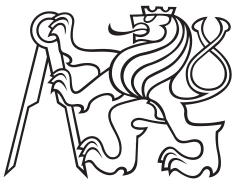
Master Thesis



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Analysis of Sleep Polysomnography Data Using Advanced Signal Processing Algorithms

Descriptive features extraction for automatic sleep stages scoring

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Declaration

I declare that the presented work was developed independently and that I have listed all sources of information used within it in accordance with the methodical instructions for observing the ethical principles in the preparation of university theses.

In Prague, 9. January 2017

Abstract

This thesis deals with the complex problematics of sleep medicine, focusing primarily on the diagnosis of sleep disorders using polysomnography. The first part covers the basics of sleep physiology and pathophysiology, followed by a chapter focused on technical aspects of sleep diagnostics. The emphasis is on the interdisciplinary approach to the main issues being reviewed and discussed. The practical part is dedicated to the extraction of descriptive features from PSG data having sufficient potential to discriminate between different sleep stages. The final set of attributes (features) is analyzed across several groups of distinct sleep disorders and the results are presented graphically. In the end, the extracted features are used to demonstrate their classification potential within a proposed approach to a semi-automatic sleep stage scoring, which aims to make the conventional tedious manual evaluation of nocturnal PSG recordings easier and more time-effective.

Keywords: polysomnography, sleep stages scoring, feature extraction, datamining, classification

Abstrakt

Tato diplomová práce se zabývá komplexní problematikou spánkové medicíny, se zaměřením především na diagnostiku spánkových poruch pomocí polysomnografie. První část pokrývá základy fyziologie i patofyziologie spánku, následovaná kapitolou věnovanou technickým aspektům spánkové diagnostiky. Důraz je kladen zejména na interdisciplinární pojetí celého tématu. Praktická část práce se věnuje extrakci popisných příznaků z PSG dat majících dostatečný potenciál diskriminace mezi jednotlivými spánkovými fázemi. Získaná množina příznaků je analyzována napříč několika skupinami různých spánkových poruch, výsledky přehledně graficky prezentovány, a v samotném závěru práce použity pro demonstraci navrženého semi-automatického přístupu k detekci spánkových fází, jehož cílem je usnadnit a zefektivnit dnes stále běžné a velmi zdlouhavé manuální hodnocení nočních PSG záznamů.

Klíčová slova: polysomnografie, hodnocení spánkových fází, extrakce příznaků, datamining, klasifikace

Překlad názvu: Analýza spánkových polysomnografických dat pokročilými algoritmy zpracování signálu

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Chapter 1

Introduction

Sleep is considered to be an unconditional necessity of our everyday lives and its quality directly affects almost all daily activities and routines. Nowadays, it is already well known that sleep deprivation and sleep disruptions lead to drowsiness and severe fatigue as well as cause cognitive and emotional problems. When the long-term effects of sleep loss in humans cumulate, they are associated with a wide range of other health consequences including increased risk of hypertension, diabetes, obesity or heart attack. Animals deprived of sleep for several weeks show temperature and weight dysregulation and eventually die of infections and tissue lesions. [RB13]

Since the beginning of the 20th century, the average sleep duration has decreased by around 20%. [CA+06] More people living in industrialized countries perform shift-work, work more hours, have multiple jobs, watch TV more often and spend a significant amount of time using the internet. These relatively recent factors are causing reversed sleep patterns and have a strong influence on circadian rhythms. Later sleep times, less sleep and daytime fatigue eventually lead to sleep disruption and chronic deprivation.

One of the most noticeable evidence of sleep loss or inadequate sleep quality is the potentially fatal outcome of operating risky equipment or drowsy driving. Nearly 20% of all serious car crash injuries are associated with driver's sleepiness and fatigue, independent of alcohol effects. [CA+06] The peak incidence of drowsy driving crashes is in the early morning hours. Its daily distribution is therefore accordant with the neurophysiology regulating sleepiness. [Car05] It was estimated that fatigue in sleep-deprived drivers is likely the cause of more than 100 000 crashes, 70 000 injuries and 1 500 deaths each year. [PG06]

In addition, sleep loss and sleep disorders have a significant economic impact. The direct medical costs are associated with doctor visits, hospital services, sleep diagnostic equipment and medications. Besides, compared to healthy subjects, individuals with chronic sleep loss or patients with various sleep disorders are less

productive, more susceptible to injuries and as a result have greater health-care needs. Other economical effects of the problem being discussed include costly sick leave or property and environmental damage.

In spite of these given facts, sleep medicine related awareness among the general public (and even healthcare professionals) is still very low. Even though many individuals report having sleep problems, it has been estimated that more than 60% of adults have never been asked about the quality of their sleep by a physician, and fewer than 20% ever initiated a discussion about it. [PG06] It is obvious, that sleep's impact on health and life quality is unfortunately still under-recognized.

Today the main issue, however, lies within the sleep diagnostics itself. The current clinical and scientific workforce is not sufficient to diagnose (and to treat afterwards) the individuals with sleep disorders while at the same time, the majority of people with sleep pathologies are yet to be diagnosed since they might be unaware of their disease.

In order to evaluate the sleep quality and thus potentially reveal a considerable number of pathologies, the patient needs to undergo a procedure consisting of spending a night in a designated sleep center and record a polysomnogram. Such overnight recording is further analyzed by an experienced doctor and used as a golden standard for clinical diagnosis of sleep disorders. The capacity needed to serve the population seeking this diagnostics procedure is, however, inadequate. The [CA+06] indicates that in many healthcare communities, the waiting time for polysomnogram may be as much as 10 weeks. For example it has been estimated that in case of sleep apnea diagnosis, at least 2 300 polysomnograms per 100 000 population are required, however, on average only about 425 polysomnograms are performed each year in the USA. [CA+06]

By increasing the awareness of the clinical consequences when sleep is lost or disturbed, and the whole problematic becoming a higher public health priority, the shortfall in available diagnostics will only worsen. Therefore an investment is critically needed to enlarge the clinical and research workforce capacity, and mostly to improve the technology for diagnosis.

Although even the sleep medicine field underlies to the current fast development of computer technology, it is still far behind the actual needs for it. Nowadays the recordings are obtained and stored in a digital form which allows for their later processing, analysis and archiving. The major issue, however, is the visual evaluation of these PSG recordings. It can take up to 2 hours to analyze one night recording even to an experienced neurologist and this evaluation is highly prone to human error and subjectivity.

Therefore, there is a huge call for development of software solutions which would either take over the PSG analysis completely or would at least make it more simple

and time effective. Another efforts are being made in developing reliable portable diagnostic technologies that would more likely meet the demand arising from greater awareness among the general public about sleep problematics.

Currently it seems that there is no software being fully able to analyze a whole night sleep recording. There is always a doctor needed, who does the scoring of sleep stages and various events detection, and who finally determines the diagnosis.

1.1 Aims and objectives

This thesis deals with the complex process of polysomnography and its subsequent analysis. Based on the obtained set of physiological signals, the doctors are able to characterize the distribution of sleep stages throughout the night or the presence of any important events associated with known pathologies. This routine consists of splitting the signal into segments with constant duration and assigning a sleep stage to each of these segments. The classification task depends on the physician being able to correctly distinguish between artifacts and the real signal, and to recognize various descriptive features typical for each sleep stage. Such visual analysis is a very tedious task and therefore any support system or an algorithm providing an automatic or semi-automatic analysis would be useful and welcomed.

One of the aims of this thesis is to describe the information available in the PSG recording with respect to sleep stages occurrences, and design a set of descriptive features which would, in addition to the raw PSG signals, provide extra information for easier and faster visual inspection and associated sleep stages scoring procedure.

It should be noted, that PSG processing performed by a clinician generally includes more than one level of analysis. Within this thesis only two main levels are considered. One consists in sleep stages scoring and thus creating the whole night hypnogram, the second one in evaluating this hypnogram and determining the final emerged diagnosis. In order to simplify the terminology used within this work, most of the time, when referring to automatic PSG analysis, only the first level of analysis (sleep stages scoring) is considered.

There are few main problems directly linked to a future development of an automatic polysomnography data analysis. The first one reflects the data quality which is usually very poor. The recordings are often full of noise and artifacts, partially due to the routines of measuring the signals that are not established well enough (although the guidelines do exist), but mostly because of the rather stochastic nature of measured signals. The second problem lies in the selection of the relevant information to be used for a subsequent classification, and the last problem deals with the classification process itself.

The artifacts issue has been studied into details as a part of my previous bache-

lor project, therefore this thesis focuses mainly on the proper features extraction computed from the available signals, their selection, and on possible approaches utilizable for the subsequent classification problem.

The last, but perhaps the most important goal of this thesis, is to study the whole problematics of polysomnography from both the medical and the engineering point of view. The great communication barrier between computer engineers and medical doctors still remains an issue preventing the development from progressing more effectively. In general, clinicians and computer scientists work in discrete departments that do not favor interdisciplinary research efforts. This work therefore does not go into extensive details within either of those fields. The main objective was not to design a powerful classification tool or to assess the polysomnography discipline from a relatively limited perspective of computer science or bioengineering, but rather to make a general research on the current situation, to some extent discuss all the steps, tools and approaches required for building any future automatic sleep stages classifier, and as a result - make the PSG problematics more comprehensible to researchers from both - medical and engineering - fields.

1.2 Thesis structure

The first part of the thesis provides the literature overview describing the sleep physiology with emphasis on different sleep patterns and changes with respect to different sleep stages. The purpose of Chapter 2 was to understand the important physiological processes of sleep and their representation as signals.

Chapter 3 covers the most common sleep disorders along with sleep-related disorders and the effect of inadequate sleep on individuals and society in general.

The sleep diagnostics including polysomnography, rules for evaluating sleep stages, known approaches to their automatic scoring, as well as alternatives to PSG are discussed and covered in Chapter 4.

The second part contains the section describing means and methods used in this work. The general process of datamining consisted of several phases corresponding to generally accepted standard CRISP-DM (Cross-Industry Standard Process for Data Mining). The data preparation phase is explained, followed by the procedure of features extraction, finalized with an introduction to the potentially used classification models along with one example implemented.

Chapter 5 contains the results, mostly represented in a graphical or tabular form.

The thesis ends with the Conclusion part where the obtained knowledge and results are discussed and summarized.

Part I

Literature review

Theoretical background and current issues in polysomnography

Chapter 2

Sleep physiology

2.1 Introduction

Sleep can be defined as a state of physiologic recovery which regularly repeats at night, while the day/night rhythm closely related to circadian rhythms is associated with an altered state of consciousness. [SD09]

Physiology of sleep, its behavioral dimensions and the consequences of insufficient amount of sleep or various sleep disorders on the general population's health and life quality are all studied by a branch of science called somnology. Sleep medicine on the other hand is the branch of clinical medicine devoted to the diagnosis and treatment of individuals suffering from chronic sleep loss or sleep disorders. [CA+06]

Sleep has been proposed to have an energy-saving function, serve as the restoration of energy resources and repairing of cell tissue, thermoregulation, metabolic regulation, and adaptive immune functions. However, these functions could be also achieved in a state of wakefulness and would not explain the loss of consciousness and responsiveness to external threats during sleep. Mentioned features of sleep therefore strongly speak for the concept of sleep being mainly for the brain. Different additional functions have been proposed though, ranging from detoxication of the brain from free radicals, glycogen replacement, to an involvement of sleep in memory and synaptic plasticity. [RB13]

2.2 Circadian rhythms

Circadian rhythms refer to the daily rhythms affecting changes both in physiology and behavior. They control the sleep-wake cycle, modulate physical and sexual

activity, food consumption, regulate body temperature, heart rate, muscle tone, and hormone secretion throughout the day. [CA+06]

These rhythms are controlled by endogenous rhythm generators located in the suprachiasmatic nucleus (SCN) of the hypothalamus - the main site functioning as the central biological clock/oscillator. The endogenous circadian rhythm occurs in cycles of approximately 24 to 25 hours which are however modulated by the outer influences (bright light) slowing or accelerating the rhythm and therefore synchronizing the biological clock to precise 24-hour cycles. [SD09]

Expression of several genes undergoes the same cyclic changes contributing to many aspects of cellular processes such as glucose and lipid metabolism, signal transduction or oxidative pathways.

The SCN receives direct inputs from nerve cells in the retina which act as light sensors that can reset the endogenous clock on a daily basis. Afterwards, the suprachiasmatic nucleus can transmit signals to the rest of the brain bringing all of the daily cycles in synchrony with the external day-night cycle. Another important output of the SCN is to a pathway controlling the secretion of melatonin, a hormone produced by the pineal gland. Melatonin is mainly secreted at night (dark environment) and acts in order to properly consolidate circadian rhythms. Though its direct effect on sleep is only limited.

Body temperature regulation is also subject to circadian system influence. It is higher during the day than at night. During the night there is a gradual decline in body temperature which promotes sleep onset and maintenance, as well as EEG slow-wave activity. Conversely, there is a gradual increase in body temperature few hours before waking. [CA+06, SR08]

2.3 Sleep architecture

Sleep architecture refers to the basic structural organization of normal sleep into different sleep stages. In general, there are two types of sleep, non-rapid eye-movement (NREM) sleep and rapid eye-movement (REM) sleep. NREM sleep is divided into stages 1, 2, 3, and 4, each representing a relative depth and having unique characteristics including variations in brain wave patterns, eye movements or muscle tone. Although the reason of the cycling sleep pattern is not yet fully understood, several sleep disorders are associated with irregular cycling and/or absent sleep stages. For example, instead of entering sleep through NREM, as is typical, individuals with narcolepsy enter sleep directly into REM stage.

Various stages of sleep can be uncovered in the EEG recordings which trace the electrical patterns of brain activity. Over the course of a sleep period, NREM and

REM sleep alternate cyclically.

A sleep episode begins with a short transient period of NREM1 progressing through stages 2, 3, 4 and finally to REM. Subjects, however, do not remain in REM sleep for the rest of the night but, rather, cycle between stages of NREM and REM. When a healthy awake person who is relaxed with the eyes closed starts to fall asleep, their level of consciousness first descends to dozing where only a few isolated alpha waves are detected. Sleepiness further descends to the next sleep stage where theta waves appear, further on a burst of fast waves, called sleep spindles, and isolated K complexes can be recorded. Finally this descend leads to a stage of deep sleep characterized by the appearance of delta waves. Their amplitude increases while their frequency drops to a minimum.

The sleep is deepest approximately 1 hour after a person falls asleep. Then it becomes lighter and the first episode of rapid eye movement occurs. This completes the first sleep cycle. [SD09]

NREM sleep constitustes about 75 to 80% of total time spent in sleep. REM sleep accounts for the remaining 20 to 25%. The average length of the first sleep cycle is 70 to 100 minutes. The later cycles last longer - approximately 90 to 120 minutes. In normal individuals, REM sleep increases in length as the night progresses. As the sleep episode progresses, stage 2 begins to account for the majority of NREM sleep, and stages 3 and 4 may sometimes disappear. [CA+06]

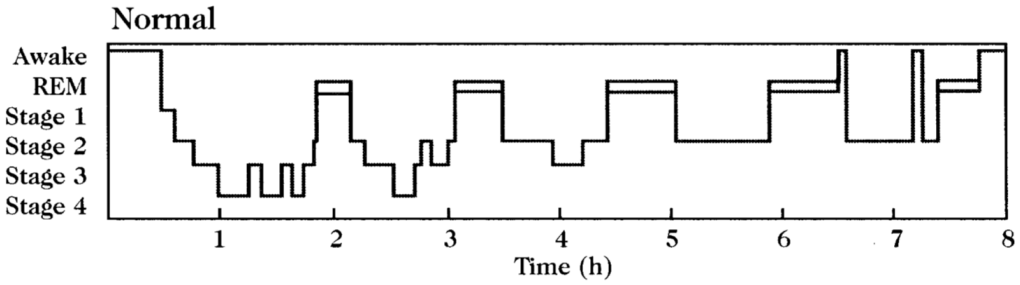

Figure 2.1: Hypnogram: sleep architecture visualisation [Sle12]

2.4 Sleep stages overview

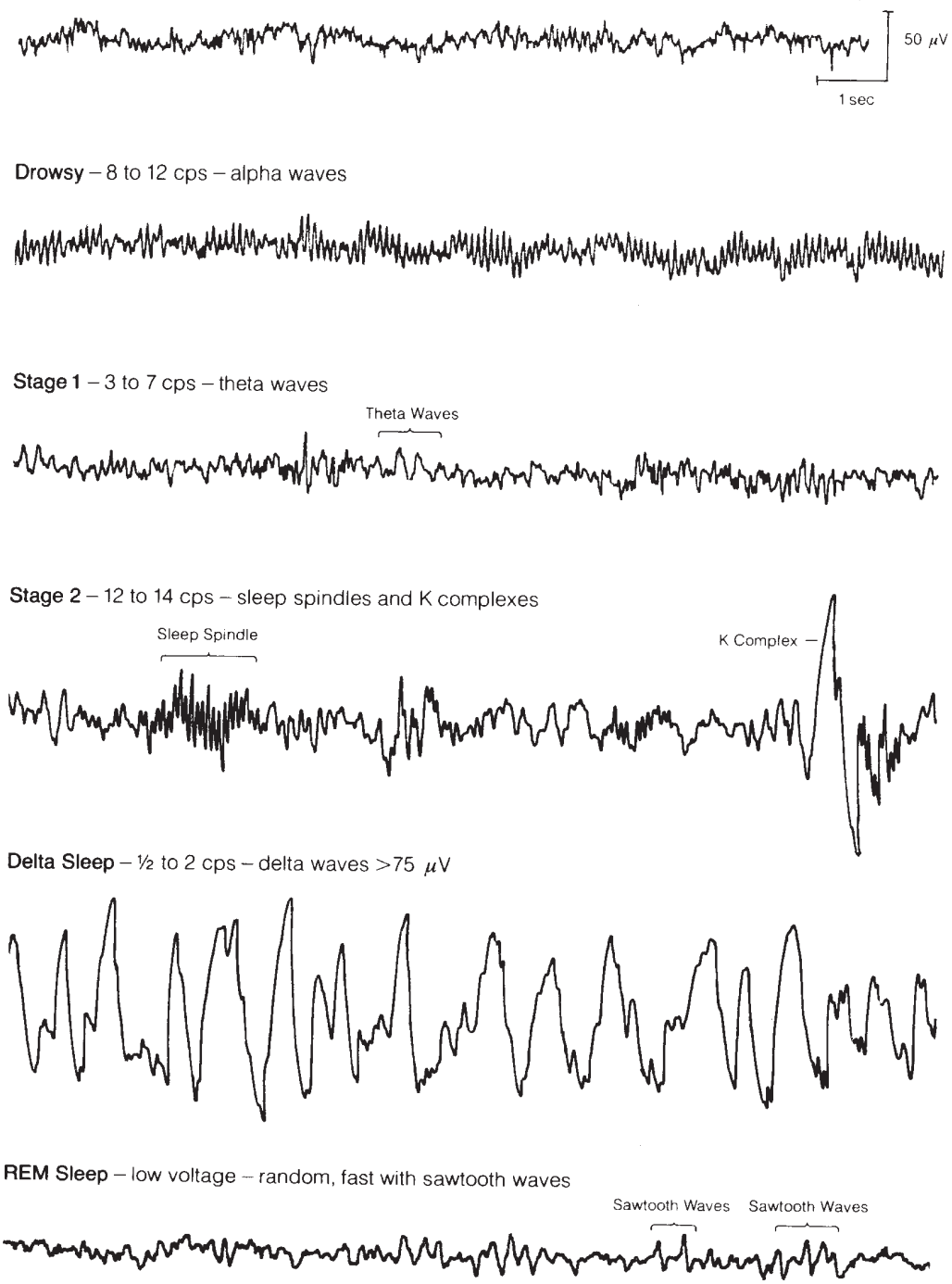

Figure 2.2: EEG waveforms in different sleep stages. [SH03]

NREM 1 The usual start of individual's sleep episode (exception are newborns and people with narcolepsy or other specific neurological disorders)

Usually lasts 1 to 7 minutes in the initial cycle

2 - 5% of total sleep

Easily interrupted by an external disruptive noise

EEG: Transitions from wakefulness (rhythmic alpha waves - approximately 8 - 12 Hz) to low-voltage, mixed-frequency waves

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NREM 2 Lasts approximately 10 to 25 minutes in the initial cycle

Lengthens with each successive cycle

Eventually constitutes between 45 to 55% of the total sleep episode

EEG: relatively low-voltage, mixed-frequency activity, presence of sleep spindles and K-complexes

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NREM 3 Part of slow-wave sleep (SWS) along with NREM 4

Most of SWS occurs during the first third of the night

Lasts only a few minutes

Constitutes ca 3 to 8% of total sleep

EEG: increased high-voltage, slow-wave activity

NREM 4 Part of slow-wave sleep (SWS) along with NREM 3

Lasts approximately 20 to 40 minutes in the first cycle

Constitutes up about 10 to 15% of total sleep

The highest arousal threshold

EEG: increased amounts of high-voltage, slow-wave activity

REM Presence of muscle atonia (inhibition of motoneurons - prevention from acting out sleeper's dreams) and bursts of rapid eye movements

Breathing and heart rate increases

Face and fingers can suddenly start to twitch

May last only 1 - 5 minutes during the initial cycle

Prolongs as the sleep episode progresses (NREM sleep periods shorten instead)

Sleepers aroused from REM sleep stage are more likely to be able to remember and describe their dreams

EEG: desynchronized, low-voltage, mixed-frequency, sawtooth waveforms, theta activity (3 to 7 Hz), slow alpha activity

[CA+06, SD09, SH03]

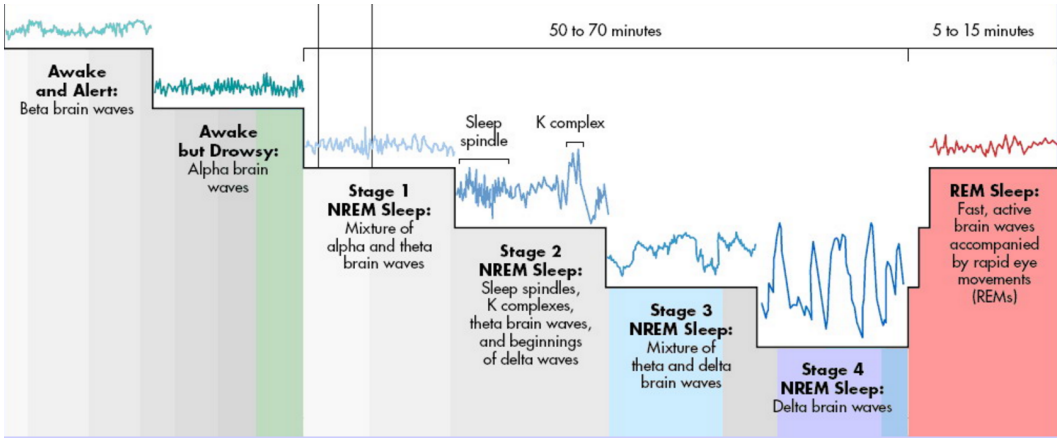


Figure 2.3: Sleep stages description with respect to EEG [1612]

2.5 Physiological changes during NREM and REM sleep

Various physiological changes associated with different sleep stages are generally well tolerated in healthy individuals, but they may start to play a significant role in individuals with certain pathologies affecting the vulnerable systems, such as for example patients with cardiovascular diseases. Few examples of affected systems are described below.

