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RECENT ADVANCES IN SLEEP RESEARCH

NEUE ERKENNTNISSE IN DER SCHLAFFORSCHUNG

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SUMMARY

The past two decades have witnessed substantial progress in methodology and knowledge in sleep research all over the world. The paper at hand will present some recent local contributions to this field. The first is a European project (SIESTA) focusing on the creation of an automatic sleep classification system and a normative database, including polysomnographic (PSG) and psychometric measures, in order to make it possible to diagnose sleep-disordered patients as compared with and age- and sex-matched healthy controls between 20 and 95 years of age. Subsequently, two trials on nonorganic sleep disorders in generalized anxiety disorder (GAD) and bruxism, as well as two trials on organic sleep disorders, i.e. snoring/sleep-disordered breathing treated with a mandibular advancement device (I.S.T.) and restless legs syndrome treated with ropinirole and gabapentin, will be discussed.

Key words: *sleep medicine – sleep research – polysomnography – psychometry – normative database – SIESTA project – sleep stage classification – generalized anxiety disorder – comorbidity – sleep bruxism – snoring – apnea – restless legs syndrome*

ZUSAMMENFASSUNG

Die letzten zwei Jahrzehnte erbrachten weltweit einen enormen Fortschritt in Methodik und Fachwissen hinsichtlich des normalen und gestörten Schlafes. Die vorliegende Arbeit gibt einen Überblick über einige rezente lokale Beiträge auf dem Gebiet der Schlafforschung und Schlafmedizin. Der erste Beitrag stellt das europäische Forschungsprojekt SIESTA vor, das sich mit der Entwicklung einer automatischen Schlafstadienklassifikation sowie einer normativen Datenbank beschäftigt, die polysomnographische und psychometrische Normdaten beider Geschlechter zwischen dem 20. und 95. Lebensjahr beinhaltet, was eine Diagnose von schlafgestörten Patienten im Vergleich mit alters- und geschlechtsentsprechenden gesunden Kontrollen ermöglicht. Danach werden 2 Studien über nichtorganische Schlafstörungen bei generalisierter Angststörung und Bruxismus sowie 2 weitere über organische Schlafstörungen beschrieben und die Behandlung von Schnarchen und schlafbezogenen Atmungsstörungen mittels eines mandibulären Protrusionsbehelfs (I.S.T. = intraorale Schnarchtherapie) sowie die Therapie des Restless-Legs-Syndroms mit Ropinirol und Gabapentin.

Schlüsselwörter: *Schlafmedizin – Schlafforschung – Polysomnographie – Psychometrie – normative Datenbank – SIESTA Projekt – Schlafstadienklassifikation – generalisierte Angststörung – Komorbidität – Schlafbruxismus – Schnarchen – Apnoe – Restless-Legs-Syndrom*

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The polygraphic and clinical database of the SIESTA project

The SIESTA project - A New Standard for Integrating Polygraphic Sleep Recordings into a Comprehensive Model of Human Sleep and its Validation in Sleep Disorders – (http://www.oefai.at/siesta) funded by the European Commission (BIOMED-2, 1997–2000) aimed at conducting extensive research on the architecture of nocturnal sleep and at developing and evaluating advanced methods for sleep analysis based on polygraphic measurements, most prominently electroencephalography (EEG) (Anderer et al. 2004). More than 600 sleep recordings in 189 healthy controls (90 males and 99 females, aged 20-95 years) and 51 patients were obtained according to a standard protocol, including in addition to the traditional polygraphic sleep data also features such as subjective ratings of sleep quality and objective measures of vigilance and cognitive performance in the evening and morning. Organized as a multi-center study, the SIESTA partnership comprised 8 clinical and 8 engineering partners in Europe. All subjects and patients were asked to document their sleep habits over 40 nights in addition to continuous activity monitoring by wrist-worn actigraphs. On days 7 and 8 of this period, subjects spent 2 consecutive nights in the sleep laboratory – one adaptation night for the first-night effect (Saletu et al. 1996) and one baseline night. Table 1 shows normative values of the main sleep parameters based on Rechtschaffen & Kales (R&K) scoring (Rechtschaffen & Kales 1968) for male and female healthy controls of different age groups (20-39, 40-59 and over 60).

Significant correlations between age and the R&K target variables presented in Table 1 were observed in 14 out of the 21 variables (Pearson correlation, $p<0.01$). While time in bed and the total sleep period did not change as a function of age, total sleep time ($r=-0.46$) and sleep efficiency ($r=-0.55$) decreased significantly with increasing age. This decrease was not due to a prolonged sleep onset latency or a longer wake period after the final awakening, but to longer wake periods

Table 1. Normative values of sleep parameters based on R&K scoring in normal healthy males and females of different age groups (mean ± standard deviation)

