Vilnius University

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Sleep and the sense of rest:

relation between sleep fragmentation

and subjective sleep quality

Summary of doctoral dissertation
Biomedical sciences, Biophysics (02 B)

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ryšys tarp miego fragmentacijos ir

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ABBREVIATIONS

AI – arousal index (number of arousals per hour of sleep)

BA - behavioural arousal

BAI – behavioural arousal index

DS – deep sleep (N3 and N4 stages of NREM)

ECG – electrocardiography

EEG – electroencephalography

EMG – electromyography

EOG – electrooculography

LS – light sleep (N1 and N2 stages of NREM)

MA - microarousal

MAI – microarousal index

NREM – non-rapid eye movement sleep

N1 – stage 1 of NREM

N2 – stage 2 of NREM

N3 – stage 3 of NREM

N4 – stage 4 of NREM

PSG – polysomnographic

PSQI – Pittsburgh sleep quality index

REM – rapid eye movement sleep

SaO_2 – oxygen saturation

SC – sleep cycle

SD – standard deviation

SE – sleep efficiency

SL – sleep latency

VA - vegetative arousal

VAI – vegetative arousal index

TIB – time in bed

TST – total sleep time

W – wake

WASO – wake after sleep onset

1. INTRODUCTION

One third of our lives we spend sleeping, but most of us know little about sleep. Although sleep importance and all the functions still remain to be ascertained, it is obvious that sleep is universal need in higher order animals and its deficit causes serious disorders. Researchers have proved that sleep is important for sound functioning of nervous system (Zeppelin et al., 2005). During the sleep brain remains active – biochemical, bioelectrical processes settle down, humans are growing while asleep, our memory strengthens and many other important processes are going on during sleep (Born et al., 2006; Tononi ir Cirelli, 2006). Very interesting and important questions are about connections of all these processes with neural mechanisms of sleep. Disruption of sleep mechanisms could lead to poor sense of rest after the sleep.

Sleep is natural need and usually we can easily satisfy it. But it appears that these days more and more people are getting troubles with sleep. Sleep usually gets disturbed because it is not a simple linear process, but it exhibits a very complex behavior which involves various areas of the central nervous system at different levels and at different times (Steriade et al., 1993a). The daily shifts from the wake state to NREM and REM sleep are under the control of interconnected processes, including the circadian timing of sleep onset, the homeostatic balance between wakefulness and sleep and the ultradian interaction between NREM and REM sleep (Achermann and Borbely, 1992).

Sleep might get disrupted by internal diseases and external factors. Sleep duration, its structure and stage composition are changing over the time (Knowles and MacLean, 1990; Rodin et al., 1998; Bliwise, 1993). Human sleep duration is very individual. It is thought that sleep duration as well as some disorders might be linked to the genetics (Marcadet et al., 1985).

Sleep disorders are one of the most common medical complaints today. Sleep disorder might last only few days, but sometimes it becomes serious problem that impacts many other life aspects. Neurologists, psychiatrists, family and other doctors are getting ever more peoples complains about insomnia, poor sleep, and poor sense of rest after the sleep (Zamit, 1999). Work medicine specialists are dealing with shift-work problems, inability to adapt to such work and diseases that are caused by sleep-wake cycle disturbances (Culebras, 1992). Sleepiness can cause many problems during wake:

car accidents, accidents at work or at home. Psychiatrists often deal with depressions, chronic fatigue syndrome, aggressive behaviour during sleep and other problems (Benca et al., 1992). And there are many other aspects why it is important to investigate sleep connections with other diseases, its impact on our psychological and social well-being.

More recently, the three processes of sleep regulation – circadian, homeostatic and ultradian – have been integrated by the definition of the arousal system (ASDA, 1992). Arousals are transient episodes of cerebral activation during sleep which involves massively the cortex regulated by interplay between cortical and subcortical neurons (ASDA, 1992; Moruzzi and Magoun, 1949). Most authors consider arousals as a transient cortical activation in responses to sleep disruptive events (Martin et al., 1996; Terzano et al., 2005; Reynolds and Banks, 2010), but there are other studies indicating that arousals punctuate both REM and NREM sleep even in the absence of detectable disturbing stimuli (Boselli et al., 1998; Halasz et al., 2004).

On one hand there are debates still going on about the nature and role of arousals in sleep and on the other hand there is question about their role for the sleeper itself – how persons sleep quality is affected by that. One of the most tedious and understudied sleep problems which might be related with arousals is non-restorative sleep. Today it becomes significant problem in medicine (Stone et al., 2008). There are various studies trying to evaluate persons rest sense after the sleep in the morning, but researchers are still debating about what determines rest sense after the sleep (Puterbaugh, 2011). There are findings which showed that subjective satisfaction after the sleep is not dependent on overall sleep length (Zamit, 1999). It was assumed that the amount of delta sleep is very important in sleep structure, but it wasn‘t exactly confirmed and even people with sufficient amounts of deep sleep might feel unrested in the morning (Martin et al., 1996). There are reports that insufficient REM sleep can also result in daytime sleepiness, poor concentration (Holcomb, 2007). A lot of attention recently is paid for a sleep integrity and a role of sleep fragmentation, which is characteristic for a primary insomnia and could have effect on the sleeps restorative function (Terzano et al., 2003; Sforza et al., 2004).

1.1 Aim and objectives

The aim of this study – to analyze sleep structure and to evaluate its relationship with subjective sense of rest after the sleep without paying attention to the type of insomnia.

Objectives:

- to analyse sleep quality through sleep cycles, phases and stages paying attention to:
    - subjective sleep parameters – subjects' sense of rest after the sleep;
    - objective sleep parameters – different arousal type indices.
- to investigate relationship between different arousal types and sleep quality data.
- to analyse dynamics of arousal indices during the night and its influence on sleep quality.

1.2 Actuality and scientific novelty

Certain aspects of sleep microstructure and their influence on subjective sleep quality were revealed for the first time:

1. For the first time relationship between arousals and subjective sleep quality was investigated through the whole night sleep, sleep cycles, phases and stages.
2. Analysis of sleep quality through sleep cycles and stages revealed significant influence of microarousals on subjective sleep quality.
3. For the first time it was shown importance of NREM 2 stage (particularly evening cycles) for the sleep quality and sense of rest after sleep.

1.3 Practical applications

This study shows that settling in central nervous and vegetative systems during NREM 2 stage (especially at the beginning of sleep – evening cycles), during which essential changes in breathing, heart rate and many other autonomic parameters take place, might be essential for subject's sense of rest after the sleep. Based on that we propose such practical applications of this study:

- In sleep research – pay more attention to the stabilization of nervous system during NREM 2 stage and especially in the first half of the sleep, which might be more important for the rest sense of sleep.
- In sleep medicine – for treating insomnias we recommend to use short working hypnotics, which would make impact on initial sleep cycles and that way might improve sense of rest after the sleep.

1.4 Defended statements

1. Sleep quality is determined by fragmentation with arousals and not by sleep length.
2. Arousal types are not equally significant – microarousals have the most significant impact on subjective sense of rest.
3. Subjective sense of rest after sleep is more related to the combination of arousal indices, but not to one particular type of arousals.
4. For the sleep quality stability of neural processes going on through the sleep stages is more important than changes between sleep cycles during the night.
5. Microstructure of NREM 2 stage is the most important for the sleep quality sense.

2. METHODS

In this chapter we describe instrumental methods used in this study, patients' inclusion/exclusion criteria, Pittsburgh sleep quality index specifics and usage. Scoring of different arousal types is described with practical examples.

2.1. Polysomnography

For this study we have used JAEGER-TOENNIES (Viasys Healthcare GmbH.) polysomnograph Somnostar PRO with software „Matrix Sleep Analysis", „SleepLab® for Windows" (version 1.70.0.3). All the parameters that were registered are listed in Table 2.1.

Table 2.1 – polysomnography parameter.

Parameter	What is registered
EEG (C4A1)	Right hemisphere EEG
EEG (C3A2)	Left hemisphere EEG
EOG L	Left eye movements
EOG R	Right eye movements
EMG (Chin)	Chin electromyogram
ECG	electrocardiogram
EMG L	Left leg movements
EMG R	Right leg movements
Trach	Microphone for snoring and sounds
Flow	Difference between in-/outgoing air temperature
Effort (Tx)	Thorax effort
Effort (Abd)	Abdominal effort
SpO2	Oxygen saturation level in blood
Pulse	Pulse
BodyPos	Body position

After the night of recording, all the polysomnograms were checked for artifacts and analysed. Basic PSG study scheme is shown in the Figure 2.1.