Cardiovascular. Autonomic nervous system activity, which varies during sleep, directly determines the shifts in blood pressure and heart rate. Sympathetic-nerve activity decreases as NREM sleep progresses, however, K-complexes, arousals or larger body movements are accompanied with its bursts leading to a consequent increase in blood pressure and heart rate. Further, due to the awakening process in the morning, both blood pressure and heart rate rise sharply increasing the risk of myocardial infarction. Activity of sympathicus also rises during REM sleep compared to wakefulness. [CA+06, SH03]

	NREM sleep	**REM sleep**
Sensitivity, perception	Sluggish to absent	Active (endogenic stimulation)
Thought	Logical, persistent	Illogical, bizarre
Motor system activity	Episodic, involuntary	Brain pathways active but alpha motoneurons inhibited
EEG wave type	Theta, delta, low frequency, high voltage	Beta, high frequency, low voltage
Heart rate	Slows from wakefulness	Increases and varies
Blood pressure	Decreases from wakefulness	Increases (up to 30%) and varies
Respiration	Decreases from wakefulness	Increases and varies, may show brief stoppages, coughing suppressed
Airway resistance	Increases from wakefulness	Increases and varies
Body temperature	Regulated at lower set point than wakefulness, shivering initiated at lower temperature than during awake state	Not regulated, no shivering nor sweating, temperature drifts toward that of the local environment

Table 2.1: Physiological differences between NREM and REM sleep

Respiratory. Ventilation and respiratory flow becomes faster and more irregular, mainly during REM sleep. Periods of hypoventilation may be quite common during both NREM and REM sleep. Factors potentially explaining lower levels of blood oxygen during NREM sleep include reduced pharyngeal muscle tone, while limited rib cage movements and increased upper airway resistance caused by loss of tone of intercostal and other breathing muscles during REM sleep may justify hypoventilation

occurring then. In general, ventilation and respiratory flow show less effective adaptive response during sleep - the cough reflex is suppressed in both NREM and REM, the hypoxic ventilatory response is reduced in NREM and further decreases during REM. [CA+06]

Blood flow. Both blood flow and metabolism significantly lower in NREM sleep, while they remain comparable to wakefulness during REM sleep. In REM sleep, however, certain brain regions show increased metabolism (and therefore a blood flow) compared to awake state. These regions include mostly limbic system (areas involved with emotions) and visual association areas, both participating in dreaming process. [SH03, CA+06]

Table 2.1 summarizes the main physiological differences between two discussed sleep forms.

2.6 Sleep regulation

The sleep-wake system is considered to be regulated by two major processes, one promoting sleep (process S, the homeostatic drive for sleep) and one that maintains wakefulness (process C, regulated by the circadian system). The need for sleep (process S) accumulates during the day, peaks before bedtime and subsequently dissipates throughout the night. Process C involving circadian influences, on the other hand, is wake/alertness promoting and builds up throughout the day counteracting the process S. During an adequate night's rest, the drive for sleep reduces, the circadian waking drive begins to increase, and the cycle can start over.

If the process C was absent, total sleep time would remain the same, however, it would be randomly distributed over the day and night. Another function of process C therefore is to consolidate sleep and wake into reasonably distinct episodes coordinated with environmental light-dark cycles through the synchronization with the circadian system.

As a homeostatic process (process S), sleep allows the body to return to equilibrium after it was disturbed (e.g. an extra compensatory sleep after a period of sleep deprivation). Sleep can therefore be called a restorative process. [SR08]

Sleep process S is mainly regulated by neurons that are able to shut down arousal systems, thus allowing the brain to fall asleep. Loss of these nerve cells would cause deep insomnia. Further also other regions of the brain influence the sleep system via inputs relaying information about the state of the body as well as from brain regions with emotional and cognitive functions. The sleep-generating system also constitutes of neurons intermittently switching from NREM to REM sleep over the course of the night. These neurons located in pons thereupon send outputs to the lower brainstem

and spinal cord causing for example muscle atonia, rapid eye movements, or chaotic autonomic activity which characterizes REM sleep. [CA+06, SR08]

2.7 Sleep patterns changes with age

Sleep architecture is continuously and considerably altered with age. Changes affect how sleep is initiated and maintained, the percentage of time spent in each stage of sleep, as well as an overall sleep efficiency which generally declines with age.

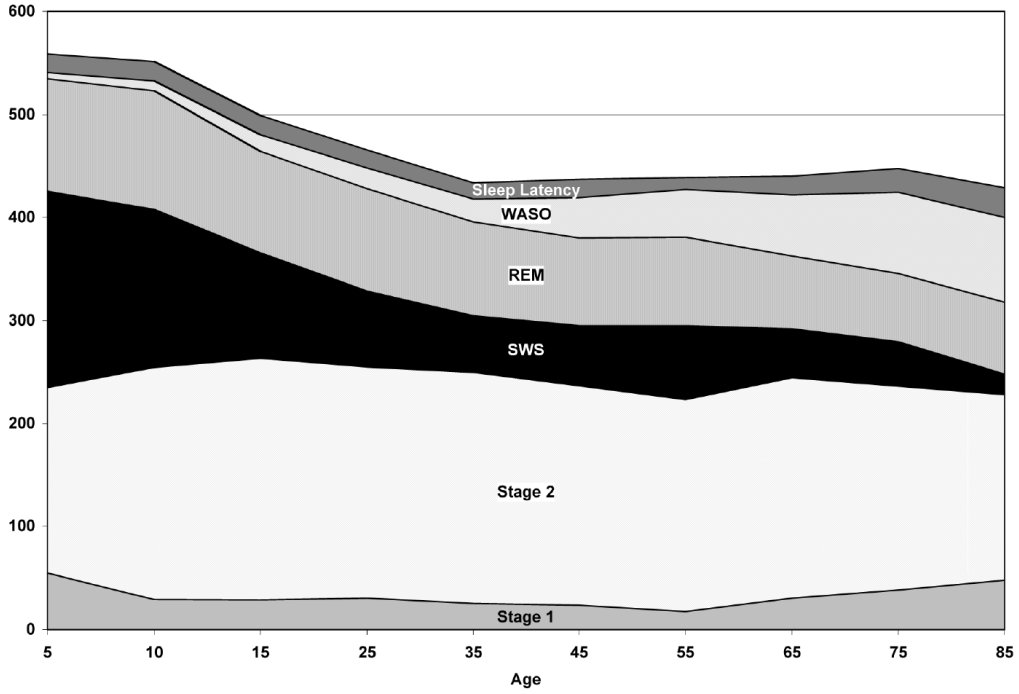


Figure 2.4: Composition of sleep over lifespan [OCGV04]

Newborns. First at birth, sleep is distributed more or less evenly across the day and night for the first few weeks, without any regular rhythm. The average duration of sleep is about 16 - 18 hours per day; however, due to its lack of consistency, the longest continuous sleep episode lasts only 2.5 - 4 hours. Newborns and infants have only three types of sleep. Those are quiet sleep, active sleep and indeterminate sleep. Sleep onset occurs through REM stage and not NREM as is usual in adults, and each sleep episode consists of one or two cycles. Main reason for these distinctive characteristics is a not yet fully developed and entrained circadian system.
Circadian rhythms begin to take an effect around 2 - 3 months of age. This leads to sleep consolidation which manifests as longer periods of wakefulness during the day and greater sleep episodes at night.
Another reason for sleep cycle changes and consolidation is a greater responsiveness

to social cues (breast-feeding, bedtime routines).
By 3 months of age, sleep onset begins with NREM, REM sleep duration decreases and shifts towards the later part of the sleep cycle. Total sleep cycle typically lasts 50 minutes. By 6 months of age, the longest continuous sleep episode lengthens to approximately 6 hours. Further on the typical muscle atonia of REM sleep occurs and so called active sleep is replaced. By 1 year old, the infant typically sleeps 14 - 15 hours per day with the majority of sleep consolidated in the evening and one or two daytime naps. [CA+06, SD09, LL]

Children. In general, several studies suggest that sleep amount decreases as a child gets older. The reduction is attributed both to changing physiologic requirements and cultural/social environments. These include decreased daytime napping and cultural factors such as how, with whom, and where children sleep, and the introduction of school time routines. Older children compared to younger ones, however, are significantly more likely to have difficulties in initiating and maintaining sleep. In addition, older children are more prone to having nightmares, which usually disrupt sleep, making it discontinuous. [CA+06, OCGV04]

Adolescents. It has been determined that adolescents require approximately 9 to 10 hours of sleep every night. Based on everybody's general experience, only few adolescents obtain adequate amount of sleep. Over a quarter of high school and college students are sleep deprived. Alterations in sleep architecture are likely due to hormonal changes that accompany the onset of puberty. For example, at mid-puberty, there is a significantly greater daytime sleepiness than earlier. Afternoon sleepiness gets greater than that in evenings in older adolescents than in younger subjects. [OCGV04, LL]

Adults. Sleep architecture continues to change with age across the whole adulthood. Two major attributes of age-related sleep changes are earlier wake time and reduced sleep consolidation. Younger adults usually awaken 1.33 hours later, and go to bed 1.07 hours later, than older subjects. One hypothesis potentially explaining why older adults experience earlier awakenings is based on an advanced circadian pacemaker that accompanies age. This could be due to older adults experiencing an increased sensitivity to light, however, the main reason still remains unclear. The consequences of the advanced circadian rhythm are a 1 hour ahead start in body temperature increase in the early morning and misaligned melatonin and cortisol secretion rhythms with the circadian clock. Younger adults may experience brief awakenings, but they are mostly minor. In addition, these arousals occur usually from REM sleep, suggesting an existence of a protective mechanism keeping younger adults from awakening during NREM sleep. This protective effect, however, also tends to decline with age. Because arousal thresholds are typically highest during SWS, and because SWS declines with age as well, older adults experience more frequent awakenings during a sleep episode. [SD09, CA+06, OCGV04]

Elderly individuals. Older people typically show an increased sleep disturbance that creates a negative impact on their quality of life, mood and alertness. Elderlies sleep approximately 36% less than children at age 5. The ability to sleep becomes less easy, although the need to sleep does not decrease with age. Individuals therefore tend to get relatively sleep deprived. Difficulty in initiating and maintaining sleep is relatively common among the elderly individuals, especially those suffering from depression, respiratory symptoms or physical disability. Long sleep episodes are generally harder to maintain. Another sleep alteration is a decrease in melatonin levels, which may be caused by the gradual worsening of the hypothalamic nuclei driving the circadian rhythms. Other important factors are for example irregular meal times, nocturia, and decreased mobility leading to a reduction in exercise. [SD09, CA+06, LL]

2.8 Gender differences

Changes in sleep patterns affect males and females differently. Despite not many studies have been made, there seem to exist differences in sleep and circadian rhythms dependent on gender. Currently available evidence is strongest in adults, however gender differences have also been observed in earlier life stages.
In adults, males spend greater time in NREM 1 stage and experience more awakenings. Although females can maintain SWS longer than men, they complain more often of difficulty falling asleep and frequent awakenings. In the contrary, men tend to complain more of daytime sleepiness.
In females, the menstrual cycle may influence sleep-wake activity. Few studies also suggest that women's sleep patterns are significantly affected during pregnancy and the postpartum period (increased daytime sleepiness and higher risk of developing restless legs syndrome).
With aging, the progressive decrease in SWS seems to be one of the most prominent changes, however, it appears to preferentially affect males. Several other gender-based distinctions can be well observed in elderly individuals. Women with ages 70 and older spend around 15 to 20% of total sleep time in stages NREM 3 and NREM 4, while men of the same age do only around 5%. Another gender difference is that older females go to bed and wake up earlier than older males. [CA+06]

Chapter 3

Sleep pathophysiology

3.1 Introduction

Nowadays, the pathophysiology of many sleep-wake disorders is still poorly understood. In general, a combination of biological, psychological, and social factors implicates the etiology of these conditions. Many sleep disorders, such as insomnia, can seriously affect the individual's personality, performance, and can even lead to psychological problems. [SR08, SL10]

The International Classification of Sleep Disorders (ICSD) divides sleep pathologies into four categories. The first category comprises the dyssomnias (disorders of initiating and maintaining sleep and the disorders of excessive sleepiness). The second category covers the parasomnias that are disorders of arousal, partial arousal, or sleep stage transition, which do not cause a primary complaint of insomnia or excessive sleepiness. The third category includes sleep disorders associated with mental, neurologic, or other medical disorders such as disorders with a prominent sleep complaint that is felt to be secondary to another condition. The fourth and last category includes those disorders for which there is no sufficient information available to consider them as definitive sleep disorders and therefore they will not be covered nor discussed within this thesis. [oSM+05]

3.2 Symptoms definitions

Following definitions were adopted and simplified from the ICSD manual [oSM+05].

Mild Sleepiness: describes sleep episodes present only during times of rest or when little attention is required. Situations in which mild sleepiness may become evident include watching television, reading while lying down in a quiet room, or being a passenger in a moving vehicle. It may not be present every day. Symptoms produce a minor impairment of social or occupational function.

Moderate Sleepiness: describes sleep episodes present daily and that occur during very mild physical activities requiring, at most, a moderate degree of attention. Examples include situations during concerts, movies, theater performances, group meetings and driving. Symptoms produce a moderate impairment of social or occupational function.

Severe Sleepiness: describes sleep episodes present daily and at times of physical activities requiring mild to moderate attention. Situations in which severe sleepiness may occur include during eating, direct personal conversation, driving, walking, and physical activities. Symptoms produce a marked impairment of social or occupational function.

Mild Insomnia: describes an almost nightly complaint of an insufficient amount of sleep or not feeling rested after the habitual sleep episode. It is accompanied by little or no evidence of impairment of social or occupational functioning. Mild insomnia often is associated with feelings of restlessness, irritability, mild anxiety, daytime fatigue, and tiredness.

Moderate Insomnia: describes a nightly complaint of an insufficient amount of sleep or not feeling rested after the habitual sleep episode. It is accompanied by mild or moderate impairment of social or occupational functioning. Moderate insomnia always is associated with feelings of restlessness, irritability, anxiety, daytime fatigue, and tiredness.

Severe Insomnia: describes a nightly complaint of an insufficient amount of sleep or not feeling rested after the habitual sleep episode. It is accompanied by severe impairment of social or occupational functioning. Severe insomnia is associated with feelings of restlessness, irritability, anxiety, daytime fatigue, and tiredness.

3.3 Dyssomnias

Disorders that produce either difficulty initiating or maintaining sleep or excessive sleepiness are called dyssomnias. They can be further divided into three groups listed below:

Intrinsic sleep disorders either originate or arise from causes within the body. Psychologic and medical pathologies producing a primary sleep disorder belong to this group.
Examples: Psychophysiologic insomnia, Sleep state misperception, Idiopathic insomnia, Narcolepsy, Hypersomnia, Obstructive sleep apnea syndrome, Central sleep apnea syndrome, Periodic limb movement disorder, Restless legs syndrome

Extrinsic sleep disorders either originate or develop from external factors outside of the body. Removal of the external factor usually leads to resolution of the sleep disturbance.
Examples: Inadequate sleep hygiene, Environmental sleep disorder, Altitude insomnia, Food allergy insomnia, Stimulant-dependent sleep disorder, Alcohol-dependent sleep disorder, Adjustment sleep disorder

Circadian rhythm sleep disorders are related to the timing of sleep within the 24-hour day. Some of them are influenced by sleep timing under the individual's control (shift work, jet-lag), whereas others are of neurologic mechanisms (irregular sleep-wake pattern). Therefore some of these disorders can have both an intrinsic and extrinsic form, however, they all have a common pathophysiologic/chronobiologic underlying mechanism.
Examples: Jet Lag syndrome, Shift work sleep disorder, Irregular sleep-wake pattern, Non-24-hour sleep-wake disorder [oSM+05, LL]

3.3.1 Insomnias

The following section describes the insomnia in general, with further details on few specific examples.

Insomnia is the most frequently reported sleep disorder, relatively more common in females. It can be characterized as a state of hyperarousal possibly caused by an activation of the hypothalamic-pituitary-adrenal axis by stress. It has been demonstrated that patients with chronic insomnia have an increased secretion of stress hormones corticotropin and cortisol throughout the sleep-wake cycle compared to healthy subjects. Additional research, using PET (positron emission tomography) imaging to assess regional cerebral glucose metabolism, showed that insomnia is also associated with greater whole-brain metabolism during both sleep and wake periods. Especially structures regulating the sleep-wake cycle (brainstem, hypothalamus, basal forebrain) appeared to be abnormally overactive during sleep. The ventral emotional neural system also was hyperactive in patients with primary insomnia and insomnia associated with depression, while this abnormal activity persisted during both wakefulness and NREM sleep. [SR08]

A hallmark of many insomnia types is the patient's focus on their sleep problem

while typically minimizing other mental or emotional concerns. This heavy focus on insomnia continually interferes with good sleep. Consequently, some types of insomnia (especially psychophysiologic insomnia) remain rather fixed over time, although occasional periods of better or worse sleep may occur spontaneously or in response to life events such as vacations or stress.

Idiopathic insomnia is another type of insomnia defined as a lifelong inability to obtain adequate sleep, and is most likely caused by an abnormality of the neurologic control of the sleep-wake system. Theoretically, either hyperactivity within the arousal system or hypoactivity within the sleep system can cause this insomnia. Either way, the lifelong and serious insomnia can be explained by neither psychologic trauma nor medical problems originating outside of the sleep-wake system.

As in all insomnias, chronically poor sleepers tend to have decreased feelings of well-being during the day. Both mood and motivation are affected, decreased attention, lack of energy and concentration. [oSM+05]

Research has shown a 350% higher risk of hypertension in insomniacs than in normal sleepers. Insomnia is also a risk factor for diabetes mellitus as well as mental disorders such as anxiety and depression or eating disorders. [CA+06]

The usual polysomnographic features which indicate objective insomnia include increased sleep latency, increased wakefulness after sleep onset, and decreased sleep efficiency. An increase of stage 1 sleep and usually a decrease of delta sleep is found. There may be increased muscle tension and increased EEG alpha activity. [oSM+05]

Unfortunately sleep studies (focused not only on insomnia) are considered complicated and uncomfortable for both patients and healthy subjects. They need to spend several nights sleeping in unfamiliar surroundings and without privacy. The results can therefore often be mispresented and out of context. [HHAAD13]

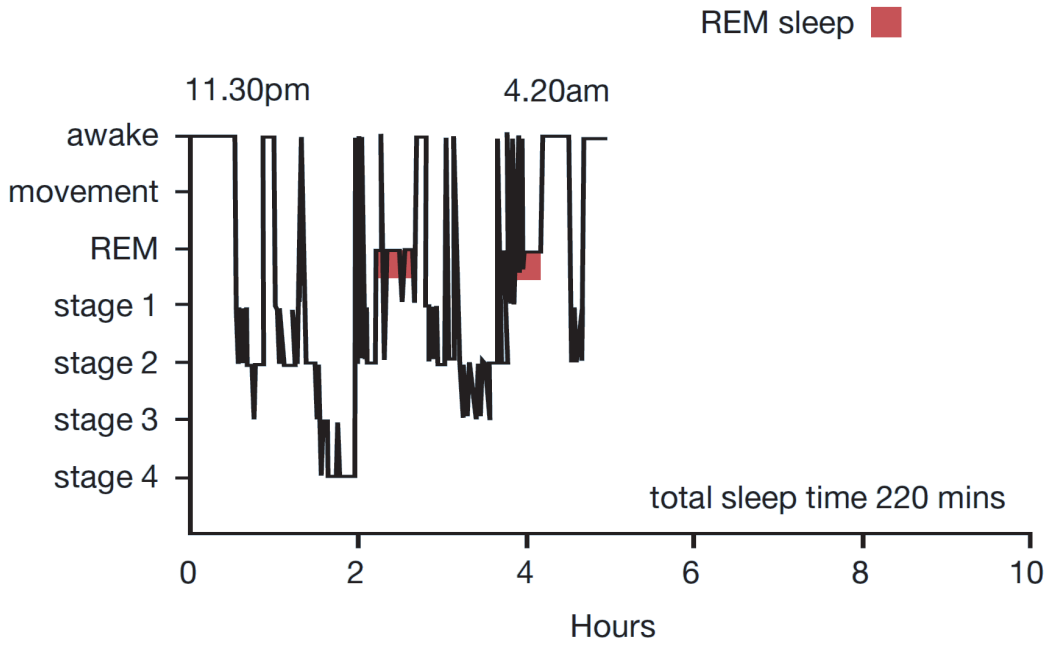


Figure 3.1: Hypnogram of an insomnia patient [WN08]

3.3.2 Narcolepsy

Narcolepsy is characterized by an excessive recurrent daytime sleepiness associated with cataplexy and abnormal REM sleep, such as sleep paralysis or hypnagogic hallucinations. [SR08]

Repeated episodes of naps or lapses into sleep of short duration, usually less than one hour, are typical. The patient characteristically sleeps for 10 to 20 minutes, wakes up relatively refreshed, but begins to feel exhausted again within the next two to three hours.

Falling asleep usually happens in situations in which tiredness is common. These include traveling in transport, monotonous meeting without active participation, listening to a lecture, watching a movie. The sleepiness can be often tolerated only with much effort and attention, however there can be sudden and irresistible sleep attacks in situations where sleep normally never occurs (during an examination, interactive talks, while eating, walking, or driving). [oSM+05]

Only little is known about the cause of the disorder, however, narcoleptic patients have marked neuronal loss (85% to 95%) in the hypothalamic regions responsible for orexin (alternative name for hypocretin) hormone production. These include the dorsal and lateral hypothalamus, as well as thalamus and the cerebral cortex. In a certain perspective, the narcolepsy can be considered as a consequence of a neurodegenerative process manifested as a gliosis in the orexin cell region. Although

the exact underlying mechanisms are not known, it is very likely that both genetic and environmental factors are involved in the onset of this disorder. Comparison of hypocretin neurons amounts in narcoleptic patients vs healthy individuals can be seen in Figure 3.2 obtained by neuronal mapping with Neurolucida software. [SR08, TNS+09]

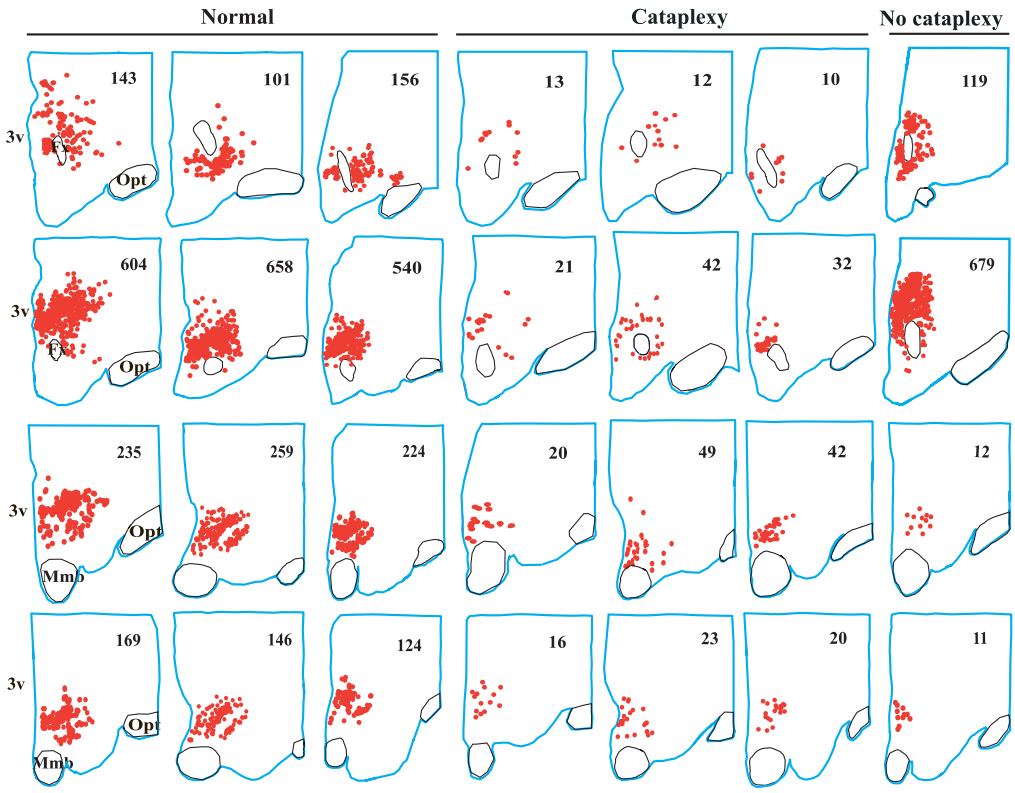


Figure 3.2: Mapping of orexin cells in 3 healthy individuals, 3 narcoleptics with cataplexy and 1 narcoleptic without cataplexy. Cell counts listed in the upper right corners. 3v - 3rd ventricle; Fx - fornix; Mmb - mammillary body; Opt - optic tract. [TNS+09]

A presence of cataplexy is a characteristic and unique feature of narcolepsy. It is characterized by sudden loss of bilateral muscle tone initiated by strong emotion. Consciousness remains clear, memory is not impaired, and respiration is intact. The duration of cataplexy is usually very short with immediate and complete recovery. The loss of muscle tone varies from a sensation of weakness, facial expression fading, jaw drop, slurred speech and buckling of the knees to complete postural collapse with a consequential fall. Respiratory and oculomotor muscles are not affected. Cataplexy is always precipitated by an emotion usually having an exciting component, such as laughter, anger or surprise.

