Arousals and macrostructure of sleep: importance of NREM stage 2 reconsidered

Despertar e macroestruturas do sono: importância de reconsiderar o estágio NREM

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ABSTRACT

Objectives: The sense of rest after sleep and its relation to various sleep parameters is still a debatable issue. The purpose of the present study was to analyse sleep fragmentation by scoring various arousals (microarousals (MA), vegetative (VA) and behavioural (BA) arousals) in all sleep stages and to evaluate their relation with subjective sleep quality without paying attention to the type of insomnia. Methods: The overnight sleep cycles of 60 subjects were analyzed according to their stage composition and arousals. Arousal indices (AI) were calculated for all types of arousals in all sleep stages and sleep cycles. The sleep quality was quantified using the Pittsburgh sleep quality index (PSQI). Results: AI differences between sleep cycles were not statistically significant. MAI value in total sleep time (TST) - 5.8 ± SD 4.1 - was the highest among all the three arousal types. Differences between AI in most sleep stages were statistically significant for all types of arousals. This suggests that human sleep development within a single sleep cycle is more important for the sleep quality than the changes between different sleep cycles. The highest AI scores for the three types of arousals were found in NREM stage 2. The strongest and significant correlation was between PSQI and MAI (r = 0.42; p = 0.001). Conclusion: The density of microarousals is important for the subjective sleep quality. The highest values of MAI and other arousal types are found in NREM stage 2. The importance of this stage might be higher than thought before and especially in initial sleep cycles.

Keywords: sleep, sleep disorders, sleep stages.

INTRODUCTION

The overnight course of sleep is not a simple linear process, and it exhibits a very complex behavior which involves various areas of the central nervous system at different levels and at different times⁴. 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 sleep⁵.

More recently, and especially to explain the clinical consequences of sleep disorders, the three processes of sleep regulation - circadian, homeostatic and ultradian - have been integrated by the definition of the arousal system⁶. Arousal are transient episodes of cerebral activation during sleep which involves massively the cortex regulated by the interplay between cortical and subcortical neurons⁷. Most authors consider arousals as a transient cortical activation in response to sleep disruptive events⁸⁹, but there are other studies indicating that...
arousals punctuate both REM and NREM sleep even in the absence of detectable disturbing stimuli\(^{8,9}\).

On the one hand, there are debates still going on about the nature and role of arousals in sleep, and on the other hand, there is a question about their role for the sleeper him/herself - how his/her sleep quality is affected by them. There are various studies trying to evaluate a person's sense of rest after the sleep in the morning, but researchers still disagree about what determines the sense of rest after the sleep\(^{10}\). There are findings which showed that the subjective satisfaction after the sleep is not dependent on the overall sleep length\(^{10}\). 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 sleep might feel unrested in the morning\(^{9}\). A lot of attention is recently paid to the sleep integrity and the role of sleep fragmentation, which is characteristic of primary insomnia and could have an effect on the sleep's restorative function\(^{12,13}\).

The aim of the present study was to analyze sleep fragmentation by scoring different types of arousals in all sleep stages and cycles and to evaluate their relationship with the subjective sense of rest after the sleep without paying attention to the type of insomnia.

**MATERIAL AND METHODS**

**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 46 ± SD 5.6 years). Subjects were recruited from clinical patients of the Sleep disorders laboratory at Vilnius Sapiegos hospital in Vilnius. All subjects were diagnosed with various sleep disorders. The only exclusion criteria were sleep apneas and heavy snoring problems. They had all night PSG study performed in the sleep disorders laboratory and woke up in the morning at their usual time. Before the study, patients had consultations with the doctor, filled out necessary questionnaires and provided written informed consents. All clinical experiments conformed to the principles outlined by the Declaration of Helsinki.

**Arousal scoring**

A monopolar derivation (C3-A2 or C4-A1) was used to score sleep stages\(^{14}\) and arousals. Arousals were scored and arousal indices (AI) (the number of arousals per hour of sleep) were calculated in three major groups to represent different levels of cortical and somatovegetative activations:

- Behavioural arousal (BA): reported in the Rechtshaffen and Kales manual\(^{14}\) as a movement arousal described as any increase in electromyographic activity that is accompanied by a change in any other EEG channel.
- Micro (cortical) arousal (MA): defined by the American sleep disorders association (ASDA) committee in 1992 as EEG arousal and characterized by transient desynchronized EEG patterns interrupting sleep. It reflects a brief awakening of the cerebral cortex regardless of any concomitant participation of the autonomic system or behavioral components\(^{9}\).
- Vegetative (autonomic) arousal (VA): identified when vegetative activation is associated with a transient EEG pattern different from a conventional ASDA arousal\(^{15,16}\).