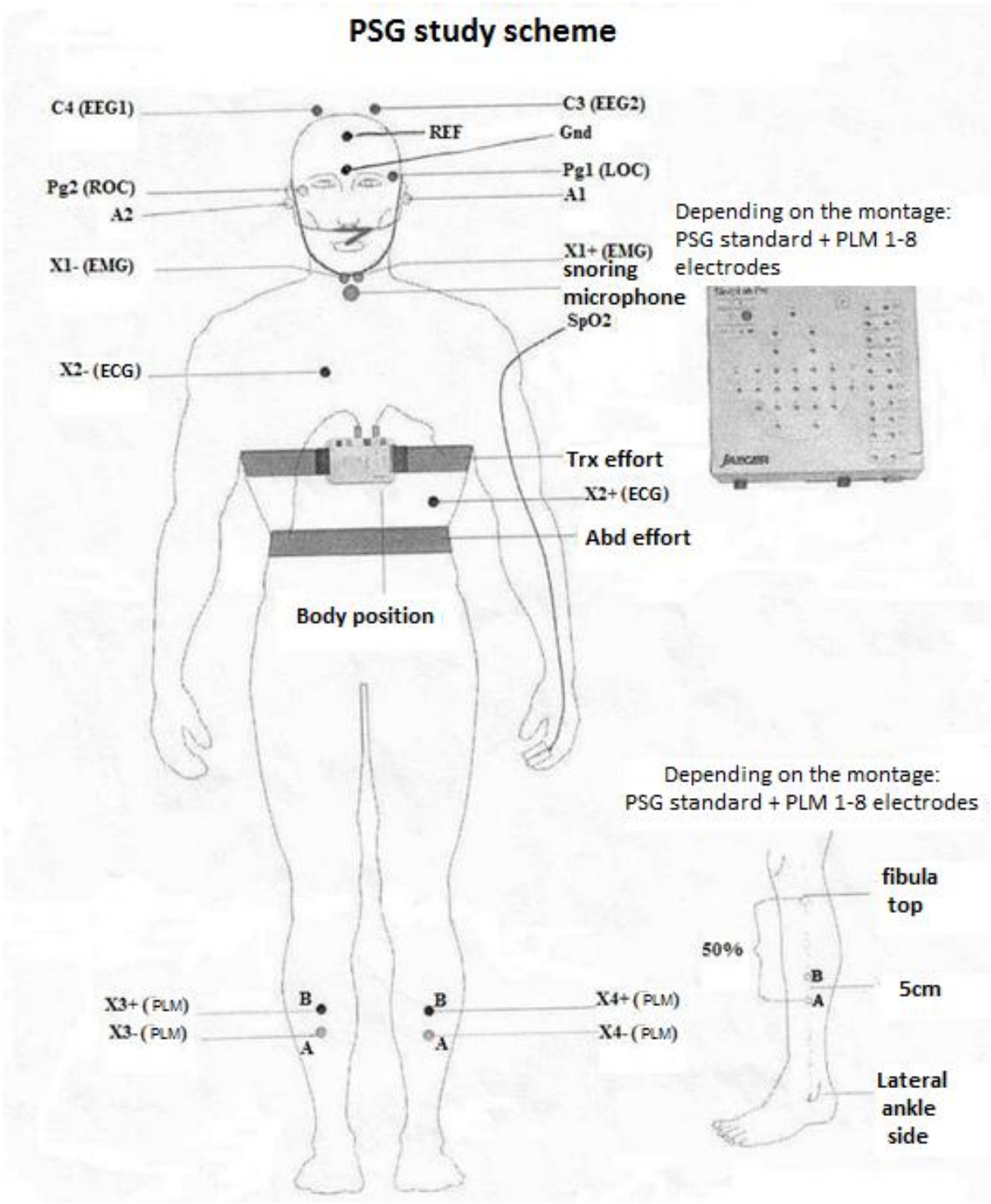

Figure 2.1. PSG study scheme. ROC – right occulogram; LOC – left occulogram; EEG – electroencephalogram; ECG – electrocardiogram; EMG – electromyogram; PLM – periodic leg movement; SpO2 – oxygen saturation in blood; Gnd – ground electrode; REF – reference electrode; A_1 – left side derivation; A_2 – right side derivation; C_3 and C_4 – international EEG derivation channels for left and right sides.

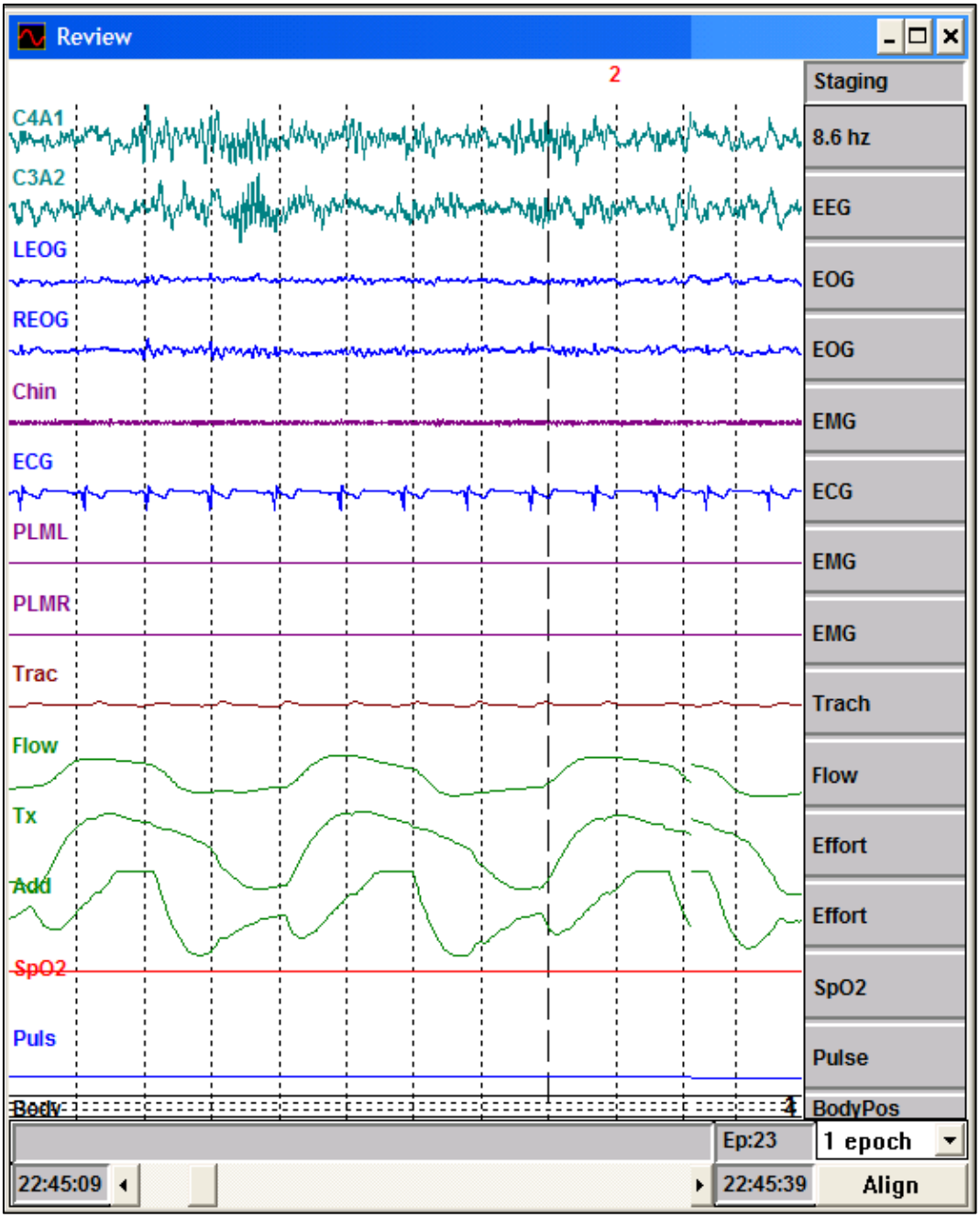

Figure 2.2. PSG recording sample. Time-distance between two vertical dashed lines – 1 sec. Channels explained in the Table 2.1.

2.2. Subjects

The data analyzed in this study were collected from the all night polysomnographic (PSG) recordings of 60 subjects (30 men and 30 women) aged between 36 and 55 years (mean 45.5 ± SD 5.7 years). All subjects were recruited from clinical patients of the Sleep disorders laboratory at Vilnius Sapiegos hospital in Vilnius. All participants provided informed agreement. Exclusive criteria were sleep apneas and heavy snoring problems.

All subjects had all night PSG study and woke up in the morning at their usual time. Before the study patients had consultations with the doctor and filed out necessary questionnaires, including questionnaires was Pittsburgh Sleep Quality Index questionnaire. More information about this form is in the next chapter.

2.3. The Pittsburgh Sleep Quality Index (PSQI)

The Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989) was developed to measure sleep quality during the previous month and to discriminate between good and poor sleepers. The PSQI has been used to measure sleep quality among truck drivers (Souza et al., 2005), to test the effects of a drug on sleep quality in a randomized placebo controlled trial (Johnson et al., 2005) and others.

Sleep quality is a complex phenomenon that involves several dimensions, each of which is covered by the PSQI. The covered domains include Subjective Sleep Quality, Sleep Latency, Sleep Duration, Habitual Sleep Efficiency, Sleep Disturbances, Use of Sleep Medications, and Daytime Dysfunction. The PSQI is designed to assess sleep quality during the past month and contains 19 self-rated questions and 5 questions rated by a bed partner or roommate (only the self-rated items are used in scoring the scale). 7 component scores that correspond to the domains listed previously are calculated and summed into a global score (Buysse et al., 1989). Higher scores represent worse sleep quality: component scores range from 0 to 3 and global scores range from 0 to 21. PSQI score of 5 represents disordered sleep (Buysse et al., 1989).

2.4. Arousal scoring

A monopolar derivation (C3-A2 or C4-A1) was used to score sleep stages (Rechtshaffen and Kales, 1968) and arousals. Arousals were scored and arousal indices (AI) (number of arousals per hour of sleep) were calculated in three major groups to represent different levels of cortical and somatovegetative activations:

- **Microarousal** (MA) was defined by the American sleep disorders association (ASDA) committee in 1992 as a rapid modification in EEG frequency well differentiated from the background EEG activity, lasting more than 2 and less than 30 seconds, which can include theta and alpha activity, and/or frequencies higher than 16 Hz but not spindles; it could be accompanied with submental muscle tone from the chin in REM sleep. It reflects a brief awakening of the cerebral cortex regardless of any concomitant participation of the autonomic system or behavioral components (ASDA, 1992; Sforza et al., 2004) (Figure 2.3).

