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Sleepiness is not always perceived prior to falling asleep in healthy sleep deprived subjects and in sleepy patients

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Objective: We prospectively evaluated the subjective awareness of sleepiness (SubS) prior to sleep onset during MWT in young healthy sleep deprived subjects and in sleepy patients.

Method: 159 patients (mean age 39.8 years; 59 females) with sleepiness of various origin and 28 young healthy students (mean age 22.4 years; 13 females) after a whole night sleep deprivation underwent 4 MWTs. They received the instruction: "Indicate your earliest symptoms of sleepiness and try to stay awake as long as possible!" Overt sleep (OS) and microsleeps (MS) of at least 3 seconds duration were scored separately.

Results: Overall 17 of 28 healthy subjects (60.7%) and 64 of 159 patients (40.3%) presented either a MS- or a OS fragment before indicating SubS at least in one of 4 MWT-trials. In both healthy subjects and patients, females demonstrated a better awareness of SubS than male subjects.

Conclusion: Our unexpected finding is in sharp contrast to the general assumption that nobody can fall asleep without prior awareness of sleepiness while driving. If the results will be confirmed in larger series, far reaching consequences will ensue. 1. the simple advice to sleepy subjects that they should not drive when sleepy would no longer be adequate. 2. Motor vehicle crashes due to microsleeps could no longer be judged as due to "reckless driving" in all cases. 3. Prevention strategies against sleepiness induced motor vehicle crashes would have to include efforts to improve perception of SubS.

Key words: Maintenance of wakefulness test; sleepiness; microsleap, motor vehicle crashes
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Circadian modulation in subjective well-being under high and low sleep pressure conditions: effects of age and gender

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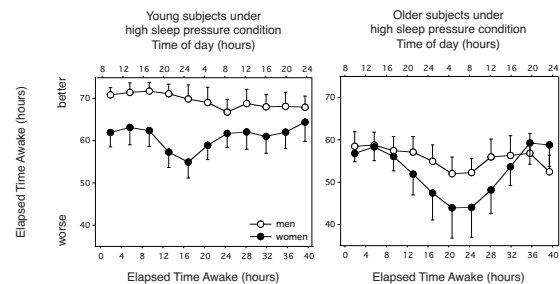
Introduction: Subjective well-being undergoes daily fluctuations. Forced desynchrony protocols with healthy young subjects have shown that subjective mood is influenced by a complex interaction between circadian phase and duration of time awake. To further investigate this interaction, we analysed the time course of subjective well-being under differential sleep pressure conditions in order to examine possible gender- and age effects.

Methods: Sixteen healthy young (8 women; 8 men, 20-35 years) and 16 older volunteers (8 women; 8 men; 55-75 years) carried out a 40-h sleep deprivation (high sleep pressure) and a 40-h nap protocol (low sleep pressure attained with a scheduled sleep-wake cycle of 75 min asleep and 150 min awake) in a balanced cross-over design under constant routine conditions. Subjective well-being was assessed at 20-min intervals during scheduled wakefulness using a composite of 100-mm bipolar visual analogue scales for mood, physical and psychic comfort.

Results: Variations in subjective well-being were significantly determined by the main factors "age", "sleep pressure condition" and "time elapsed" (p at least 0.012, repeated measures ANOVA). In both the high and low sleep pressure protocols, the elderly felt significantly less well than the young (p=0.01). Overall, subjective well-being ratings were significantly lower during the high compared to the low sleep pressure condition (p=0.009). Significant two-way interactions between sleep pressure condition and age (p=0.012), and between sleep pressure and gender (p=0.003), indicated that the elderly responded with a greater impairment in well-being under high sleep pressure than the young and women (but not men) more under high than low sleep pressure. All subjects displayed a significant circadian rhythm of subjective well-being, which was more prominent in women than in men, particularly during the high sleep pressure protocol.

Conclusions: Our results demonstrate significant age and gender-related modulation of circadian and sleep-wake-homeostatic contributions to subjective well-being. These results point towards a possible age- and/or gender specific tolerance with respect to sleep deprivation and circadian phase. This could have important ramifications on the capacity for night work.

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Effect Of A High Altitude Sojourn On Vigilance And Attention In Untreated Patients with Obstructive Sleep Apnea Syndrome

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Background: Many patients with the obstructive sleep apnea syndrome (OSA) enjoy vacations in mountain areas and choose to discontinue CPAP treatment during this period. The purpose of the current study was to evaluate the hypothesis that vigilance and attention deficits of untreated OSA patients are aggravated during hypoxic exposure at high altitude compared to low altitude.

Methods: 40 OSA patients (median age 61y, apnea/hypopnea index 38/h) residing at <600 m discontinued long-term CPAP therapy for 8-9 days. They spent days 1 to 4 at low altitude and days 5 to 9 at high altitude in 2 mountain resorts (Davos Schatzalp, 1850 m, and Davos Jakobshorn, 2590 m), 2 days and nights each. They were

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randomized to undergo testing either during the last day in Zurich (490 m) before ascent to altitude and during 4 days in Davos, or during 4 days in Davos and on the first day after their return to Zurich, respectively. The Oxford sleep resistance test (OSLER, one 40 min session), the Divided Attention Steering Simulator test (DADS, one 30 min session) and subjective sleepiness by the Karolinska scale were evaluated each morning days 5-9.

Results: Although the patients felt moderately sleepy, the OSLER sleep resistance time was not reduced at any altitude and the number of missed stimuli was low. However, performance in the DADS test was deteriorated at 2590 m compared to the lower altitudes (see table).

Conclusion: Exposure to hypoxia during a high altitude sojourn deteriorates attention deficits in OSA patients that discontinue CPAP therapy. This may have implications for their performance during activities requiring attention including driving.

	Zurich, 490 m 40 tests, one day	Schatzalp, 1850 m 80 tests on 2 days	Jakobshorn, 2590 m 80 tests, on 2 days
Karolinska scale	4 (3;6)	3 (3;4)#	3 (2;3)#
OSLER sleep resistance time (min)	40 (40;40)	40 (40;40)	40 (40;40)
OSLER missed stimuli	4 (0;19)	2.5 (0;10)	1 (0;11)
DADS reaction time (sec)	3.4 (2.3;15)	3.1 (2.5;15.0)	10 (2.7;15.0)¶
DADS off-road events	79 (10;600)	41 (9;600)	600 (56;600)*
DADS tracking impairment	0.46 (0.32;1.50)	0.43 (0.33;1.50)	1.50 (0.51;1.50)*

Medians (quartiles); # P<0.05 vs. 490m; * P<0.05 vs. 490 and 1850 m; ¶ P=0.08 vs. 490 m and P<0.05 vs. 1850 m

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Deal or no deal?**Circadian alterations in investment behaviour during sustained wakefulness**

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There is recent evidence that higher cognitive functions such as decision making are impaired under sleep loss. It is not known however, whether circadian aspects contributed to these impairments, since circadian markers of the human timing system have not been investigated so far. Here we investigated the repercussions of circadian phase and elevated sleep pressure on decision making during a simple multistage investment decision task. Six healthy young males (20–29y) spent 40h awake in a chronobiology facility under constant light and temperature conditions. Every 3 hours they carried out a multistage investment decision task. Each participant started with a specific capital in each test session and was asked to increase it. Each session comprised a maximum of 20 trials during which participants could put a percentage of the current available capital at stake. The success rate was presented to the participant at each trial. However, unbeknownst to the subjects, win and loss were randomly distributed. If a winning event occurred the capital increased according to the stake proportion of the capital which was chosen by the participant. In a loss event the stake proportion was subtracted from the capital. As circadian marker, salivary melatonin was sampled every hour. The time of each test session was assigned to either biological day or biological night in accordance to each participant's melatonin profile.

Investment task variables such as capital and stake were averaged separately for each session and then subjected to a one way rANOVA with the factor 'time'.

Results disclosed a main effect for the factor 'time' for the variables capital ($p < 0.01$, $F_{10,50}=9.1$) and stake ($p < 0.001$, $F_{10,50}=5.7$). A post-hoc cross-correlation between the mean salivary melatonin and the mean capital showed significance for lag 0 ($r = -0.77$, $p < 0.05$) and lag 1 ($r = -0.69$, $p < 0.05$). A two-sided t-test revealed a significant lower mean capital during the biological night compared to the biological days (day 1: $p < 0.05$; day 2: $p < 0.05$). Furthermore, compared to the specific start capital of each session the mean capital during the biological night was significantly lower ($p < 0.05$) whereas the mean capitals during the biological days did not significantly increase. The impairment of investment decision and the willingness to take more risky decisions occurred mainly during the biological night. Moreover, it seems that on average the capital loss during the biological night is more pronounced than a possible capital gain during the biological day. Taken together, our data indicate pronounced circadian effects on investment behaviour under conditions of sustained wakefulness.

Research supported by the Swiss National Science Foundation (SNF# 320000-108108).