**The Pittsburgh Sleep Quality Index (PSQI)**

The Pittsburgh Sleep Quality Index (PSQI)\(^{17}\) 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\(^{18}\), to test the effects of a drug on sleep quality in a randomized placebo controlled trial\(^{19}\) 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). Seven component scores that correspond to the domains listed previously are calculated and summed into a global score\(^{17}\). A score of 5 and more indicates poor sleep quality; the higher the score, the worse the sleep quality. Component scores range from 0 to 3 and global scores range from 0 to 21.

**Protocol**

All patients who took part in the study were patients of the Sleep disorders laboratory in 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., Viysys 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. The 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\(^{14}\) using 30-second epochs, with the investigator blind to subject and experimental conditions. 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.
Statistics and data evaluation
All PSG recordings were analyzed and conventional PSG measurements that were obtained from that analysis were: 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). Stages 1 and 2 together are referred to as light sleep (LS), Stages 3 and 4 together are referred to as deep sleep (DS).

Each PSG recording was subdivided into sleep cycles. The first sleep cycle started at sleep onset and the following sleep cycle started with the first epoch of NREM sleep after a completed REM sleep episode. All sleep cycles ended with the last epoch of the included REM sleep epoch. According to adopted procedures, 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 sleep cycle 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 sleep cycle. Before every calculation subjects with calculated parameters exceeding ± 3SD were excluded from data analysis, therefore the number of analysed subjects (N) differs in different calculations.

Examination of the data and the Kolmogorov-Smirnov and Chi-square tests for normality suggested that variables were 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. The PSG data from different sleep cycles was 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).

RESULTS
General sleep parameters
Total sleep time in general group (N = 55) was 418 min. Sleep efficiency was 85%, which was less than reported 94% in the study by Terzano et al. with normal healthy subjects.

In 22 subjects, sleep was organized in four completed sleep cycles, in 27 subjects - in five, and only 4 patients had six sleep cycles. Subjects with parameters exceeding ± 3SD were excluded from the data analysis. Table 1 reports the structural parameters of five sleep cycles derived from 24 subjects, four sleep cycles derived from 40 subjects, three sleep cycles from 41 and two sleep cycles from 44 subjects. The sixth sleep cycle was not taken into consideration as it was found only in two subjects.

The average duration of the sleep cycle was 90 min. The third sleep cycle was the longest and the fifth sleep cycle was the shortest, but the length of the fifth sleep cycle did not differ significantly (Table 1). The amount of deep sleep declined from the first to the last sleep cycle (in N3 p < 0.001, F = 1.717 and in N4 p < 0.05, F = 0.439) with especially sharp reduction between the second and the third sleep cycles. The duration of light sleep was lower in the first two sleep cycles becoming more stable in the third and fourth sleep cycles and rising in the fifth. Differences of N2 durations in different sleep cycles were significant (p < 0.001, F = 1.342) and those of N1 were not. REM sleep duration increased from the first to the last sleep cycle (p < 0.05, F = 3.293) (Table 1 and Figure 1).

Arousals
All AI rose from the first to the second sleep cycle during the night and then varied, but there were no significant differences between Alis in different sleep cycles. MAI in TST - 5.8 ± SD 4.1 - was the highest among all the three arousal types. BAI in TST was 4.8 ± SD 2.7 and VAI in TST was 3.0 ± SD 2.4 (Table 2).

Looking from sleep staging perspective, the situation with AI is different. Differences between Alis in most sleep stages are significant for all types of arousals. The highest AI scores are found in NREM stage 2 and the 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 of stages (Table 3).

Subjective sleep quality
Average Pittsburgh Sleep quality index (PSQI) for all subjects was 13.0 ± SD 4.4. This is normal in our case, because all the subjects have been diagnosed with some sleep disorders.

The correlation between conventional sleep staging parameters (stage duration, % from TIB, % from TST) and PSQI gradually progresses from light sleep into deep sleep (Figure 2). Significant correlations for all the 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 2).