Other symptoms associated with narcolepsy include sleep paralysis, hypnagogic hallucinations and automatic behavior. Hypnagogic hallucinations are vivid dream-like experiences occurring at sleep onset including visual, tactile, kinetic and auditory

phenomena. These are usually accompanied with fear. Usual reports state hallucinatory experiences such as being caught in a fire, flying through the air or being endangered by someone or something in general.

Narcolepsy is a condition with various complications. Accidents due to sleepiness and cataplexy may happen often in casual situations. Most commonly while driving, operating heavy or dangerous equipment. Serious social consequences must be taken into consideration as well.

All-night polysomnography recordings usually contain sleep-onset REM period sometimes associated with reports of hypnagogic hallucinations or sleep paralysis. NREM 1 sleep stage is relatively more presented and there might be visible disruptions of the normal sleep pattern with frequent arousals and awakenings. [oSM+05, LL]

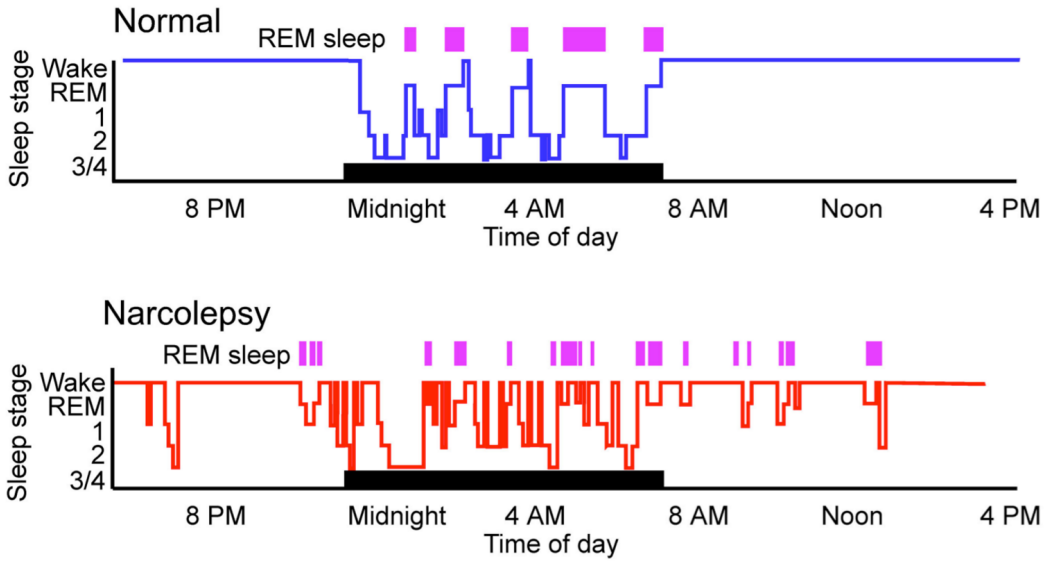


Figure 3.3: Hypnogram of a narcoleptic patient compared to a healthy individual [Sch]

3.3.3 Obstructive sleep apnea syndrome

Obstructive sleep apnea syndrome is characterized as repetitive episodes of upper airway obstruction occurring during sleep. A characteristic snoring pattern is typically associated with this disorder and manifests as loud snores or brief gasps alternating with episodes of silence. The snoring is often so loud that the patient can sometimes hear it, but is usually unaware of its intensity. Ingestion of alcohol before bedtime or an increase in body weight may exacerbate the snoring. More severe apnea cases can have prolonged episodes of breathing cessation sometimes associated with cyanosis which are afterwards terminated with loud snores and gasp sounds or mumbling. The accompanying body movements can be violent, rarely, patients can even fall out of bed.

After waking up, subjects typically do not feel refreshed, they describe feelings of disorientation or grogginess. Severe dryness of the mouth is common and often makes the patient get something to drink during the night. Morning headaches, characteristically dull and generalized, are often reported.

Children with obstructive sleep apnea syndrome may show loud snoring, arousals and unusual sleep postures such as sleeping on the hands and knees. Daytime mouth breathing and poor speech articulation are also common features in affected children.

Often patients with the obstructive sleep apnea syndrome are overweight. When this disorder occurs in patients of normal or below-normal body weight, a definable localized structural abnormalities such as maxillomandibular malformation or adenotonsillar enlargement should be suspected as a potential cause of upper airway obstruction. Cardiac arrhythmias commonly occur during sleep and range from sinus arrhythmia to premature ventricular contractions, atrioventricular block and sinus arrest. In children, learning difficulties and behavioral disorders (hyperactivity alternating with excessive sleepiness) exhibit rather often.

Polysomnographic features include apneic episodes monitored by nasal and oral airflow. They are typically 20 - 40 s in duration and whenever greater than 10 seconds, they are considered clinically significant. These episodes occur mainly in stages NREM 1 and NREM 2, rarely during stages NREM 3 or NREM 4. PSG monitoring of patients suspected of obstructive sleep apnea syndrome should consist of EEG, EOG, EMG, airflow, respiratory muscle effort, ECG and blood oxygen saturation channels. Visible changes associated with apneic episode are often sudden changes in cardiac frequency, fall in oxygen saturation level (usually with 10 - 20 second detection delay) and various arousals disrupting the sleep. [oSM+05, LL]

3.3.4 Central sleep apnea syndrome

Central sleep apnea syndrome is defined as periods of cessation or decrease of ventilatory effort during sleep and is usually associated with oxygen desaturation. Various central nervous system lesions affecting either the cerebral hemispheres or the brainstem are behind the respiratory center failure. Specific anatomic abnormalities, however, usually cannot be identified. Thus, in this case, the predominant respiratory disturbance lies within the central nervous system and central apneic episodes, however, it may be associated with few obstructive apneas too.

Compared to obstructive sleep apnea syndrome, snoring is not prominent, although it can occur.

The main complication is grounded on hemodynamic consequences of this syndrome. Systemic hypertension, cardiac arrhythmias, pulmonary hypertension and cardiac failure can all occur. [oSM+05]

3.3.5 Periodic limb movement disorder

Periodic limb movement disorder is characterized by periodic episodes of repetitive and stereotypic limb movements occurring during sleep. Usually the legs are affected and carry out the movements consisting of extension of the big toe in combination with partial flexion of the ankle, knee, and sometimes the hip. The movements are often associated with a partial arousal or awakening, but the patient is rarely aware of these. Between the episodes, the legs do not move.

This disorder can be associated with a variety of medical conditions, metabolic disorders especially. For example, episodes of limb movements can develop in patients with chronic uremia.

Fragmented, restless sleep and complaints of insomnia or excessive sleepiness are common results of the periodic limb movement disorder. In severe cases, some patients also have the movements while awake.

Limb movements can appear immediately with the onset of NREM 1 stage. They are frequent during NREM 2 and decrease in frequency in NREM 3 and NREM 4. During REM sleep, the movements are usually absent. EEG channel on polysomnography recordings may show association of the leg movements with a K-complex, an arousal or an awakening. An increase in heart rate and blood pressure can accompany the movements as well. The EMG channels from anterior tibialis muscles show repetitive contractions, each lasting 0.5 - 5 seconds. There may often be myoclonic jerks occurring at the beginning of each movement. Usually both of the lower limbs are involved, but only one leg could be affected. [oSM+05, LL]

3.3.6 Restless legs syndrome

Restless legs syndrome is a disorder characterized by disagreeable leg sensations that usually occur prior to sleep onset and that cause an almost irresistible urge to move the legs. Leg motion brings a partial or complete relief, however, symptoms return upon cessation of leg movements. Patients describe the sensations using words like ache, discomfort, pulling or itching. The sensations are mainly felt between the ankle and the knee, however, they can be elsewhere, in rare cases including even the arms. These events usually interfere with sleep onset since they characteristically occur only at rest prior to the subject's sleep period and can last up to several hours. However, even the very severely affected individuals fall asleep eventually.

The disorder can be associated with pregnancy, anemia or uremia. When associated with pregnancy, it usually appears after the 20th week. Severe insomnia, psychologic disturbance and depression can be sometimes a serious outcome of this sleep disorder. [oSM+05]

3.4 Parasomnias

The parasomnias are defined as disorders intruding into the sleep process. They are not primarily disorders of sleep/wake states per se, instead they could be described as manifestations of the central nervous system's activation, usually transmitted through skeletal muscle or autonomic nervous system pathways, and therefore leading to an undesirable physical phenomena occurring predominantly during sleep. They are further divided into four groups: [oSM+05, LL]

Arousal disorders manifest as partial arousals occurring during sleep.
Examples: Confusional arousals, Sleepwalking, Sleep terrors

Sleep-wake transition disorders occur usually during the transition from wakefulness to sleep or from one sleep stage to another.
Examples: Rhythmic movement disorder, Sleep starts, Sleep talking, Nocturnal leg cramps

Parasomnias usually associated with REM sleep are defined as those that have their onset during the REM sleep stage.
Examples: Nightmares, Sleep paralysis, Sleep-related painful erections, REM-Sleep-related sinus arrest

Other parasomnias .
Examples: Bruxism, Sudden infant death syndrome, Benign neonatal sleep myoclonus, Nocturnal paroxysmal dystonia

3.4.1 Bruxism

Sleep bruxism is defined as a stereotypic movement disorder characterized by grinding or clenching of the teeth during sleep. Even though the first signs of this disorder are often discovered by a dentist, usually the patient seeks for a medical attention to eliminate the disturbing sounds caused by teeth grinding.

Bruxism can cause an abnormal wear of the teeth, damage to the periodontal tissue, or jaw pain. Additional symptoms include various muscle and tooth sensations, facial pain and headaches.

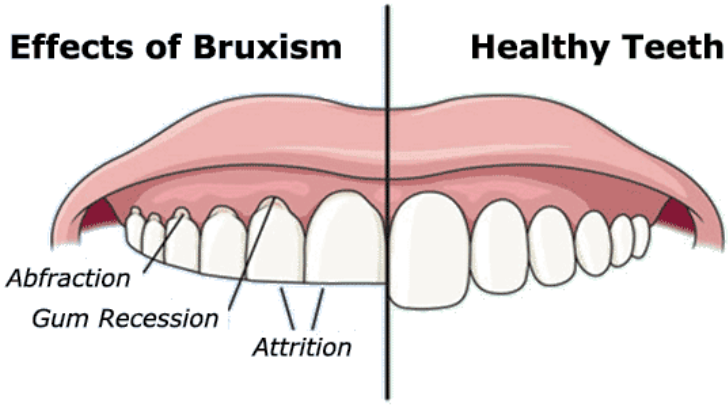


Figure 3.4: Teeth wear caused by bruxism [bru]

Bruxism events vary in the intensity and duration, but typically hundreds of events occur during one night. The patient usually does not awaken, but the sleep is fragmented with associated arousals.

Approximately 85 - 90% of the whole population present minor sleep bruxism events during their lifetime. In otherwise healthy individuals, various studies suggest a close correlation between stress from psychological sources and teeth grinding during sleep. Only in cca 5% of these subjects, bruxism will present as a clinical condition.

Sleep bruxism can occur during all stages of sleep, but it is most common in NREM 2 stage. The polysomnographic recording demonstrates increased masseter and temporalis muscle activity. [oSM+05]

3.5 Sleep disorders associated with mental, neurologic or other medical disorders

Pathologies belonging to this group are not primarily sleep disorders but are mental, neurologic, or other medical issues that have either sleep disturbance or excessive sleepiness as one of their major symptoms. [oSM+05]

Examples: Psychoses, Mood disorders, Anxiety disorders, Panic disorder, Alcoholism, Dementia, Parkinsonism, Sleep-related epilepsy, Cerebral degenerative disorders, Nocturnal cardiac ischemia, Chronic obstructive pulmonary disease, Sleep-related asthma, Peptic ulcer disease, Sleep-related gastroesophageal reflux

3.6 Sleep related disorders

Various sleep disorders per se along with insufficient sleep amount or quality can be directly linked to other medical disorders. Either by increasing the risk of their development or causing them directly. Eventually, even not so serious primary sleep problem can have some fatal consequences.

For example it has recently been recognized that restless legs syndrome and sleep apnea may be a major cause of attention deficit hyperactivity disorder and other behavioral problems in children. [CA+06] Other studies have shown that insomniacs have a 350% higher risk of developing hypertension than normal sleepers. Insomnia is also a risk factor for diabetes. [HHAAD13]

3.6.1 Sleep deprivation

In the United States, normal sleep duration has decreased from approximately 9 hours in 1910 to an average of 7 hours in 2002. Today, many individuals are in bed 5 - 6 hours per night on a chronic basis. [KGW+02] In general, chronic sleep restriction may lead to accidents, cardiovascular dysfunction or obesity and diabetes. Although it can also cause mood disorders, cognitive deficits in attention and alertness, and the failure of sleep-dependent learning and memory consolidation. In the following section, examples of some effects of sleep on neurocognitive functions are discussed.

Sleep consolidates perceptual learning. When a subject undergoes a visual learning task, a following sleep period turns out to be necessary in order to see an improvement. If no sleep is obtained within 30 hours after the training, the potential benefits of the training are lost. Both deep SWS sleep and REM sleep are needed for this improvement, and they can be obtained either across an 8 hour night, or with a nap of as little as one hour. [Car05]

Sleep consolidates motor skill learning. As with the visual perceptual task discussed above, motor skill learning also shows a sleep dependent component, now appearing to require rather light NREM 2 sleep. On the finger tapping motor sequence task, subjects show a 20% improvement in speed, and up to a 50% reduction in error rates after a night of sleep. [Car05]

Sleep consolidates complex learning. Sleep-dependent learning apparently is not limited only to simple tasks. In learning a complex technique for analyzing strings of digits, subjects develop insight into a simpler technique for completing the analysis as the result of a night of post-training sleep. In the absence of such sleep, the

number of subjects gaining insight into this simpler solution drops from 60% to less than 30%. [Car05]

In our culture, major sources of sleep deprivation include medical problems[1], psychophysiological insomnia (usually due to stress or anxiety), circadian phase delay in adolescents producing later bedtimes and a drive for later mornings, "sleep bulimia" in college and graduate students[2], and a culture of late-night TV and internet use.

Another feature that has been proven to be particularly sensitive to sleepiness and fatigue are reaction times. For example, lapses of attention increase after being awake for 18 hours. At approximately 22 hours of wakefulness psychomotor performance is equivalent to a 0.08 blood alcohol concentration. Other recent studies showed that when subjects slept less than 7 hours nightly, the performance lapses got progressively worse each day. Such psychomotor performance deficits were also observed with people working night shifts.

Sleep deprivation is therefore associated with many neurobehavioral and cognitive effects including previously mentioned increased working memory errors, reduction in learning and acquisition, preservation on ineffective solutions, but also cognitive slowing and loss of situational awareness. [Car05]

3.6.2 Cardiovascular diseases

Although sleep is generally perceived as a state of rest, the pathophysiology of cardiovascular diseases may be closely linked to state changes related to sleep. Autonomic and hemodynamic measures are strongly influenced by normal sleep, by presence of arousals, and by disordered sleep.

Normal sleep constitutes a remarkably heterogenous autonomic and hemodynamic profile, with blood pressure, heart rate and sympathetic activity closely dependent on current sleep stage. During non-REM sleep, there is a gradual decrease in blood pressure, heart rate and sympathetic activity, with the deepening of sleep stages. On the other hand, REM is accompanied by marked increases in sympathetic activity and intermittent surges in both blood pressure and heart rate. Since REM stage is more prevalent later during the sleep (closer to the waking time) and cardiac and vascular events manifest clear circadian rhythms with peak occurrences between 6 - 11 am, the relationship between these events and sleep arousal is rather evident, though still poorly understood. Sympathetic excitation and hemodynamic responses during REM or a sleep arousal may contribute to early morning cardiovascular presentations and to cardiac ischemia during sleep.

[1] e.g. sleep apnea, chronic pain

[2] characterized by shorter sleep during the week and prolonged sleeping on weekends

The most compelling data linking sleep to heart disease is in the case of sleep apnea. Obstructive sleep apnea induces profound derangements in arterial blood chemistry. Chemoreflex activation by hypoxemia and hypercapnia is a powerful mechanism for sympathetic activation and surges in blood pressure. Related cardiovascular diseases include hypertension, heart failure and atrial fibrillation. [SDMA93]

3.6.3 Obesity and diabetes

Sleep has modulatory effects on many components of the endocrine system. The secretion of growth hormone and prolactin is markedly increased during sleep, whereas the release of cortisol and thyrotropin (TSH) is inhibited.

For example, decreased slow wave sleep in young men is associated with decreased production in growth hormone. Because the growth hormone plays an important role in controlling the distribution of fat and muscle during adulthood, having less of it increases the tendency towards becoming overweight with age.

Other short term studies have found a correlation between inadequate sleep and insufficient levels of the hormone leptin, which regulates carbohydrate metabolism. Low levels of leptin cause the body to crave carbohydrates regardless of the amount of calories consumed. [PG06]

Awakenings interrupting sleep also inhibit growth hormone and prolactin secretions, and are associated with increased TSH and cortisol concentrations. The modulatory effects of sleep on hormones release are, however, also observed for the hormones controlling water balance and glucose regulation. There are also important interactions between a function of the immune system and sleep. [Car05, VPB+00]

Due to the very complex problematics of sleep, at the basic research level, somnology must be considered an interdisciplinary field involving genetics, environmental sciences, epidemiology, cardiology, immunology, endocrinology, neurosciences and otolaryngology. [CA+06] Nowadays, this field is being even enriched with disciplines such as psychology, bioengineering or computer science.

Chapter 4

Sleep diagnostics

4.1 Introduction

From previous sections and paragraphs, the importance of sleep and sleep medicine in general has been already emphasized. Not only specific sleep pathologies call for adequate diagnostics and treatment, but also socio-psychological impact and other disorders arising on top of a present sleep pathology require particular attention.

As well as everything else, the health service also underlies to the development of digital technologies. Not so long time ago the polysomnographic recordings were still printed on a paper and then assessed by the doctor. Today, the recordings can be stored in a digital form, which allows their later processing, analysis and easier archiving.

The major ongoing problem is the visual evaluation of such recordings. It is still a very tedious task even for an experienced doctor. Therefore, the software solutions for work with digital data are constantly developing, however currently there is always a doctor needed to finally analyze the recording and determine the right diagnosis. [LBL09]

Following sections further describe the PSG examination, its main purpose and associated issues, alternative tools for sleep diagnosis, and subsequent analysis of the obtained data.

4.2 Polysomnography

Polysomnography was first developed in 1960s when also known as sleep scoring. Since then this method has become a golden standard and a classic approach to studying the patient's sleep behavior including sleep disorders.

While patients are sleeping or trying to fall asleep, three concurrent physiological signals monitoring physiological changes are collected using non-invasive surface electrodes: electroencephalography (EEG), electrooculography (EOG) and electromyography (EMG). This method therefore requires a whole night recording in a sleep laboratory. Often additional signals are being recorded too. These include signals related to breathing - nasal/oral airflow, thoracic effort and abdominal effort. Further channels include blood oxygenation, electrocardiography (ECG) and leads measuring limb motion. [ZWW10, CSP+15]

Sensors for measuring mentioned signals are typically conductive electrodes attached to the patient's skin. Thermal or pressure sensors attached to the nose or mouth usually serve to measure respiratory airflow, while piezoelectric or impedance change straps often measure chest/abdomen movements to assess respiratory effort. Blood oxygenation (SpO2) is obtained through a pulse oximeter attached to a finger. Limb motion is most often recorded with accelerometers attached to the wrist or the ankle. [LBL09]

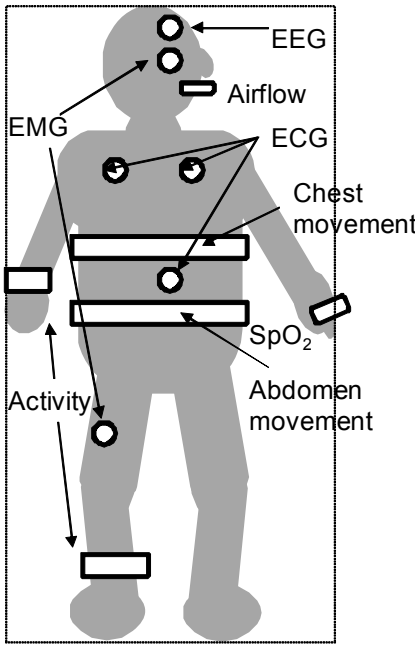


Figure 4.1: PSG sensors attachement scheme [LBL09]

Today, PSG technique is widely used in hospitals to monitor patients' sleep cycles. Based on the signals analysis, sleep-wake states and sleep stages can be recognized by human expert (see 4.3). These may exhibit abnormal qualitative and quantitative changes associated with clinical conditions and environmental situations, and be useful in diagnosing various sleep pathologies. [LT+11, ZWW10]

In this setup, where many electrodes are mounted to patient's body parts including face and scalp, subjects may feel uncomfortable during sleep. This can lead to distortion or misinterpretation of the whole test because one night recording is simply taken out of individual's sleep routine context. As a result, there are efforts to design and build other more easily implemented and transported monitoring systems.

The standard PSG which is performed in a sleep laboratory is categorized as a Type I. Table 4.1 describes other systems including wireless technologies providing a more versatile approach. [LBL09]

Type I	monitoring devices perform in-lab; technician is present; overnight
Type II	monitoring devices can perform full PSG outside of the laboratory; technician is not present; comprehensive portable devices
Type III	monitoring devices do not record the signals needed to determine sleep stages or sleep disruptions; typically only respiratory movement and airflow, heart rate and arterial oxygen saturation is measured; some devices may record snoring, detect light or monitor the body position
Type IV	monitoring devices record one or two variables (eg. arterial oxygen saturation and airflow); can be used without a technician; continuous single or dual bio-parameter devices

Table 4.1: Categories of sleep monitoring devices [LBL09]

Today, the capacity needed to serve the population seeking sleep diagnosis and treatment is unfortunately not adequate. It is indicated that in many places, the waiting time for a PSG examination may be as much as 10 weeks. As public awareness of the clinical consequences of poor sleep or sleep disorders increases, this diagnostics shortfall will even worsen. A substantial investment is therefore needed to enlarge the clinical and research workforce and improve the diagnosis technology. [CA+06]

4.2.1 EEG

Electroencephalogram is the summation of electrical signals generated by millions of brain neurons. It is usually divided into different frequency bands: delta (0.5 - 2 Hz), theta (3 - 7 Hz), alpha (8 - 12 Hz) and beta (12 - 20 Hz). Sometimes additional bands such as fast beta (20 - 40 Hz) or gamma band are set aside.

According to many studies, spectral powers of different frequency bands highly correlate with different sleep stages and therefore serve as a well known pattern in PSG studies. For example, deep sleep is recognized by the presence of high amplitude delta waves. [ZWW10]

Sleep specific electrical oscillations

Sleep and sleep stages are characterized by specific rhythms of brain activity.