	20-39 years		40-59 years		60-95 years	
	Males (n: 29)	Females (n: 30)	Males (n: 27)	Females (n: 30)	Males (n: 34)	Females (n: 39)
Total sleep period (min)	445±38	457±28	454±37	452±34	456±37	451±28
Total sleep time (min)	420±34	433±29	407±37	409±36	375±48	378±50
Sleep efficiency (%)	90±6	92±4	85±6	86±7	79±9	80±9
Sleep onset latency (min)	19±24	13±8	20±19	21±20	16±14	16±10
REM latency (min)	76±18	86±36	87±38	81±34	87±47	79±42
Number of sleep cycles	4.2±0.7	4.3±0.7	4.0±1.0	4.2±0.8	3.7±0.9	3.5±0.9
Wake within TSP (min)	26±19	21±18	46±27	41±24	78±43	71±36
Wake after final awakening (min)	3±4	4±8	4±6	6±9	6±11	9±17
Frequency of awakenings	16±7	13±8	23±9	19±7	29±15	23±8
Frequency of stage shifts	136±37	121±29	155±33	138±36	174±50	155±36
S1 (min)	31±15	27±11	47±16	38±18	62±29	45±18
S1 (% TST)	7±4	6±3	12±4	10±5	17±8	12±5
S2 (min)	225±29	226±34	235±39	223±39	207±50	207±45
S2 (% TST)	54±6	52±7	57±6	54±8	55±10	55±8
S3 (min)	34±13	32±12	29±9	34±13	26±22	37±19
S3 (% TST)	8±3	7±3	7±2	8±3	7±6	10±5
S4 (min)	41±20	51±23	16±16	26±24	13±19	21±22
S4 (%TST)	10±5	12±5	4±4	6±6	3±5	6±6
REM (min)	89±16	98±20	81±22	88±25	66±24	68±22
REM (%TST)	21±3	23±4	20±5	22±5	18±6	18±5
Movement time (min)	3±2	3±3	1±2	1±2	2±2	1±1

within the total sleep period (r=0.60) and more frequent awakenings (r=0.47). Thus, with increasing age sleep was more fragmented, which is also seen in a significant increase in the number of stage shifts (r=0.35). Concerning the effect of normal aging on sleep architecture, an increase in light sleep (S1 (%): r=0.53) and a decrease in deep sleep was observed (S4 (%): r=-0.42), while stage-2 sleep remained relatively unchanged. Moreover, REM sleep was reduced in older subjects (REM (%): r=-0.35).

Sex differences were observed in 7 out of the 21 variables (independent samples t-test). Females generally showed a more stable (fewer awakenings, t=-2.83, p<0.01 and fewer stage shifts t=-2.71, p<0.01) and deeper sleep (less S1 (%), t=-2.85, p<0.01 and more S4 (%), t=2.38, p<0.01). Concerning sleep efficiency, sleep latencies, wake within the total sleep period and wake after awakening no significant differences between males and females were seen.

In 2005, Anderer et al. presented an automatic sleep classification system (Somnolyzer 24x7) based on the SIESTA project. Five hundred and ninety recordings, split into development and validation samples, were used. The final validation in 286 PSGs of 95 healthy subjects and 49 patients with sleep disorders revealed an overall epoch-by-epoch agreement of 80% (Cohen's kappa: 0.72) between the Somnolyzer-assisted and the human expert scoring, as compared with an interrater reliability of 77% (Cohen's kappa: 0.68) between 2 human experts scoring the same dataset. Two Somnolyzer analyses (including a structured quality control by two human experts) revealed an interrater reliability close to 1 (Cohen's kappa: 0.99).

In 2007, the AASM Manual for the Scoring of Sleep and Associated Events (Iber et al. 2007) was published by the American Academy of Sleep Medicine (AASM). Concerning the visual classification of sleep stages, these new rules are intended to replace the rules by R&K. We adapted the automatic R&K sleep scoring system Somnolyzer 24x7 to comply with the AASM rules and subsequently performed a validation study based on 72 PSGs from the SIESTA database (56 healthy subjects, 16 patients, 38 females, 34 males, aged 21-86 years) (Anderer et al. 2010). The AASM version of the Somnolyzer revealed an agreement between semi-automated and human expert scoring comparable to that published for the R&K version with a validity comparable to that of human experts, but with a reliability close to 1, thereby reducing interrater variability as well as scoring time to a minimum.

Danker-Hopfer et al. (2009) found an overall agreement of 82% for the new AASM standard (Kohen's kappa =0.76) and of 80.6% (Kohen's kappa =0.68) for the R&K standard. Agreements increased from R&K to AASM for all sleep stages, except N2. The results of this study underline that the modification of the scoring rules on the one hand improves interrater reliability as a result of the integration of occipital, central and frontal leads, but on the other hand declines interrater reliability specifically for N2 due to the new rule that cortical arousals with or without a concurrent increase in the submental electromyogram are critical events for the end of N2.