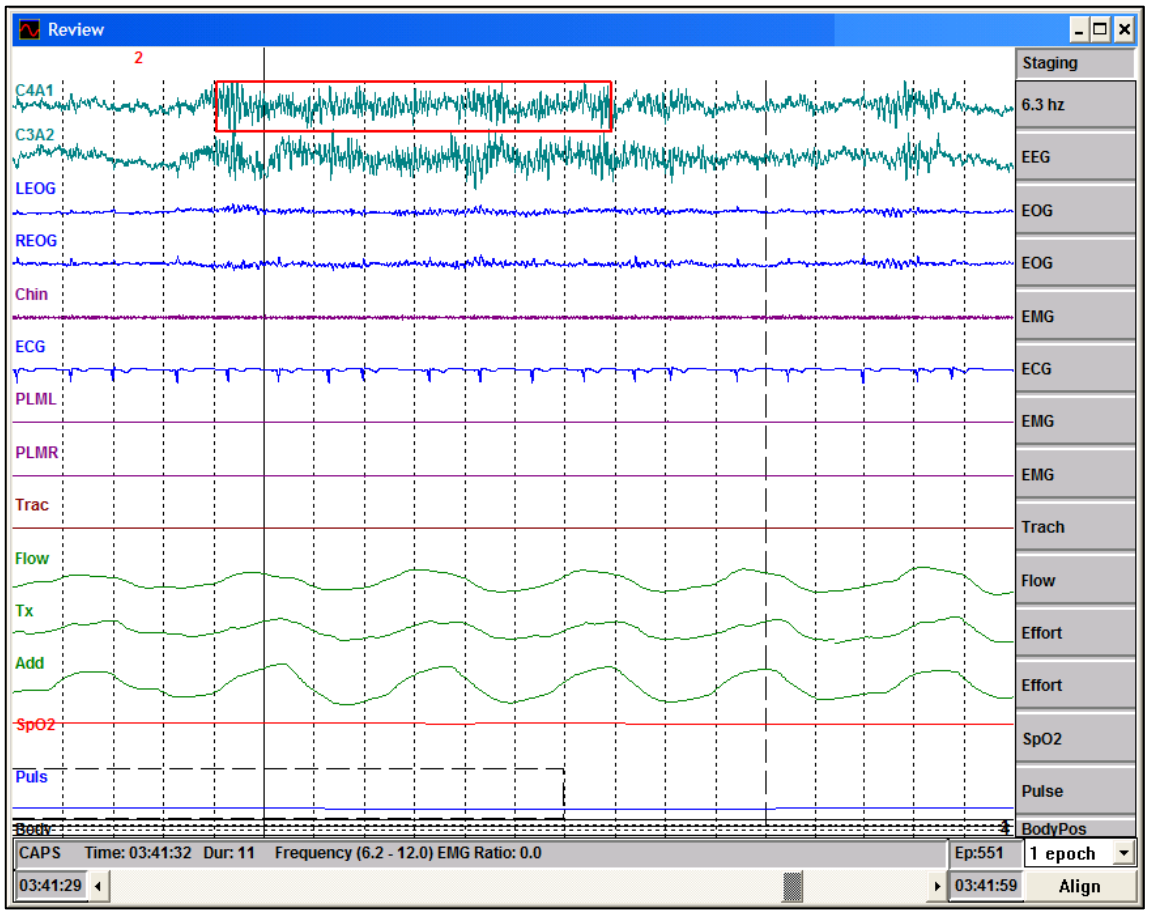

Figure 2.3. Microarousal in the NREM2 stage (marked red at the top). Channels explained in the Table 2.1.

- **Vegetative arousals** (VA): identified when vegetative activation is associated with a transient EEG pattern different from a conventional ASDA arousal (Rees et al., 1995; McNamara et al., 2002) (Figure 2.4).

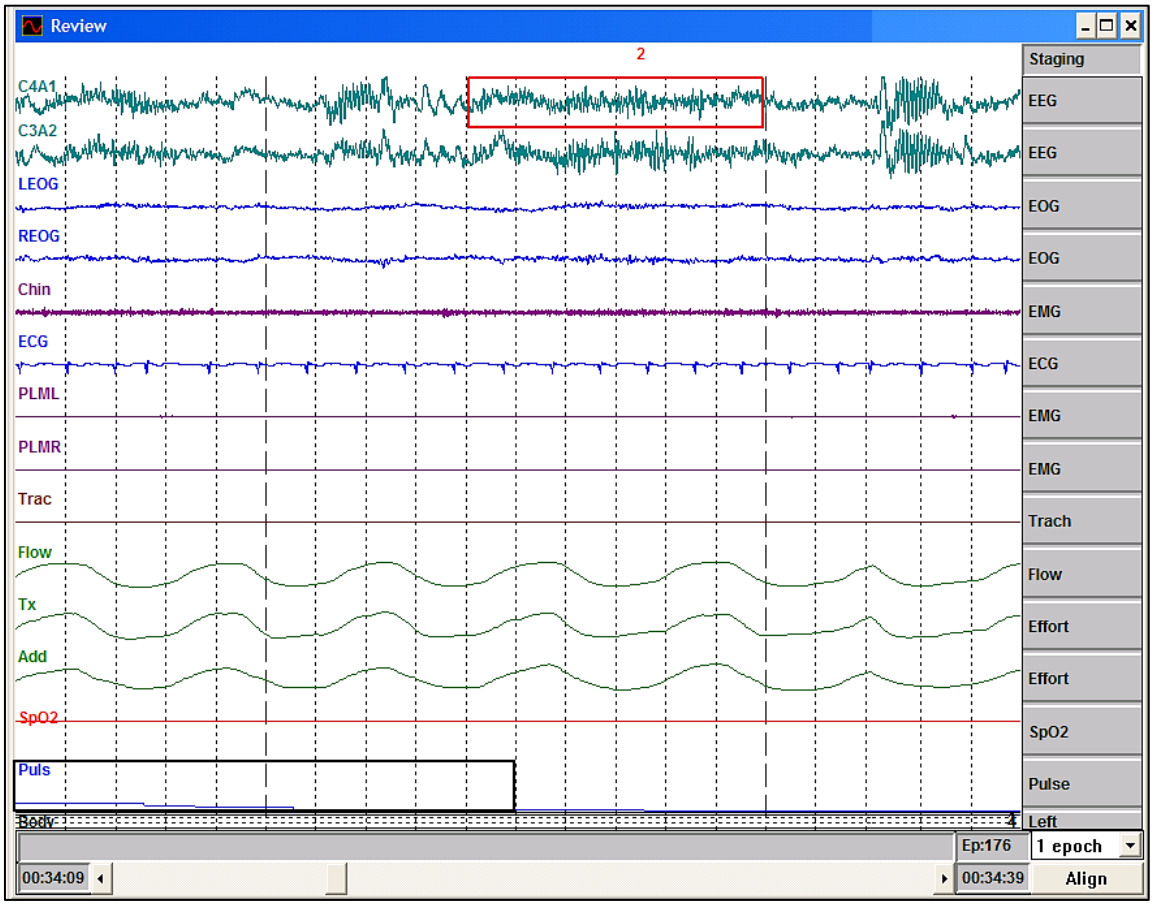

Figure 2.4. Vegetative arousal in NREM 2 stage. Pulse drops so much (marked black at the bottom), that cortical activation is generated (marked red at the top). Channels explained in the Table 2.1.

- **Behavioural arousal** (BA) was reported in the Rechtshaffen and Kales manual (Rechtshaffen and Kales, 1968) as a movement arousal described as any increase in electromyographic activity that is accompanied by a change in any other EEG channel (Figure 2.5).

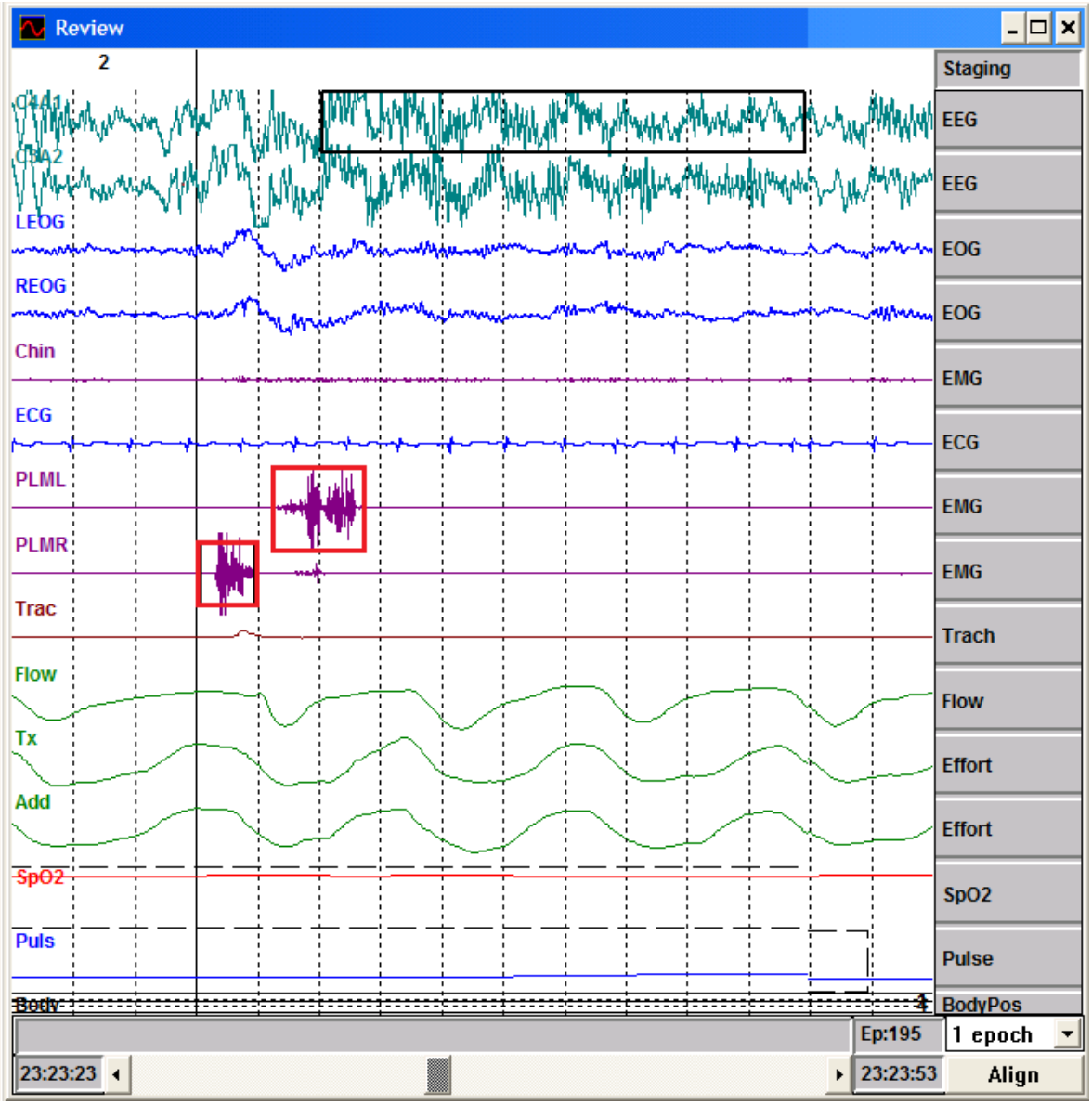

Figure 2.5. Behavioural arousal in NREM 2 stage. After leg movement (marked red in the middle) cortical activation is generated (marked black at the top). Channels explained in the Table 2.1.