SWA = slow wave activity. During slow wave sleep (SWS = NREM 3, NREM 4), the EEG shows dominant slow wave activity defined as frequencies within 0.5 - 4.0 Hz band and including the slow oscillations with a peak frequency of 0.8 Hz. Delta activity belong to SWA. Slow oscillations are generated based on switching between periods of neuronal membrane depolarization accompanied by sustained firing and periods of membrane hyperpolarization associated with neuronal silence. Basically every neuron of the brain cortex (both excitatory and inhibitory neurons) engages in the synchronous generation of slow oscillations especially prevalent during NREM 2 stage.
K-complexes during NREM 2 sleep stage appear to represent isolated slow waves. The slow oscillation is generated in cortical networks and can occur in isolated cortical slices, however, it very likely reflects an interaction between both cortical and thalamic network. High-density EEG recordings suggest that the slow oscillation behaves like a travelling wave originating mostly in the frontal regions and propagating towards posterior regions. Slow waves activity is considered as a marker of the homeostatically regulated sleep pressure which increases after prolonged sleep deprivation and decreases from early to late sleep. This decrease in SWA across sleep may be explained by a decrease in the incidence of high-amplitude slow waves. Independent of the decrease in amplitude, the slope of the slow waves also decreases from early to late sleep, possibly reflecting a decrease in the synchrony and speed of depolarization and hyperpolarization of neurons. [RB13]

Spindles. Spindle activity refers to regular EEG oscillatory activity which occurs in a frequency range 10 - 15 Hz. It is expressed in NREM 2 as discrete spindles lasting 0.5 – 3 s. They can be temporally locked to a vertex sharp wave or a K-complex. Spindles are also present during SWS and superimposed on delta activity, and then

form less clearly discrete spindles. Despite the spindle activity in SWS being able to reach levels similar to those in stage NREM 2, on average it is lower. There is a reciprocal relationship between sleep spindles and slow wave activity. While SWA progressively decreases throughout the night, sleep spindles and power in the 12 – 15 Hz band tend to increase. Sleep deprivation typically reduces spindle activity during subsequent recovery sleep, together with an increase of SWA. Studies have revealed the presence of two kinds of spindles: fast spindles (13 – 15 Hz) and slow spindles (10 - 12 Hz). The fast type shows a more widespread distribution concentrating over the central and parietal cortex, whereas slow spindles are more focused over the frontal cortex and are more frequently present during SWS compared to NREM 2. These two types differ in aspects such as circadian and homeostatic regulation, sensitivity to pharmacotherapy and dominance in different age groups. [RB13]

Theta activity. Theta activity, defined as periods of synchronized activity within 3 – 7 Hz is a hallmark of tonic REM sleep[1]. Theta activity also modulates the amplitude of high-frequency gamma oscillations (ca 40 Hz). This rhythm is thought to favor neuronal encoding through the theta-phase coupling of faster gamma oscillations differing between phasic and tonic REM periods. Phase-locking of gamma band activity during coherent theta activity is thought to have a key role in memory information encoding and consolidation. [RB13]

4.3 Sleep stages scoring

Distinct sleep stages are associated with different physiological and neuronal features which are generally used to identify the sleep stage a subject is in. This process called sleep scoring, or sleep staging, is a critical step in PSG signal processing pipelines used in clinical routine as well as in sleep research.

The scoring of sleep-wake stages is performed by a trained human expert on the basis of an epoch-by-epoch visual interpretation of the PSG signals. The analysis generally follows established guidelines, such as a set of R&K criteria (published in 1968 by Rechtschaffen and Kales) where each segment of 30 s is labelled as either Awake, S1–S4 (as for NREM 1 - NREM 4) or REM. These rules were later updated by the American Academy of Sleep Medicine (AASM) resulting in merging stages NREM 3 and NREM 4 into a single stage of deep sleep called NREM 3, also known as slow wave sleep (SWS). [LCR+15]

Sleep stages are scored in 30 second sequential epochs commencing at the start of the recording, with each epoch being assigned a sleep stage. If two or more stages coexist during a single epoch, the stage comprising the greatest portion is assigned.

[1] REM sleep without actual rapid eye movements

The following section documents definitions of sleep stages along with the rules for their manual scoring derived from [Ibe07].

4.3.1 Scoring rules

Wake. An epoch is scored as stage W when more than 50% of the epoch has alpha rhythm over the occipital region. Epochs without visually recognizable alpha rhythm are scored as stage W if any of the following are present: Eye blinks[2] at a frequency of 0.5 - 2 Hz; Reading eye movements[3]; Irregular conjugate rapid eye movements associated with normal or high chin muscle tone.
Stage W represents the waking state, ranging from full alertness through early stages of drowsiness. The majority of individuals with eyes closed will demonstrate alpha rhythm. About 10% of subjects do not generate alpha rhythm on eye closure, and a further 10% may generate limited alpha rhythm. In these subjects, the occipital EEG activity is similar during eye opening and eye closure. The EOG during wakefulness may demonstrate rapid eye blinks at frequency of about 0.5 - 2 Hz. As drowsiness develops, the frequency of blinking slows, and eye blinks may be replaced by slow eye movements, even in the presence of continued alpha rhythm. If the eyes are open, voluntary rapid eye movements or reading eye movements may be seen. The chin EMG during stage W is of variable amplitude, but is usually higher than during sleep stages. [Ibe07]

NREM 1. Stage NREM 1 is scored in subjects who generate alpha rhythm if it is attenuated and replaced by low amplitude, mixed frequency activity for more than 50% of the epoch. In subjects who do not generate alpha rhythm, stage NREM 1 is scored commencing with the earliest of any of the following phenomena: Vertex sharp waves[4] or slow eye movements[5].
Vertex sharp waves may be present but are not required for scoring a stage as NREM 1. The EOG will often show slow eye movement in this stage but these are not required either. During this stage, the chin EMG amplitude is variable, but often lower than in stage W. [Ibe07]

NREM 2. The following rule defines the start of a period of sleep stage NREM 2. Beginning of stage NREM 2 is scored respectively if one or both of the following occur during the first half of that epoch or the last half of the previous epoch: One

[2] Conjugate vertical eye movements at a frequency of 0.5 - 2 Hz present in wakefulness with the eyes open or closed.

[3] Trains of conjugate eye movements consisting of a slow phase followed by a rapid phase in the opposite direction as the subject reads.

[4] Sharply contoured waves with duration < 0.5 seconds maximal over the central region and distinguishable from the background activity.

[5] Conjugate, reasonably regular, sinusoidal eye movements with an initial deflection usually lasting > 500 ms.

or more K-complexes[6] unassociated with arousals or one or more trains of sleep spindles[7].
The following rule defines continuation of a period of sleep stage NREM2. Epoch is continued to be scored as NREM2 if it presents with low amplitude, mixed freqency EEG activity without K-complexes or sleep spindles and they are preceded either by K-complexes unassociated with arousals or by sleep spindles.

The following rule defines the end of a period of sleep stage NREM 2. Scoring as NREM 2 is ended when at least one of the following events occurs: Transition to stage W; an arousal (change to stage NREM 1 until a K-complex unassociated with an arousal or a sleep spindle occurs); a major body movement followed by slow eye movements and low amplitude mixed frequency EEG without non-arousal associated K-complexes or sleep spindles (the epoch following the major body movement is scored as stage NREM l; transition to stage NREM 3, transition to stage REM.
The EOG usually shows no eye movement activity during the NREM 2 sleep stage, but slow eye movements may persist in some subjects. In this stage, the chin EMG is of variable amplitude, but is usually lower than in stage W, and may be as low as in REM sleep. [Ibe07]

NREM 3. An epoch is scored as stage NREM 3 when 20% or more of an epoch consists of slow wave activity, irrespective of age.
Sleep spindles may also persist in this stage, eye movements are typically not seen. The chin EMG is of variable amplitude, often lower than in stage NREM 2, and sometimes as low as in stage REM. [Ibe07]

REM. REM stage is scored in epochs with all the following phenomena: low amplitude, mixed frequency EEG; low chin EMG tone; rapid eye movements.
Scoring as stage REM is continued, even in the absence of rapid eye movements, for segments following one or more epochs of stage REM as defined above, if the EEG continues to show low amplitude, mixed frequency activity without K-complexes or sleep spindles, and the chin EMG tone remains low.
The following rule defines the end of a period of REM sleep stage: Scoring is stopped when one or more of the following occur: there is a transition to stage W or NREM 3; tone of chin EMG increases above the standard REM stage level; an arousal occurs followed by low amplitude, mixed frequency EEG and slow eye movements; a major body movement followed by slow eye movements and low amplitude mixed frequency EEG without non-arousal associated K-complexes or sleep spindles; one or more non-arousal associated K-complexes or sleep spindles are present in the first half of the epoch in the absence of rapid eye movements, even if chin EMG tone

[6] A well-delineated negative sharp wave immediately followed by a positive component standing out from the background EEG, with total duration higher than 0.5 seconds, usually maximal in amplitude when recorded using frontal derivations. For an arousal to be associated with a K-complex, it must commence no more than 1 second after termination of the K-complex.

[7] A train of distinct waves with frequency 10 - 15 Hz (most commonly 12 - 14 Hz) with a duration higher than 0.5 seconds, usually maximal in amplitude using central derivations.

remains low. [Ibe07]

PSG records usually use a fixed 30s epoch duration. Manual scoring relies on previously described visual extraction of specific features mostly in EEG channels, two channels of EOG and one channel of chin EMG. [LT+11]

In general, the process of sleep diagnostic examination and the consequent manual scoring is very complex and very time-consuming. A complete visual inspection of the recordings acquired during nocturnal polysomnography can last approximately 1 to 2 hours per patient, although the main issue is a high sensitivity to a subjective judgement of the scorer. Despite the scorer being a highly trained personnel, the reliability of manual sleep scoring is still very low because of intra and inter scorer variability and human error. It is very unlikely that two different though trained professionals would score one sleep recording identically. This leads to an inconsistency in diagnosis assessment and an absence of a real ground truth in sleep stages classification.

In order to overcome problems associated with manual scoring, development of an automatic sleep scoring system is highly desirable. However, one of the issues this thesis is trying to discuss and emphasize is the previously mentioned lack of reliable ground truth in sleep stages scoring which could be used as a training set for future automatic classifiers. Researchers and developers are therefore finding themselves rather in a philosophical position within a vicious circle, where they are trying to design an automatic scoring system and later evaluate its success rate based on questionable reference data.

Automatic sleep stages classification systems are, however, still the future of polysomnography and sleep diagnostics over all. They would not only save time and costs associated with sleep testing, but would also make the examination more accessible to a larger population. Eventually the interscorer variability would be overcome too.

A typical algorithm involves basic signal processing, signal segmentation and extraction of representative features followed by a classification task where the system automatically assigns one of the sleep stages to each segment based on the extracted set of features. [IRV15]

The description of few approaches and algorithms already presented in the literature is covered in the following section.

4.3.2 Approaches to automatic sleep stages scoring

While visual scoring still remains the gold standard, recent years have witnessed a rise in algorithm developments for automatic or semi-automatic sleep staging systems.

Across existing methods, a wide range of physiological features is usually extracted from PSG signals. These include time-domain, frequency-domain, time–frequency-domain features, and both linear and nonlinear features. While some studies rely only on one or two features to perform sleep stage classification, others extract exhaustive amount of features and later search for their optimal subset combination.

The standard classification process consists of three main steps: feature extraction from PSG channels (EEG, EOG and EMG) covering both time and frequency domain features; dimension reduction and feature subset selection; classification itself using various machine learning techniques.

Study [LCR+15] used support vector machines as a classifier. In principle, SVMs are designed for binary classification (into two target classes), therefore in order to automatically score into more than two sleep stages, a multi-class SVM framework needed to be implemented. In general, two main approaches can be used: either One-Against-All (OAA) or One-Against-One (OAO). The OAA framework uses a binary SVM to distinguish each class from all other classes and the final decision is obtained by applying a "winner takes all" strategy. By contrast, OAO trains a dedicated classifier for each of all possible pairs of classes and the decision is obtained by performing a majority vote. Study [LCR+15], however, proposed a decision-tree-based support vector machine approach. The structure of the decision tree was designed using hierarchical clustering. In other words, this decision-tree classification framework had a binary SVM at each node. The rationale of this study was to combine the advantages of the efficient computation of decision trees and the high classification accuracy of SVMs.

Three different schemes to extract features from EEG signals were presented in study [ENN+04]. These were relative spectral band energy, harmonic parameters and Itakura Distance.

Itakura distance is used widely in speech processing applications to measure the distance between two autoregressive processes. In this study, the Itakura distance was used to measure the similarity of a base line EEG epoch (specific sleep stage) with the rest of the epochs in the EEG vector. The Itakura distance shows that when the subject falls into a deeper sleep stage, the distance increases as a consequence of the autoregressive process change.

Additionally, it was shown that the awake state was related to higher frequencies of the spectra, while the stage NREM 4 was linked to slow waves. It was observed that the percentage of relative energy band of beta waves was a good feature for

distinguishing between different sleep stages.

Features set describing sleep-related attributes based on wavelet analysis was introduced by [CJCL06]. Each segment of PSG was represented by following parameters: amplitude and frequency-weighted energy of three primary EEG rhythms and the EMG channel, presence of sleep spindles in the frontal EEG lead, alpha-slow-wave index, theta-slow-wave index, and presence of eye movements in the EOGs. Study [CJCL06] further used unsupervised clustering k-means algorithm. The main problem associated with this approach was that the users were incapable to know the true number of clusters in a recording, because in general not every sleep recording includes all sleep stages.

More detailed overview of the applicability of the wavelet transform compared to Fourier transform to EEG signals for sleep analysis is provided in [JTPS94]. Furthermore, the paper describes the application of the wavelet transform to EEG signal analysis in context of analyzing a synthetic composite signal, pattern-oriented analysis, analysis of arousal reactions, analysis of EEG in different sleep stages and analysis of an all-night sleep recording. [EM15]

Other methods have also used artificial neural networks and decision trees for classification with a variety of time, frequency, entropy, and wavelet based features.

All sleep scoring algorithms in literature report their classification performance by evaluating their method on sleep data either recorded by the researchers or using signals available from public sleep databases. It is generally difficult to compare the performance of algorithms that have been evaluated using different datasets. Therefore it is highly desirable to use a public database since it is easily accessible for all researchers for algorithms comparison. [IRV15]

Overall, the performance of classification can be severely degraded by the presence of irrelevant features. Moreover, it might not be optimal to use the same feature set to classify all the different sleep stages because even AASM scoring manual identify each sleep stage using distinct feature sets. [HLK+13]

4.4 Other goals of automatic PSG analysis

Apart from efforts to design an automatic tool for sleep stages scoring, there are several other features important for sleep diagnosis that are worth studying and aiming for their automatic analysis. These include evaluation of sleep dynamics, sleep microstructure, detection of arousals and estimation of associated sleep fragmentation, or automatic apneas recognition.

4.4.1 Sleep arousals

An arousal (short awakening[8]) event and arousal index (ArI[9]) are often used as a measure for quantifying the sleep fragmentation. [JRL08] In fact, sleep arousal is known as any intrusion of wakefulness into the sleep, but is accounted a part of normal sleep and rarely results to awakening. [SDPC15] Other approaches for quantifying sleep quality include summarizing the distributions of specific sleep stages including time spent in light, deep, slow wave and REM sleep, or calculating sleep efficiency as a ratio of total sleep time to total time in bed. [KMW+12]

In traditional PSG studies, events like sleep arousals, delta waves, eye movement, limb movement, obstructive apnea or SpO2 desaturation are used by sleep experts to deduce various sleep disorders such as hypopnea, obstructive sleep apnea and restless leg syndrome, where an arousal event follows events such as oxygen desaturation, an increase in breathing effort and leg movements. [EM15] Having a possibility of their automatic detection is therefore highly desirable.

The objective of studies [EM15] and [SDPC15] was to develop an algorithm for automatic detection of sleep arousals without distinction between the types of each arousal. The first case of interest was to detect whether the person was being aroused from sleep. The continuous night-long signal was first segmented into smaller windows, subsequently descriptive features characterizing the signal were extracted from each segment and in the end these were used to classify each segment as containing an event of interest or not. The supervised learning methods were used.

Study [EM15] though used a different classifier for each type of event, thus forming a binary classification problem. The added benefit of this approach was that in each segment more than one type of event could be detected. For example, a segment could include both a leg movement and an arousal event, which is actually very common in sleep studies. The supervised learning algorithms used and compared in this work were Naive Bayes, Logistic Regression and Decision Trees.

The event detection problem from study [EM15] can be reduced to a classification problem by taking each segment of the signal and testing it against a classifier that decides if that segment contains an event of interest or not, as it was done in study [SDPC15].

[8] Defined as an abrupt shift of any particular frequency of EEG that lasts at least 3 seconds [Ibe07]

[9] The number of arousals per hour

4.4.2 Sleep microstructure and dynamics

Sleep microstructure is expressed by Cyclic Alternating Pattern (CAP), and its possible alterations in pathological sleep.

Despite CAP being a physiological phenomenon, it is also a marker of sleep instability and can be correlated with several sleep-related pathologies. Increased amounts of CAP are often observed in sleep-disordered breathing, as well as in insomnia, sleep movement disorders, parasomnias, and epileptic diseases such as nocturnal frontal lobe epilepsy. Pathological amounts of CAP can also be found in hypersomnias of central origin such as narcolepsy.

CAP is a periodic EEG activity occurring during NREM sleep. It is characterized by cyclic sequences of cerebral activation (phase A) followed by periods of deactivation (phase B) which separate two successive phase A periods with an interval <1 min. Phase A period and the following phase B period define a CAP cycle, and at least two CAP cycles are required to form a CAP sequence. [TPS+01]

There are three subtypes of phase A and each of them has different characteristics: subtype A1 promotes EEG synchronisation, accompanying the transition from light to deep sleep, while, subtypes A2 and A3 are expressed with more desynchronised EEG patterns towards the onset of REM sleep. CAP sleep has been regarded as an essential mechanism in modulating onset, consolidation and disruption of sleep stages, and thus its detailed study may be useful in understanding the mechanisms of various sleep disorder, especially insomnia. [CGM+13]

The different distributions of CAP A phases with respect to sleep stages can be measured in sleep centers to characterize such pathologies. These indexes can be valuable as measures of sleep quality, but it is usually very time-consuming to determine them. Another trend in automatic PSG analysis therefore is the development of software capable of accurate and efficient analysis of CAP sequences. [TPS+01]

4.5 Alternatives to PSG

Conventional PSG measurements are typically made through a variety of sensors mounted directly to the patient's skin in a sleep laboratory, where he or she needs to spend one or more nights. These unfamiliar sensors, associated wiring and overall invasiveness can impose significant discomfort and movement restrictions on the patient, which can adversely have an impact on the recorded data and results of the study. [KVMS15, LBL09]

Polysomnography thus results to be expensive since it is time consuming and

necessitates costly appliances and expert technicians to observe the patient during the night. Moreover, its use is limited to clinical laboratories and the home use is not yet fully possible. [PDlPA15, CSP+15]

As a result, many patients with sleep-related problems may avoid testing and go undiagnosed. Even those undergoing a full sleep study cannot be monitored over longer periods of time to assess longitudinal variations as the one or two night sleep study represents only a "snap-shot" of the actual underlying sleep issue. [EM15]

All the points mentioned above, emphasize the need for automatic, non-intrusive methods for sleep diagnostics.

These new methods should have a reduced number of channels in order to save time, reduce costs and enable the use in patient's homes so it helps increase the number of diagnosed subjects. [KVMS15]

Wireless technologies have been recently introduced to alleviate some of these complications and make the consideration of home based sleep studies possible. A straightforward approach to bringing wireless solutions to PSG monitoring systems can be applied by directing all the wiring to a body-worn wireless communications device. While sensor related problems and some of the wiring issues still remain, this approach reduces the electromagnetic interference and allows the patient greater degree of unrestricted movement including rolling over and even leaving the bed. [LBL09]

In recent years many non-contact measurements (especially for the tracking of breathing) have been proposed. Specifically, the use of systems based on digital imaging is very promising since it removes all the wiring of the patient to the instrumentation, and the patient does not need to be in a known position and static conditions throughout the whole night. [CSP+15]

In addition, polysomnography is not suitable for continuous monitoring so it could improve the diagnosis and the treatment outcome. Therefore other systems, such as actigraphy, are also used to measure sleep parameters and estimate sleep problems. This is an unobtrusive method, however, the hardware is too simple and only considers sleep efficiency to estimate sleep quality based on gross motor activity throughout the night.

Pressure sensor arrays are another alternative for monitoring patients during the night. They are used to record the time in bed and they acquire the respiratory signal. Such device allows noninvasive monitoring, can be easily installed in standard beds, and can be used for a continuous monitoring of sleep quality for many nights. [PDlPA15]

Part II

Methodology

PSG data analysis

Chapter 5

Introduction

This chapter provides a brief overview of the structure and contents of Part II. The general workflow is shown in Figure 5.1. All data processing and analysis was performed in MatLab R2016b environment.

Beginning with the original database consisting of 108 files, first a usable subset of recordings has been selected, and then seven channels common for all 70 recordings from the new subset extracted. In the next step, a way to transform raw data into a feature space has been found. The extracted feature space was expected to bring a clear difference between classes (stages of sleep). In addition, mutual information has been computed in order to evaluate the 'quality' of extracted features. Any regularities or patterns found in the extracted data are, among other results, reported in Chapter 9.

All partial analysis was performed on each pathology group separately.

As was already mentioned before, this thesis' purpose was not to focus on sleep stages classification, therefore the contents of Chapter 8 are more about verifying the classification potential of extracted features, rather than about complex design of multiple classifiers from scratch. In other words, the aim of the Classification chapter is to validate whether extracted features are suitable for discrimination between different sleep stages in various clinical recordings.

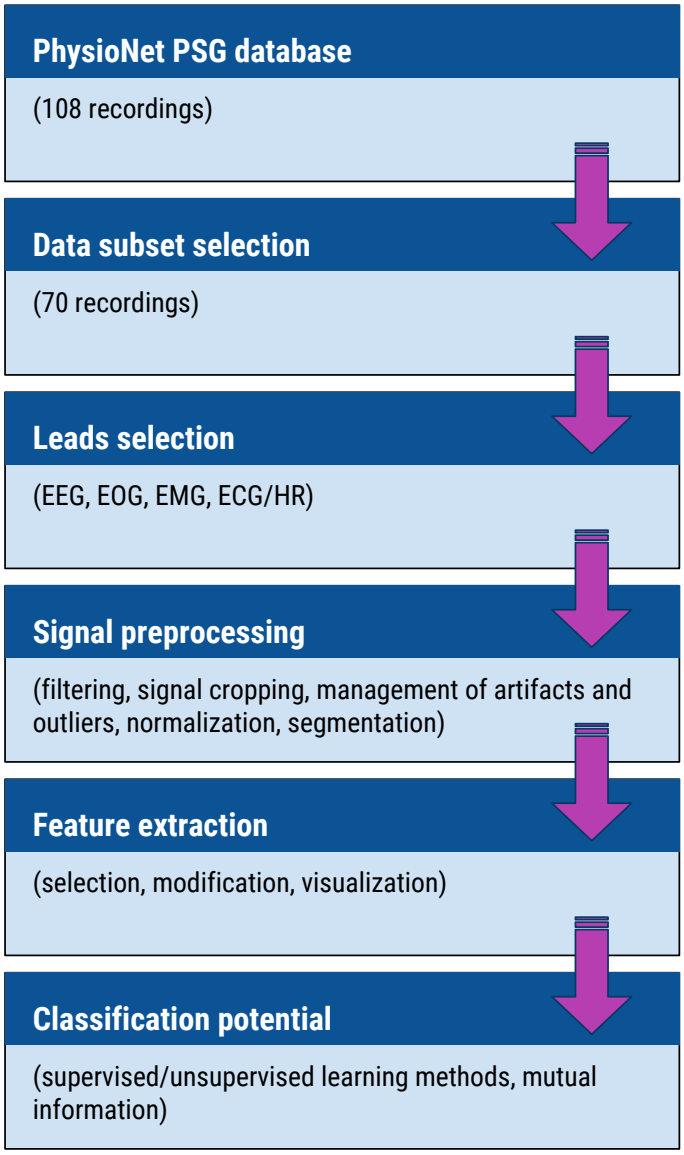


Figure 5.1: Methodology workflow

Chapter 6

Data preprocessing

6.1 PSG Database

The CAP Sleep Database available as a part of online public PhysioNet library was used as the main dataset for this thesis. [TPS+01, GAG+00] The database consists of 108 polysomnographic recordings stored in the European Data Format (.edf). The waveforms always include EEG, EOG and submentalis muscle EMG channels. Many of the recordings contain additional channels representing the anterior tibial EMG, respiration signals and ECG, however, the available leads are not consistent across the whole database. The data was collected with different sampling frequencies (different signal types withing single recording were sampled with different sampling frequency and also different recordings had different sample rates used for the respective signals), however, these, as well as used filters and other recording and post-recording specifications, are available as a part of the edf file structure. The scoring of the sleep macrostructure was provided by expert neurologists in a form of attached hypnograms, reported as 0 for wake, 1 to 4 for the NREM sleep stages and 5 for REM. The R&K Rules were applied.