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A functional polymorphism of Catechol-O-Methyltransferase (COMT) affects modafinil efficacy during sleep deprivation

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Catechol-O-Methyltransferase (COMT) is a major breakdown enzyme of catecholamines, in particular dopamine. A common, functional single nucleotide polymorphism (SNP) of COMT leads to a valine to methionine substitution at codon 158 of the COMT protein, which is associated with 34 fold decrease in enzyme activity. Studies in narcoleptic patients revealed that this SNP affects disease severity and response to the stimulant modafinil (Dauvilliers et al., 2001 & 2002). Extracellular dopamine is increased by modafinil in narcoleptic dogs, whereas dopamine transporter knock-out mice are unresponsive to this stimulant (Wisor et al., 2001). These findings suggest that dopamine plays a role in the mode of action of modafinil. We investigated whether the Val158Met SNP of COMT influences modafinil efficacy in healthy men during sleep deprivation. Ten homozygous Val/Val and 12 Met/Met allele carriers (23.4 ± 0.5 years) completed two blocks of 40 hours extended wakefulness. They

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Homer1a is a core brain molecular correlate of sleep loss

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Background: Sleep is regulated by a homeostatic process that determines its need and a circadian process that determines its timing. A highly reliable index of the homeostatic process is provided by the amplitude and prevalence of EEG delta oscillations (delta power). We have shown that the homeostatic regulation of sleep need, quantified as delta power, varies with genetic background and is associated with a locus on mouse chromosome 13. Here we show that Homer1a, localized within this locus, is the best transcriptional index of sleep need.

Methods: Sleep deprivation and transcriptome profiling was performed in 3 inbred mouse strains with differential delta power response to sleep deprivation. A transgenic mouse model was generated that expresses a Flag-tagged poly(A) binding protein under the control of the Homer1 gene enabling us to study gene expression in Homer1 expressing cells.

Results: We show that genetic background affects susceptibility to sleep loss at the transcriptional level in a tissue-dependent manner. In the brain, Homer1a expression best reflects the response to sleep loss. Time course gene expression analysis suggests that 2032 brain transcripts are under circadian control. However, only 391 remain rhythmic when mice are sleep deprived at four time points around the clock. Using our transgenic mouse line we show that in Homer1-expressing cells specifically, apart from Homer1a, three other activity-induced genes (Ptgs2, Jph3, and Nptx2) are over-expressed after sleep loss.

Conclusions: Our findings suggest that most diurnal changes in gene transcription are sleep-wake dependent rather than clock dependent. The four genes identified play a role in recovery from glutamate-induced neuronal hyperactivity. The consistent activation of Homer1a suggests a role for sleep in intracellular calcium homeostasis and in the protection from neuronal activation imposed by wakefulness.

received two doses of 100 mg modafinil and placebo according to a randomized, double-blind, cross-over design. In each block they performed at 3-h intervals 14 sessions of a 10-min psychomotor vigilance task (PVT) followed by a 10-min random number generation task (RNG).

Modafinil maintained stable PVT reaction times throughout the 40-h waking period in Val/Val homozygous individuals, whereas it was hardly effective in the Met/Met genotype. Moreover, modafinil reduced the wakefulness-induced increase in redundancy on the RNG in Val/Val allele carriers. In contrast, redundancy did not differ between modafinil and placebo in Met/Met homozygotes. The differential efficacy of modafinil on objective measures of sustained attention and executive functions was accompanied by differential subjective effects between the genotypes.

In conclusion, the functional Val158Met COMT SNP influences modafinil efficacy during prolonged wakefulness. These data suggest that mechanisms involving dopamine and/or other catecholamines contribute to sleep loss-induced impaired vigilant attention and executive functions in healthy men.

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Familial narcolepsy, obesity, and type 2 diabetes with hypocretin deficiency

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Introduction: Narcolepsy is mainly a sporadic disease and believed to be autoimmune-mediated. This is underlined by the fact that 75% of reported monozygotic twins are discordant for narcolepsy-cataplexy suggesting, as in autoimmune disorders, a multi-factorial and therefore complex rather than a simple genetic condition. Nevertheless, up to 10 % of cases may be found in a familial context with an autosomal dominant mode of inheritance. We describe the first dizygotic twin pair concordant for narcolepsy in a family in which narcolepsy cosegregates with obesity and type 2 diabetes with an autosomal dominant mode of transmission.

Methods: A Spanish family was clinically investigated and underwent whole night polysomnography and MSLT based on the standard methods. Laboratory investigations included high resolution HLA DQB1 genotyping, mutation analysis of Prepro-hypocretin (HCRT), Hypocretin-Receptor-1 and -2 (HCRTR1, HCRTR2) gene as well as CSF hypocretin-1 measurements.

Results: The pedigree consists of four generations including a dizygotic male twin pair in the third generation concordant for narcolepsy with cataplexy and obesity. Four additional family members were also diagnosed with narcolepsy and cataplexy while at least 7 other family members were known to have suffered for excessive daytime sleepiness (EDS). Furthermore, the family consists of several members affected by type 2 diabetes and/or obesity, which partially cosegregates with narcolepsy or EDS. HLA genotyping in twins showed no association with DQB1*0602 while CSF measurements revealed hypocretin deficiency. Mutation analysis ruled out any pathogenic mutation in the coding regions and exon-intron boundaries of the hypocretin ligand and receptor genes.

Conclusion: This unique familial case clearly represents a genetic form of narcolepsy with an autosomal-dominant mode of inheritance, not necessarily associated with HLA-DQB1*0602 but with hypocretin deficiency without any pathogenic mutation in hypocretin ligand or receptors. Our findings raise the possibility of a common genetic contribution to narcolepsy, obesity, and type 2 diabetes as already suggested in sporadic narcolepsy.

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Green Tea Catechin Polyphenols Attenuate Behavioral and Oxidative Responses to Intermittent Hypoxia in Rats

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Introduction: The intermittent hypoxia (IH) that characterizes sleep-disordered breathing (SDB) is known to impair spatial learning and to increase NADPH oxidase activity and oxidative stress in rodents. Green tea catechin polyphenols (GTP) have emerged not only as radical scavengers, but also as potentially promising neuroprotective agents in the context of treatment for neurodegenerative diseases. We hypothesized that green tea catechin polyphenols (GTP) may attenuate IH-induced neurobehavioral deficits by reducing IH-induced NADPH oxidase expression, lipid peroxidation and inflammation.

Methods: Male Sprague-Dawley rats were administered an extract containing a mixture of polyphenolic compounds (Polyphenon-60, >60% polyphenols) in their drinking water or water alone (W) as a

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Effect of average reference in EEG recordings with just a few derivations

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Background: EEG signals depend on the position of reference electrode. In studies of topographical differences, re-referencing to average reference is common. To examine the validity of this procedure when only a few derivations are available, we compared linked mastoid recordings with average reference data based on four derivations.

Methods: Baseline PSG recordings (12h time in bed) of 11 subjects from a previous study (Tucker et al., 2007; JSR 16, 170-180) were investigated. Four derivations (Fz/C3/C4/Oz) were recorded against linked mastoids. Sleep stages (30s epochs) were scored using R&K criteria. EEG signals were re-referenced to the average of the four derivations. Power spectra were determined for 30s epochs (FFT, 4s subepochs, cosine taper, 1s overlap) and averaged across artifact-free vigilance states.

Results: Re-referencing to average reference reduced total power in the NREM sleep EEG at Fz (24.1% of power of linked mastoid), C3 (13.6%) and C4 (13.2%), but not at Oz (100.1%). The fast spindle peak (>12Hz) in the NREM sleep EEG was reduced in all recordings. Six subjects showed in addition slow spindle activity (peak in spectrum <12Hz) in the frontal derivation independent of the reference. The alpha peak in the waking EEG increased at Oz in 9 out of 11 recordings after re-referencing to average reference.

Conclusions: Using average reference resulted in reduction of total power relative to linked mastoid reference. Importantly, EEG topography differed between the two referencing procedures, and rhythmic activity patterns were affected. Caution is needed in the interpretation of EEG signals referenced to an average reference based on only a few electrodes.

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control group. Animals were then exposed to 14 days of IH exposure (oscillating between 21% and 10% O₂ every 90 seconds during sleep hours). Following IH exposure, all rats underwent cognitive assessment in the spatial, reference version of the Morris water maze. Then, levels and expression of Malondialdehyde (MDA), PGE and p47^{phox} sub-unit of NADPH oxidase in brain tissue was measured.

Results: GTP-IH rats displayed greater spatial bias for the hidden platform in the MWM during probe trials in comparison to the control group. An increase in p47^{phox} expression occurred in W-IH compared to W-RA. In contrast, GTP-IH animals exhibited only minor increases in p47^{phox} expression. Similarly, W-IH rats showed doubling of cortical MDA levels compared to room air (W-RA) animals, while GTP-IH animals showed a 40% reduction in MDA levels.