Data collected from PSGs, microarousal indices (MAI), behavioural arousal indices (BAI) and vegetative arousal indices (BAI) were objective data; Pittsburgh sleep quality indices (PSQI) were subjective data. Relationships between these objective and subjective data and their dynamics will be further analysed in this study.

2.5. Protocol

All patients who took part in the study were regular patients of the Sleep disorders laboratory at Vilnius Sapiegos hospital. As part of their standard clinical assessment they completed the PSQI at their initial patient consultation and a clinical history was taken. An overnight sleep study was then performed using the electrophysiological recording equipment (SleepLab Applications from VIASYS® Respiratory Care Inc., Viasys Healthcare GmbH, Hoechberg, Germany) to measure 4 EEG leads (C3, C4, P3, P4 referenced to linked ears), an electrooculogram (EOG), an electromyogram (EMG), and an electrocardiogram (ECG). Also arterial oxygen saturation (SaO_2) was determined, respiration was monitored with thermistors and thoracic movements, and tibialis electromyographic activity was recorded using surface electrodes placed on the right and left legs. Sleep laboratory was equipped with video and sound recording devices for additional monitoring of body movements and sounds. All equipment was time synchronized.

Subjects went to bed at their usual time and were asked to refrain from drinking beverages containing caffeine or alcohol in the previous afternoon and evening hours. In the morning they also awakened at their usual time.

Sleep stages were visually scored according to standard criteria (Rechtshaffen and Kales, 1968) using 30-second epochs, with the investigator blind to subject and experimental condition. Standard sleep parameters were computed over the complete sleep time period, and all recordings were analyzed for sleep staging and arousal scoring with the Matrix Sleep Analysis SleepLab® for Windows (version 1.70.0.3) software package.

2.6. Statistics and data evaluation

PSQI was calculated for each patient using standardized key to the questionnaire – total scores could vary from 0 to 21.

All PSG recordings were analyzed and conventional PSG measures were included: total sleep time (TST), time in bed (TIB), sleep efficiency (SE), sleep latency (SL), wake after sleep onset (WASO), total duration and percentages of non-rapid eye movement sleep (NREM) stage 1 (N1), stage 2 (N2), stage 3 (N3) and stage 4 (N4) and rapid eye movement sleep (REM). Stage 1 and 2 together are referred to as light sleep (LS), Stage 3 and 4 together are referred to as deep sleep (DS).

Each PSG recording was subdivided into sleep cycles (SC). The first SC started at sleep onset and the following SC with the first epoch of NREM sleep after a completed REM sleep episode. All SC ended with the last epoch of the included REM sleep episode. According to adopted procedures (Feinberg and Floyd, 1979; Merica and Gaillard, 1991) a REM sleep period was considered completed when the duration of the NREM stage following the last epoch scored as stage REM exceeded 15 min. The sleep time preceding the final awakening not completed by REM sleep episode was not included in the cycle calculation. For each SC the total duration, stage composition and percentages were analyzed. Arousal indices (AI) were quantified in TST, NREM sleep and in each of NREM sleep stages, REM sleep, separately and in every SC.

In every calculation subjects with parameters exceeding ± 3SD were excluded from data analysis.

Examination of the data and the Kolmogorov-Smirnov and Chi-square tests for normality suggested that most of the variables were likely to be normally distributed. Pearson correlation thus was used to examine the relationships between each of the arousal indices and PSQI in all sleep stages and sleep cycles. Level of confidence (p) less than 0.05 was considered as significant.

The PSG data from different SCs were analyzed and compared by a factorial ANOVA followed by a post-hoc Bonferroni test. All the statistics were calculated using the STATISTICA v 8.0 software (StatSoft Inc., USA).

3. RESULTS

In this chapter general sleep parameters, arousal statistics and their dynamics during the night will be reviewed. At the end of this chapter relationships between sleep structure and subjective sleep quality will be analysed. Total of 60 patients were analysed. In every calculation subjects with parameters exceeding ± 3SD were excluded from data analysis, therefore number of subjects (N) could differ in every analysis stage.

3.1. General sleep parameters

Conventional sleep and staging parameters for the whole night sleep are presented in Table 3.1 and Table 3.2. SE was 85%, which was less than reported 94% in the study by Terzano et al. with normal healthy subjects (Terzano et al., 2005).

Table 3.1 – Conventional sleep parameters. Average ± SD

TST (min)	417.5±57.9
SE (%)	85.1±9.2
SL (min)	18.6±23.2
WASO (min)	54.5±39.5
NREM duration (min)	325.5±51.7
REM duration (min)	87.1±29.1

TST – total sleep time; SE – sleep efficiency; SL – sleep latency; WASO – wake after sleep onset; NREM – non-rapid eye movement sleep; REM – rapid eye movement sleep; (N=55).

Table 3.2 – Conventional sleep staging parameters. Average ± SD

	Latency (min)	Duration (min)	% from TIB	% from TST
W	-	78.1±56.6	15.7±11.2	-
N1	-	56.0±39.9	11.2±7.5	13.4±8.6
N2	11.3±14.4	152.0±38.7	31.0±7.4	37.1±8.0
N3	30.1±25.2	83.7±27.1	17.1±5.5	20.5±6.6
N4	43.1±37.8	33.8±26.7	7.0±5.7	8.2±6.5
REM	83.1±46.9	87.1±29.1	17.7±5.8	20.8±5.6

TIB – time in bed; TST – total sleep time; N1, N2, N3, N4 – stages 1, 2, 3, 4 of NREM (non-rapid eye movement sleep); REM – rapid eye movement sleep; W – wake; (N=51).

More detailed information about conventional sleep parameters and sleep phases (NREM and REM) is provided in the Table 3.3.

Table 3.3 – Descriptive statistics of conventional sleep parameters

	Total sleep time (min)	Sleep efficiency (%)	Sleep latency (min)	Wake after sleep onset (min)	NREM duration (min)	REM duration (min)
Number of subjects	55	55	55	55	55	55
Mean	417.49	85.10	18.60	54.50	325.58	87.11
Standard Error	7.80	1.24	3.13	5.32	7.24	4.07
Standard Deviation	57.88	9.23	23.22	39.46	51.68	29.08
Minimum	282.00	62.90	0.50	3.00	196.50	18.50
Maximum	510.00	98.20	108.50	191.50	423.00	143.00

NREM – non-rapid eye movement sleep; REM – rapid eye movement sleep

In 22 subjects, sleep was organized in four completed SC, in 27 subjects – in five, and only 4 patients had six SC. Tables 3.4 and 3.5 report the structural parameters of five SC derived from 24 subjects, four SC derived from 40 subjects, three SC from 41 and two SC from 44 subjects. The sixth SC was not taken into consideration as it was found only in two subjects.

Due to this reason and to the definition of SC (see above in chapter 2.6), the sum of values expressed in Tables 3.3 and 3.4 do not coincide with the total values derivable from Table 3.1 and 3.2.

The average duration of the SC was 90 min. The third SC was the longest and fifth SC was the shortest, but the length of the five SC did not differ significantly (Table 3.4). The amount of DS declined from the first to the last SC (in N3 $p < 0.001$ and in N4 $p < 0.05$) with especially sharp reduction between the second and the third SC. The duration of LS was lower in the first two SC becoming more stable in the third and fourth SC and rising in the fifth. Differences of N2 durations in different SCs were significant ($p < 0.001$) and of N1 not. REM sleep duration increased from the first to the last SC ($p < 0.05$) (Table 3.4 and Figure 3.1).

Table 3.4 – Stage duration in sleep cycles. Average ± SD

	I cycle	II cycle	III cycle	IV cycle	V cycle	p	Significantly differing sleep cycles
Number of subjects	N=44	N=44	N=41	N=40	N=24		
TST (min)	86.4±21.8	92.3±19.6	94.8±30.0	92.6±18.2	83.5±24.3	n. s.	
WASO (min)	6.4±8.1	4.0±6.7	6.9±9.6	4.6±8.7	4.9±8.2	n. s.	
N1 (min)	11.5±8.6	6.6±7.2	9.5±13.5	9.1±9.1	12.5±2.3	n. s.	
N2 (min)	23.0±11.4	29.7±12.9	36.8±12.3	37.1±13.2	34.6±14.3	**<0.001**	3>1; 4>1; 5>1
N3 (min)	23.9±12.7	23.9±12.7	18.9±15.8	11.3±9.7	4.5±6.1	**<0.001**	1>4; 1>5; 2>4; 2>5; 3>5
N4 (min)	12.8±12.5	10.8±11.1	4.1±6.9	3.8±7.6	1.4±4.9	**<0.05**	1>5;
NREM (min)	71.1±16.5	70.9±17.2	69.3±21.3	61.3±15.4	53.0±16.4	n. s.	
REM (min)	8.8±8.0	17.4±12.6	18.7±13.4	26.6±15.0	25.6±14.6	**<0.05**	3>1; 4>1; 5>1;

TST – total sleep time; WASO – wake after sleep onset; N1, N2, N3, N4 – stages 1, 2, 3, 4; NREM – non-rapid eye movement sleep; REM – rapid eye movement sleep; p – significance of inter cycle differences.