Recordings, unfortunately, vary in both the number of channels and their type. The channel labels stating the lead type were often different in used language or capitalization. Therefore a manual inspection of each recording had to be done in order to analyze which channels were actually available and through which labels/names they could be accessed. This manual inspection further included controlling the presence of hypnogram since most of the recordings did not contain a full night scoring. Usually only 60 - 80% of the night was assigned with a sleep stage class. Fully classified recordings although did exist.

There were 16 healthy subjects without any known neurological disorders and free of drugs affecting the central nervous system. The rest of the database consists of 92 pathological recordings including patients diagnosed with nocturnal frontal lobe

epilepsy (NFLE), REM behavior disorder (RBD), periodic limb movements (PLM), insomnia, narcolepsy, sleep disordered breathing (SDB), and bruxism. The overview can be seen in Table 6.1 along with the actual number of recordings finally used for further analysis in this thesis. The selection criteria are described in following sections.

Pathology	Number of recordings	Gender [F/M]	Age	Included
No pathology	16	9/7		4
Bruxism	2	0/2		0
Insomnia	9	5/4		5
Narcolepsy	5	3/2		3
NFLE	40	19/21		35
PLM	10	3/7		7
RBD	22	3/19		15
SDB	4	0/4		1
Total	**108**	**42/66**		**70**

Table 6.1: PSG Database Overview

6.2 Final dataset selection

Due to the previously described inconsistency in the available data - different channels recorded across the dataset, missing hypnograms or simply some leads being too noisy - only a subset of the original database was used. The criteria for data selection was chosen so the final number of recordings used for further processing was maximal.

Only the recordings meeting the following requirements have been selected:

1. Channels labeled ROC-LOC (EOG), F4-C4 (EEG), P4-O2 (EEG), EMG1-EMG2 (chin EMG), DX1-DX2 (right leg), SX1-SX2 (left leg), HR (heart rate) are present in the recording [1]

2. Channels stated in (1) contain only a reasonable amount of noise and artifacts

[1] These channels were used for further analysis.

3. A referential hypnogram is available for at least 50% of the total signal duration

This procedure of database inspection was a very tedious task due to the original number of recordings, their length, and complexity of biological signals that needed to be studied in order to determine a "subjective signal to noise ratio".

6.3 Data preparation

In order to obtain comparable results from any type of automatic signal analysis, the data needs to be preprocessed. This includes removing as much noise as possible, detecting and removing artifacts, outliers, offsets, and preferably normalizing the amplitude range.

6.3.1 Artifacts and outliers

Various approaches on how to deal with artifacts in PSG signals have been considered since this problematics had been studied within a previous bachelor project. Main issues lie in first detecting the artifact and later in the way it is handled - whether replaced with a native signal estimate, or removed completely.

Many artifacts occurring in a channel are often a manifestation of another physiological signal suddenly producing higher voltages. For example, in EEG signals we can typically observe artifacts caused by muscle activity, eye blinks, chewing, snoring or body movements. Other artifacts can be caused by electrodes and wires temporary detachments, which are often produced, again, by body movements. These all are indeed artifacts per se, however, they reflect important events occurring during the night (examination period), and therefore it was decided not to remove them, but rather to exploit their presence as another type of information about "what is going on". In real clinical settings, avoiding the presence of these artifacts is merely impossible anyway. Thus cleaning the signal for research purposes could be relatively contra-productive, because these ideal signals obtained from theoretical set-up could never be reproduced in practice.

The only artifacts handled in this thesis were those manifesting as obvious outliers. Preserving them would significantly reduce further possibility to compare any useful information contained in signals between distinct recordings.

Based on the visual observation of available signals, the relative amount of outliers in each channel type was estimated. In other words, this estimate reflected how often do outliers usually occur in EEG, EOG, EMG and other signals, and was used to compute respective percentiles.

$$K_{low} = \text{prctile}(signal, p_{low}) \quad \text{where} \quad p_{low} = P(signal \leq K_{low})$$

$$K_{high} = \text{prctile}(signal, p_{high}) \quad \text{where} \quad p_{high} = P(signal \leq K_{high})$$

Parameters K_{low} and K_{high} represent the thresholds specifying the range of accepted values. All the signal datapoints having a value lower than K_{low} or higher than K_{high} were marked as outliers. For all signals apart for HR (heart rate) channel, p_{low} was set to 0.1% and p_{high} to 99.9%. HR channel p_{low} and p_{high} values were set to 1% and 99% respectively.

The identified outliers were replaced with mean values computed from the remaining signal.

6.3.2 Filtering and normalization

The provided data has been already filtered, therefore this task did not have to be performed in this work. The filters used were saved in the edf file structure, along with respective sampling frequencies, and could be easily accessed. EEG and EOG leads were usually filtered with 30 Hz low-pass and 0.3 Hz high-pass filters, EMG signals with 10 Hz high-pass, 50 Hz notch, and variable cut-off low-pass filters.

All signals but the heart rate were further normalized into the range between -1 and 1 and their DC offset was removed.

6.4 Hypnogram constraints

Because not all the recordings had a hypnogram provided for the whole examination duration, the unscored parts of each recording have been excluded. The separate channels extracted and preprocessed in the previous steps were cropped, so all data for further analysis had their reference scoring available.

Provided hypnogram scoring was modified in order to match the updated scoring rules, where stages NREM 3 and NREM 4 are merged into one slow wave sleep - SWS. New scoring is: 0 for Wake, 1 for NREM 1, 2 for NREM 2, 3 for SWS, 4 for REM sleep.

6.5 Segmentation

Analysis of any long-term signals requires that the signals are segmented into, ideally, stationary-like frames. There are two main approaches to segmentation - adaptive or fixed-length. The main disadvantage of fixed-length segmentation is the risk of creating a segment boundary in the middle of an important event, and thus loosing the possibility of its detection and subsequent extraction. Another con is that the window size might be much larger than the actual event duration. As a result, the extracted feature for this segment will include a lot of irrelevant information, which can cause the event being missed again. This should not happen when performing adaptive segmentation due to its ability to detect segments containing data that are relatively more stationary-like.

However, in case of multi-channel data, the advantages of adaptive segmentation cannot be that easily and effectively applied anymore. The main reason for this is that there are most likely different events location in different channels, and simply that adaptive segmentation would produce different epochs in each of those channels. The final segmentation, however, must be consistent across the channels so time-matching features from all of them can be used for later analysis and classification.

For the reason of having multi-channel signal, the fixed-length segmentation into 30s long windows has been chosen and performed. Additional advantage of this approach was a simple implementation and an easier way of matching and comparing these segments to referential hypnograms. These were, in fact, created by scoring the original signal segmented into fixed 30s long epochs as well.

Chapter 7

Feature extraction

This chapter describes processes of data transformation and feature extraction. The main purpose of this procedure is to find unknown and potentially useful information or relationships in the large data. Preprocessed data is used as an input in order to obtain knowledge information as an output.

Theoretically, each PSG-signal segment obtained in part 6.5 should be described with multiple attributes (features), so that all segments belonging to one class have similar attribute values.

The selection methods were applied on all signals among EEG, EOG, EMG and a heart-rate signal.

Overall, there were 64 features extracted from the physiological signals. The features can be categorized into two main groups. The first one contains information about the frequency domain computed by the means of Fourier transform (27 attributes), the second one represents all features computed from the time domain (37 attributes).

The relevant feature sets are presented and summarized in Chapter 9, Section 9.2.

7.1 Frequency-space features

Spectral powers in the EEG frequency bands (absolute or relative) are expected to be the key information extracted from the EEG channels. Based on the literature review, almost each sleep/wake stage should be characterized by a typical pattern of some frequency. Besides, the initial visual analysis performed by a neurologist is in compliance with this approach, since he or she is first looking at the EEG activity with respect to waves frequencies.

To simplify the extraction process, a method based on spectrogram has been chosen. A spectrogram with window length corresponding to the size of one segment was computed. The resulting spectrogram thus had as many columns as the number of epochs the original signal was segmented to. The relative powers for each band have been computed by dividing the sum of PSDs (power spectral density) within the desired band range by the total power (sum of PSD values for all frequencies (s̃pectrogram rows) in each segment. This spectrogram-based principle of extracting spectral features was applied on all signal types (EEG, EOG, EMG).

An example of computing the relative spectral power of alfa band for a segment i is given below:

$$\text{relative\_power}(\alpha) = \frac{\text{power}(\text{EEG}[i], \sum_{f=8}^{12} \text{PSD}(f))}{\text{power}(\text{EEG}[i], \sum_{f=0}^{f_{max}} \text{PSD}(f))}$$

Used spectral bands ranges are presented in Table 7.1.

	EEG F4-C4, P4-O2	**EOG** ROC-LOC	**EMG** Chin	**LEGS** DX1-DX2, SX1-SX2
Band 1 (delta) [Hz]	0.5 - 2	0.1 - 2	10 - 17	10 - 22
Band 2 (theta) [Hz]	3 - 7	2 - 6	17 - 30	22 - 40
Band 3 (alfa) [Hz]	8 - 12	6 - 8	30 - 47	40 - 47
Band 4 (beta) [Hz]	12 - 30	8 - 10	53 - 74	53 - 100
Band 5 [Hz]	–	10 - 12	76 - 110	–
Band 6 [Hz]	–	12 - 14	–	–

Table 7.1: Spectral bands used for features extraction

Used spectral bands can be seen in following Figures 7.1, 7.2, 7.3 and 7.4 in forms of spectrograms. One can see, that in case of chin EMG, two frequencies were considered as artifacts and therefore excluded. These were power line noise (50 Hz) and an artifact having a frequency of 75 Hz occurring in many recordings. Power lines noise was also excluded from lower limbs EMG.

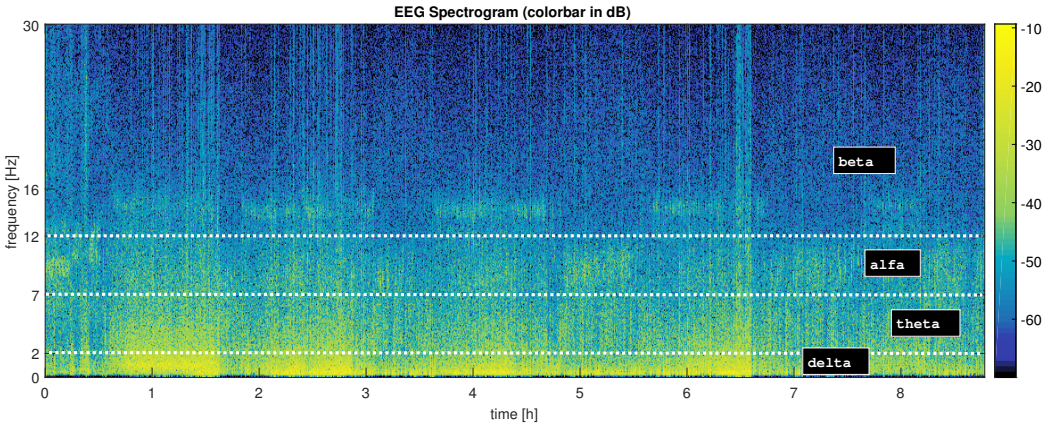


Figure 7.1: EEG Spectrogram for N11 recording: Extracted spectral bands

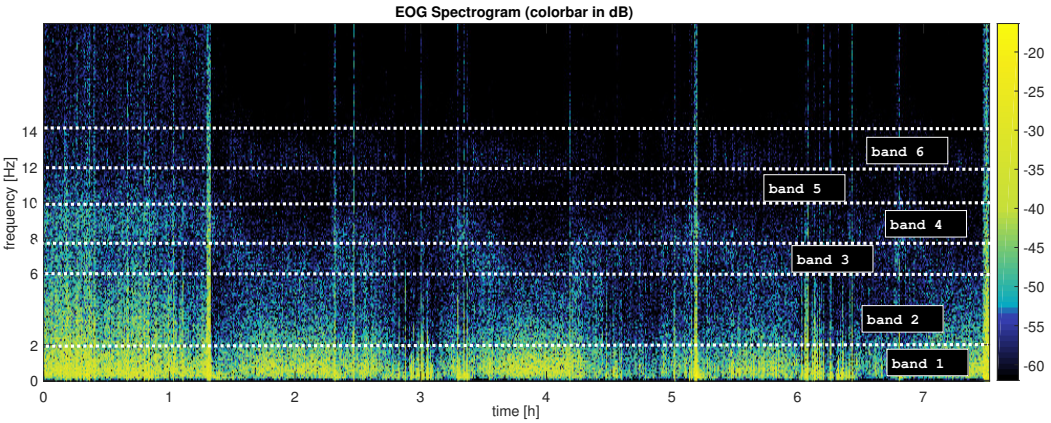


Figure 7.2: EOG Spectrogram for PLM2 recording: Extracted spectral bands

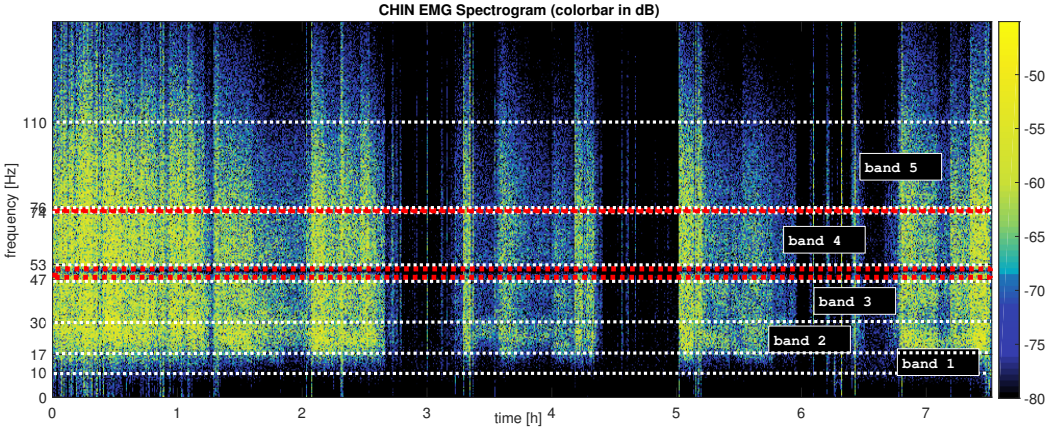


Figure 7.3: Chin EMG Spectrogram for PLM2 recording: Extracted spectral bands

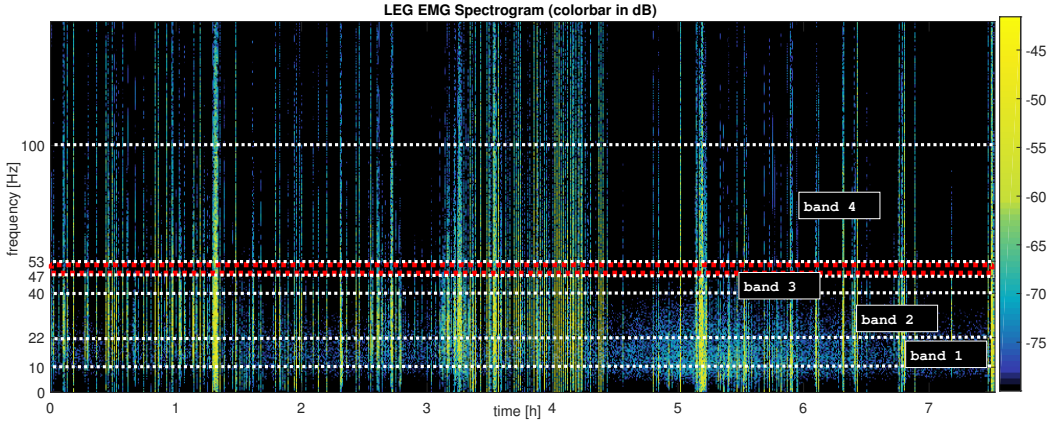


Figure 7.4: Legs EMG Spectrogram for PLM2 recording: Extracted spectral bands

7.2 Time-space features

One of the challenging problems for physiologic data (EEG in particular) feature extraction is that these signals are complex, non-linear, non-stationary, and stochastic. They are considered quasi-stationary only within short intervals. This, among others, was a reason for segmenting the original data.

However, the assumption of smaller segments meet the quasi-stationary requirement holds only during a "normal brain" condition. During any mental or physical activities, changes in alertness and wakefulness, or during eye-blinking, this assumption is no longer valid and the observed signal is non-stationary again. [PTM+14]

As a result, the chosen approaches to extract features from time-domain included both linear statistical measures and non-linear such as entropy. These are defined in the following section.

Originally, additional statistical features including mean, median or kurtosis values were also computed, however, these, based on a visual inspection, did not present enough of a distinctive potential between sleep stages, and therefore were dropped out.

Zero crossing rate. In each segment, the number of zero crossings is computed. The utilization of this feature required the signal to be normalized into a symmetric range around zero (for example -1 to 1) and to have a zero mean value. Both requirements were fulfilled in previous steps (see 6.3.2).

Variance. For a vector x made up of N scalar observations, the variance is defined as

$$V = \frac{1}{N-1}\sum_{i=1}^{N}(x_i - \mu)^2$$

where μ is the mean of x

$$\mu = \frac{1}{N}\sum_{i=1}^{N} x_i$$

RMS. The root-mean-square value of a vector X is defined as

$$X_{\text{RMS}} = \sqrt{\frac{1}{N}\sum_{i=1}^{N}(X_i)^2}$$

Peak to peak value. The difference between the maximum and minimum values are computed for each segment.

Skewness. Skewness is a measure of the asymmetry of the data around the sample mean. If skewness is negative, the data are spread out more to the left of the mean than to the right. If skewness is positive, the data are spread out more to the right. The skewness of the normal distribution (or any perfectly symmetric distribution) would be zero. [MAT16]

Skewness is defined as

$$S = \frac{\frac{1}{N}\sum_{i=1}^{N}(x_i - \mu)^3}{\left(\sqrt{\frac{1}{N}\sum_{i=1}^{N}(x_i - \mu)^2}\right)^3}$$

Shannon information entropy. Entropy is a non-linear measure of complexity and uncertainty and it can be used to study the level of chaos of the system. It is expected to have the potential to reflect how well we can predict the behavior of the system. Basically, higher entropy indicates more complex or chaotic systems, thus, less predictability. [PTM+14]

Shannon entropy for a finite set of variables $X = x_1, x_2, ..., x_m$ is defined as

$$H(X) = -\sum_{i=0}^{m} p(x_i)\ln p(x_i)$$

where $p(x_i)$ is a probability of $x_i \in X$. The signals were partitioned into bins prior to the entropy computation.

All time-domain features described above have been extracted from channels EEG (F4-C4, P4-O2), EOG (ROC-LOC) and EMG (Chin, DX1-DX2, SX1-SX2). For HR (heart rate) channel, only one attribute consisting of a mean value of each segment was extracted.

7.3 Mutual information

In order to evaluate the quality of extracted features, mutual information (MI) parameter was computed. This value measures how much an attribute contributes in order to make the correct classification decision.

It is defined as:

$$MI(A_i, hyp) = H(A_i) + H(hyp) - H(A_i, hyp)$$

where A is a discrete random variable representing values of the attribute i, and hyp is a vector of referential hypnogram scoring. $H(A_i), H(hyp)$ are the respective entropies and $H(A_i, hyp)$ is a joint entropy of A_i and hyp.

Features (attributes), having their MI value higher than the mean of all MI values from the set of features, were considered as "good" attributes and marked green in the respective plots in Section 9.4. On the contrary, those attributes having their MI lower than the mean minus respective standard deviation, were considered as "bad" and marked red. Red attributes should be rejected from further analysis and potential classification since they can significantly worsen the classification performance.

Chapter 8

Classification

The purpose of this chapter was to verify the classification potential of extracted features on real clinical data. The aim was to present a simplified approach that could be applicable in practice. The selected procedure is based on an idea of a semi-automatic classification system, which presents a certain number of signal epochs to the sleep expert to score them. This labeled subset is afterwards used as a training set for a Naive-Bayes classifier.

The whole process consisted of few steps described in more details below.

8.1 Attributes selection

Attributes were selected based on the mutual information criterium computed in Section 7.3. Depending on which recording was being used for the classification task, respective features had been excluded. This can be better understood when seeing results in 9.4. In the end, only disorder-specific green and blue attributes were used.

8.2 Training set selection

The main idea was to present the physician with X segments from each class and then use these as a training set. There were however few issues that needed to be considered before choosing the final approach. No matter how many segments were about to be presented, they needed to be found first. One possibility was, that the physician would find them manually. However, he or she could never know for sure whether all sleep stages were present in the signal, and thus could spend way too much time on searching for such epochs.

Second, when using Bayesian classifier, the relative proportions of classes in the training set should correspond to the respective proportions in the recording which is about to be scored automatically, since this type of classifier operates with prior probabilities. This brings another problem for the physicians, because not only they need to find segments representing unknown number of classes, they also should know their expected proportions, and thus find and score the respective number of epochs.

To overcome these issues, clustering method based on k-means algorithm has been used. The data represented as a set of attributes were segmented into C clusters and a specific number of each cluster representatives (segments), proportional to the cluster size, was chosen randomly as a training set (to be presented for manual scoring).

Therefore there were two parameters needed to be estimated. Number of target clusters C and a scaling factor X specifying how many segments from each cluster should be used for training. Number of training segments from a cluster i was defined as:

$$N(i) = \text{round}\Big(X \cdot \text{size}(i)/\text{size}(s)\Big)$$

where s represents the smallest cluster.

Parameter C was set to have minimal value of 5 (the case when all sleep stages are present). All higher values logically produce more clusters than is the possible number of classes, however, this would only lead to a higher number of segments being presented to the physician.

The dependency of classification accuracies on choice of C and X was visualized in a form of color-mapped matrices in Section 9.6.

8.3 Prediction

Since the data being used in this thesis had the referential sleep scoring already available, no actual sleep expert was necessary in this phase.

Because this thesis was not focused on classification, the theory of Bayesian classifiers has not been covered any further in this text. It is well described in [FK].

Naive-Bayes classifier was trained on modified dataset with attribute values being divided into discrete bins, otherwise the probability of a datapoint, belonging to a

specific class and having one exact set of attribute values, would have been close to zero.

This task have been performed on two whole groups - subjects with no pathology, and narcolepsy patients. In clinical practice, this way of classification would not be useful, however, it has been used here to study the mutual dependency of factors C and X since single recordings had been too short to produce enough outputs.

In the end, the described approach has been applied on few single recordings, in order to simulate "how well" the semi-classification could perform in a real-life (with respect to daily work of sleep experts who analyze the signals) situation. Results are visualized in the according chapter.

8.4 Evaluation

In order to evaluate the classification results and grade the model, the confusion matrix was first created, where TN stands for True Negatives, TP for True Positives, FN for False Negatives and FP for False Positives. Sensitivity (TPR, true positive rate) and specificity (TNR, true negative rate) were computed afterwards.

$$\mathrm{TPR} = \frac{\mathrm{TP}}{\mathrm{TP+FN}}$$

$$\mathrm{TNR} = \frac{\mathrm{TN}}{\mathrm{TN+FP}}$$

The case of sleep stages scoring is a multiclass problem, thus approach "one against all" is used and TPR and TNR are computed for each class separately. TP of C1 (class 1) represents all C1 instances that are classified as C1. TN of C1 is all non-C1 instances that are not classified as C1. FP of C1 is all non-C1 instances that are classified as C1, and finally FN of C1 is all C1 instances that are not classified as C1.