Conclusions: Thus, oral GTP attenuates IH-induced spatial learning deficits and mitigates IH-induced oxidative stress through multiple beneficial effects on oxidant pathways. Since oxidative processes underlie neurocognitive deficits associated with IH, the potential therapeutic role of GTP in SDB deserves further exploration. Research supported by Swiss National Science Foundation and National Institutes of Health grants HL-69932 and 2P50 L60296.

Loss of Hypocretin (Orexin) Neurons with severe Traumatic Brain Injury

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Objective: To better understand the causes of sleep-wake disturbances in TBI, we aimed to test whether hypothalamic hypocretin neurons are lost after severe traumatic brain injury.

Background: Traumatic brain injury (TBI) frequently results in excessive daytime sleepiness and hypersomnia, but the underlying causes of posttraumatic sleep-wake disturbances are unknown. Narcolepsy is caused by a loss of the hypocretin-producing neurons in the hypothalamus, and in the first days after TBI, cerebrospinal fluid levels of hypocretin-1 are often very low, suggesting injury to the hypocretin system. Similarly, six months after TBI, there is an association between low cerebrospinal fluid hypocretin levels and excessive daytime sleepiness.

Methods: We immunostained hypothalamic sections and counted hypocretin neurons from 4 deceased patients with severe TBI and from 4 control subjects. Control hypothalami contained an average of 44,838 ± 3,988 hypocretin neurons (range 40,700–49,625). In TBI patients, the number of hypocretin neurons ranged from 23,800 to 47,600 (mean 32,106 ± 7,618), representing an approximately 30% cell loss ($p < 0.001$). Cell densities in TBI patients were reduced by 27%, and perivascular spaces frequently contained hypocretin-immunoreactive debris. In controls, the number of hypocretin neurons differed by no more than 2–4% between the right and left hypothalami, but in TBI brains, cell counts varied by 10–29% between sides, possibly reflecting asymmetric trauma.

Conclusion: The loss of hypocretin neurons in patients with severe TBI suggests that disturbed hypocretin signaling may contribute to posttraumatic sleep-wake disturbances.

Increased slope of sleep slow-waves in pre-pubertal children compared to mature adolescents

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Slow-wave activity (SWA, 1–4.5 Hz) during NREM sleep is a reliable indicator of sleep pressure (Borbély, 2001). A recent hypothesis suggests that SWA reflects synaptic strength (Tononi and Cirelli 2006). Evidence for the hypothesis comes from a large-scale thalamocortical model showing that a change in synaptic strength is sufficient to account for the change in SWA. In the model, the change in SWA was predicted by a change in the synchronization of cortical neurons, which is best reflected in a change of the slope of slow waves (Esser et al., 2007). Such a relationship between SWA and the slope of slow waves was also found in rats and humans (Vyazovskiy et al., 2007; Riedner et al., 2007). Here we asked the question, whether the increased SWA level observed in pre-pubertal children compared to mature adolescents (Jenni and Carskadon 2004) is associated with increased synaptic strength as measured by the slope of sleep slow-waves.

Slow Oscillations In the NonREM Sleep EEG: Do They Reflect Sleep Homeostasis?

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Background: Slow waves represent the most prominent feature in the electroencephalogram (EEG) of non-rapid eye movement (NREM) sleep. They are characterized by fluctuations at frequencies ranging from slow (< 1 Hz) to delta (1–4 Hz) oscillations.

Slow wave activity (SWA, power in the 0.75–4.5 Hz range) is a marker of sleep intensity. It increases as a function of the time spent awake and decreases in the course of sleep, indicating that sleep is homeostatically regulated.

On the other hand, it was shown that slow oscillations (< 1 Hz; SO) constitutes a different activity. These intracortically generated fluctuations consist of rhythmic depolarizing components (up states) separated by prolonged hyperpolarizations (down states) at the cellular level. SO were hypothesized to be involved in the temporal organization of other sleep rhythms such as spindles and delta waves. Their role in sleep regulation, however, is uncertain. In the present study the response of SO to sleep deprivation is investigated.

Methods: EEG data (C3A2) of baseline and recovery sleep after sleep deprivation (40 hours of prolonged wakefulness) were analyzed (N=8). Half waves were determined as positive or negative deflections between consecutive zero crossings (SO: 0.5–1 Hz; low delta activity: 1–2 Hz) in the band-pass filtered signal (–3 dB at 0.4 and 2.26 Hz). Spectral analysis of the EEG was also performed (0.1 Hz resolution).

Results: Slow oscillations and low delta activity occurring during the slow wave sleep (stages 3 and 4) of the first NREM sleep episode were compared between baseline and recovery sleep. Preliminary analysis revealed that the number of SO per minute significantly decreased after sleep deprivation. In contrast, the number of low delta waves was increased. Power spectra did not show any significant change in the SO range, while activity in the low delta range was significantly increased.

Conclusions: The present findings suggest that sleep deprivation alters the distribution of oscillatory events between SO and low delta activity.

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All night sleep recordings were performed for the C3A2 derivation in 8 pre-pubertal children (Tanner 1/2, 11.9±0.3 years) and 6 mature adolescents (Tanner 4/5, 14.3±0.6 years) for a baseline and after sleep deprivation. The EEG was visually scored, artefact rejected, and bandpass filtered (0.5–4 Hz). Slow-waves were detected as negative signal deflections between two consecutive positive peaks.

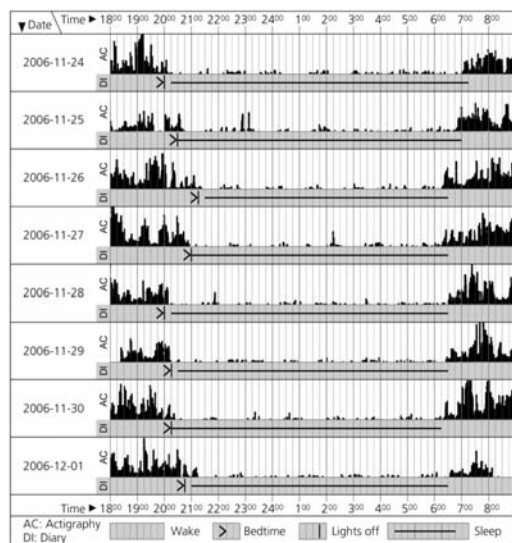
SWA showed the well-known homeostatic response in both groups and was, during the baseline and after sleep deprivation, higher in pre-pubertal children compared to mature adolescents. We found concurrent differences in the slope of slow-waves between pre-pubertal children and mature adolescents (baseline: pre-pubertal children, 335.6±26.8 µV/s; mature adolescents, 205.1±22.2 µV/s; $p < 0.005$). Moreover, even when controlling for the amplitude of slow-waves, pre-pubertal children exhibited steeper slope slow-waves than mature adolescents.

The increased slope of slow-waves in pre-pubertal children compared to mature adolescents suggests increased synaptic strength of neurons involved in the generation of sleep slow-waves. Such increased synaptic strength in pre-pubertal children could be due to increased density and/or increased efficacy of synapses.

Agreement rates between actigraphy, diary, and questionnaire for children's sleep patterns: recommendations for clinical and research practice

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Background: The evaluation of children's sleep-wake patterns is essential for the identification and management of sleep problems which affect 20% to 30% of children one or more times during childhood (see for a recent review¹). Sleep-wake patterns of children can be assessed by different methods. However, none of previous reports provide the clinician or sleep researcher with information about the interchangeable use of the most common used methods (actigraphy, diary, and questionnaire). Do parents accurately report on their child's sleep? How well do actigraphy, diary and questionnaire data agree? Can these methods be interchangeably used? These questions can only be answered by the statistical approach proposed by Bland and Altman^{2,3}. The aims of this study were [1] to describe



Blue-enriched light improves self-reported alertness and performance in the work place

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Decrements in alertness and performance compromise health and safety in the workplace. Adequate exposure to light can reduce decrements in alertness and performance. These effects are thought to be mediated, in part, by a recently discovered melanopsin dependent photoreceptive system. The spectral sensitivity of this system is shifted towards shorter wavelengths (blue light), compared to the classical visual system. Specifications and standards for existing light installations in the work place, however, are based on the spectral sensitivity of the classical visual system. We investigated the effects of blue-enriched light (17000K), in comparison to standard lighting (4000K), on self-reported measures of alertness, performance and sleep quality. 104 participants (aged 18-60) divided into two groups took part in an 8 week cross-over. After completion of baseline questionnaires, participants completed morning, midday and late afternoon questionnaires during one day per week. These tests measured subjective sleep quality, alertness, mental effort, headaches, eye strain, recovery and mood. The two groups did not differ with respect to demographics (i.e. age, sex and BMI) or sleep characteristic (Karolinska sleep diary). Preliminary analyses of questionnaires completed during the first leg of the trial revealed that the group under blue-enriched light reported enhanced subjective alertness and performance ($p < 0.03$) and decreased sleepiness and negative mood. ($p < 0.05$). There were no differences in the incidence of headaches or eye strain between the conditions. These preliminary analyses show that blue-enriched light can improve subjective alertness and performance and decrease sleepiness and negative feelings during the normal working day. Research grant from Philips Lighting.