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. It could be that for the subjective sense of sleep quality not just one particular type of arousals might be important, but the combination of all of them. Grouped arousal indices (e.g. MAI + BAI) had stronger significant correlations with PSQI (r = 0.5; p < 0.0001) than single type arousals.

No significant AI differences between sleep cycles (Table 2) and significant AI differences between sleep stages (Table 3) suggested that the sleep stage is a more important factor for AI than the sleep cycle. So we calculated three types of AI for all sleep stages in every sleep cycle and analysed them. Factorial ANOVA showed that the sleep stage (F(4, 3117) = 20.825; p < 0.0001; η² = 0.026), but not the sleep cycle (F(4, 3117) = 0.676; p = 0.6; η² = 0.001) is a significant factor for AI value. The arousal type was also a significant factor for AI (F(2, 3117) = 13.290; p < 0.00001; η² = 0.008). For factorial ANOVA test, AI was a dependent variable and the sleep cycle (I-V), the stage (N1-N4, REM), and the arousal type (MA vs. VA vs. BA) were categorical predictors (factors).
Arousal indices in sleep cycles.

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

MAI in TST showed the highest correlation with PSQI (r = 0.42; \( p < 0.001 \)) (Figure 2). This was in accordance with similar previous studies by other authors \(^{(5,25)}\). And this is not a static effect. During the course of night - going from the first to the last sleep cycle - this relation gets weaker, indicating the importance of initial sleep cycles to the overall sleep quality sense (Figure 3).

The correlation between different types of AIs and PSQIs changes during the night. MAI correlation rises during the night while BAI and VAI decrease (Figure 4). Statistically significant correlation with PSQI showed only BAI (r = -0.34; \( p = 0.02 \)) and VAI (r = -0.33; \( p = 0.03 \)) in the fifth sleep cycle.

Correlations between the amount of light sleep and deep sleep in sleep cycles with PSQI were not significant. This relation in case of deep sleep from negative (r = -0.20) becomes neutral (r = 0.04) going from the first to the fifth cycle and in case of light sleep - from positive (r = 0.23) to more neutral (r = 0.12). The correlation between the amount of REM sleep and PSQI values varies a lot from one sleep cycle to another over the night (Figure 3).

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 the 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, the decline of deep sleep and the increase of light sleep during the night are the most relevant contributions supplied by the conventional criteria to understand the structure of sleep \(^{(22-24)}\). Our study showed that this holds true also in subjects with sleep disorders. The composition of the single sleep cycle varies in the course of the night - the period length of deep sleep decreases from the first to the last sleep cycle and at the same time light sleep and REM sleep undergo a progressive increase (Figure 1). But the question to us was how all this relates to the person's sense of rest in the morning.

The importance of deep sleep for the 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 2). This was in accordance with similar previous studies by other authors \(^{(5,25)}\).

And this is not a static effect. During the course of night - going from the first to the last sleep cycle - this relation gets weaker, indicating the importance of initial sleep cycles to the overall sleep quality sense (Figure 3).

From all the three arousal types that we have studied MAI in TST showed the highest correlation with PSQI (r = 0.42; \( p = 0.001 \)). 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 an important role in sleep regulation and express not negative sleep disturbances, but maintenance of internal body functions instead \(^{(9)}\).
<table>
<thead>
<tr>
<th>Number of subjects</th>
<th>N1</th>
<th>N2</th>
<th>N3</th>
<th>N4</th>
<th>REM</th>
<th>p</th>
<th>F</th>
<th>Significantly differing sleep stages</th>
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<tbody>
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<td>BAI</td>
<td>45</td>
<td>45</td>
<td>45</td>
<td>45</td>
<td>45</td>
<td></td>
<td>2.275</td>
<td>1 &gt; 3; 1 &gt; 4; 2 &gt; 1; 2 &gt; 3; 2 &gt; 4; REM &gt; REM; REM &gt; 4</td>
</tr>
<tr>
<td>MAI</td>
<td>45</td>
<td>45</td>
<td>45</td>
<td>45</td>
<td>45</td>
<td></td>
<td>3.702</td>
<td>1 &gt; 4; 2 &gt; 1; 2 &gt; 3; 2 &gt; 4; 2 &gt; REM; REM &gt; 3; REM &gt; 4</td>
</tr>
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<td>VAI</td>
<td>45</td>
<td>45</td>
<td>45</td>
<td>45</td>
<td>45</td>
<td></td>
<td>5.369</td>
<td>2 &gt; 1; 2 &gt; 3; 2 &gt; 4; 2 &gt; REM</td>
</tr>
</tbody>
</table>

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; F: F-ratio variance; Average ± SD.