Chapter 9

Results

9.1 Introduction, Data exploration report

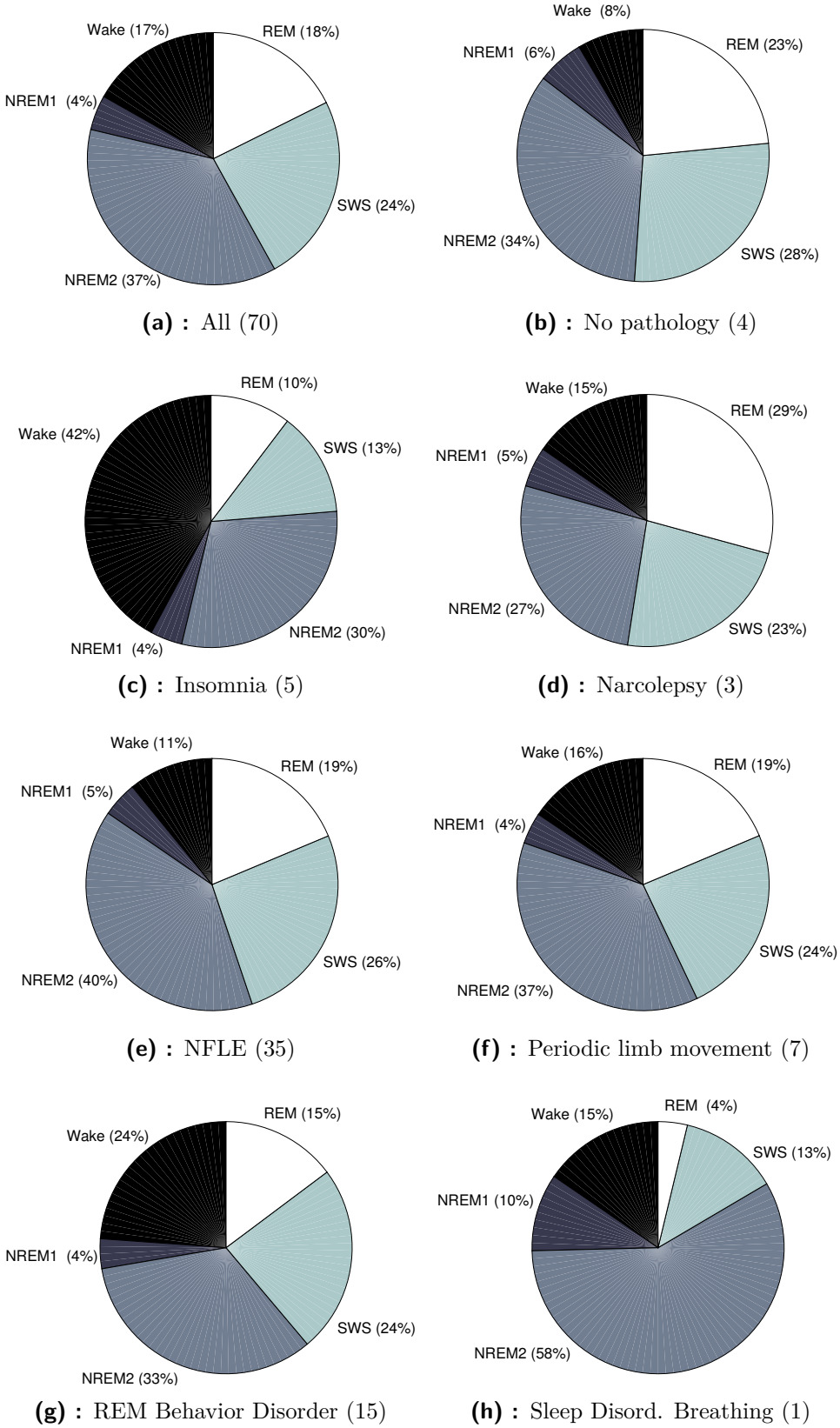
Figure 9.1 shows the relative distribution of sleep stages in different groups of pathologies. Marked differences are visible for example as an increased portion of Wake state in subjects with insomnia, or REM stage in subjects with narcolepsy. Although subfigure (h) shows a significantly higher portion of NREM 2 for sleep disordered breathing (SDB) compared to other groups, this pathology group consisted only of one recording, and therefore these findings were not trustworthy enough. The SDB group was also excluded from further analysis and reporting for the same reason.

The individual figures and statistics have been plotted for each pathology group separately, because merging them would devalue the potential to reveal any hidden patterns specific for the respective sleep disorder.

Section 9.2 contains box plots for main EEG, EOG and EMG spectral bands and their distributions with respect to different sleep stages. Following section 9.3, on the other hand, presents box plots representing the features extracted from time domain. These figures should indicate which features have average values for distinct sleep stages different enough, and thus could be useful for a classification task. The reader should note different y-axis ranges used throughout these plots.

Box plots revealed that most of the attributes contained a high amount of outliers and therefore some smoothing should have been applied. However, the more the feature arrays were smoothed, the more they were loosing their discrimination potential in terms of distinct medians for each class (sleep stage). For this reason, in the phase of box plots generation, the set of features was not smoothed nor altered in any other way.

Intermediate results and findings are stated and discussed below the respective sections.



(a) : All (70)

(b) : No pathology (4)

(c) : Insomnia (5)

(d) : Narcolepsy (3)

(e) : NFLE (35)

(f) : Periodic limb movement (7)

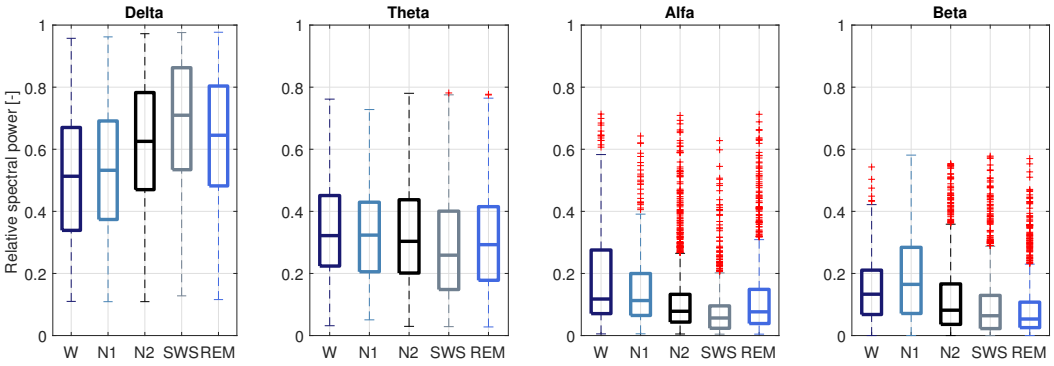
(g) : REM Behavior Disorder (15)

(h) : Sleep Disord. Breathing (1)

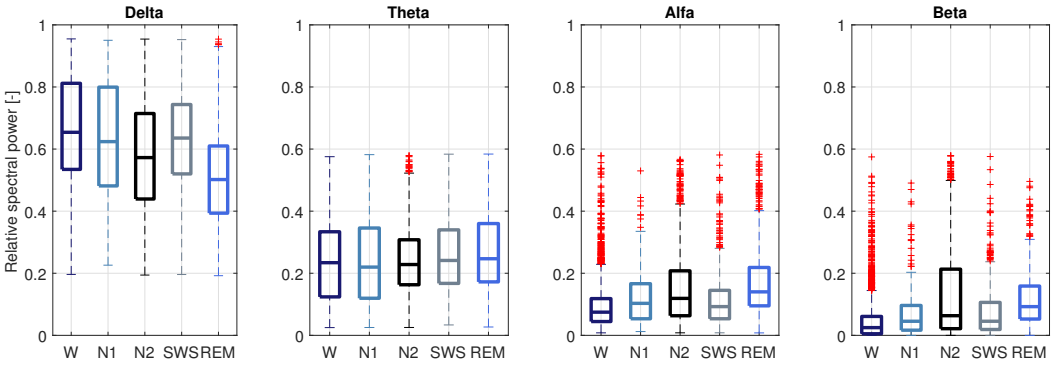
Figure 9.1: Sleep stages distribution for different pathology groups, and respective number of recordings.

9.2 Frequency-domain features

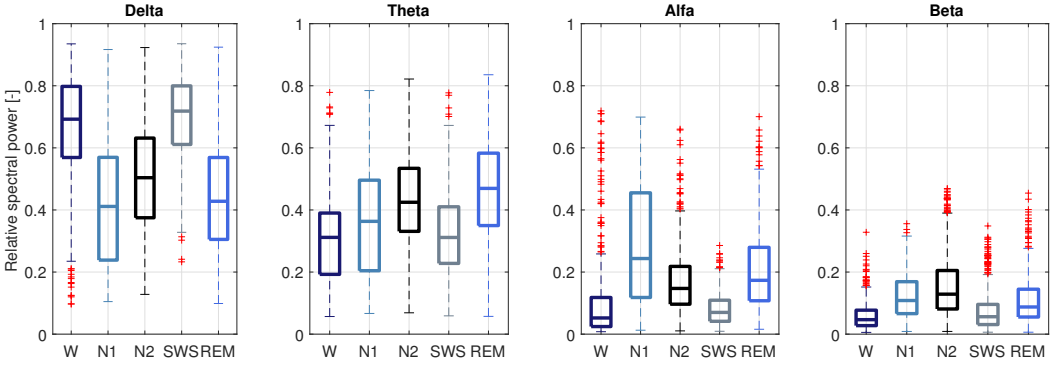
9.2.1 EEG



(a) : No pathology

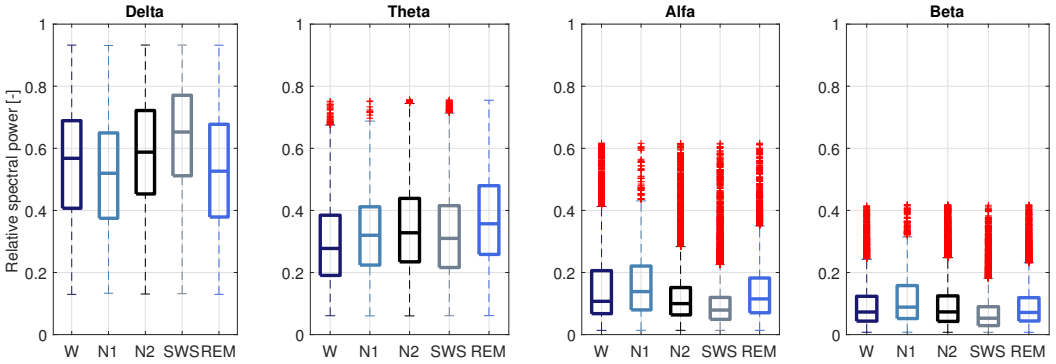


(b) : Insomnia

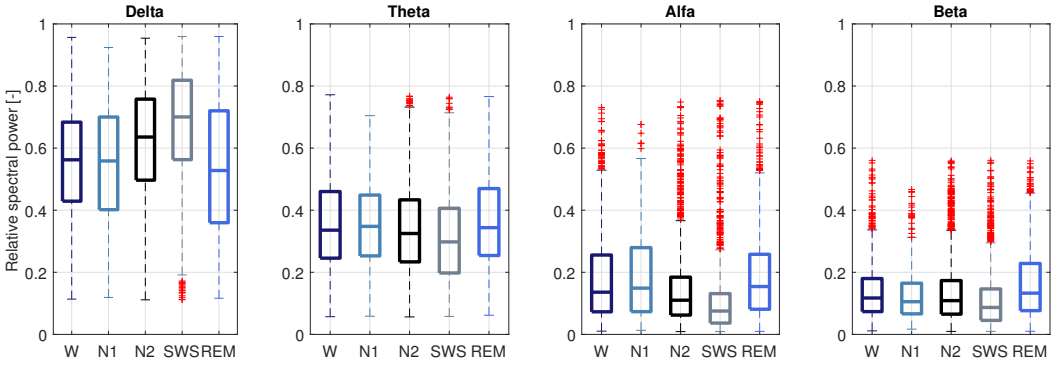


(c) : Narcolepsy

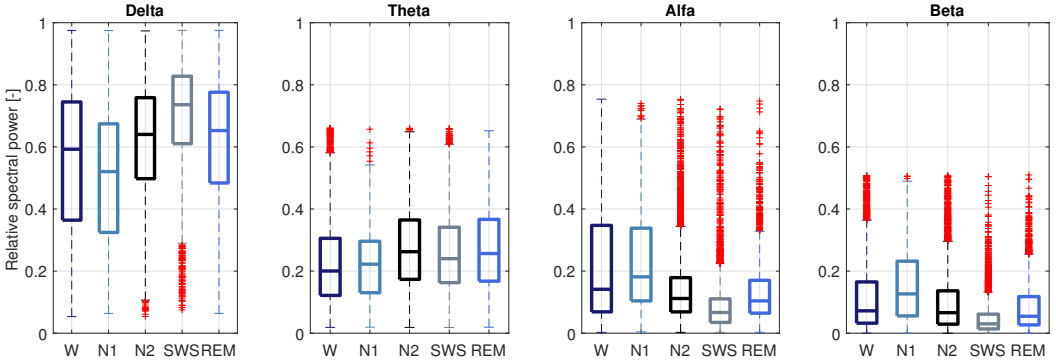
Figure 9.2: EEG relative spectral bands, part 1



(a) : NFLE



(b) : Periodic Limb Movement

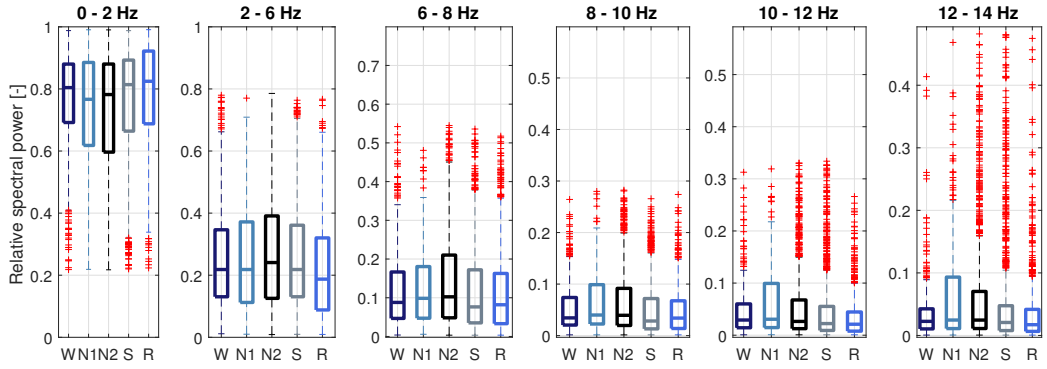


(c) : REM Behavior Disorder

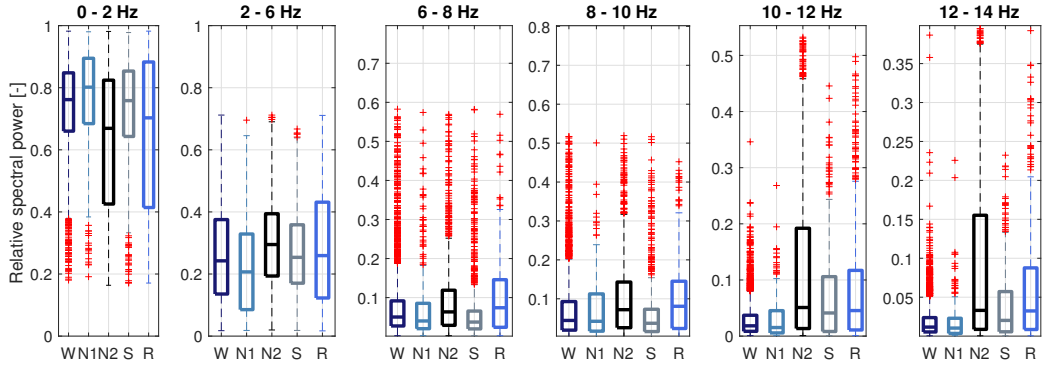
Figure 9.3: EEG relative spectral bands, part 2

Delta and alfa spectral bands seem to have the highest discrimination power. On the other hand, median values of the theta band do not differ very much across different sleep stages.

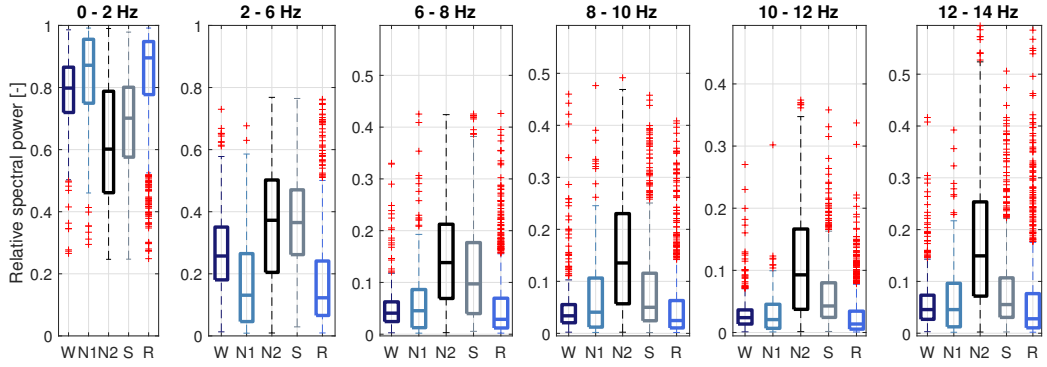
9.2.2 EOG



(a) : No pathology

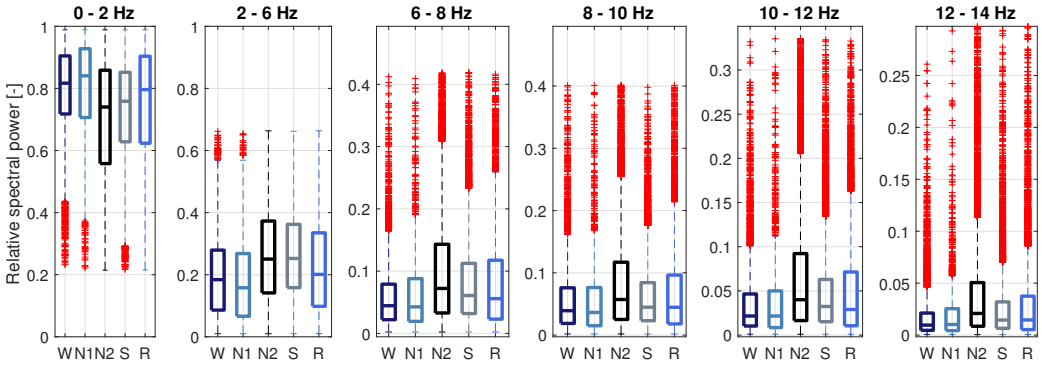


(b) : Insomnia

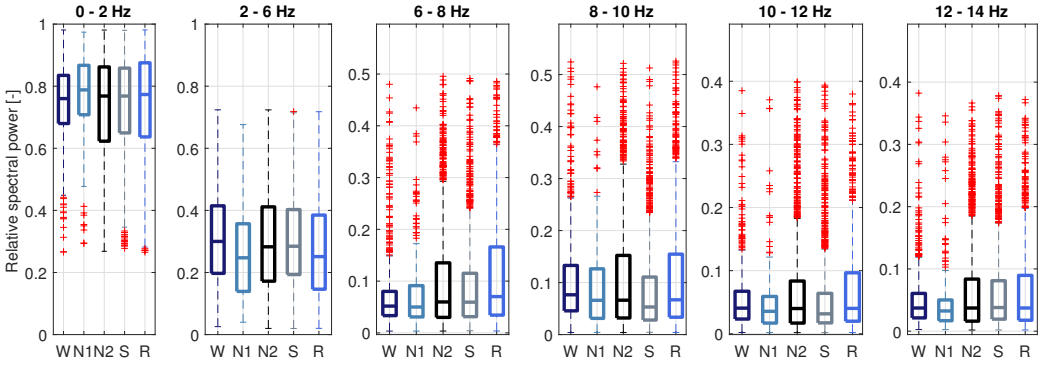


(c) : Narcolepsy

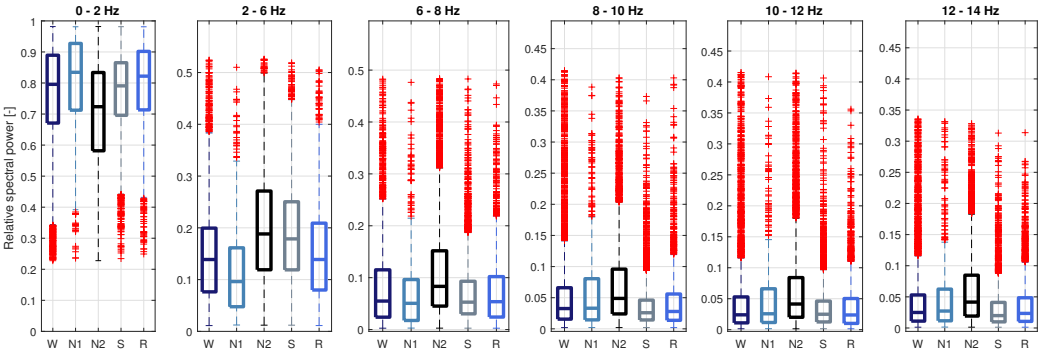
Figure 9.4: EOG relative spectral bands, part 1



(a) : NFLE



(b) : Periodic Limb Movements

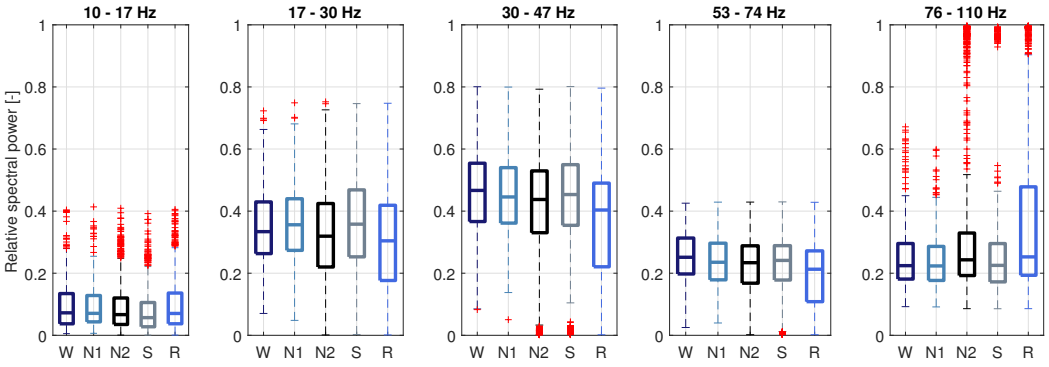


(c) : REM Behavior Disorder

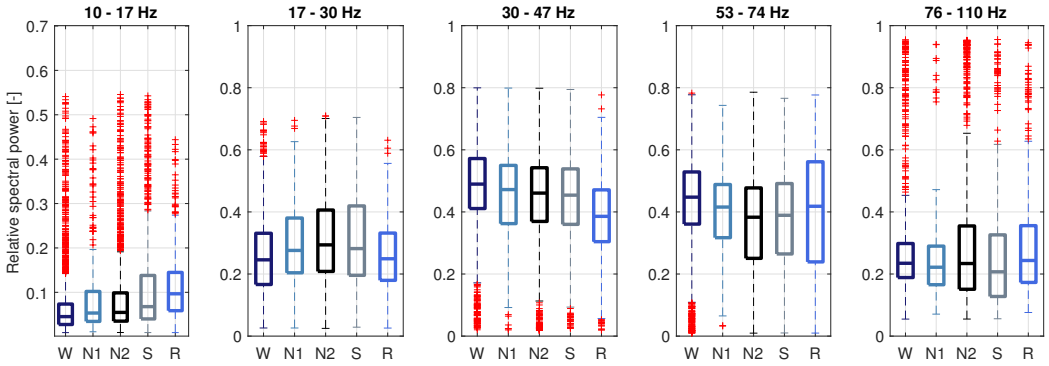
Figure 9.5: EOG relative spectral bands, part 2

Only spectral bands 0.1-2 Hz and 2-6 Hz show reasonable differences between classes. The higher frequencies seem to have too many outliers and possibly consist of noise.