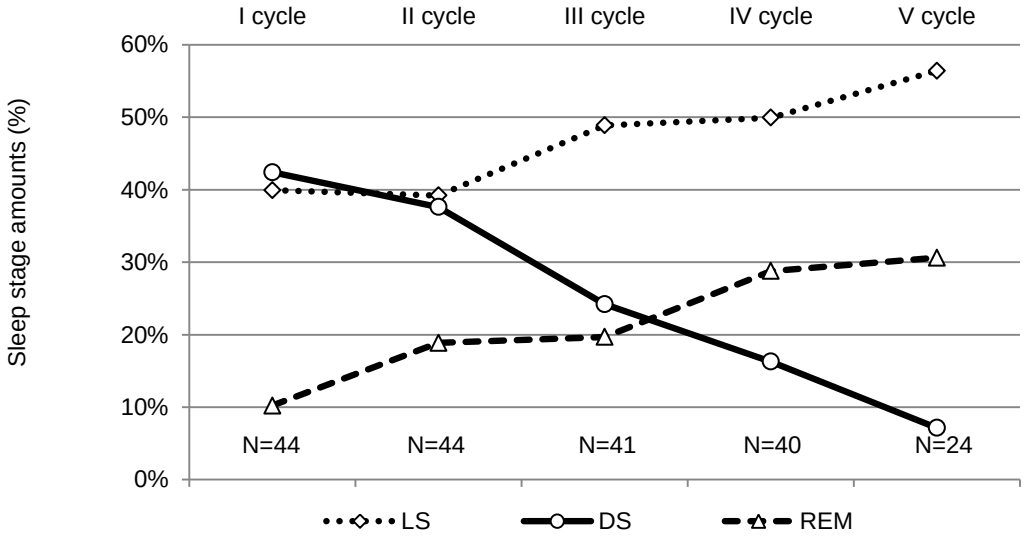

Figure 3.1. Average proportions of light sleep (LS), deep sleep (DS) and REM sleep in different sleep cycles; N – number of subjects.

Interim summary: the amount of light sleep and REM sleep increases with every cycle, while amount of deep sleep decreases. Significant differences of sleep stage durations were found only between some sleep cycles. Most dramatic changes in stage durations happen between the second and the third SC.

3.2. Arousals and their dynamics

The first step was to compare arousal statistics between men and women. Analysis of arousal indices and arousal distribution in sleep stages and cycles in men and women (t-test for two independent samples) revealed that in most of the parameters there were no significant differences ($p > 0.02$) (Figures 3.2-3.4). That gender is not significant factor for AI was confirmed by the factorial ANOVA analysis (see further). Due to these reasons it was decided to analyse men and women as one group

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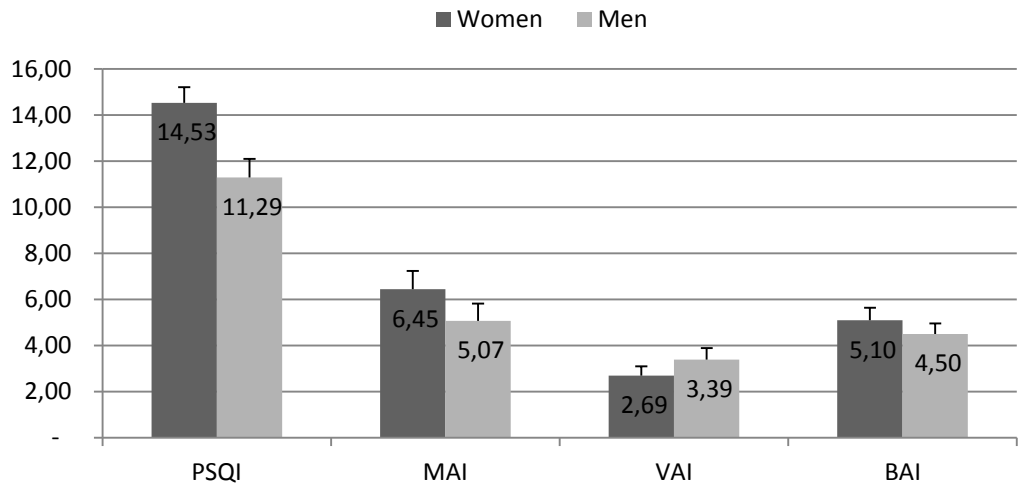

Figure 3.2. Women (N=30) and Men (N=28) group indices comparison. Vertical error bars represent Standard errors (SE).

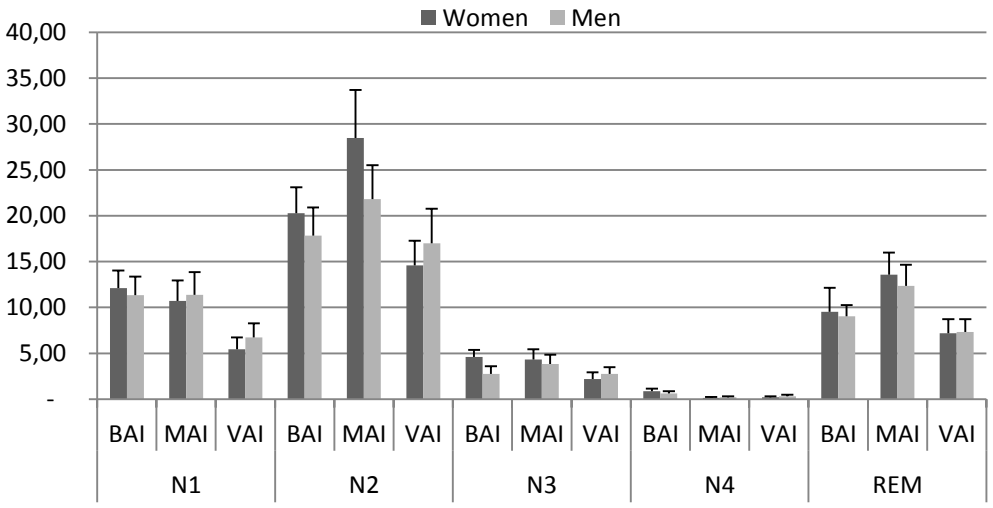

Figure 3.3. Women (N=30) and Men (N=28) group AI averages comparison in different sleep stages. Vertical error bars represent Standard errors (SE).

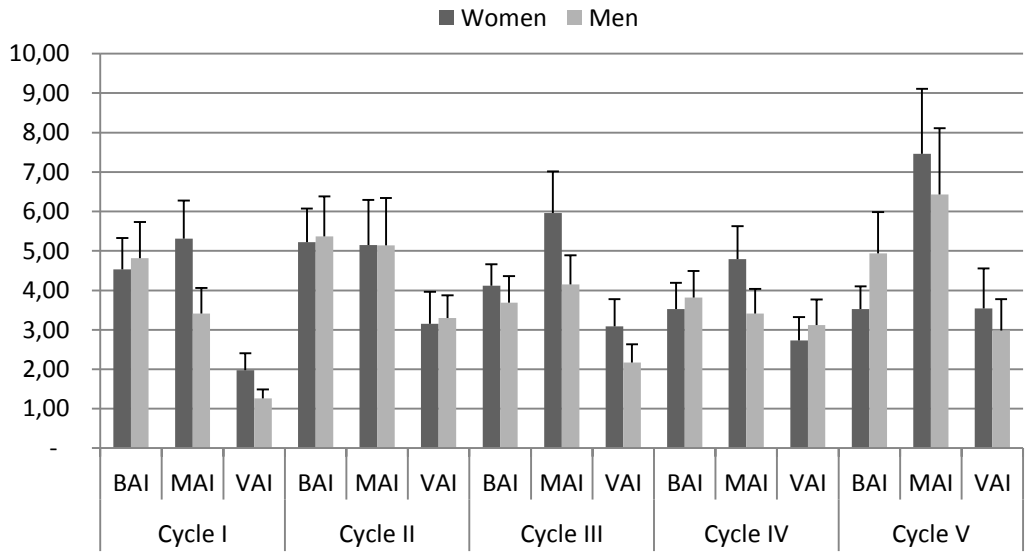

Figure 3.4. Arousal indices in women (N=30) and men (N=28) groups in different sleep cycles. Vertical error bars represent Standard errors (SE).

Three different arousal type indices were analysed separately in present study, but combinations of different arousal type indices and their effect on sleep quality were examined as well. The highest AI in TST was MAI 5.8 ± SD 4.2. The combination of all three arousal types had AI not exceeding 14 (Table 3.5).

Table 3.5 – Arousal indices and their combinations. Average ± SD

	MAI	VAI	BAI	MAI+VAI	MAI+BAI	MAI+VAI+BAI	VAI+BAI
AI average	5,8±4,2	3,0±2,4	4,8±2,7	8,8±4,2	10,6±4,7	13,6±4,7	7,8±3,6

MAI – microarousal index; BAI – behavioural arousal index; VAI – vegetative arousal index; N=58.

Descriptive statistics of Pittsburgh sleep quality index (PSQI), different arousal indexes (AI) and combinations of different AIs are provided in the table 3.6.

Table 3.6 – Descriptive statistics of Pittsburg sleep quality and arousal indices

	PSQI	MAI	VAI	BAI	MAI+VAI	MAI+BAI	MAI+VAI +BAI	VAI+BAI
Nbr of subjects	58	58	58	58	58	58	58	58
Mean	13,0	5,8	3,0	4,8	8,8	10,6	13,6	7,8
Standard Error	0,6	0,5	0,3	0,4	0,6	0,6	0,6	0,5
Standard Deviation	4,3	4,1	2,4	2,7	4,2	4,7	4,7	3,6
Minimum	5,0	0,5	0,1	0,6	1,8	1,9	2,9	1,4
Maximum	19,0	17,0	9,8	12,2	17,8	21,4	22,8	14,9

PSQI – Pittsburgh sleep quality index; MAI – microarousal index; BAI – behavioural arousal index; VAI – vegetative arousal index. N=58.

All AI rose from first to second SC during the night and then varied, but there were no significant differences between AIs in different sleep cycles. MAI in TST – 5.8 ± SD 4.1 – was the highest among all three arousal types. BAI in TST was 4.8 ± SD 2.7 and VAI in TST was 3.0 ± SD 2.4 (Table 3.7).

Table 3.7 – Arousal indices in sleep cycles

	I cycle	II cycle	III cycle	IV cycle	V cycle
Number of subjects	N=46	N=45	N=42	N=40	N=24
BAI	4.7±4.1	5.3±4.4	3.9±2.7	3.7±3.0	4.2±3.0
MAI	4.4±4.0	5.2±5.5	5.1±4.2	4.1±3.3	6.9±5.7
VAI	1.6±1.7	3.2±3.3	2.6±2.7	2.9±2.8	3.3±3.1

BAI – behavioural arousal index; MAI – microarousal index; VAI – vegetative arousal index; Average ± SD.

Looking from sleep staging perspective situation with AI is different. Differences between AI in most sleep stages are significant for all types of arousals. The highest AI scores are found in NREM stage 2 and lowest in NREM stage 4. AI values rise from N1 to N2 and then decline as sleep gets deeper. AI values in REM are in between N2 and N3 values. MAI values are higher than BAI and VAI values in the most stages (Table 3.8).