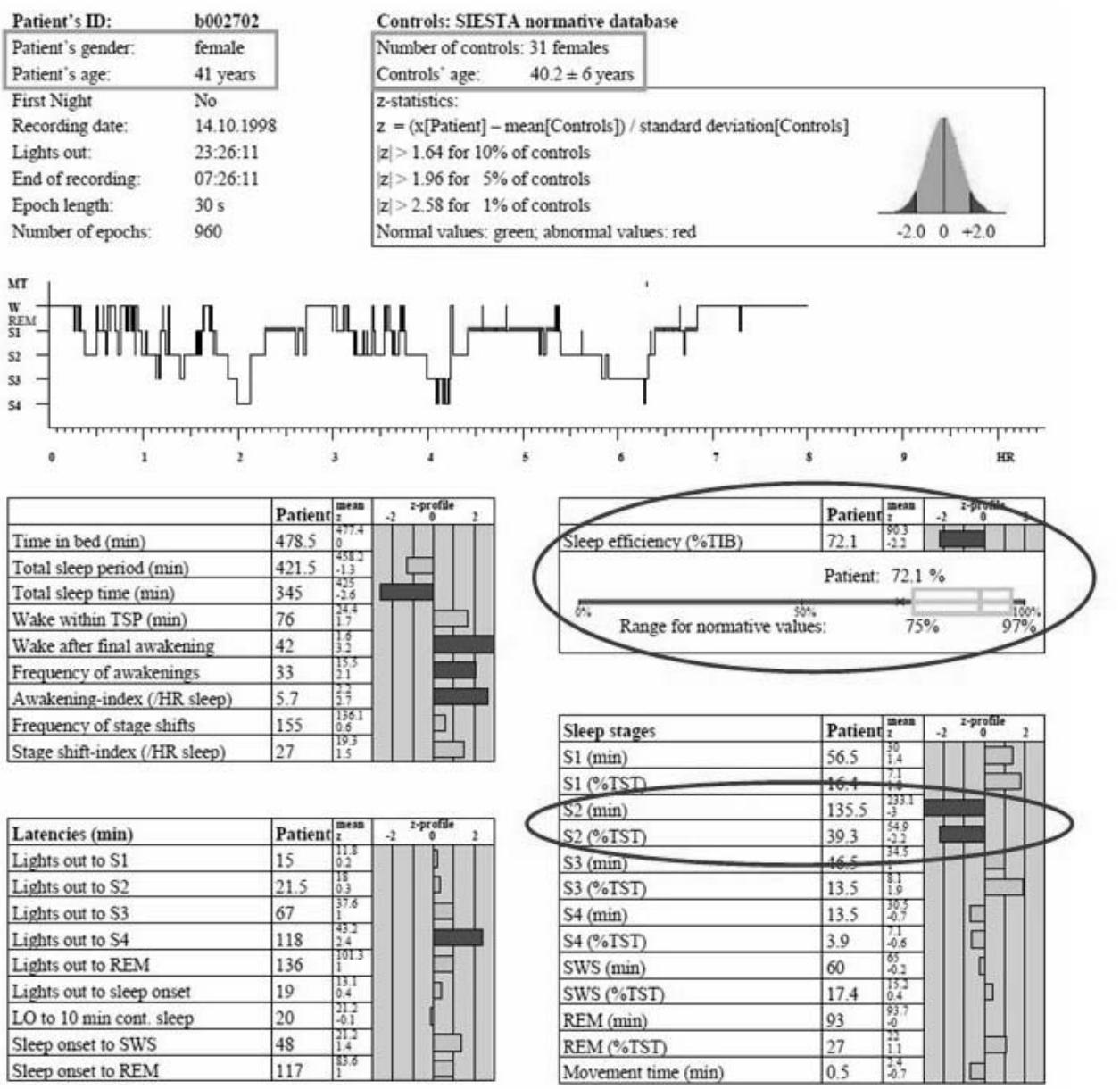

Figure 1. Page 1 of the Siesta Spot Report™ showing the deviations from normative values in R&K variables for a 41-year-old female patient with nonorganic insomnia related to generalized anxiety disorder

Comparison between patients and age- and sex-matched healthy controls

The Siesta Spot Report™ compares patients' sleep profiles with the SIESTA normative database of polysomnographic recordings. On three pages, all important target variables describing an individual patient's sleep profile are summarized and compared with normative values.

The control nights used for the analysis are selected individually according to the patient's age and sex. This is done separately for the adaptation night (first night in the sleep lab) and the diagnosis/therapy nights (following at least one adaptation night). The resulting individual control group comprises all subjects of the SIESTA normative database that are of the same sex as the patient and maximally 10 years younger or older. The database includes approximately 200 controls, and thus an individual control group comprises between 28 and 32 normal healthy controls.

In the output, the patient's values are presented in comparison with the mean values (mean) of the control group and the deviation (z-value) from these normative mean values (Figure 1). The z-values relate the difference between the patient's value and the normative value to the variance observed in healthy subjects. Usually, a z-value between -2 and +2 is considered normal. Based on these deviations, a clinician is able to select a drug or a therapeutic intervention that induces changes in sleep parameters opposite to those caused by the disease (key-lock principle) (Saletu-Zyhlarz et al. 2002) (Table 2).