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sleep-wake patterns in a non-clinical sample of healthy kindergarten children by measures derived from questionnaire, diary, and actigraphy and [2] to report rates of agreement between methods according to Bland and Altman^{2,3}.

Methods: Cross-sectional study of 50 kindergarten children, age 4 to 7 years. Sleep-scheduled times (sleep start, sleep end, assumed sleep, actual sleep time, and nocturnal wake time) were assessed by different methods. The study included data from 7 nights of actigraph recordings and sleep diary over the same time period (see Figure), and from a questionnaire, asking about children's normal sleep scheduled times. Children were studied in their homes.

Results: Differences between actigraphy and diary were ± 28 minutes for sleep start, ± 24 minutes for sleep end, and ± 32 minutes for assumed sleep indicating satisfactory agreement between methods, while for actual sleep time and nocturnal wake time agreement rates were not sufficient (± 106 minutes, ± 55 minutes, respectively). Agreement rates between actigraphy and questionnaire as well as between diary and questionnaire were insufficient for all variables. Sex and age of children, and SES did not influence the differences between methods for all variables.

Conclusions: Actigraphy and diary may be interchangeably used for the assessment of sleep start, sleep end, and assumed sleep, but not for nocturnal wake times. The diary is a cost-effective and valid source of information about children's sleep scheduled times, while actigraphy may provide additional information about nocturnal wake times or may be used if parents are unable to report in detail. It is insufficient to collect information by a questionnaire or an interview asking about children's normal sleep patterns. Therefore, we recommend that the diary should be a standard tool in the assessment of children sleep-wake patterns.

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Profiling drug action on the waking EEG and brain gene expression of three wake-promoting drugs in inbred strains of mice.

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Introduction: Stimulants are widely used to treat excessive daytime sleepiness associated with sleep disorders. We tested the effects of R228060 (R22), a new stimulant, and of d-amphetamine (AMP) and modafinil (MOD) on the waking EEG and gene expression, in three inbred mouse strains [AKR/J (AK), C57BL/6J (B6), DBA/2J (D2)] that differ in their capacity to sustain wakefulness.

Methods: For each drug a dosage was selected aimed at inducing a similar wake duration (R22 and MOD: 150; AMP: 6mg/kg). In study 1 drug-induced changes in the waking EEG were analyzed between drug injection and sleep onset. EEG spectra were expressed as % of baseline. In study 2 the same drug doses (or saline) were administered and mice were kept awake for 5h by handling. Brain RNA was used in an Affymetrix gene profiling study. A clustering analysis was performed using a Pearson correlation distance metric to evaluate the effects of drug and strain.

Results: EEG analysis during drug-induced wakefulness revealed a transient ~2Hz slowing of theta and an increase in beta2 (20-35Hz) only after R22 while for the other drugs a prolonged, faster and higher theta was observed. R22 failed to induce beta2 in AK mice. Gamma (35-60Hz) was increased by all drugs.

Among the 500 genes that were affected the most by strain and drug, cluster analysis identified 8 distinct patterns of change in gene expression for the 9 conditions (3 strains x 3 drugs). Interestingly, in 2 clusters, R22 and AMP had opposite effects on gene expression for B6 and D2, whereas the changes for AK after R22 matched the changes observed after AMP in B6 and D2. In two others clusters, the effects of R22 and MOD were similar.

Conclusions: Expression profiles after R22 importantly differed from AMP. The changes in the waking EEG after R22 differed from that of the other drugs. These results suggest that different neuronal pathways are activated to achieve wake promotion. Genetic background affected the response to R22 both for the waking EEG and gene expression. Establishing and comparing drug induced EEG and gene expression profiles might help identify the mode of action of compounds for which this is unknown. Work supported by J&J PRD, R&D Europe.

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Women with difficulties initiating sleep and vasospastic syndrome exhibit lower heart rate variability in the high frequency band (>0.15Hz)

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Introduction: Women with primary vasospastic syndrome (VS), a functional disorder of vascular regulation in otherwise healthy subjects (main symptom: cold hands and feet), often suffer from difficulties initiating sleep (DIS) without any other sleep complaints. DIS belongs to the DSM-IV criteria for primary insomnia, but also occurs secondarily during other sleep disorders e.g. Delayed Sleep Phase Syndrome. Chronic primary insomnia has been characterized as a state of hyperarousal seen for example in higher sympathetic nervous activity as measured by spectral analysis of heart rate variability (HRV). The low frequency band (LF=0.04-0.15Hz) of the HRV-spectrum mirrors the influence of both sympathetic and parasympathetic nerve activity, whereas the high frequency band (HF=0.15-0.4Hz) is associated with pure parasympathetic nerve activity.

Aim of the study: In a controlled laboratory study we aimed to compare women having both VS and DIS (WVD) with controls (CON) to test the hypothesis whether WVD exhibit a sympathetic dominance in the HRV spectrum similar to primary insomniacs.

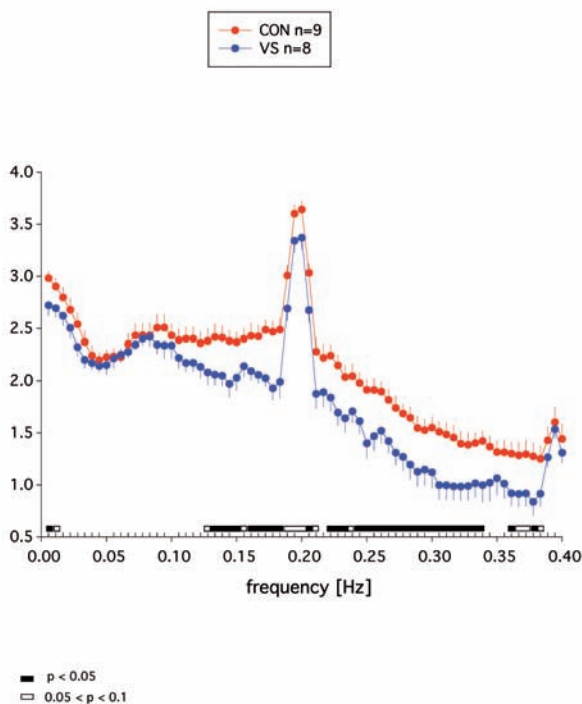
Methods: 9 CON and 8 WVD (luteal phase; 20-33yr) completed two protocols, either carried out with paced (0.2Hz) or unpaced (spontaneous) 3min breathing episodes at hourly intervals distributed throughout a 40h constant routine (CR). Power spectral analysis of log-transformed purified inter-beat interval data was carried out by FFT.

Results: In comparison to CON, WVD showed significantly ($p<0.05$) lower power values in both LF and HF from spectral analysis of 'spontaneous breathing'-data (main effect). Spectral analysis of 'paced breathing'-data revealed significantly ($p<0.05$) lower power values predominantly in HF but not in LF, leading to a significantly ($p<0.05$) reduced HF/LF-ratio.

Conclusion: This finding indicates a sympathetic predominance in WVD compared with CON which could represent a pathophysiological correlate for the syndrome of combined VS and DIS.

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log Powerspectrum - paced breathing



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Actigraphy For Assessing Sleep Disturbances In High Altitude Field Studies

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Background: Polysomnography, the gold standard for evaluating sleep, is technically demanding and expensive. To investigate sleep disturbances of large cohorts under field conditions simple techniques are desirable. Therefore, the aim of this study was to evaluate whether sleep duration in mountaineers can be accurately measured by actigraphy in comparison to polysomnography and whether subjective sleep disturbances at high altitude correlate with measures from actigraphy and polysomnography.

Methods: 23 mountaineers underwent polysomnography and actigraphy during 5 nights, one at 490 m (Zurich), and 4 at 4559 m (Capanna Regina Margherita). Subjective sleep quality was assessed on a visual analogue scale with a range of 0 to 100. The results of the actigraphy and polysomnography were compared to each other as well as to subjective sleep quality.

Results: Polysomnography revealed a mean sleep duration of 440 to 554 min, Sleep efficiency was 88 to 92% and not different between the two altitudes and over the course of consecutive nights. Mean nocturnal oxygen saturation in Zurich was 95% and decreased significantly, i.e., to 72-79%, at 4459m. There was a close correlation between actigraphy and polysomnography for total sleep time ($R=0.97$, $p<0.05$) and sleep efficiency ($R=0.96$, $p<0.05$) and, to a minor degree, for sleep latency ($R=0.65$, $p<0.05$). In 66 comparisons, the mean difference between actigraphy and polysomnography was 1 minute for total sleep time and 0% for sleep efficiency. 95% confidence intervals of the mean differences were ± 20 min for total sleep time and $\pm 4\%$ for sleep efficiency. At 4559 m, sleep efficiency measured by actigraphy and polysomnography were correlated with the oxygen desaturation index ($R=0.37$, $p<0.05$ and $R=0.40$, $p<0.05$, respectively). No significant correlation existed between subjective sleep quality and the objective sleep efficiency or sleep latency.