Table 3.8 – Arousal indices in sleep stages. Average ± SD

	N1	N2	N3	N4	REM	p	Significantly differing sleep stages
Number of subjects	N=45	N=45	N=45	N=45	N=45		
BAI	11.7±9.3	19.0±14.0	3.6±4.0	0.7±1.2	9.3±9.4	**<0.05**	1>3; 1>4; 2>1; 2>3; 2>4; 2>REM; REM>4.
MAI	11.1±11.0	25.1±21.3	4.1±5.0	0.2±0.5	12.9±11.1	**<0.001**	1>4; 2>1; 2>3; 2>4; 2>REM; REM>3; REM>4.
VAI	6.1±6.7	15.8±15.6	2.5±3.6	0.3±0.6	7.3±6.9	**<0.01**	2>1; 2>3; 2>4; 2>REM.

BAI – behavioural arousal index; MAI – microarousal index; VAI – vegetative arousal index; N1, N2, N3, N4 – stages 1, 2, 3, 4 of non-rapid eye movement sleep; REM – rapid eye movement sleep; p – significance of inter-cycle differences.

Not significant AI differences between SC (Table 3.4) and significant AI differences between sleep stages (Table 3.8) suggested that sleep stage is more important factor for AI than SC. So we calculated three types of AI for all sleep stages in every sleep cycle and analysed them. Factorial ANOVA showed that sleep stage ($F(4, 3117)= 20.825$; $p < 0.0001$; $\eta^2 = 0.026$), but not sleep cycle ($F(4, 3117)= 0.676$; $p = 0.6$; $\eta^2 = 0.001$) is significant factor for AI value. Arousal type was also a significant factor for AI ($F(2, 3117)= 13.290$; $p < 0.00001$; $\eta^2 = 0.008$). For factorial ANOVA test AI was dependent variable and SC (I-V), stage (N1-N4, REM), and arousal type (MA vs. VA vs. BA) were categorical predictors (factors).

Interim summary: not significant AI differences between SC but significant AI differences between sleep stages and factorial ANOVA analysis showed that sleep stage but not sleep cycle is significant factor for AI value. Highest AI scores were found in NREM stage 2 and MAI values are higher than BAI and VAI values in the most stages. There were no gender differences.

3.3. Subjective sleep quality

Pittsburgh Sleep quality index (PSQI) score of 5 or higher represents disordered sleep (Buysse et al., 1989). The higher score, the worse sleep quality. Average PSQI for all subjects in this study was 13.0 ± SD 4.4. This is normal in our case, because all the subjects had sleep problems.

Correlation between conventional sleep staging parameters (stage duration, % from TIB, % from TST) and PSQI gradually progresses from LS into DS. Significant correlations for all three parameters were only between wake (W) duration and PSQI ($r = 0.3$; $p < 0.05$) and between N4 duration and PSQI ($r = -0.3$; $p < 0.05$) (Figure 3.5). REM numbers in the figures are presented between N2 and N3 values, because entry in to the REM sleep is usually happening from N2 stage (Figure 3.5).

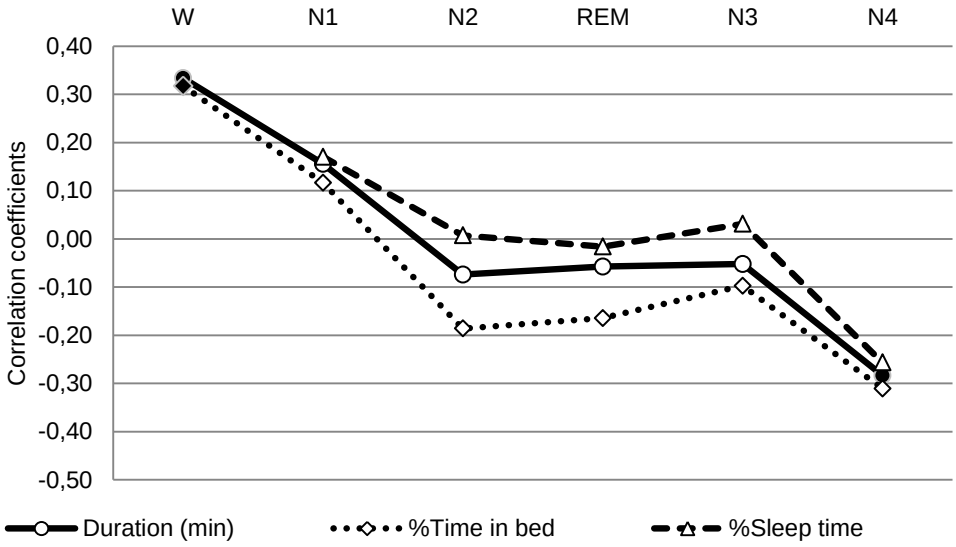

Figure 3.5. Pittsburgh sleep quality index correlations with conventional sleep parameters (N=51). W – wake; N1, N2, N3, N4 – stages 1, 2, 3, 4 of NREM (non-rapid eye movement sleep); REM – rapid eye movement sleep. Statistically significant values are marked black.

The strongest and significant correlation was between PSQI and MAI ($r = 0.42$; $p = 0.001$). There was no significant correlation between PSQI and other types of AI (Table 3.9). It could be that for subjective sense of sleep quality might be important not one particular type of arousals, but the combination of all of them. Grouped arousal indices (e.g. MAI + BAI) had stronger significant correlations with PSQI ($r = 0.5$; $p < 0.001$) than single type arousals (Table 3.9).

Table 3.9 – Pittsburgh sleep quality index correlations with arousal indices

Correlation combinations	r	p
PSQI & MAI	0.42	**0.001**
PSQI & VAI	- 0.17	0.192
PSQI & BAI	0.21	0.118
PSQI & MAI+VAI	0.31	**0.018**
PSQI & MAI+BAI	0.49	**<0.001**
PSQI & VAI+BAI	0.04	**0.002**
PSQI & MAI+VAI+BAI	0.40	0.773

PSQI – Pittsburgh sleep quality index; BAI – behavioural arousal index; MAI – microarousal index; VAI – vegetative arousal index; r – correlation coefficient; p – level of significance; N=58.

After analyzing subjective sleep quality relations with separate sleep cycles and their different stage durations we found that statistically significant correlations are only between duration of N1 in first SC and PSQI ($r = 0.32$; $p < 0.05$). That means the more time we spend in stage N1 during the first SC, the poorer our general sleep quality would be (Figure 3.6). It is interesting that going from the first to the last SC this correlation gets weaker. This supports the idea that the first sleep cycles are more important for the good rest sense after the sleep (Figure 3.6).

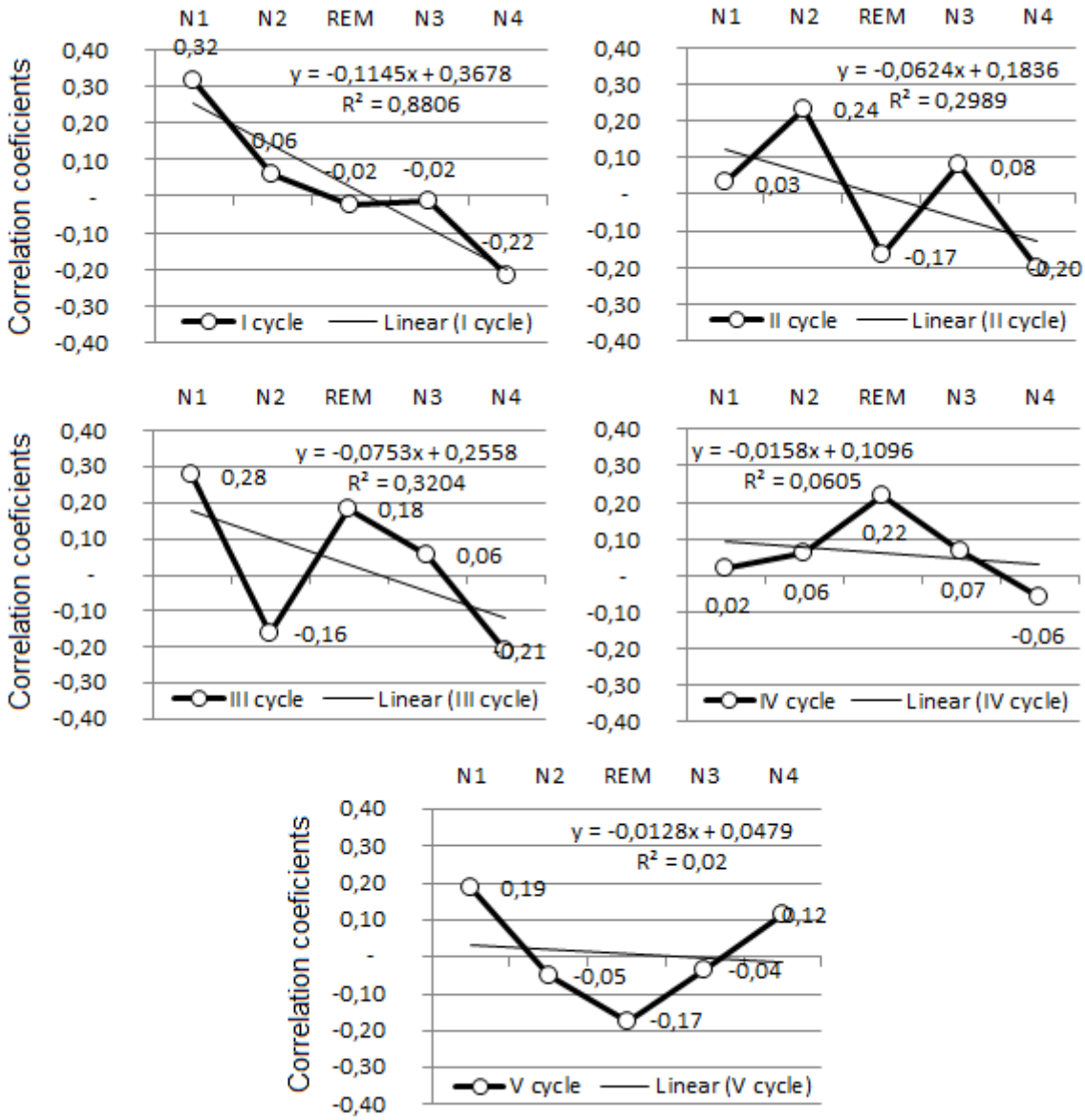

Figure 3.6. Correlations between sleep stage durations and PSQI in different sleep cycles. On the vertical axis – correlation coefficients; N1, N2, N3, N4 – stages 1, 2, 3, 4 of NREM (non-rapid eye movement sleep); REM – rapid eye movement sleep; thin black lines – linear regressions.