Table 2. Polysomnographic differences between mental disorder patients and controls as well as between drug treatment and placebo in normals. Alterations in the sleep architecture of patients with nonorganic insomnia due to psychiatric disorders as compared with normal controls are opposite to changes induced by psychotropic drugs intended for their treatment as compared with placebo (key-lock principle)

	POLYSOMNOGRAPHY — SLEEP VARIABLES								
MENTAL DISORDERS	SE %	E min	M min	L min	S1 %	S2 %	S3+4 %	SREM %	REML min
Anxiety disorder	-	+	+	+		-	+		
Depression	-	+	+	+			-	+	-
Mania	-	+	+	+			-	0/+	0/-
Schizophrenia	-	+	+			-	-	(-/+)	0/-
Obsessive-compulsive disorder			+				-		0/-
Post-traumatic stress disorder	-	+						-	+
Borderline personality					+		-	+	-/0
Anorexia	-	+	+				-		(-)
Bulimia									
Alcohol - acute use		-	+	+			+/	-/+	
- subacute use	-							-	
- chronic use	-		+	+			-	+	
- abstinence		+	+	+	+	-	-	-	
Opiates - acute use	-						-	-	
Hypnotics - chronic use					-	+	-	-	
Cocaine - acute use	-	+	+	+	+	-	-	-	+
TREATMENT									
Anxiolytics	+	(-)	-	-		+	(-)		+
Hypnotics						+	-/+	-	+
Antidepressants - sedative	+	-	-	-			+	-	+
Antidepressants - non-sedative	-	(+)	+		+			-	+
Neuroleptics - sedative								+	
Stimulants	-	+	+	+	+	-	-	-	+

SE = sleep efficiency; E = early insomnia; M = middle insomnia (W_{TSP}); L = late insomnia (W_{BB}); REML = REM latency

On the impact of comorbid insomnia on electrophysiological brain function

Comorbidity is increasingly regarded as important for both diagnosis and treatment of psychiatric disorders. Thus, the aim of one of our recent investigations was to compare EEG tomographic data obtained in GAD with and without nonorganic insomnia.

In the first study, low-resolution brain electromagnetic tomography (LORETA) was performed in 44 untreated patients (25 females) with the primary diagnosis of nonorganic insomnia (F51.0) associated with GAD (F41.1) and 44 age- and sex-matched normal controls (Saletu et al. 2005). In the second study, 18 patients (9 females) with the primary diagnosis of GAD without mandatory insomnia were compared with 18 controls.

While patients with F51.0 and concomitant F41.1 showed an increase in LORETA power in the delta, theta, alpha-1 and alpha-2 frequencies (Figure 2), GAD patients without mandatory insomnia demonstrated a decrease in LORETA power - specifically in delta (more left than right hemisphere, involving occipital cortex, insula, cingulate and frontal cortex) and beta (occipital cortex), mirroring neuroimaging findings on the neural circuitry of anxiety (Figure 3).

Conclusion: Different EEG LORETA findings were obtained in GAD patients, depending on the comorbidity: While in daytime recordings patients with nonorganic insomnia demonstrated increased slow activities reflecting daytime tiredness and sleepiness, GAD patients without insomnia exhibited a decrease in slow activity and thus hypervigilance. According to the key-lock principle different pharmacological strategies have to be applied (Saletu et al. 2010a).

Polysomnographic, psychometric and neuropsychopharmacological studies in sleep bruxism

Sleep bruxism (SB) was classified as a parasomnia (i.e. an undesirable physical phenomenon occurring during sleep) (306.8) in the first version of the International Classification of Sleep Disorders (ICSD-1), with stereotyped movements such as grinding or clenching of the teeth during sleep being the essential feature (American Sleep Disorders Association 1997). Interestingly, in the second edition (ICSD-2), SB is listed as a sleep-related movement disorder (780.58, G 47.64) (American Academy of Sleep Medicine 2005). On the other hand, in the ICD-10 (International Classification of