Conclusion: Sleep duration and sleep efficiency estimated by actimetry agreed closely with corresponding polysomnographic measures. Therefore, actigraphy is a valuable and simple tool for assessment of altitude related sleep disturbances under field conditions as an adjunct to symptom scales.

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Are there age-related changes in dream recall?

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Background: There is converging evidence that the ultradian NREM-REM sleep cycle together with the circadian-modulated activation of REM sleep sum to generate the main characteristics of dreaming. In this study, it was investigated whether this circadian modulation of dream recall changes with age.

Methods: Dream recall was investigated in 17 young (20-31 year) and 15 older (57-74 year) volunteers under a 40-hour multiple-nap paradigm (75/150 min sleep/wake schedule) under constant-routine conditions. Dream recall was assessed at the end of each nap trial with the Sleep Mentation Questionnaire, which addresses characteristics of dream recall, such as number of dreams, dreams during the time falling asleep, emotionality, vividness, pleasantness, physical activity, hostility and colourfulness.

Results: The number of dreams recalled varied significantly both across the naps and between the age groups, with older subjects exhibiting less dreams ($p<0.05$). Concomitantly, older participants had comparatively lower levels of the following characteristics of dream recall: dreams during the time falling asleep, emotionality, vividness, pleasantness, physical activity and colourfulness ($p<0.05$). Furthermore, these dream characteristics, varied significantly across the circadian cycle ($p<0.05$), showing a circadian modulation which was closely associated with the circadian rhythm of REM sleep during the naps.

Conclusions: This study revealed an age-related decline in the number of dreams recalled, coupled with an age reduction in some of the core characteristics of dreaming. Furthermore, these central characteristics of dream recall fluctuated in accordance with the circadian cycle, thus suggesting that the circadian modulation of dream mentation can possibly be modified by age.

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Validation of a German Version of the Fatigue Severity Scale

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Study Objectives: To validate a German version of the FSS in healthy subjects and different disorders known to be commonly associated with fatigue.

Background: Fatigue is highly prevalent and negatively impacts life quality and performance in a large variety of disorders. The English 9-item Fatigue Severity Scale (FSS) is one of the most commonly used self-report questionnaires to measure fatigue, but has only been validated in small sample-sized studies and in single disorders.

Patients and Methods: The German version of the FSS was administered to 454 healthy subjects, 429 patients with sleep-wake disorders, 188 patients with multiple sclerosis, and 235 patients with recent ischemic stroke.

Results: FSS scores were 4.7 ± 1.6 (mean \pm SD) in patients with multiple sclerosis, 3.9 ± 1.9 in patients after ischemic stroke, 4.3 ± 1.6 in patients with sleep-wake disorders. Compared to patients, values were significantly lower in healthy subjects (3.0 ± 1.1 , $p < 0.001$). Scores did not correlate with gender, age, or education. Item analysis showed an excellent internal consistency and reliability (Cronbach's alpha = 0.934).

Conclusions: This first validation of a fatigue scale in a large sample size demonstrates that the German version of the FSS is a simple and reliable instrument to assess and quantify fatigue for clinical and research purposes.

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PER3 Polymorphism Affects Cardiac Autonomic Control in Healthy People

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A variable number tandem repeat polymorphism in the coding region of the PERIOD3 gene has been shown to affect several markers of sleep homeostasis as well as the decline in performance when the wake episode is extended into the circadian night. The objective of the current investigation was to characterize variations in autonomic nervous system activity during sleep and wakefulness through analysis of heart rate variability (HRV) in subjects homozygous for the long (PER3-5/5) or short (PER3-4/4) variant of this polymorphism.

The ECG and respiratory activity of 24 subjects was recorded continuously during a baseline sleep episode, a 40-h constant routine and a recovery sleep episode.

Preliminary analyses of the ECG data revealed that the PER3-5/5 and PER3-4/4 subjects differ in various HRV indices. In NREM sleep during the baseline night, parasympathetic activity, reflected by the pNN50 and RMSSD, was significantly lower in PER3-5/5 subjects than in PER3-4/4 subjects ($P < 0.05$). This difference was confirmed by power spectral analysis of RR intervals which showed differences in the time course of HF between the two genotypes. A decrease in normalized HF/(LF+HF) was observed during NREM in the PER3-5/5 subjects ($P < 0.05$), suggesting a loss of parasympathetic control on autonomic balance. Analyses of waking ECG during the constant routine confirmed these different levels of autonomic drive to the heart.

The data show that this polymorphism in the circadian clock gene PER3 modulates the parasympathetic control on the autonomic balance during sleep and wake in humans.

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Sleep in mice lacking the GABA_A receptor α 3-subunit

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Most hypnotics, including benzodiazepines (BZ) and BZ-like compounds, target the gamma-aminobutyric acid (GABA)_A receptors. The heterogeneity of subunits constituting the hetero-pentameric GABA_A receptor leads to an extensive diversity of GABA_A receptor subtypes with specific functional and pharmacological properties. Characterizing the contribution of a specific receptor subtype in sleep regulation may provide further insights into the understanding of mechanisms underlying physiological sleep. GABA_A receptors containing the α 3-subunit are markedly expressed in several neuronal networks involved in sleep regulation (i.e., arousal activation systems as well as sleep-promoting circuitries). Interestingly, the thalamic reticular nucleus (nRT), a structure playing a crucial role in the thalamo-cortical network, exclusively expresses the α 3-subtype. To determine whether the loss of these receptors may alter sleep and sleep regulation, we investigated sleep in mice lacking the alpha3-subunit (α 3KO mice).

Sleep deprivation is a well-established method to enhance sleep pressure and thereby uncover differences in sleep regulation. Thus, we performed baseline EEG recordings in wild-type and α 3KO mice for 24 h, followed by 6 h SD and 18 h recovery (α 3KO, $n=12$; wild-type, $n=11$).

The genotypes did not differ in their vigilance states. Spectral analysis of the baseline EEG showed no difference between the genotypes in the NREM sleep EEG spectrum or at the waking-NREM sleep transition. At the NREM-REM sleep transition (last 12-sec epoch) EEG power in the spindle frequency range (10-15 Hz) was significantly lower in α 3KO mice than in wild-type. Enhancement of sleep pressure by 6 h SD did not reveal differences in the NREM sleep spectra or at transitions between α 3KO mice and wild-type. Finally, analysis of the wake EEG showed slightly but significantly larger power in the 11-13-Hz band in α 3KO mice versus wild-type. Overall, sleep regulation and cortical NREM sleep EEG activity was unaltered in α 3KO mice. Further studies are required to determine how functions of nRT neurons are preserved in the absence of GABA_A α 3-containing receptors in the nRT and neocortex.

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Impact of sustained wakefulness and circadian phase on temporal production and reproduction

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Temporal duration judgments are known to depend on a variety of factors, both cognitive and physiological in nature. Several studies have reported circadian and wake dependent modulations of short-term interval timing i.e., the ability to judge durations in the seconds-to-minutes range. Here, we aimed at investigating the effects of sustained wakefulness and circadian phase on duration production and duration reproduction for multiple time intervals. Since there is evidence that different processes and mechanisms are involved in duration production and reproduction respectively, we hypothesized that the tasks respond unequally to homeostatic and circadian challenges.

In order to obtain a differentiated view of the impact of temporal dynamics in physiology on short-term interval timing, we probed production of 5-s, 10-s and 15-s intervals and reproduction of 3.75-s, 5-s, 7.5-s, 10-s and 15-s intervals in parallel at 3-h intervals in 12 young male subjects (mean age 24.9 ± 2.96 years; age range 21–29 years during 40-h of sustained wakefulness under near-constant routine conditions).

The two methods employed i.e., production and reproduction, yielded antidromic response curves across the 40-h episode. RM ANOVA using factors time (elapsed time into protocol) stimulus (stimulus duration) and task (task type) yielded no significant effect of factor time, but significant effects of factors task and stimulus and significant interactions of factors stimulus x task, stimulus x time and stimulus x task x time. ($p < 0.05$) Reproduction displayed wake-dependent changes combined with a general overestimation for shorter (3.75-s, 5-s) and circadian modulation combined with a general underestimation for longer intervals (10-s, 15-s); 7.5-s intervals were reproduced accurately during the entire protocol. In contrast, produced durations were consistently underestimated and did not exhibit consistent wake-dependent or circadian dynamics. The findings reveal a complex interaction between task type, interval length, circadian phase and state of the sleep-wake homeostat, which need to be incorporated into current models of interval timing.

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Drops in pulse wave amplitude, a microarousal scoring surrogate.