After grouping sleep stages in to light (LS) and deep (DS) sleep picture becomes clearer. Correlations between amount of LS and DS in SCs with PSQI were not significant (Figure 3.7). This relation in case of DS from negative (r = -0.20) becomes neutral (r = 0.04) going from the first to the fifth SC and in case of LS – from positive (r = 0.23) to more neutral (r = 0.12). Correlation between amount of REM sleep and PSQI values varies a lot from SC to SC over the night (Figure 3.7).

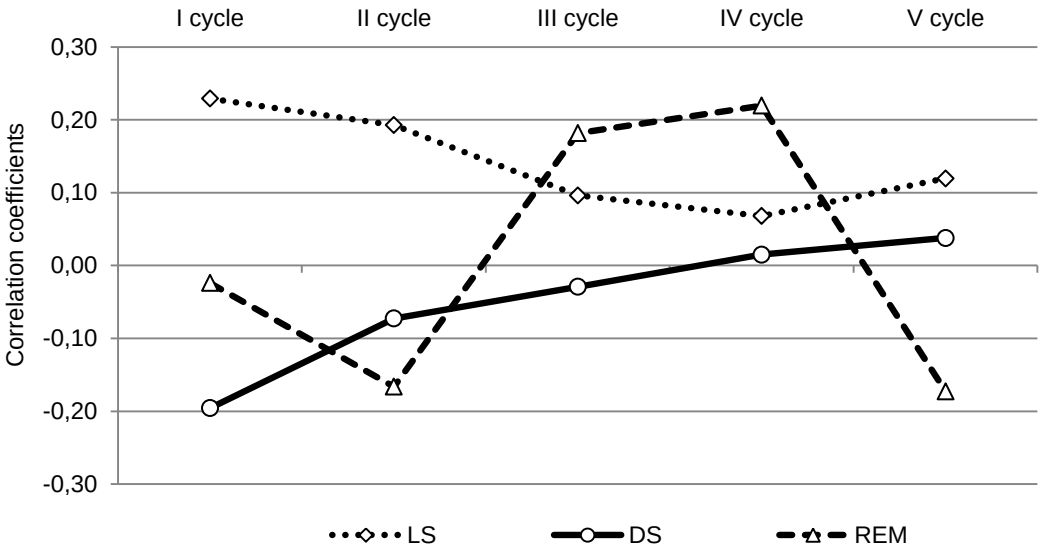

Figure 3.7. Pittsburgh sleep quality index correlations with light sleep and deep sleep duration in different sleep cycles (N=44). LS – light sleep; DS – deep sleep; REM – rapid eye movement.

Correlation between different types of AIs and PSQIs changes during the night. MAI correlation rises during the night, BAI and VAI – decreases (Figure 3.8). Statistically significant correlation with PSQI showed only MAI ($r = 0.64$; $p = 0.001$) and only in the fifth SC. This means that for the good sleep quality it is more important whole sleep structure and not just certain type separate sleep stage in different SCs.

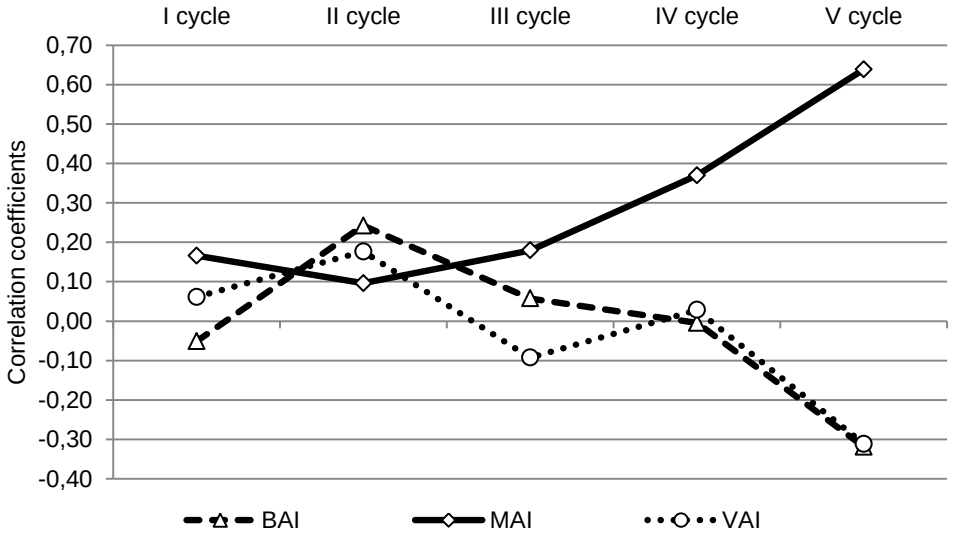

Figure 3.8. Pittsburgh sleep quality index correlations with different type arousals in sleep cycles. BAI – behavioural arousal index; MAI – microarousal index; VAI – vegetative arousal index. N=46.

Interim summary: study results showed that amount of deep sleep (N3 and especially N4) is important for subjective sense of rest after the sleep. Positive correlation between LS and PSQI shows negative effect of LS for sleep quality and negative correlation between DS and PSQI shows positive effect of DS for sleep quality. Going from the first to last sleep cycle both of these correlations become neutral – importance for the sleep quality becomes weaker – therefore we assume that initial sleep cycles are more important for good rest sense after the sleep. MAI correlation with PSQI becomes stronger with every SC and in the end of the night it is statistically significant. This could be related to the increasing amount of N2 in every consecutive SC. On the other hand relation of VAI and BAI with PSQI tend to be more negative with every SC, which formally would mean more positive impact for sleep quality sense with every SC.

4. DISCUSSION

The present study was undertaken to analyse sleep structure and fragmentation in terms of arousals (behavioural, micro and vegetative) and their distribution during the night and to evaluate if there is any relation with subjective sense of rest after the sleep without paying attention to the type of insomnia.

Stage-dependent EEG modifications, the cyclic alternation between NREM and REM sleep, which develops in four to six 90-min ultradian cycles, decline of DS and increase of LS across the night are the most relevant contributions supplied by the conventional criteria to understand the structure of sleep (Brunner, 1990; Preud'homme, 2000; Ohayon, 2004). Our study showed that this holds true also in subjects with sleep disorders. The composition of the single SC varies in the course of the night – the period length of DS decreases from the first to the last SC and at the same time LS and REM sleep undergo a progressive increase (Figure 3.1). But the question was how all this relates to persons rest sense after the sleep. Sleep structure, all the relations and proportions of sleep structural parts are important not as such, but how they let us evaluate the quality of person's sleep and wake.

The importance of deep sleep for subjective sense of rest after the sleep was shown as a significant negative correlation between Pittsburgh sleep quality index (PSQI) and deep sleep (N4) amount ($r = -0.3$; $p < 0.05$) (Figure 3.5). This was in accordance with similar previous studies by other authors. (Martin et al., 1996; Pitson and Stradling, 1998). What is important that this is not static effect – during the course of night – going from the first to the last SC – this relation gets weaker, indicating the importance of initial SCs to the overall sleep quality sense (Figure 3.7). Such a tendency makes sense looking from evolutionary perspective – it is vital to get good sleep sooner.

From all three arousal types that we have studied MAI in TST showed the highest correlation with PSQI ($r = 0.42$; $p = 0.001$). But even stronger correlation was found between PSQI and general index of MAI+BAI ($r = 0.5$, $p < 0.001$) (Table 3.9). VAI in TST showed negative correlation with PSQI and this means that the more vegetative arousals patient has, the better his sleep quality is. That was unexpected, but it could be that internally generated vegetative arousals to some extent play important role in sleep

regulation and express not negative sleep disturbances, but maintenance of internal body functions instead (Halasz et al., 2004).

AIs dynamics during the night is closely related to the duration of sleep stages in each SC. MAI correlations with PSQI increases from cycle to cycle, but it is significant only in the V cycle ($r = 0.64$; $p = 0.001$) and is mainly related to increasing proportion of LS (especially N2) with each SC. Correlations between BAI, VAI and PSQI become more negative over the night in parallel with decreasing amount of DS in each SC (Figure 4.1). This negative trend is similar to the negative correlations between PSQI and VAI in TST. That could be related to the maintenance and preparation of internal body functions before the morning time awakening.

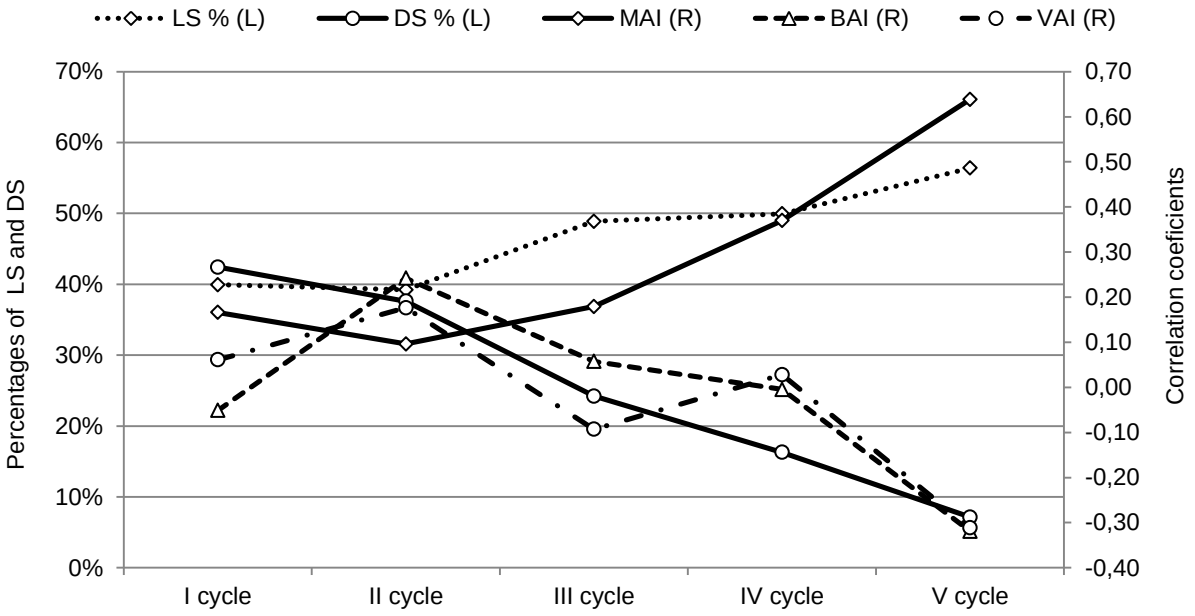

Figure 4.1. Pittsburgh sleep quality index correlations with different type arousals through the sleep cycles (N=46).
LS % - percentage of light sleep; DS % - percentage of deep sleep; BAI – behavioural arousal index; MAI – microarousal index; VAI – vegetative arousal index; L – left hand side axis; R – right hand side axis.