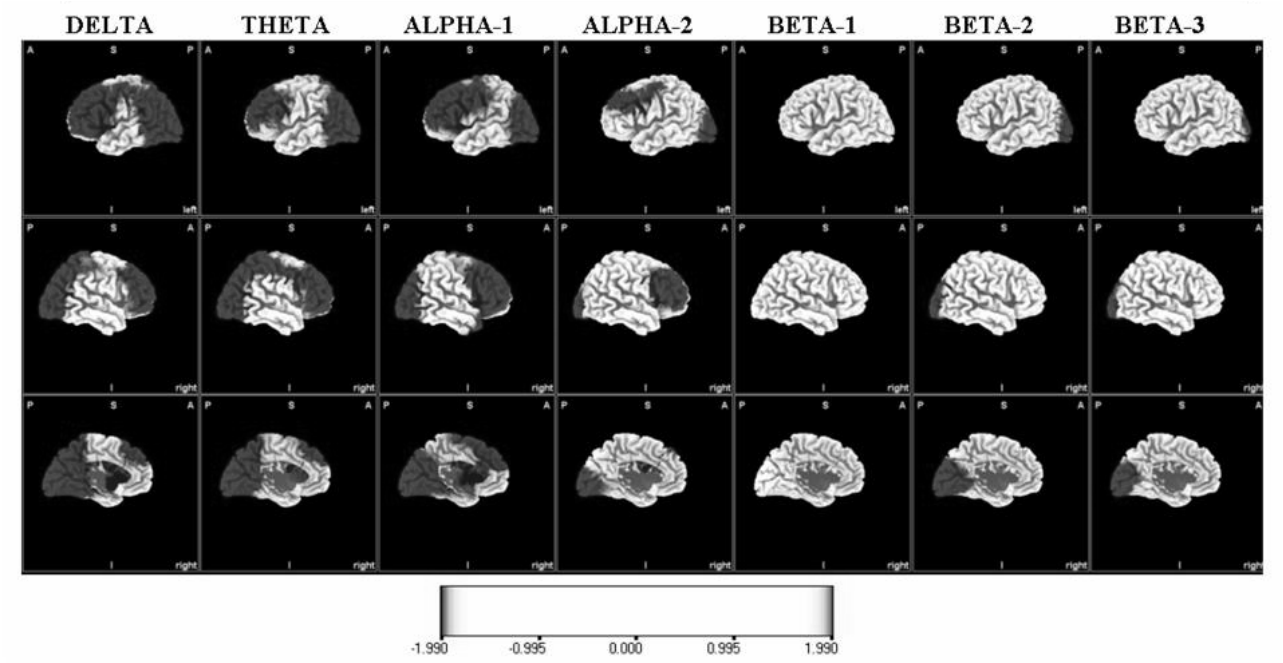

Figure 2. LORETA-maps on differences between generalized anxiety disorder (GAD) patients and normal controls (n=44, 44) (pre-treatment; vigilance-controlled EEG with eyes closed); significant probability maps (SPM) based on t-values ($p<0.05$)

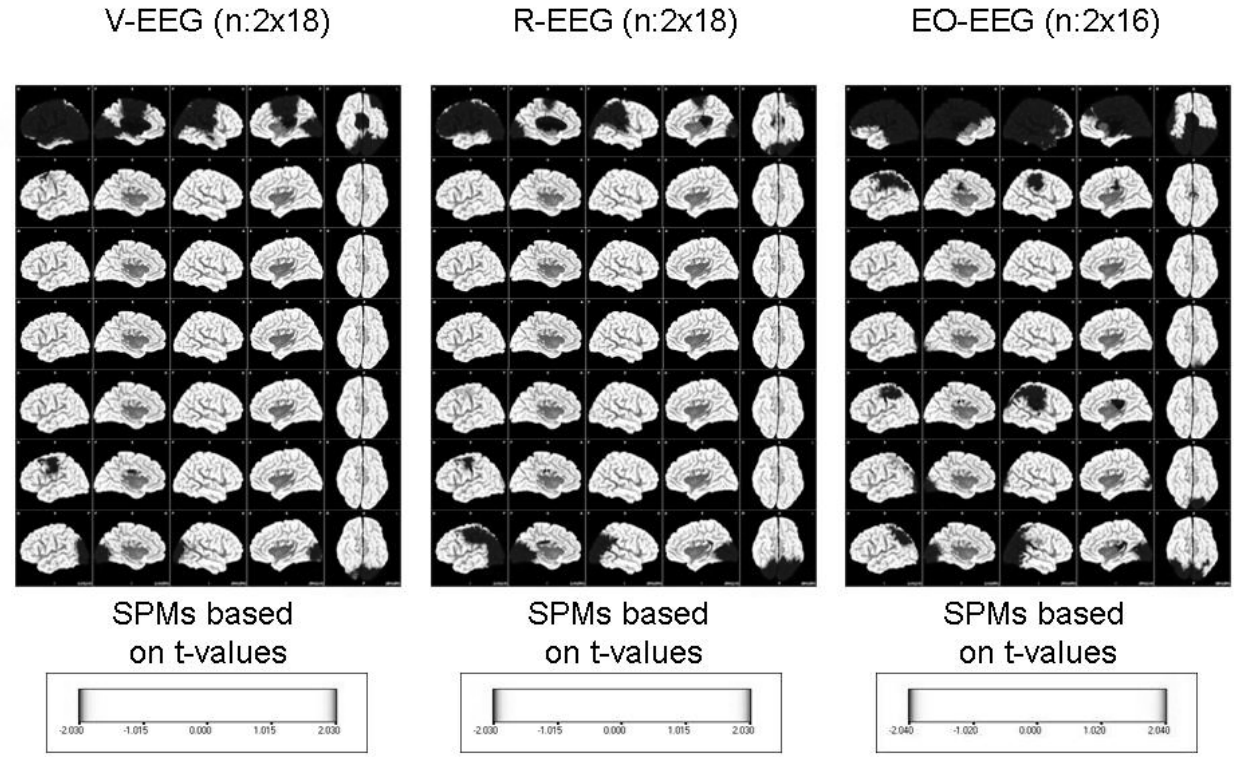

Figure 3. EEG LORETA images on the differences between drug-free GAD patients and age- and sex-matched healthy controls

Diseases, 10th revision) by the WHO, teeth grinding appears in chapter F "Mental and Behavioral Disorders" under F45.8 "Other Somatoform Disorders" (WHO 1992), which indicates that in the pathogenesis of SB, stress and psychosocial variables play a role. SB was suggested to be a sequel of microarousals during sleep (sudden brain and cardiac activation).

The prevalence of sleep bruxism is approximately 8%, that of wake bruxism is around 20%. SB decreases with increasing age, with an incidence rate of 14% in children and 3% in the elderlies.