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Introduction: During sleep, sudden drops in pulse wave amplitude are commonly observed simultaneously with microarousals. Their presence is thought to result from a vasoconstriction induced by an autonomic central nervous system activation. We sought to determine if pulse wave amplitude drops are associated with cortical activation as quantified by EEG spectral analysis.

Methods: EEG spectral analysis was performed over 5 consecutive epochs of 5 seconds before, #1+2: during #3 and after # 4+5 the pulse wave amplitude drops (> 20%). A total of 1084 events, from 10 consecutive sleep polygraphic recordings were analysed. The presence or absence of visually scored EEG arousals was also determined (according to AASM criteria). EEG spectral analysis was performed over five wave lengths: (beta 17-30 Hz, alpha 8-12 Hz, theta 4-8 Hz, sigma 12-16 Hz and delta). The power density of each type of EEG wave was compared between the five epochs using repeated measures ANOVA with a Tukey post hoc test.

Results: The global analysis of all drops in pulse wave revealed a significant increase in EEG power density of all EEG wave for the epoch #3 in comparison to the preceding (#1-2) and subsequent (#4-5) ones ($p < 0.001$). Further analysis of pulse wave drops not associated with a visually recognized microarousal also revealed a significant increase in EEG power for all types of waves during the pulse wave drops (epochs #3; $p < 0.001$).

Conclusion: Pulse wave amplitude drops, observed on polygraphic sleep recordings, are associated with a sudden increase in EEG power density in all wave length. This suggests that drops in pulse wave amplitude are concomitant to central nervous system activation, even in absence of microarousal. Supported by the "Swiss Pulmonary Society" fund for research.

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Running wheel availability and sleep (rest) homeostasis in mice

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Exercise leads to sleep consolidation in mice. Rest epochs recorded with infra-red sensors can approximate sleep data obtained by polysomnography. To investigate the impact of exercise on sleep homeostasis, C57BL/6 mice ($n=11-12$ per group) with (RW) and without a wheel (noRW) were sleep deprived (SD) by 'gentle procedures' either during the first (SD1-6) or second 6 h of the light period (SD7-12). Motor activity (IR-sensor resolution 0-200 counts/min) and running wheel revolutions were recorded at 1-min intervals. The amount of rest (activity counts = 0), duration of rest episodes, intensity of IR-activity and running wheel revolutions were determined during 5 d baseline and for 12-18 h recovery after the SD's.

RW mice rested 2 h less and were more active than noRW mice. The reduction in the amount of rest was due to a significantly lower amount of short rest episodes (<16 min) in RW mice. Intensity of activity per 24 h correlated negatively with the amount of short rest episodes lasting ≤ 1 min in all mice, and correlated positively with the amount of rest episodes >16 min in mice without a wheel.

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Structural equation modeling of sleep apnea, inflammation, and metabolic dysfunction in children

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Obstructive sleep apnea (OSA), often concomitant with obesity, increases the risk for the metabolic syndrome. One mechanism that may participate in this association is upregulation of inflammatory pathways. We used structural equation modeling to assess the interrelations between childhood obesity, OSA, inflammation, and metabolic dysfunction. One hundred and eighty-four children (127 boys, mean age: 8.5 ± 4.1 years) had height and weight measured, underwent overnight polysomnography and had fasting blood taken. The blood was analyzed for insulin, glucose, lipids, leptin, and cytokines [interferon (IFN)- γ , granulocyte macrophage-colony stimulating factor, interleukin (IL)-1 β , IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, tumor necrosis factor]. Structural equation modeling (SEM) was used to evaluate associations between the outcomes of interest including hypoxia, arousal (related to respiratory and spontaneous), obesity, metabolic dysfunction, and inflammatory markers. Two cytokine factors and one metabolic factor were derived for the SEM. These factors provided good fit in the structural equation model ($\chi^2/df = 2.855$; comparative fit index = 0.90, root mean squared error of approximation = 0.10) and all factor loadings were significantly different from zero ($P \leq 0.01$).

Overall, our results indicate that while obesity (as measured by body mass index z-score) has a major influence on the metabolic dysfunction associated with OSA, arousal indices, and cytokine markers may also influence this association. Our results support the hypothesis that OSA is a contributor to the mechanisms that link sleep, systemic inflammation and insulin resistance, and show that the interrelations may begin in childhood.

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The two groups differed in the amount of rest and activity level during recovery (hours 7-12). In noRW mice SD1-6 induced a massive delayed reduction in intensity of activity and an increase in the amount of rest in recovery hours 7-18, while in RW mice the activity level was unchanged, and the increase in rest was restricted to recovery hours 13-18. The amount of rest episodes was similar in both groups after SD compared to baseline. After SD7-12 intensity of activity was reduced for the entire 12 h in noRW mice, while in RW mice the reduction lasted only 6 h. However, the magnitude of reduction was higher during hour 1 of recovery in RW mice than in noRW mice. Rest was increased during the entire 12 h recovery in noRW mice and during hour 1 and 7-12 in RW mice. Significant group differences in the amount of rest occurred in the first 4 h recovery.

Summarized, running wheel availability affected the amount and distribution of rest. Interestingly, active wakefulness led to enhanced rest consolidation. Although both SDs induced a homeostatic increase in the amount of rest, RW availability influenced the time course of recovery as well as rest consolidation.

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Follow-up on Metabolic Markers in Children Treated for Obstructive Sleep Apnea

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Rationale: In adults, obstructive sleep apnea (OSA) is associated with metabolic dysfunction that improves with treatment of OSA. No equivalent studies exist in children.

Objective: To examine the relationship between metabolic markers and OSA with time and treatment in children.

Methods: Metabolic markers measured on a fasting morning blood sample at diagnostic polysomnography and follow-up 1.3 ± 0.6 yr later.

Measurements and Main Results: Forty-five children (34 males), aged 6.9 ± 3.5 yr, and including 12 obese subjects, were in the final analysis. There were no differences in metabolic markers between children with and without OSA at initial study; however, obese children had significantly higher insulin (106.1 ± 72.1 vs. 66.7 ± 37.6 pmol/L; p = 0.028), insulin/glucose ratio (23.7 ± 14.3 vs. 14.7 ± 8.0; p = 0.02), and significantly lower high-density lipoprotein cholesterol (1.3 ± 0.2 vs. 1.6 ± 0.4 nmol/L; p = 0.005) than nonobese children. Twenty children underwent surgical removal of adenotonsillar tissue, whereas 12 children with OSA elected not to have treatment. OSA persisted after treatment in five children, and resolved in 27. Thirteen children did not have OSA on initial or follow-up studies. At follow-up, there was a small but significant improvement in total cholesterol in those children whose OSA was resolved (4.8 ± 0.8 to 4.7 ± 0.6 nmol/L; p = 0.005) and a trend for obese children with persisting OSA to have elevated insulin levels compared with obese children without OSA (p = 0.07).

Conclusion: Obesity appears to be the major influence on metabolic dysfunction in children with OSA, but these preliminary data also suggest that resolution or persistence of OSA may affect changes in metabolic function over time.

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Symptomatic narcolepsy after encephalitis lethargica syndrome in a school-age child

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Background: An encephalitis lethargica syndrome has been recently described in patients with basal ganglia autoimmunity, possibly triggered by streptococcal infections (Dale, 2004). Moreover, symptomatic narcolepsy may rarely develop following various inflammatory brain diseases, and its idiopathic form is probably also linked to immune mediated mechanisms.

Case description: Two weeks after a transitory upper airways infection, a previously healthy 8 year-old boy developed progressive hypersomnia, hyperphagia, apathy, irritability and night sleep disturbances. On neurological examination he appeared hypomimic, with lips and tongue dyskinesia, dysarthria, and head tremor. He never showed frank parkinsonism, cataplexia, sleep paralysis, or hallucinations. Conventional CSF analysis was normal except for few oligoclonal bands in both CSF and serum, but hypocretine was undetectable. Antistreptococcal antibodies were elevated at 1360 UI/L; a brain MRI was normal. Determination of HLA DQB1 0602 was positive. PSG showed an extremely fragmented night sleep with incomplete muscle atonia during REM; the patient had an apnea-hypopnea index just above the upper limit for his age (4/h, mostly hypopneas). The MSLT disclosed a clearly shortened sleep latency (1 minute) with 4/4 SOREM. The patient improved under prednisone, administered for 5 months.

Conclusion: We assume that this child had secondary narcolepsy without cataplexy, symptomatic of an encephalitis lethargica syndrome triggered by a streptococcal infection. This observation, including the partial response to immunosuppressive therapy, may contribute to enlarge the spectrum of post-streptococcal neurological and neuropsychiatric disorders, and underlines the potential link between auto-immune mechanism and neural circuits involved in sleep regulation (Bentivoglio, 2007).