Not significant AI differences between SC (Table 3.7) and significant AI differences between sleep stages (Table 3.8) suggested that development of human sleep within the single SC is more important for the sleep quality than the changes between SCs. Factorial ANOVA confirmed that – sleep stage and arousal type were significant factors for the AI values, whereas sleep cycle was not (see above in chapter 3.2).

The highest AI values were found in N2 stage and MAI in this stage was higher than the other two AIs (Table 3.5). Based on this we suggest that not only the sleep stage proportions (the amount of DS) are important to feel good after the sleep, but the microstructure of each stage, and especially N2, might be significant for that also.

What is happening during N2 stage that we could think of its importance?

The average cerebral metabolism and blood flow begin to decrease in N2 compared to wakefulness (Madsen, 1991a; Maquet, 1992). Comparing the influence of high (34-37^{o}C) and low (21^{o}C) ambient temperatures on sleep, Haskell et al. pointed out that the duration of wakefulness and N1 sleep increased in cold exposure whereas the duration of N2 sleep decreased (Haskell et al., 1981). They concluded that cold was more disruptive to sleep than heat. A similar observation has been reported by Palca et al. (Palca et al., 1986). For naked subjects exposed for five consecutive nights at 21^{o}C cold exposure increased wakefulness and decreased N2 sleep without any change in other sleep stages. That shows that sleep disruption might be expressed as the reduction in N2 sleep (Palca et al., 1986).

The increase in slow wave activity during NREM sleep is associated with low adrenocorticotropic activity and low sympathetic activity, whereas N2 clearly reveals its hormonal and autonomic duality, depending on whether it prepares deep sleep or REM sleep (Shannahoff-Khalsa et al., 1996). It could be that sleep disorders might result from an alteration of the autonomic nervous system activity, or from inadequate coupling between endocrine, autonomic, and EEG ultradian rhythms (Parmeggiani and Velluti, 2005).

In healthy nocturnal young subjects, oral administration of exogenous melatonin before going to bed increased N2 amount significantly, with slight hypothermic action (Shirakawa et al., 2001). The effect of a high melatonin dose (80 mg p.o.), when tested in subjects with insomnia induced by exposure to recorded traffic noise, was a reduction of sleep latency and of the number of awakening episodes and the increase of N2 sleep and sleep efficiency (Waldhauser, 1990). Administration of 3-mg dose of melatonin during 14 nights to elderly patients with chronic primary insomnia brought about a significant reduction in WASO while TST and SE increased, with an increase of N2 stage (Monti, 1999). It turns out that pharmaceutical improvement of sleep influences mostly N2 stage.

Individuals who learn a new task have a significantly higher density of sleep spindles, which are one of the markers of N2 stage, than those in a control group (Gais, 2002) and the improvement of performance after a period of sleep is correlated with the percentage of N2 sleep (Walker, 2002).

From all these findings we can see that N2 stage is associated and correlated with good sleep quality and sleep disruptive conditions make most impact also on N2 stage. This and recent findings about sleep mechanism disruptions and its possible connection with some pathologies (from cognitive to metabolic defects) (Wulff, 2010; Wulff 2009) raise new thoughts. Stabilization of sleep and especially in NREM stage 2 might help to reduce symptoms of these pathologies and give way for other specialists to intervene more effectively with their therapy. Moreover, the importance of this stage gets new meaning in light with emerging concepts of sleep-wake cycle regulation and transition from NREM to REM sleep and vice versa, which usually is happening through NREM stage 2 (Fort et al., 2009; Datta and MacLean, 2007).

In summary, it can be concluded that microarousal density is important for the subjective sense of rest after the sleep. Highest values of MAI and other arousal types are found in NREM stage 2. That is why we point out that the importance of this stage might be higher than anticipated and especially in initial sleep cycles. This stage plays role of a certain distributor between light and deep sleep. If during this stage all main processes in the brain and body are stable and sleep is undisrupted, then deep sleep can restore brain's electrolytic homeostasis; ionic balance, macromolecules are restored in the cells – brain rests. But if processes during this stage are unstable, e.g. sleep is fragmented with microarousals, then sleep quality becomes poorer and deep sleep cannot compensate that.

CONCLUSIONS

1. For the subjective sense of rest after the sleep the stability of sleep in the initial sleep cycles is more important than in the last sleep cycles.
2. Sleep stage and arousal type regardless of sleep cycle are significant factors for the arousal index values.
3. Sense of rest after the sleep is influenced more by combination of different arousal type indices (strongest – microarousals plus behavioural arousals), than by the single type of arousals. Taking single type arousal indices the strongest correlation with the sense of rest is in case of microarousals.
4. Increase of all arousal indices in N2 stage (especially increase of microarousal index) has the strongest impact for the sense of rest after the sleep.

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SANTRAUKA

Įvadas: poilsio jausmas po miego ir jo ryšys su įvairiais miego parametrais dar vis yra plačiai diskutuojamas klausimas, ir mokslininkai iki šiol nesutaria, kas lemia gerą savijautą po miego.

Tikslas: išnagrinėti miego struktūrą bei įvertinti jos ryšį su poilsio jausmu po miego nepriklausomai nuo nemigos tipo.

Metodai: 60 pacientų (30 vyrų ir 30 moterų) nakties polisomnogramos išnagrinėtos pagal jų ciklus, fazes ir stadijas. Registruoti trijų rūšių nubudimai – elgesiniai, vegetaciniai ir mikronubudimai. Skirtingų tipų nubudimų indeksai nagrinėti visuose miego cikluose ir stadijose, taip pat visame miege. Miego kokybė vertinta pasitelkus Pitsburgo miego kokybės indekso (PMKI) anketą.

Rezultatai: Giliojo miego svarba subjektyviam miego kokybės jutimui buvo parodyta kaip statistiškai reikšminga neigiama koreliacija tarp Pitsburgo miego kokybės indekso (PMKI) bei gilaus miego (LM4 stadijos) trukmės ($r = -0,3$; $p < 0,05$). Nereikšmingi NI skirtumai tarp miego ciklų ir reikšmingi NI skirtumai tarp miego stadijų leidžia teigti, kad miego kokybei reikšmingesnis yra miego stadijų viduje vykstančių nervinių procesų stabilumas nei kitimai tarp miego ciklų nakties eigoje. Iš visų trijų nagrinėtų nubudimų indeksų bendroje miego trukmėje didžiausia koreliacija su PMKI nustatyta MNI atveju ($r = 0,42$; $p = 0,001$). O labiausiai subjektyvų miego kokybės jausmą įtakojo mikronubudimų ir elgesinių nubudimų bendras indeksas MNI+ENI ($r = 0,5$, $p < 0,001$). Didžiausios NI reikšmės buvo registruotos LM2 stadijoje, o MNI lenkė kitus nubudimų indeksus daugelyje miego stadijų. Atsižvelgiant į tai, galima teigti, jog geram miego kokybės jausmui svarbu yra ne vien miego stadijų proporcijos miego cikluose (gilaus miego kiekis), bet ir kiekvienos miego stadijos, o ypač LM2 stadijos, mikrostruktūra.

Išvados: miego kokybė priklauso nuo jo suskaidymo nubudimais. Didžiausią įtaką poilsio jausmui turi visų tipų nubudimų, ypač žievinių mikronubudimų, indeksų padidėjimas antroje lėtojo miego stadijoje. Šios stadijos reikšmė miego kokybei gali būti didesnė nei manyta iki šiol ir ypač pirmaisiais miego ciklais.

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- Liesiene V, Liesiene R, Uloziene I, Zakevicius M. „Prognostic value of EEG and BAEP evaluation in children’s coma.“ Abstract book of „6th Baltic Congress of Neurology (BALCONE) “ Vilnius, 2009, S64.

Conference presentations

- 12th international conference „Biomedical Engineering“. 23-24th October, 2008, Kaunas, Lithuania. Oral presentation: „Relationship between EEG parameters and subjective sleep quality“ (in Lithuanian).
- 6th Baltic Congress of Neurology (BALCONE) 13-16th May, 2009, Vilnius, Lithuania. Oral presentation: „Prognostic value of EEG and BAEP evaluation in childrens coma“. Poster: Correlation studies between the degree of quantitative neurophysiological patterns variation and recovery of consciousness in children‘s traumatic brain coma.
- 3rd scientific conference of Lithuanian association of neurosciences. 2nd December, 2011, Vilnius, Lithuania. Oral presentation: „Microstructure of sleep and its relationship with subjective sense of rest after the sleep“ (in Lithuanian).

Other publications and science promotion activities

- Popular science article “Sleep science: mysteries and paradoxes” (in Lithuanian). Lietuvos Žinios. pp. 14-15; 2010 09 06 (and www.lzinios.lt).
- Popular science video reportage “Dream masters” (in Lithuanian) in the cycle “Science Express with R.Maskoliūnas”. 2010 Vilnius, Lithuania. (Delfi TV).
- Science festival “Space-ship Earth 2010”. 2010 September 9-17; Vilnius, Kaunas and Klaipėda, Lithuania. Oral presentation: „Animal and human sleep – what we have in common" (in Lithuanian).

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