The pathogenesis, pathophysiology and pharmacotherapy of SB is still not fully understood. We investigated symptomatology, objective and subjective sleep

and awakening quality of middle-aged bruxers compared with normals and acute effects of clonazepam 1 mg compared with placebo by polysomnography and psychometry (Saletu et al. 2010b). Twenty-one drug-free bruxers spent 3 nights in the sleep lab, 21 age- and sex-matched controls 2 nights. Clinically, bruxers exhibited deteriorated measures in the Pittsburgh Sleep Quality Index (PSQI), Zung Self-Rating Scale for Anxiety (SAS), Zung Self-Rating Scale for Depression (SDS) and International Restless Legs Syndrome Study Group Scale (IRLSSG), polysomnographically impaired sleep maintenance, increased movement time, stage shift index, periodic leg movements (PLM) and arousals (Figure 4) and psychometrically deteriorated subjective sleep and awakening quality, evening/morning well-being, drive, mood, drowsiness, attention variability, memory, and fine motor activity. As compared with placebo, clonazepam significantly decreased the SB index in all patients (mean: –42+15%) (Figure 5). Sleep efficiency, maintenance, latency, awakenings and nocturnal waketime, the stage shift index, S1, PLM, the arousal index, subjective sleep and awakening quality and fine motor activity improved.

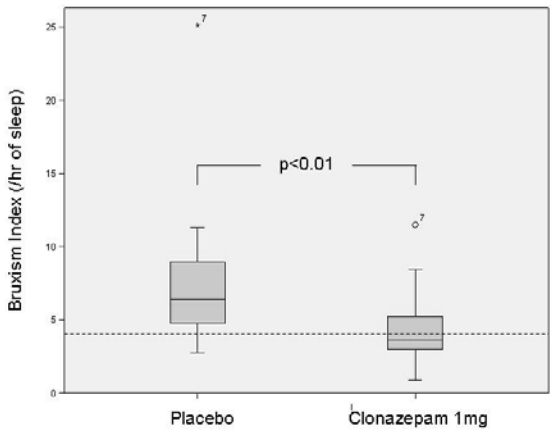

Figure 5. Improvement of the sleep bruxism index after acute bedtime administration of 1 mg clonazepam as compared with placebo ($p<0.01$, Wilcoxon, N:20) and normal values