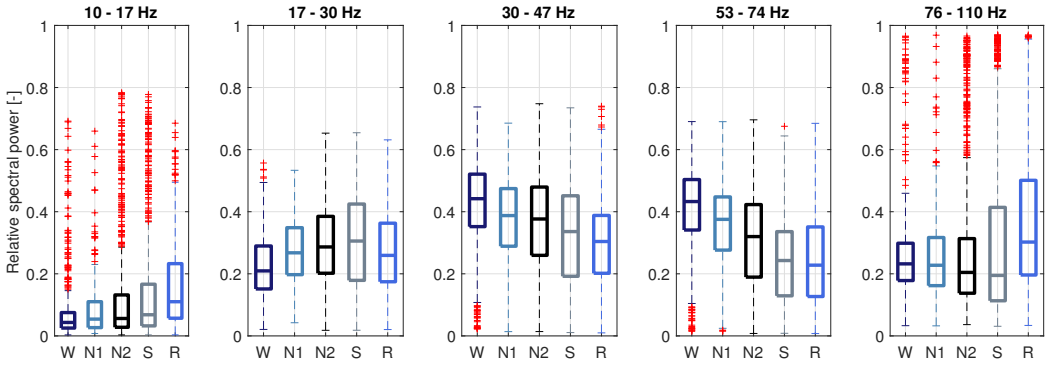
9.2.3 Chin EMG



(a) : No pathology

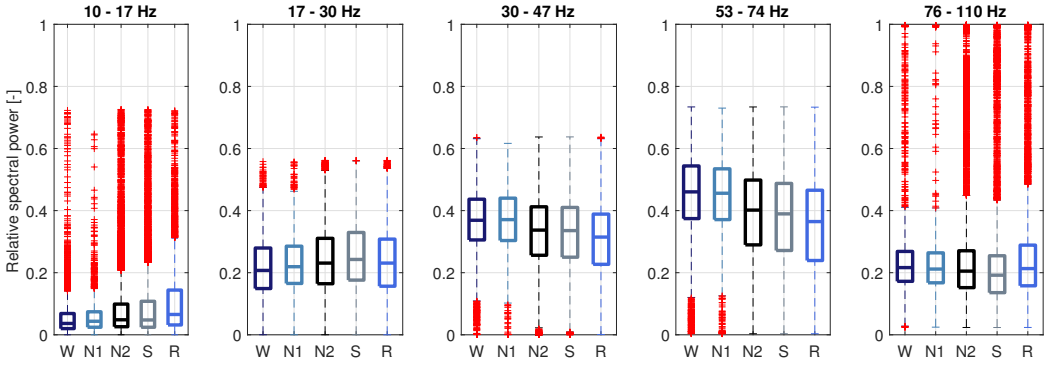


(b) : Insomnia

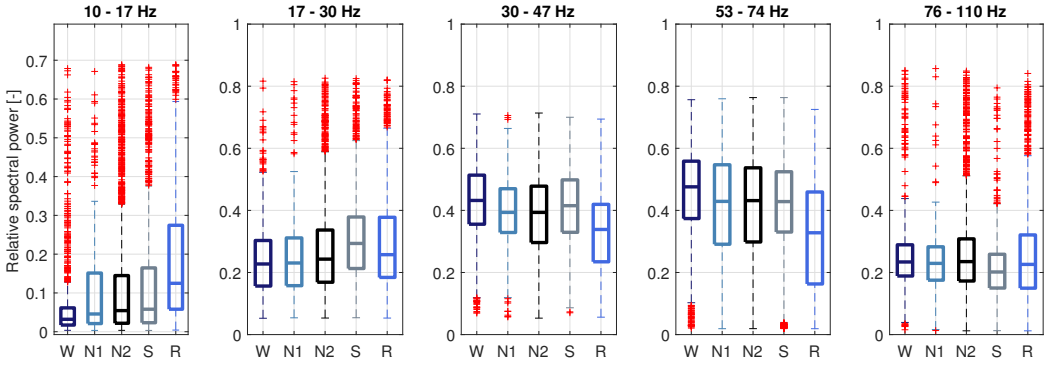


(c) : Narcolepsy

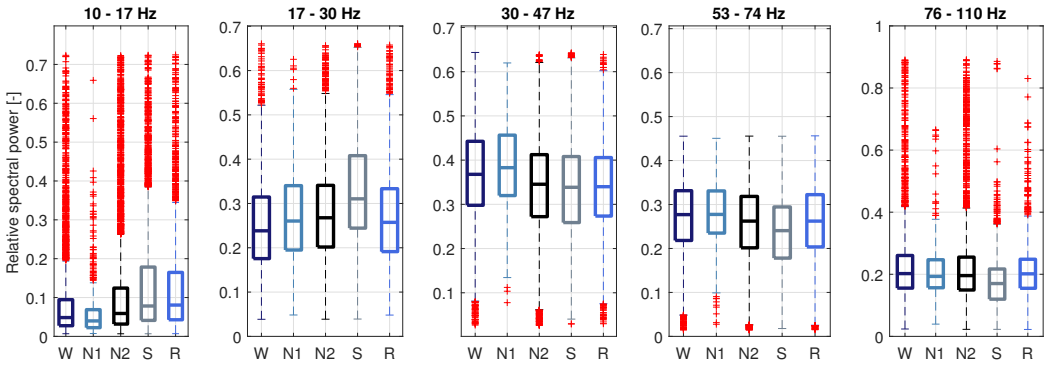
Figure 9.6: Chin EMG relative spectral bands, part 1



(a) : NFLE



(b) : Periodic Limb Movement



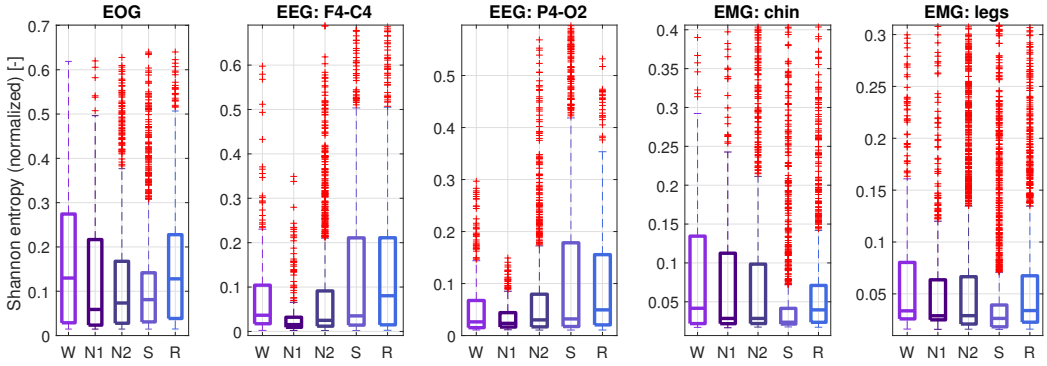
(c) : REM Behavior Disorder

Figure 9.7: Chin EMG relative spectral bands, part 2

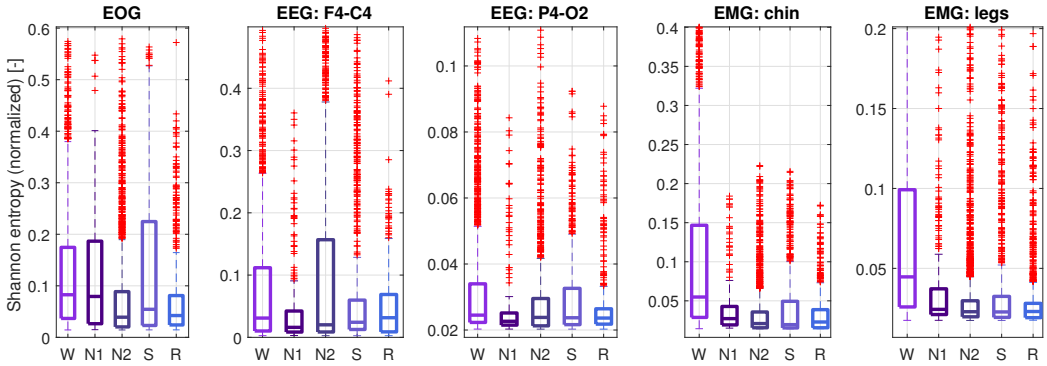
Based on the above plots, bands 10-17 Hz and 76-110 Hz seem to be rather irrelevant for sleep stages scoring.

9.3 Time-domain features

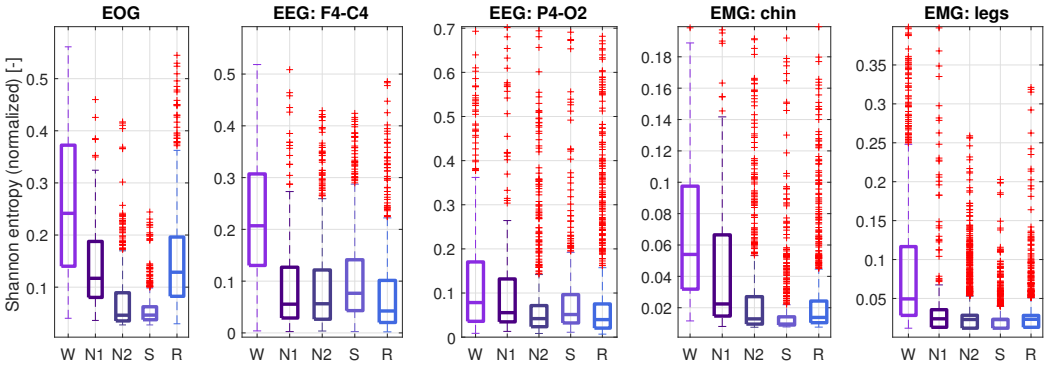
9.3.1 Entropy



(a) : No pathology

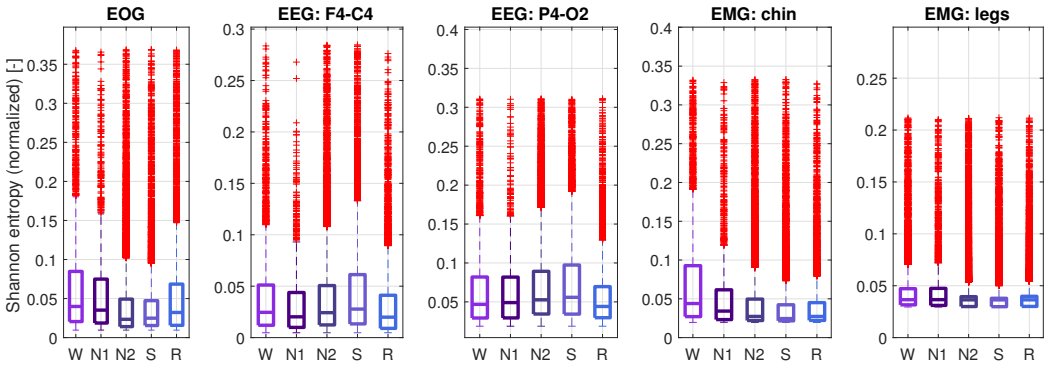


(b) : Insomnia

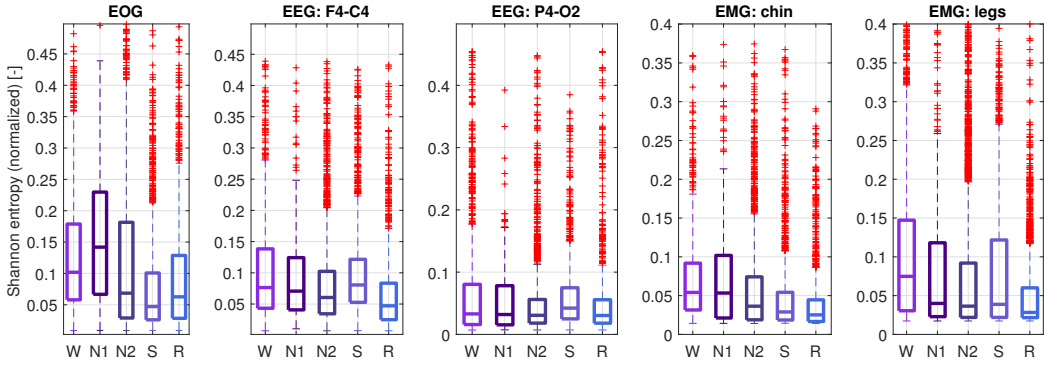


(c) : Narcolepsy

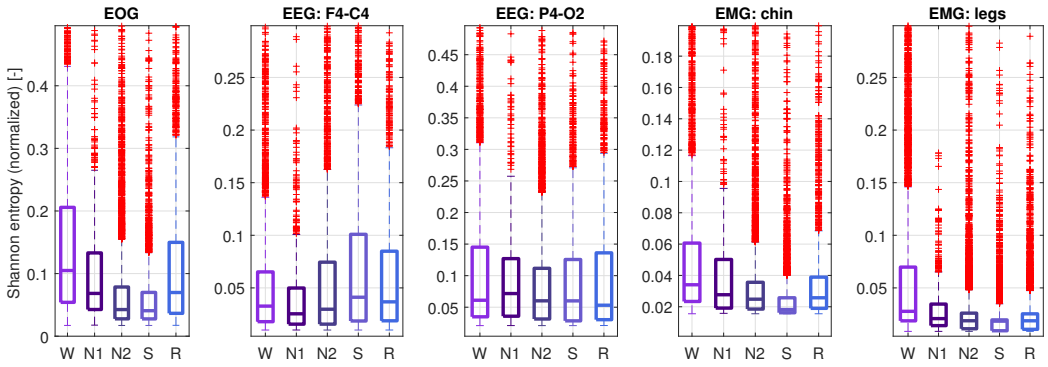
Figure 9.8: Entropy, part 1



(a) : NFLE



(b) : Periodic Limb Movement

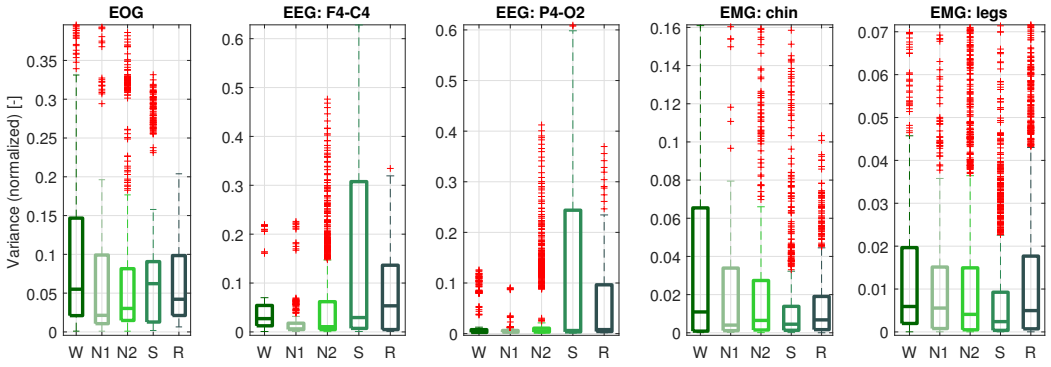


(c) : REM Behavior Disorder

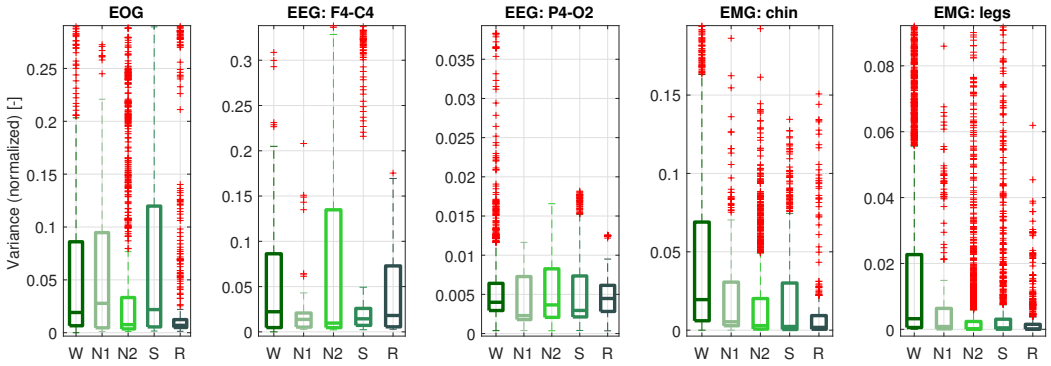
Figure 9.9: Entropy, part 2

Entropy values should be higher when the signal is relatively more chaotic or dominated by higher frequencies. Controversially, when the signal is rather consolidated, the entropy takes its minimum values. However, results show that basically only EOG entropy had any discrimination power.

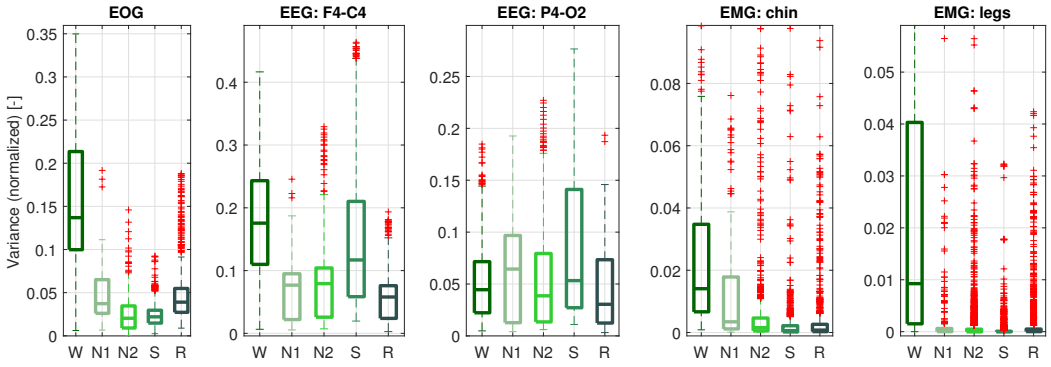
9.3.2 Variance



(a) : No pathology

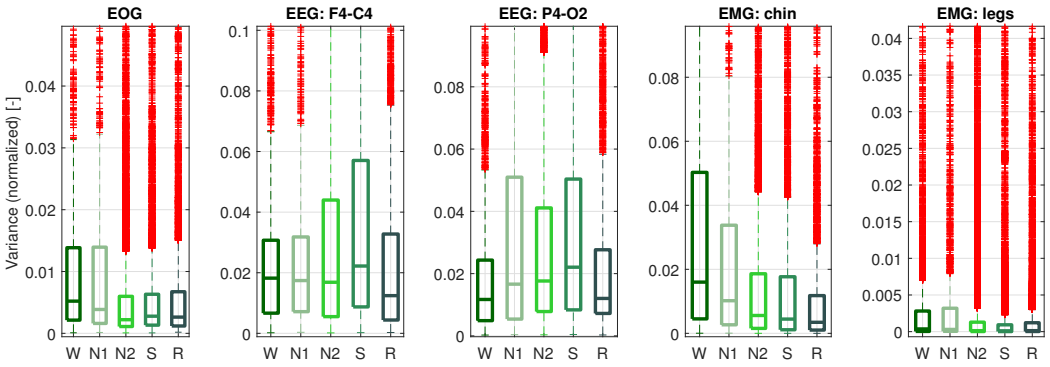


(b) : Insomnia

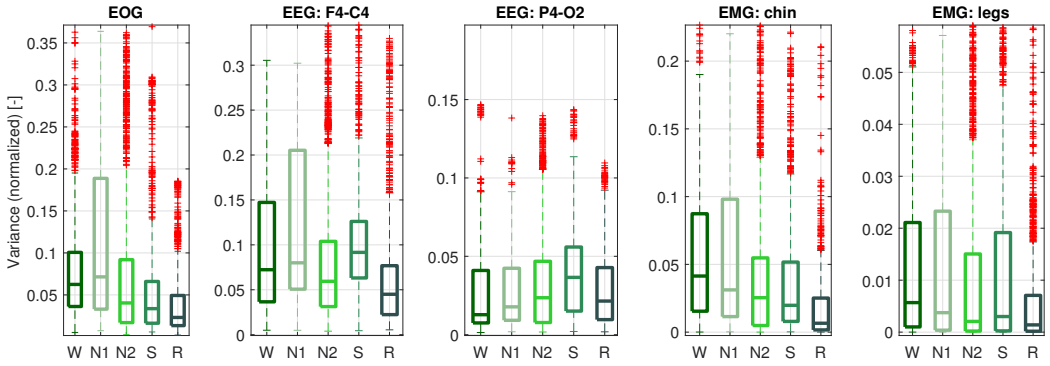


(c) : Narcolepsy

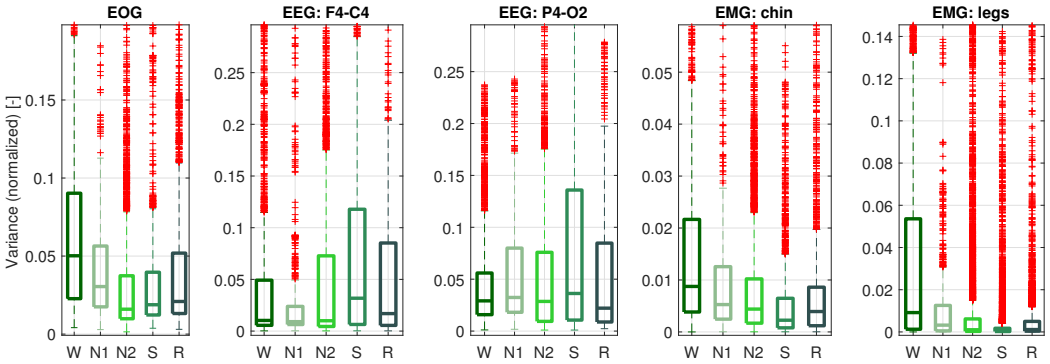
Figure 9.10: Variance, part 1



(a) : NFLE



(b) : Periodic Limb Movement

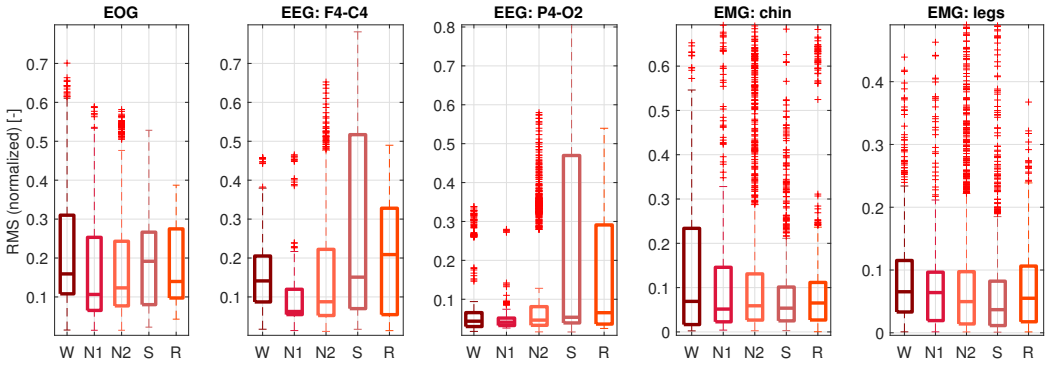


(c) : REM Behavior Disorder

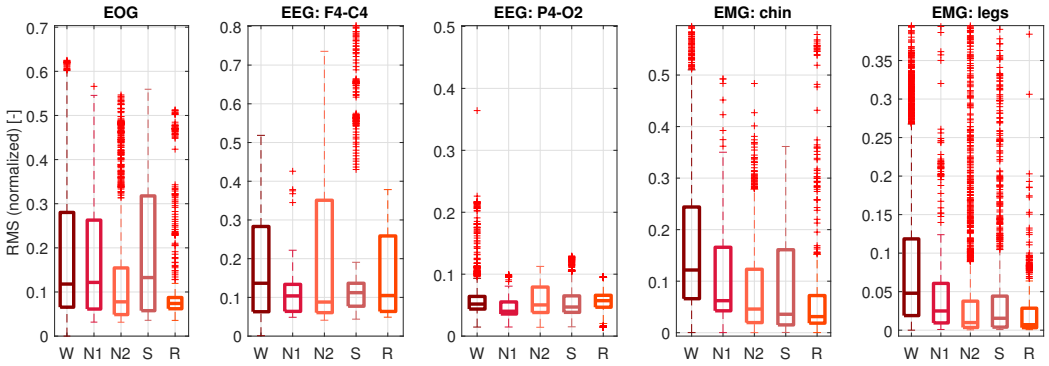
Figure 9.11: Variance, part 2

At first sight, EOG and EEG variance attributes seem to be useful, especially for characterizing wake state and slow wave sleep. Variance of limb EMG is very noisy and except for PLM (periodic limb movements) group shows different (higher) values only during wake state and only for narcolepsy, insomnia and REM behavior disorder groups.

