomnia. The latter finding does indicate a higher susceptibility for auditory stimuli. The current study indicates that this does not translate to lower awakening thresholds. Key press–based awakening thresholds may not be optimal because of the unknown and possibly group and sleep stage–specific effect of time needed for orienting (cf. Ref. 61), but using EEG-based awakening thresholds instead led to the same result.

Sleep perception

Confirming our second main hypothesis, the perception of sleep upon awakening differed significantly between GSC and ID. For stage N2, the judgment of having been asleep or awake was similar in both groups. However, in REM sleep, there were significantly more judgments rating the presleep state as awake compared with asleep in patients with ID compared with GSC. Furthermore, those ID patients who did give the asleep judgment when awoken from REM sleep were significantly less certain of it than GSC. These two observations indicate that ID patients are more likely to perceive REM sleep as waking.

GSC hardly reported having been awake at all when awoken from REM sleep (2.6 per cent on average compared with 16.7 per cent for ID),

whereas the figure was around 20 per cent for both groups for N2 awakenings. Weigand et al. [25] found figures of 20 and 38 per cent for REM and N2, respectively, for healthy participants awoken by a single loud tone. Mercer et al. [27], using a signal detection framework for sleep–wake discriminability after a continuous tone, reported false-alarm rates (wake judgment from PSG sleep) of 20 and 40 per cent for REM and N2 sleep, respectively, in GSC and 60/80 per cent in ID. Therefore, there is a common finding of clearly lower probability of awake judgments after awakenings from REM sleep than from N2 sleep, with higher numbers in ID, which was not specific for REM sleep in the study of Mercer et al. [27].

In both groups, mentations (something was on my mind) were reported for about a quarter of awakenings from N2 but two thirds of awakenings from REM sleep. In REM sleep, the rate was independent of concomitant awake or asleep judgments, whereas in N2 sleep, a higher rate (40 per cent) was associated with the awake judgment. The lack of group differences indicates that the frequency of mentations (including possible rumination) is not different and also not their association with awake or asleep judgments.

Interestingly, the emotional tone rated as positive and negative feelings associated with the sleep mentation showed that patients with ID rated specifically negative feelings more strongly than good sleepers when they had experienced mentation in REM sleep. The few previous studies on sleep mentation in insomnia indicate that, as in other groups of sleep-disordered patients [62], mentation content reflects current daytime stressors and more negative emotionality [63, 64]. This corresponds with previous work showing increased daytime negative emotionality in patients with ID compared with GSC (see Refs. 30, 65, and 66).

Effect of phasic REM sleep

Within REM sleep, no influence of phasic or tonic REM sleep phase on waking thresholds was found. This is in contradiction to Ermis et al. [67] who, in 10 healthy participants, found clearly increased waking thresholds from phasic REM sleep (comparable to slow–wave sleep) than from tonic REM (comparable to N2). In that study, each participant was awoken 31 times in one night on average, resulting in clearly more intraindividual data but also much more sleep disturbance by the awakenings.

Event–related potential studies have evidenced clearly blunted EEG responses to auditory stimuli within phasic phases of REM sleep [18, 19, 68–70], suggesting that waking thresholds should also be higher during these phases. Therefore, the amount of intraindividual data available in the current study may not have been sufficient to show a possible difference.

However, the subjective judgment of having been awake was clearly less probable after awakenings from phasic than from tonic REM sleep. No other aspect of the subjective report, including presence of sleep mentation or its emotional tone, differed between tonic and phasic REM sleep. This corresponds to results from other studies [71] noting that dream reports are more vivid during this sleep stage, suggesting that awakenings from phasic REM sleep can be more clearly identified as such rather than being experienced as wake.

Limitations

Power analysis suggested a sample size of $n = 28$ per group to confirm the primary hypothesis of reduced waking thresholds in insomnia. This aim was almost achieved with one participant less in each group than initially planned. Sample characteristics of patients with ID were similar to our previous work (e.g. Ref. 8). The sample had a predominance of females and participants on average were in their mid-forties. The mean duration of insomnia was almost 15 years, reflecting the long duration of the illness in this patient group and a high chronicity of the disorder.

Our inclusion criteria required the subjective sleep duration as derived from the sleep diary to be 60 min less than PSG-derived sleep duration. Although this requirement ensured that we would observe a sample similar to our typical clinical insomnia population, it does not translate to a selected sleep state misperception sample since the discrepancy within the study nights was much smaller (Table 2). We cannot exclude that the lack of misperception in the experimental nights may have contributed to the negative finding regarding awakening thresholds.

Although the ID sample had significantly higher depression values as measured by the BDI compared with GSC, none of the ID participants was clinically depressed as documented by a clinical psychiatric interview (exclusion criterion). There was also more anxiety in the ID group as reflected by significantly increased values of the STAI. However, the psychopathological changes observed in the ID group were all clinically subthreshold and as such typical for PI and ID insomnia samples [72].

Conclusions

Summarizing, these data indicate that, on the one hand, there is no difference in the waking thresholds as measured by auditory waking thresholds between patients with insomnia and good sleepers when woken from sleep stages N2 or REM, but on the other hand patients with insomnia experienced the preceding REM sleep state as awake significantly more often than good sleepers.

Regarding the REM sleep instability hypothesis of insomnia [12], this study failed to add direct support through waking thresholds, despite several studies showing that REM sleep in insomnia is characterized more strongly by microarousals and wake intrusions [8, 11, 64]. However, the sleep perception aspect of this hypothesis, following our previous finding that reports of increased wake time in ID are related specifically to time spent in REM sleep [8], is strongly supported by the current study.

This follows the general observation that objective peculiarities in ID are scant and need large studies to be detected reliably (e.g. Ref. 8 with a group size of 100), whereas the subjective complaints are robust. It appears that directly using these robust differences increases the chance to relate to objective correlates (such as REM sleep).

Another opportunity to relate to objective findings in ID may be to use more EEG channels: Colombo et al. [73] and Riedner et al. [74] used high density (256 electrodes) EEG during waking and NREM sleep and confirmed increased high frequency activity in insomnia during the waking state and NREM sleep. The findings were primarily interpreted as reflecting hyperarousal during day- and nighttime in insomnia, though REM sleep was unfortunately not assessed in these studies.

The importance of REM sleep for subjective experience of ID was indicated early—in a case history, Calef [75] speculated that the severe self-reported insomnia in his patient might not be due to actually being awake at night but just to dreaming to be awake. Cartwright et al. [76] summarized evidence of how dreams or dream content are related to waking concerns in good sleepers and patients with depression during an acute illness episode and remission. A similar description was given by Schredl [62] who studied dreams in different types of sleep disorders. Thus, it might be justified to conclude that the typical presleep concern of being unable to sleep in insomnia might express itself as an increased frequency of awake judgment when woken from REM sleep because this mentation continues into REM sleep. Although we have seen no difference in the absolute rate of something was on my mind judgments in patients with ID, the contents is emotionally more negative and possibly closer to the daytime rumination and thus may be harder to discriminate from waking than REM sleep containing more dreamlike and bizarre mentations. How this may translate into future insomnia treatment remains to be further studied [1, 2].

Data from a PET study [77] which, however, looked only at NREM sleep in good sleepers and patients with ID, reflect increased activation in the precuneus and posterior cingulate cortex areas in insomnia. These changes were interpreted as reflecting difficulties in cognitive, self-referential, and affective areas. At least this might be considered indirect evidence that also in REM sleep the experience of dreaming or consciousness is altered in insomnia.

Supplementary Material

Supplementary material is available at *SLEEP* online.

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Conflict of interest statement

None declared.

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