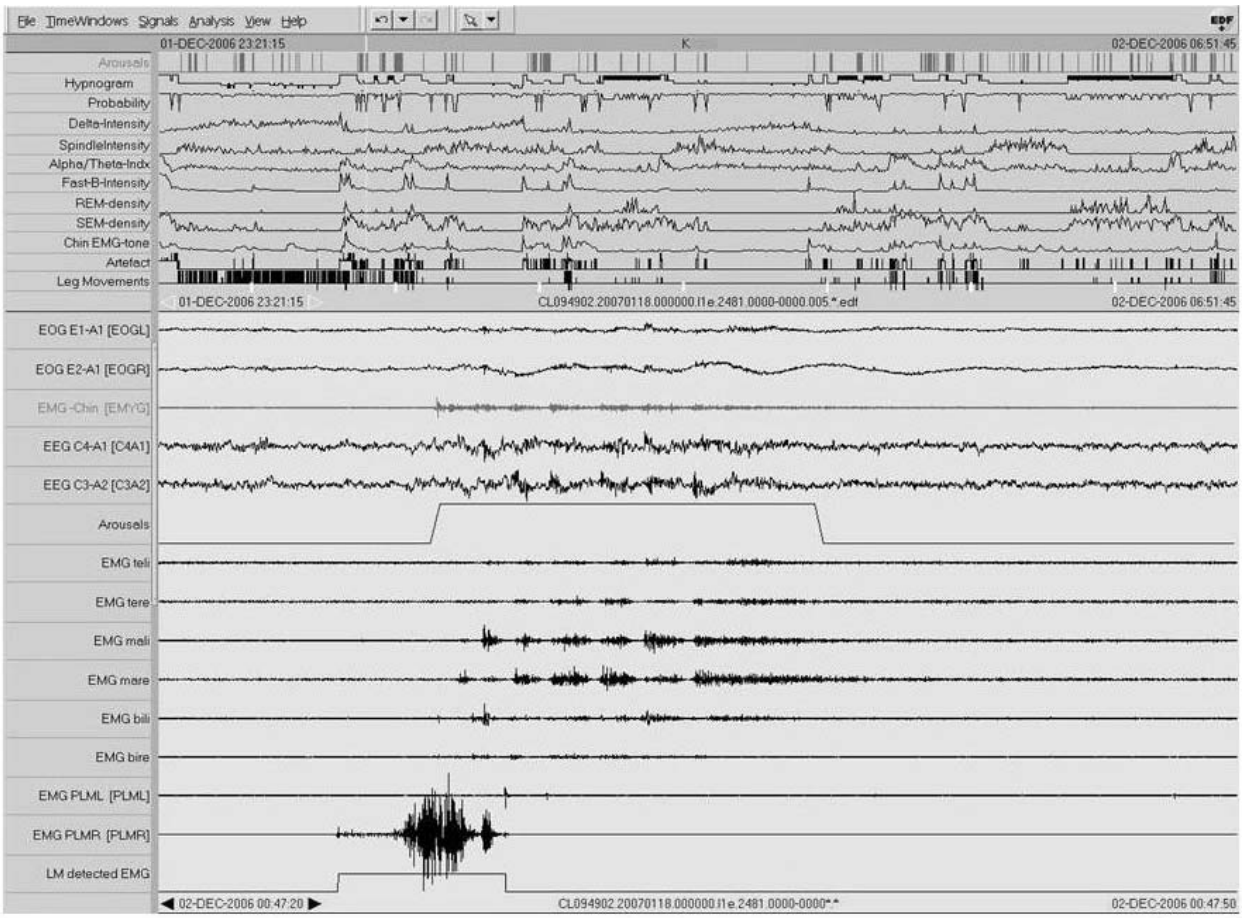

Figure 4. Example of a 30-second polysomnogram demonstrating one sleep bruxism episode between 00:47:20 and 00:47:50. The 15 polygraphic traces in the lower part of the figure demonstrate from the top to the bottom: the left and right electrooculogram (EOG), the submental electromyogram (EMG), the right (C4) and left (C3) central and vertex (CZ) electroencephalogram (EEG), the arousal classification, the left and right temporalis, masseter and biventer muscles, the left and right periodic leg movement (PLM) recordings from the respective anterior tibial muscle and finally the LM detected EMG. In the upper part of the figure the following complex all-night measures are shown: arousals, hypnogram, probability delta intensity, spindle intensity, alpha/theta index, fast beta intensity, REM density, SEM density, chin EMG tone, artefact and leg movements. Note the relationship between the periodic leg movement, the central arousal and sleep bruxism motor activity.

Effects of a mandibular repositioning appliance on sleep in patients with snoring and sleep apnea

Mandibular repositioning appliances (MRAs) have become an established treatment for snoring and sleep-disordered breathing – though most studies only focused on the evaluation of respiratory variables.

In a single-blind, placebo-controlled case-series study we investigated the effects of an individually adjustable MRA (I.S.T. = Intraoral Snoring Therapy) (Figure 6) on psychopathology, macro/microstructure of sleep, PLM, morning performance, mood/affect and psychophysiology (Saletu et al. 2007).

Fifty patients (37 males) aged 59.7+10.3 years, suffering from primary snoring (7), mild (22), moderate (15) and severe apnea (6), spent 4 nights in the sleep laboratory (adaptation, placebo, drug and MRA night).

Confirmatory statistics showed an improvement of the snoring index (SI) by 72%, the apnea index (AI) by 73% and the apnea-hypopnea index (AHI) by 59% (Table 3). Clinical improvement was seen in the PSQI, SAS, SDS and the Epworth Sleepiness Scale (ESS). The restless legs syndrome also improved. Polysomnographically, sleep stages REM and 4 as well as REM latency increased, stage 3, movement time, stage shifts and PLM decreased, as did all arousal measures.

Subjectively, morning well-being, drive, affectivity and wakefulness improved. Objectively, attention, motor and reaction time performance, critical flicker frequency as well as muscular strength increased, diastolic blood pressure and the pulse rate decreased.

Conclusion: Apart from its good therapeutic effects on snoring and respiratory variables (snoring showed complete or partial response in 68%, the AHI in 67% of the apnea patients), the MRA also improved psychopathology, objective and subjective sleep and awakening quality.

Effects of gabapentin and ropinirole in restless legs syndrome

Sleep disturbance is the primary co-morbidity of restless legs syndrome (RLS) and is mainly caused by frequent brief arousals due to periodic leg movements in sleep (PLMS). PLMS occur in approximately 80% to 90% of RLS patients. They support the diagnosis of RLS and correlate with its severity.

In a placebo-controlled sleep laboratory study we compared the acute effects of gabapentin (GBT) and ropinirole (ROP) in RLS (Saletu et al. 2010c). In a parallel-group design, 40 RLS patients received 300 mg GBT and another 40 patients 0.5 mg ROP as compared with placebo. Polysomnographic and psychometric