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Melatonin in treatment of chronic sleep disorders in adults with pervasive developmental disorders: a retrospective study

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Background: The circadian rhythm of pineal melatonin secretion, which is controlled by the suprachiasmatic nucleus (SCN), is reflective of mechanisms that are involved in the control of the sleep/wake cycle. Melatonin can influence sleep-promoting and sleep/wake rhythm-regulating actions through the specific activation of MT(1) (melatonin 1a) and MT(2) (melatonin 1b) receptors, the two major melatonin receptor subtypes found in mammals. Therefore, Melatonin may be used to treat sleep disorders in both children and adults with intellectual disability (ID), although it has no product license for such use. The evidence for its efficacy, potential adverse effects and drug interactions are reviewed in the context of prescribing to people with ID.

Methods: This study presents the use of melatonin to treat severe circadian sleep-wake disturbances in 6 adults with pervasive developmental disorders. Melatonin was initiated at a daily dose of 3 mg at nocturnal bedtime. If this proved ineffective, the melatonin dose was titrated over the following 4 weeks at increments of 3mg/2weeks up to a maximum of 9 mg, unless it was tolerated. Assessments included the Clinical Global Impression-Severity (CGI-S) and the CGI-Improvement (CGI-I).

Results: Melatonin administered in the evening dramatically improved the sleep-wake pattern in all patients. Melatonin appears to be effective in reducing sleep onset latency and is probably effective in improving nocturnal awakenings and total sleep time in adults with pervasive developmental disorders. Its effectiveness remained stable for the 6-months period of administration. Melatonin was well-tolerated in all patients and no side effects were noted during the therapy.

Conclusions: Melatonin appears to be promising as an efficient and seemingly safe alternative for treatment of severe circadian sleep disturbances in adults with intellectual disability. There may be heterogeneity of response depending on the nature of the sleep problem and cause of the ID or associated disabilities. Further studies are necessary before firm conclusions can be drawn and guidelines for the use of melatonin for people with ID formulated.

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Triggers for Cataplexy – Sexual Intercourse

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Background: Strong positive emotions such as joking, laughing and elation are specific triggers for cataplexy in patients with narcolepsy-cataplexy (NC). Cataplexy during sexual intercourse and orgasm (orgasmolepsy), though less often reported, can be a serious problem in NC patients.

Objective: To describe frequency and features of loss of muscle tone during sexual intercourse in a series of NC-patients, patients with mixed sleep disorders and healthy controls.

Patients and methods: Review of sleep questionnaires and Stanford cataplexy questionnaires of 75 subjects (29 with NC, 26 with mixed sleep disorders and excessive daytime sleepiness (EDS)/fatigue and 20 healthy controls) followed by an interview with specific focus on muscle loss during sexual activity in suspicious cases.

Results: Muscle weakness during sexual intercourse, was reported by three NC patients (two female, age 23 and 24 years, one male, age 25 years), one male patient with behaviorally induced sleep insufficiency and cataplexy-like symptoms and none of the healthy controls. In four NC patients and three patients with other sleep disorders and EDS the occurrence of muscle weakness during sexual intercourse remained uncertain. For the two female NC-patients this specific type of cataplexy occurred by each sexual intercourse as complete bilateral loss of muscle tone. The male patient reported complete bilateral loss of muscle tone during sexual intercourse only when in a relationship involving emotional commitment and trust. One female NC patient reported no more orgasmolepsy under treatment with sodium oxybate. In the patient with behaviorally induced sleep insufficiency and orgasmolepsy, cataplexy-like symptoms affected one or the other upper or lower limb and were usually triggered by negative emotions and sports activities.

Conclusion: We suggest that cataplexy during sexual intercourse is a distinct feature in NC patients, but may also occur in other sleep disorders. Deficient arousal and reward dysregulation due to hypocretin deficiency may contribute to emotional motor dysfunction in orgasmolepsy. EDS may represent a gating mechanism for emotional muscle dyscontrol in orgasmolepsy and cataplexy-like symptoms.

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Sodium oxybate in pharmaco-resistant chronic cluster headache (CCH).

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Background: Pain attacks in cluster headache (CH) have a striking circadian distribution with a close relation to sleep. Patients with chronic CH (CCH) are specifically refractory to pharmacological treatment and suffer from severely disturbed sleep. Only a few (mostly unsuccessful) attempts have been made to influence nocturnal pain attacks via pharmacological induced changes in sleep structure or sleep quality. Sodium oxybate (SO, Xyrem®) is a compound known to affect GABA-ergic transmission and to consolidate sleep.

Objectives to evaluate the effects of SO on sleep structure and on nocturnal pain attacks in patients with pharmaco-resistant CCH
Design and Methods: Three consecutive CCH-patients (21-47 years, 1 female, 2 males) participated this open-labelled prospective study. They were intractable to pharmacotherapy (at least to four substances of different classes) and to electrical hypothalamic stimulation in one patient. At baseline they presented with multiple nocturnal (2-6) and diurnal (3-6) pain attacks per 24 hours and suffered from disturbed nocturnal sleep. SO (3.0-8.5 g/night) was administered in two nightly doses, the first at bedtime and the second 4 hours later. Response to SO was monitored by serial polysomnography (PSG), hand wrist actimetry, pain and sleep diaries.

Results: Long term administration of 5-8.5 g SO/night resulted in a persistent reduction of pain frequency (>90%) and intensity (>50%) of nocturnal attacks in two CCH-patients as documented by diary, serial PSG and wrist actigraphy. Pain attacks during daytime remained unaffected in the first and only mildly improved in the second patient. In both patients PSG documented an increase in sleep efficiency, a marked decrease of wake after sleep onset and an increase of slow wave sleep. In the remaining patient pain intensity of nocturnal attacks decreased ($\geq 50\%$) while the number of attacks per night remained unchanged. By contrast, a substantial reduction of pain frequency and intensity during the day could be achieved. Interestingly in this patient sleep structure only slightly improved after the administration SO. Mild to moderate side effects (dizziness, vomiting, amnesia, weight loss) occurred. No loss of efficacy was observed at follow up (longest observation period 15 months) so far.

Conclusions: Sodium oxybate improved sleep quality and reduced nocturnal and diurnal pain attacks in pharmaco-resistant CCH. A substantial reduction of nocturnal cluster pain could only be achieved in CCH-patients who improved sleep quality. The effects of SO on CCH needs to be corroborated in a placebo controlled trial.

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Sleep, neuronal plasticity and functional recovery after stroke

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Background: Ischemic stroke is a leading cause of death and disability in industrialized countries and one of the main causes of long-term disability. Currently, few effective medical interventions are available in the acute phase. Promotion of neuronal plasticity during rehabilitation may represent a new perspective for improving long-term outcome. Clinical and experimental data suggest that sleep plays a role in mediating neuronal plasticity after stroke.

As a first step to understand sleep function after stroke, the present study was set up to examine correlates between sleep, EEG spectrum and motor function recovery in a rat ischemia model.

Methods: Focal cortical ischemia was induced by coagulating the distal middle cerebral artery (MCA). EEG was recorded over the motor cortex (M1). Motor function was assessed by a battery of tests including single pellet reaching, paw placement in a cylinder and tape removal.

Preliminary results: Coagulation of the MCA resulted in a small infarct in the somatosensory cortex and deficits in motor function, such as pellet reaching. EEG spectral analysis showed a marked reduction in the high frequency bands (12-25Hz), particularly in the hemisphere ipsilateral to the damage.

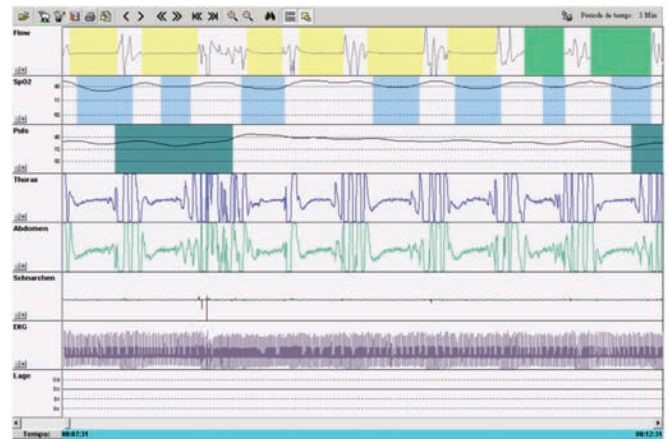
Conclusions: The results suggest involvement of high frequency EEG activities in neuronal reorganization after cortex injury. Further investigation is needed to characterize the relation between the altered EEG spectrum and function recovery.

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Central sleep apneas and high coffee intake. A case report

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A 48-year old man complained of excessive daytime somnolence, nervousness, irritability, dizziness and poor sleep for several weeks. His spouse described irregular breathing during sleep with respiratory pauses as well as intermittent snoring. He was experiencing major psychological stress at work, and was given a medical leave. He had also been treated for mild arterial hypertension for one month. He had been smoking 15 cigarettes a day since age 15, he rarely drank alcoholic beverages and there was no drug abuse. He had no regular sport activity. Epworth score was 8/24, on the visual analog scale he was 8/10 (0= fully awake, 10=sleepy) upon awakening. Physical examination was normal, BMI 26 kg/m², neck circumference 42 cm. Lung function tests showed a mild obstructive pattern. An ambulant polygraphic exam revealed mild intermittent snoring, AHI 48/min (1/3 central 1/3 mixed 1/3 obstructive apneas and hypopneas, longest apnea 32s), Desaturation index (DI) 10/h, mean SpO₂ 94% lowest 85%, mean HR 79/min.