Not significant AI differences between sleep cycles (Table 2) and significant AI differences between sleep stages (Table 3) suggested that developments of human sleep within the single sleep cycle are more important for the sleep quality than the changes between sleep cycles. Factorial ANOVA confirmed that the sleep stage and the arousal type were significant factors for the AI values, whereas the sleep cycle was not (see above in Subjective sleep quality).

Figure 2. 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.

Figure 3. 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 sleep.

Figure 4. Pittsburgh sleep quality index correlations with different type arousals in sleep cycles (N = 46). BAI: Behavioural arousal index; MAI: Microarousal index; VAI: Vegetative arousal index.

Figure 5. Pittsburgh sleep quality index correlations with different type arousals in 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.

As dynamics during the night is closely related to the duration of sleep stages in each sleep cycle. MAI correlations with PSQI increase from cycle to cycle, but it is not significant and is mainly related to increasing proportion of light sleep in each sleep cycle and especially N2. Correlations between BAI, VAI and PSQI become more negative over the night in parallel with decreasing amount of deep sleep in each sleep cycle (Figure 5). 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.
The highest AI values were found in N2 stage and MAI in this stage was higher than the other two AIs (Table 3). On this basis, we suggest that not only the sleep stage proportions (the amount of deep sleep) 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 in the human body that we could think of its importance? The average cerebral metabolism and blood flow begin to decrease in N2 compared to wakefulness. Comparing the influence of high (34-37°C) and low (21°C) ambient temperatures on sleep, Haskell et al. pointed out that the durations of wakefulness and N1 sleep increased in cold exposure whereas the duration of N2 sleep decreased. They concluded that cold was more disruptive to sleep than heat. A similar observation has been reported by Palca et al. For naked subjects exposed for five consecutive nights at 21°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.

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 for sleep or REM sleep. 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.

In healthy nocturnal young subjects, oral administration of exogenous melatonin before going to bed increased N2 amount significantly, with slight hypothermic action. The effect of a high melatonin dose (80 mg p.o.), when tested in subjects with insomnia induced by traffic noise, was a reduction of sleep latency and of the number of awakening episodes and the increase of N2 sleep and sleep efficiency. 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. 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 is one of the markers of N2 stage, than those in a control group and the improvement of performance after a period of sleep is correlated with the percentage of N2 sleep.

From all these findings we can see that N2 stage is associated and correlated with good sleep quality and sleep disruptive conditions make the most impact on N2 stage also. That and recent findings about sleep mechanism disruptions and its possible connection with some pathologies (from cognitive to metabolic defects) 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 the 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.

In summary, it can be concluded that microarousal density is important for the subjective sense of rest after the sleep. The 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. It is well known that during N2 essential changes in thalamo-cortical circuits take place and temporary de-connection of sensory influx to cortex occurs. It is assumed that this creates special conditions for cortical restorative processes. The stability of N2 defines how deep sleep which is responsible for the metabolic-bolistic restorative unfolds. If during this stage everything goes well in the brain and sleep is undisrupted, then deep sleep plays its role and sleep quality is good, but if something goes wrong in this stage, e.g. sleep is fragmented by microarousals, and then sleep quality becomes poorer.

There are a few limitations in our study that we would like to point out. First of all, age. Subjects’ age in this study varied from 35 to 55 years and this might have had some impact on the study results. It would be useful to collect a larger group of subjects in a narrower age range. The second is the type of sleep disorders. We wanted to see if there is any relation between the sleep microstructure in terms of arousals and the subjective sense of rest after the sleep without paying attention to the type of a sleep disorder. But a different type of a sleep disorder might have variable effects on the sleep microstructure and then on the sense of rest.

Even though we analysed the data from patients who had various sleep disorders, we think that general concept that sleep fragmentation has a negative impact on sleeper’s sense of rest after the sleep applies for both people with and without sleep disorders.

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REFERENCES