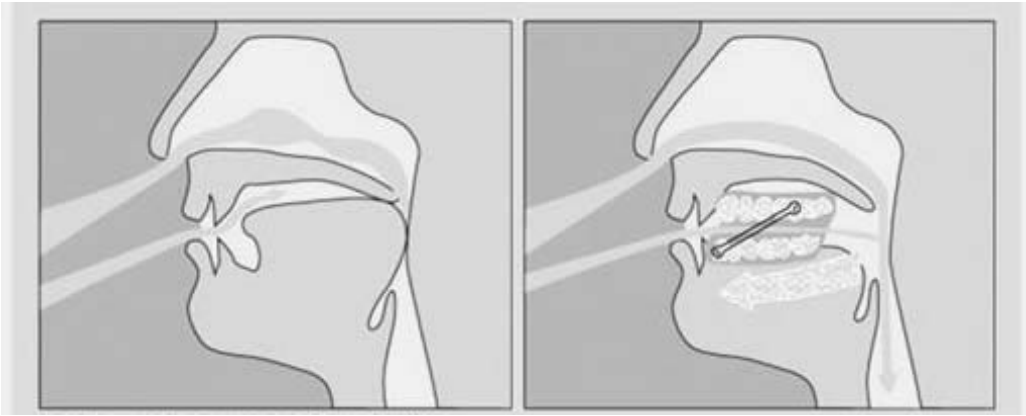

Figure 6a. Mode of action of the mandibular advancement device

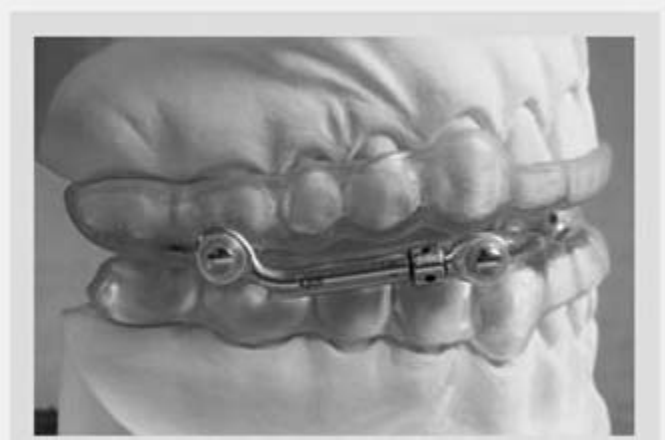

Figure 6b. Mandibular advancement device

Figure 6. Mandibular advancement device and its mode of action. The mandibular advancement device slightly moves forward the lower jaw ("protrusion"), which induces a widening of the pharynx, thus improving the airflow

Table 3. Respiratory, PLM and arousal variables in patients with snoring and SDB before and during treatment with an MRA (n=50)

Variables	Adaptation night	Placebo night	MRA night	Percent change from placebo MD (25/75)
Snoring index, n/h sleep ↓	66.5±45.8	71.9±48.1	28.8±36.2***	-72 (-89/-37)
AI, n/h sleep↓	8.6±10.6	9.4±10.9	3.9±6.3***	-73 (94/-16)
AHI, n/h sleep ↓	16.8±15.2	17.6±16.5	7.7±9.8***	-59 (-81/-14)
Desaturation index, n/h sleep ↓	21.8±17.9	23.0±20.6	12.2±13.5***	-39 (-71/-11)
Minimal 0_2 saturation, % ↑	78.1±9.6	79.6±9.7	82.4±8.4***	+3 (-1/7)
PLM, total n/TIB ↓	216.9±150.3*	200.5±156.8	140.6±122.5***	-24 (-58/23)
PLM index, n/h sleep ↓	20.6±18.6	21.0±20.7	14.3±13.9**	-31 (-63/21)
Arousal index total, n/h sleep ↓	20.4±13.6*	18.4±13.0	14.7±8.2*	-19 (-34/12)
Arousals with respiratory events ↓	22.5±25.6	23.8±27.8	8.5±12.1***	-66 (-94/-33)
Arousals with 0_2 desaturation ↓	1.7±1.9	2.6±4.3	2.0±2.5	-50 (-100/0)
Arousals with snoring ↓	16.4±16.6	16.6±18.1	7.7±l0.2**	-67 (-95/0)

↑↓ = Direction of improvement; Wilcoxon (differences to placebo): * $p<0.05$, ** $p<0.01$, *** $p\leq0.001$.
Values are expressed as mean ± SD, unless otherwise indicated; MD = Median; TIB = time in bed

Table 4. Comparative placebo-controlled polysomnographic and psychometric findings on the acute effects of gabapentin (GBT) vs. ropinirole (ROP) in restless legs syndrome

1. Sleep initiation and maintenance was improved more after GBT than ROP
2. Sleep architecture was changed differentially:
   GBT: SE% ↑; S1 ↓; S2 ↑; S3+4 ↑; REM ↑; REM-L ↓
   ROP: SE% ↓; S1 ↑; S2 ↓; S3+4 ↓; REM ↓; REM-L ↑
3. PLM improved more after ROP (-64%) than GBT (-41%)
   Snoring improved more after ROP (-43%) than GBT (+3%)
   Arousal index decreased more after GBT (-34%) than ROP (+12%)
4. Subjective sleep improved more after GBT than ROP
5. Awakening quality, thymopsyche and noopsyche did not differ

measures were obtained in three sleep laboratory nights (screening/placebo/drug). Statistics included a Wilcoxon test for differences between drug and placebo and a U-test for inter-group differences. Sleep efficiency and latency were found significantly improved after GBT, while they remained unchanged after ROP, with significant inter-drug differences. Sleep architecture showed oppositional changes after the two drugs: While GBT decreased S1, increased slow-wave sleep and SREM and shortened REM latency, ROP increased S2, decreased slow-wave sleep and SREM and increased REM latency. Periodic leg movements (PLM) showed a significantly greater decrease after ROP (-73%) than after GBT (-35%). Subjective sleep quality improved significantly only after GBT, mental performance improved after both drugs with no inter-drug differences.

Conclusion

The dopamine agonist ROP showed acute therapeutic efficacy in regard to PLM measures only, whereas GBT had a less pronounced effect on these measures, but improved objective and subjective sleep and awakening quality as compared with both placebo and ROP. Differential acute drug effects may serve as prognostic indicators of therapeutic response of individual patients (Table 4).

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Conflict of interest:

Bernd Saletu has received research support from Abiogen Pharma, GlaxoSmithKline and Medichemie. He is a shareholder of The Siesta Group Schlafanalyse GmbH, Austria.

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