The neurological and cardiological work-up were normal. A therapeutic trial with an automated CPAP machine (Autoset-CS) brought a complete suppression of apneas and hypopneas with little change in daytime sleepiness. A subsequent history taking, revealed a heavy coffee consumption of 30-40 cups a day. After reducing the coffee consumption to <3 cups /day (caffeine level 13 mmol/L), the nervousness and daytime sleepiness improved. A repeat nocturnal polygraphic exam showed: snoring and mostly obstructive apneas and hypopneas, AHI =13, longest apnea 27s, DI 11/h, mean SpO₂ 91% lowest 84%.

A possible explanation for the transformation of this mild obstructive sleep apnea syndrome into a severe, predominantly central and mixed SAS is the high coffee intake. The pathophysiological mechanism of this possible deleterious effect on respiration is unclear. Although caffeine is routinely being used in premature infants to reduce sleep apneas, a very high coffee intake in adults may induce central sleep apneas through ventilatory instability caused by a high loop gain due to activation of the central chemoreceptors, i.e. increase in carbon dioxide sensitivity and decrease in the carbon dioxide threshold during sleep.

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Disturbances in Sleep-Wake Rhythms Correlate with Impairment in Cognitive Functioning in Schizophrenic Patients

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Background: Cognitive impairments are frequently observed in schizophrenic patients who may suffer from negative symptoms characterised by anhedonia, lack of motivation and interest, flattened affect, and social withdrawal. These symptoms may also occur in the absence of psychotic episodes with positive symptoms such as delusions. In an ongoing study we are investigating the relationship between characteristics of the circadian rest-activity cycle, negative symptoms and cognitive functioning in schizophrenic patients.

Methods: Rest-activity cycles were recorded by wrist actimetry along with sleep diaries throughout a period of 20±3.7 days in 9 schizophrenic patients (age range 30-56 y). Saliva samples were collected during 2 days (interspersed by a 7-day interval) to determine the onset of melatonin secretion as an objective marker for circadian phase. Moreover, clinical interviews documented medication and sociodemographic data and standardised questionnaires and interviews (BPRS, PANSS, PSQI) assessed clinical status. Cognitive capacities such as attention, executive functioning and verbal fluency were assessed by the Trail Making Test A+B, the Stroop interference task, and the Supermarket test.

Results: The circadian rest-activity cycles in six of the nine patients showed abnormalities such as frequent awakenings during the main sleep episode, frequent napping during daytime, or hypersomnia. So far, we have not found any relationship between negative symptoms and the degree of rest-activity cycle disturbance as measured by the interdaily stability index (IS) and the relative amplitude (RA) of the daily 10h-period with most activity and the 5h-period with least activity. However, we have found significant correlations between all three neuropsychological measures mentioned above and IS and RA (see table).

Conclusion: These findings indicate that in our patient cohort poor cognitive functioning is related to disturbed rest-activity rhythms. Thus, the degree of synchronisation and stabilisation of the rest-activity cycle by light and daily structure as well as the timing of medication may all be important factors to be considered when treating schizophrenic patients. This study was supported by Bristol-Myers Squibb and the Velux Foundation.

	interdaily stability (IS)		relative amplitude (RA)	
	r	p	r	p
Trail Making Test A [s]	-0.83	0.005	-0.68	0.042
Trail Making Test B [s]	-0.68	0.042	-0.7	0.036
Stroop interference task [s]	-0.83	0.005	-0.92	0.001
Supermarket test	0.69	0.038	0.85	0.004

Obstructive Sleep Apnea in Patient with Haemangioma of the Oral Cavity and Neck – A Case Report

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An uncommon cause of obstructive sleep apnea syndrome (OSAS) is soft tissue tumours of the head and neck, which may create anatomic abnormalities that interfere with the maintenance of upper airway patency. The surgical removal of tumour is usually the treatment of first choice, but in cases of high risk surgical intervention, the patient can be treated by continuous positive airway pressure (CPAP). Herein we describe a 6 years follow up of one patient with a large haemangioma of the oral cavity and neck who is treated by CPAP.

A 44 years old man was referred to our sleep centre because of a long standing history of snoring and daytime sleepiness. His past medical history was notable for a congenital hemangioma involving the right side of his face and neck, right side of his tongue, oral cavity, pharynx, larynx and subglottic region. First polysomnography showed the apnea/hypopnea index (AHI) 54.4 per hour, severe oxygen desaturations (minimal saturation 48%) and the absence of deep sleep. At this time the patient refused CPAP, the treatment by mandibular advancement device (MAD) was started one year after the diagnostic. New polysomnographic recording (with MAD) showed the inefficacy of this treatment (AHI 48.4/h) and treatment by nasal CPAP (10 cm of water pressure) was finally accepted by the patient. Polysomnographic recording with CPAP showed a very good treatment efficacy (AHI 5/h), but after 2 years the patient noted the reappearance of daytime sleepiness and snoring. New polysomnographic titration established the efficacy pressure at 13 cmH₂O. Now, 3 years after the last titration, we observe again the loss of efficacy of the CPAP therapy and new titration of CPAP under polysomnographic control is necessary.

Our experience leads us to conclude that nasal CPAP therapy is effective and well tolerated in the patients with hemangiomas, but an appropriated and regular monitoring is necessary.

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Hypersomnia, disturbed REM sleep regulation and loss of motivation in a patient with hypothalamic lesion

Poryazova R, Werth E, Bassetti CB, Khatami R

We report a case of a 40-year old hypersomnolent patient with an extensive bilateral lesion of posterior hypothalamus and pituitary gland most probably due to Langerhans cell histiocytosis. Fourteen years ago he was diagnosed with pituitary microadenoma and panhypopituitarism. Despite adequate hormone substitution therapy he developed severe excessive daytime sleepiness (EDS), memory deficit, hyperphagia and loss of motivation over a six-months period. MRI at admission showed bilateral tumor infiltration with slight enhancement of gadolinium in the posterior hypothalamus including the mammillary bodies. The patient did not report on cataplexy, sleep paralysis or hypnagogic/hypnopompic hallucinations. During a 24-hour polysomnography sleep latency with sleep onset REM period (SOREMP), numerous bouts of REM sleep and high sleep fragmentation were observed. The overall amount of REM sleep was not increased. Hypocretin-1 level in cerebrospinal fluid was decreased (112 pg/ml). This case suggests that lesions in the posterior hypothalamus associated with hypocretin deficiency may present as a combination of a sleep-wake disturbance, loss of motivation and emotional impairment.

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Sleep Quality in a Polysomnography-Night. An Assessment by Patients.

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Background: Many patients wonder how they would sleep or wether at all they would sleep during a polysomnography (PSG) night. The routine answer at the Interdisciplinary Center of Sleep Medicine at the Cantonal Hospital of St. Gallen is a comforting: not different from home. This approach is taken because of fewness of data on subjective sleep quality in the polysomnography night and in order to take away pressure from the patient who fears to fail to fall asleep, thus possibly invalidating the test.

Methods: 49 patients seen because of a tentative diagnosis of sleep apnea were exposed to a structured questionnaire within 24 hours after the PSG-night.

Results: 45 questionnaire were available for analysis of data. Mean age was 52 years, 27% female, 63% male. Mean sleep efficiency was 76% (range 45-97%) The return to the global question: how did you sleep in the Sleep Laboratory compared to home? gave 45% of the surveyed persons rating sleep in the Sleep Lab better or identical, and 55% worse than at home. Rating sleep quality on an numerical scale of 0 to 10 gave better or identical sleep in the Sleep Lab in 39%, and worse in 61% of the surveyed population. 81% felt wake time in the PSG-night was more, 73% felt that sleep onset was later and 67% indicated that falling asleep was more difficult in the Sleep Lab compared to home. „Unaccustomed circumstances“ (83%), head electrodes (60%) and nasal canula (52%) were mentioned as interfering with sleep. Only minorities mentioned belts (31%), finger probe of pulse oxymetry (31%) and noise (27%) as hindering sleep.

Discussion: more than half of the 45 tested people slept less well in the Sleep Lab compared to home, despite noise control measures, detailed written information about the procedure, invitation to bring along private bedding, soft toys and alcohol. In retrospect smoking withdrawal may have been an unnoticed problem. However, in no case did subjectively disturbed sleep seriously reduce the diagnostic value of the PSG.

The numbers refer to the pages of this supplement.

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Chellappa S 8 S	Leemburg S 12 S	Vella S 10 S, 11 S
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