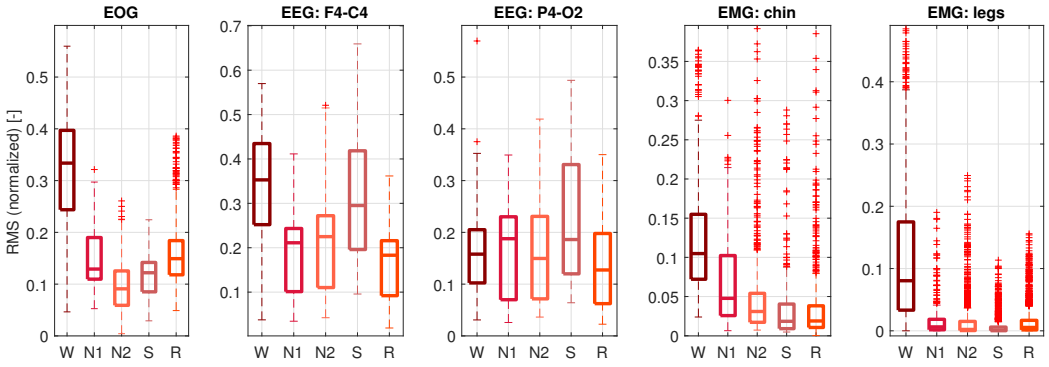
9.3.3 RMS



(a) : No pathology

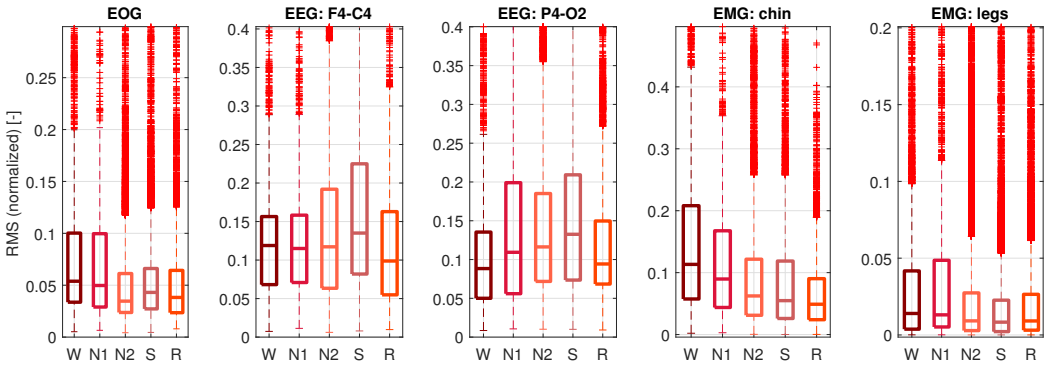


(b) : Insomnia

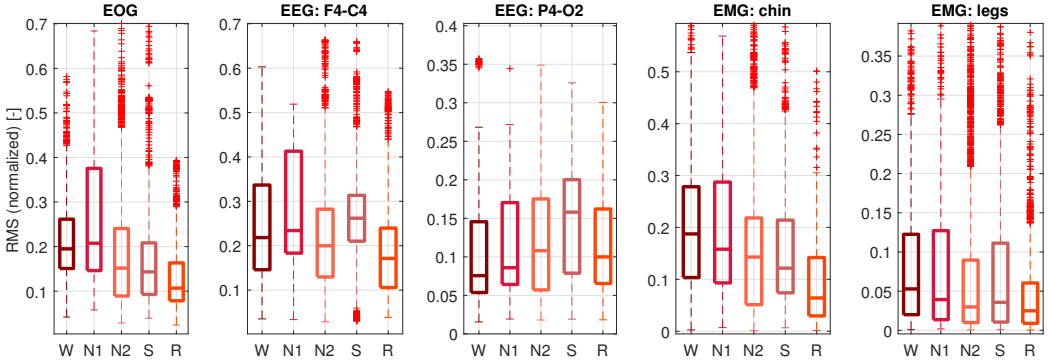


(c) : Narcolepsy

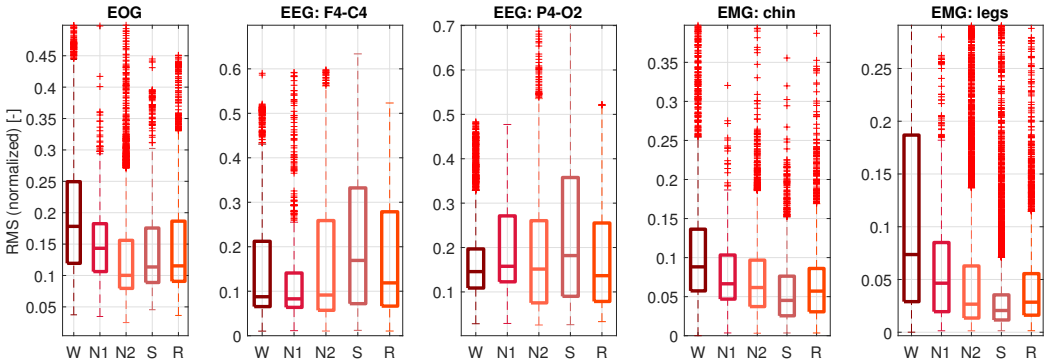
Figure 9.12: RMS, part 1



(a) : NFLE



(b) : Periodic Limb Movement

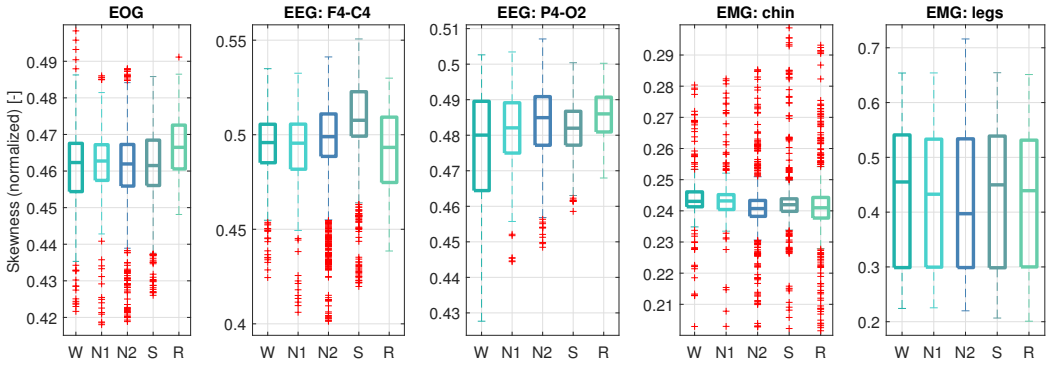


(c) : REM Behavior Disorder

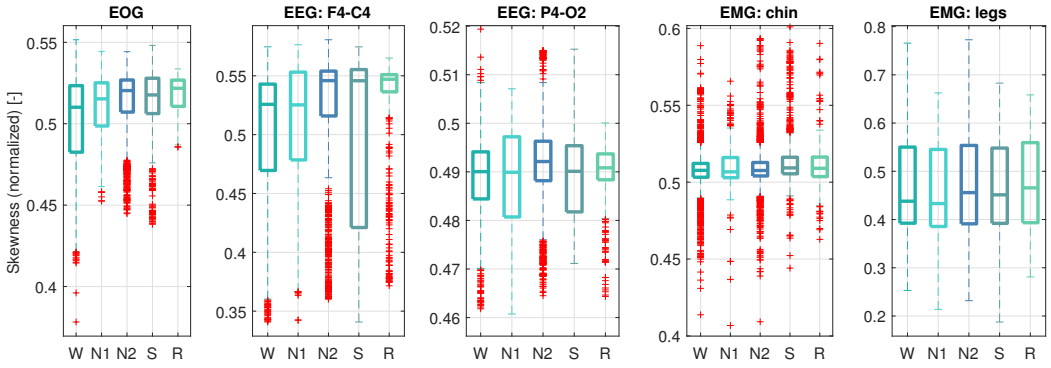
Figure 9.13: RMS, part 2

Again, most of the results for limbs EMG show only very small discrimination power and only for some groups, namely for periodic limb movements and REM behavior disorder. RBD is characterized by lack of muscle atonia during the REM sleep stage. As a result, patients typically act out their dreams. Some level of characteristic patterns in limb EMG leads was, therefore, more or less expected. Other than that, very promising discrimination power yields from both EOG and EEG channels.

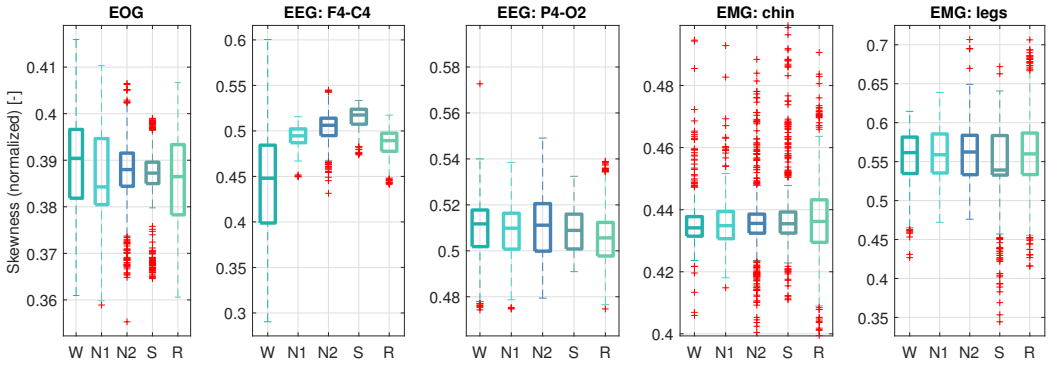
9.3.4 Skewness



(a) : No pathology

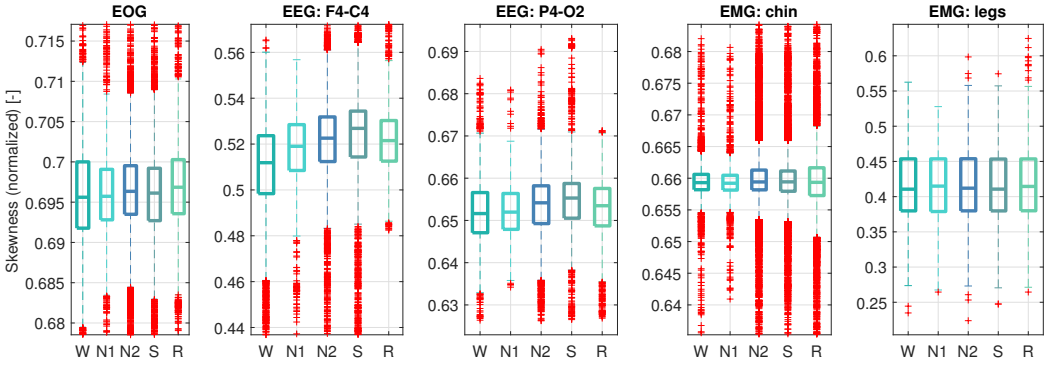


(b) : Insomnia

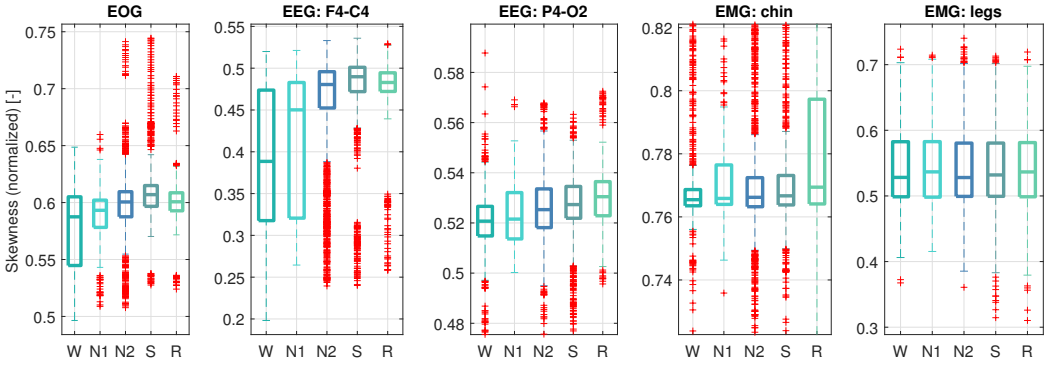


(c) : Narcolepsy

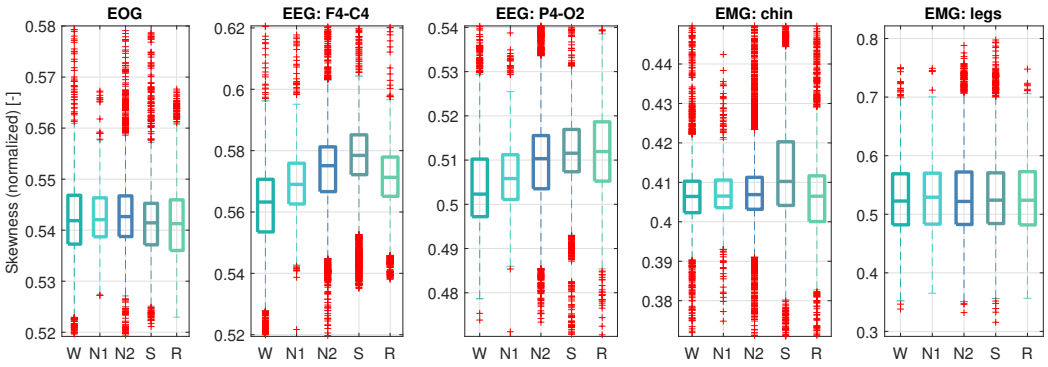
Figure 9.14: Skewness, part 1



(a) : NFLE



(b) : Periodic Limb Movement



(c) : REM Behavior Disorder

Figure 9.15: Skewness, part 2

Skewness seem to have a very poor discrimination potential in all but EEG leads. Especially EMG leads show no discrimination power whatsoever.

9.3.5 Heart rate

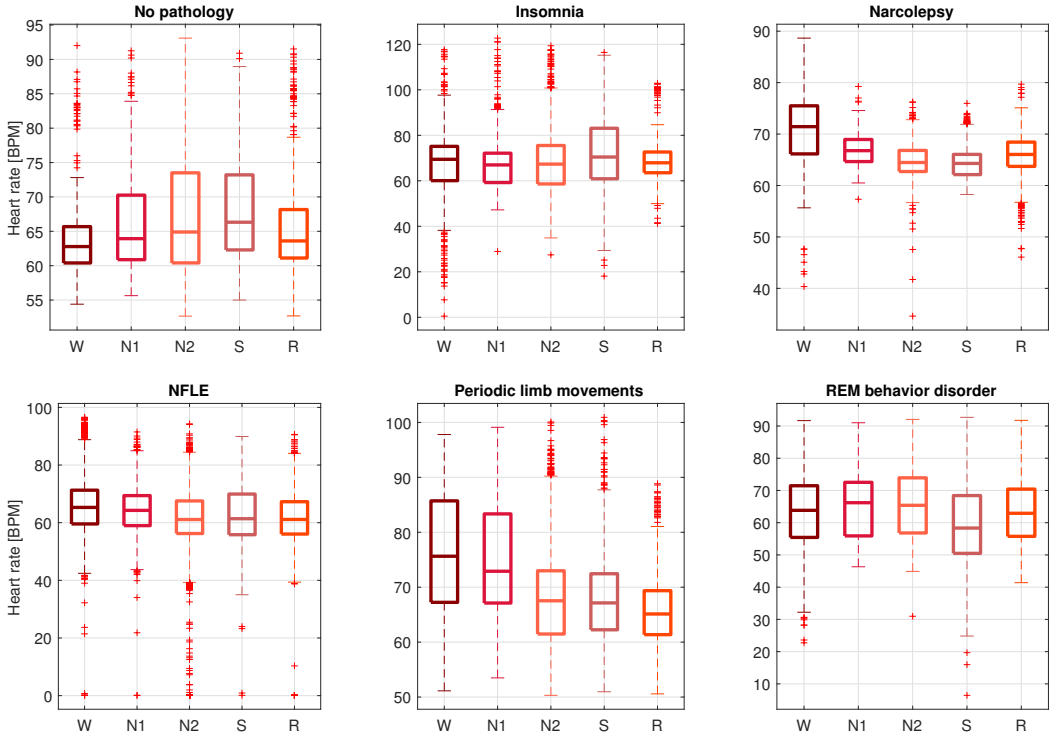


Figure 9.16: Heart rate

There are obvious differences in heart rate across different sleep stages. This finding is also consistent with facts learned within the literature review.

9.4 Mutual information

The resulting mutual information between different features and referential scoring was visualized in a form of stem plots shown below. The coloring represents the relative quality of each attribute, as it has been described in 7.3. The horizontal lines stand for the computed thresholds. The set of features was first smoothed in order to optimize the results. The final values, as well as attributes type (instead of plain numbers-encoding), are summarized in Table 9.1.

Section 9.5 then shows examples where the "best" attributes were plotted against the referential hypnograms.

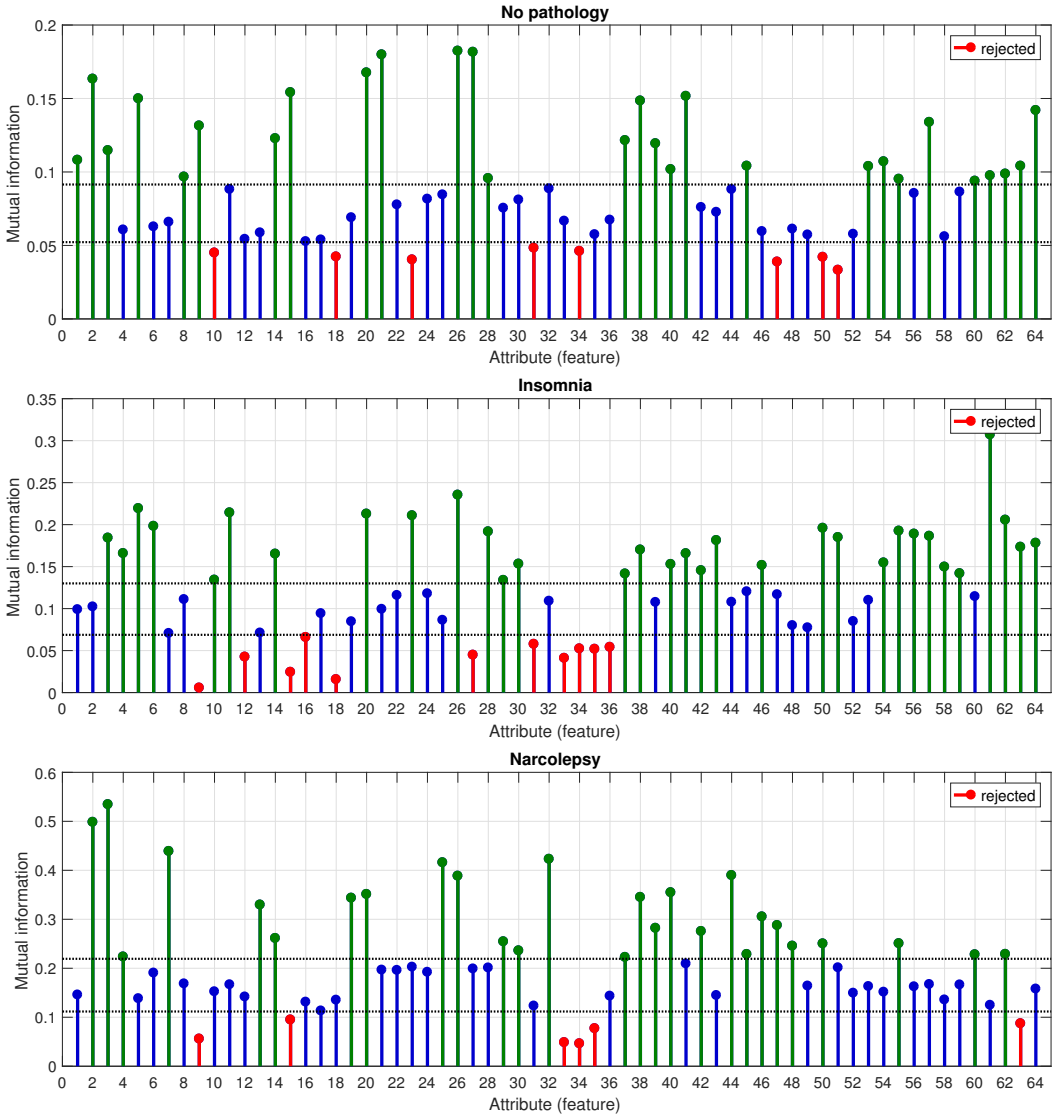


Figure 9.17: Mutual information, part 1

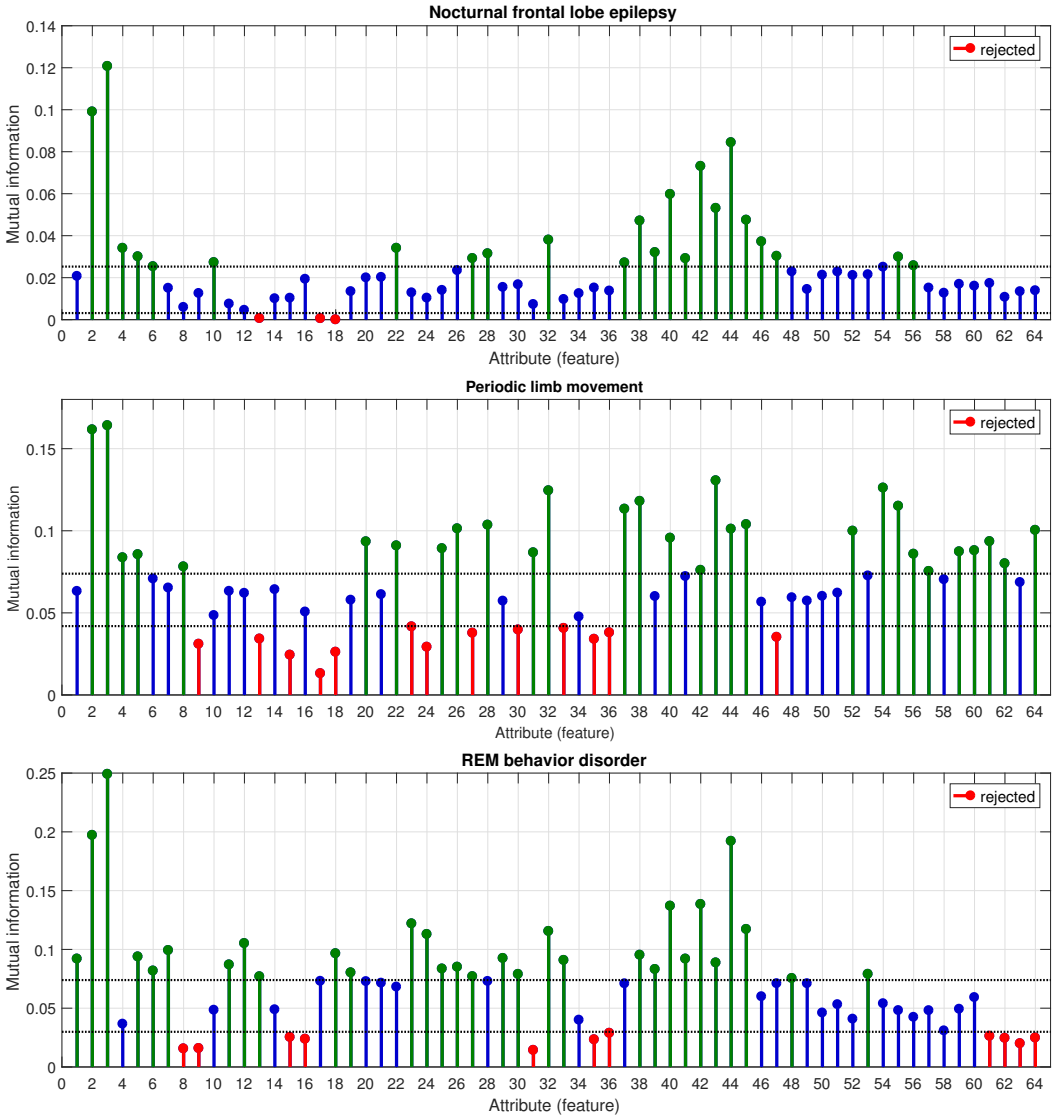


Figure 9.18: Mutual information, part 2

In the end, it was shown, that only zerocrossing rate of EEG, heart rate, delta/alfa frequency bands and chin EMG band of 53-74 Hz were considered as "good" attributes for all studied groups. On the other hand, the thresholds for determining whether an attribute was good or bad were different for each group. Because of that, it would be most correct to state, that different groups require different set of features in order to maximize the total mutual information between those attributes and class-scoring.

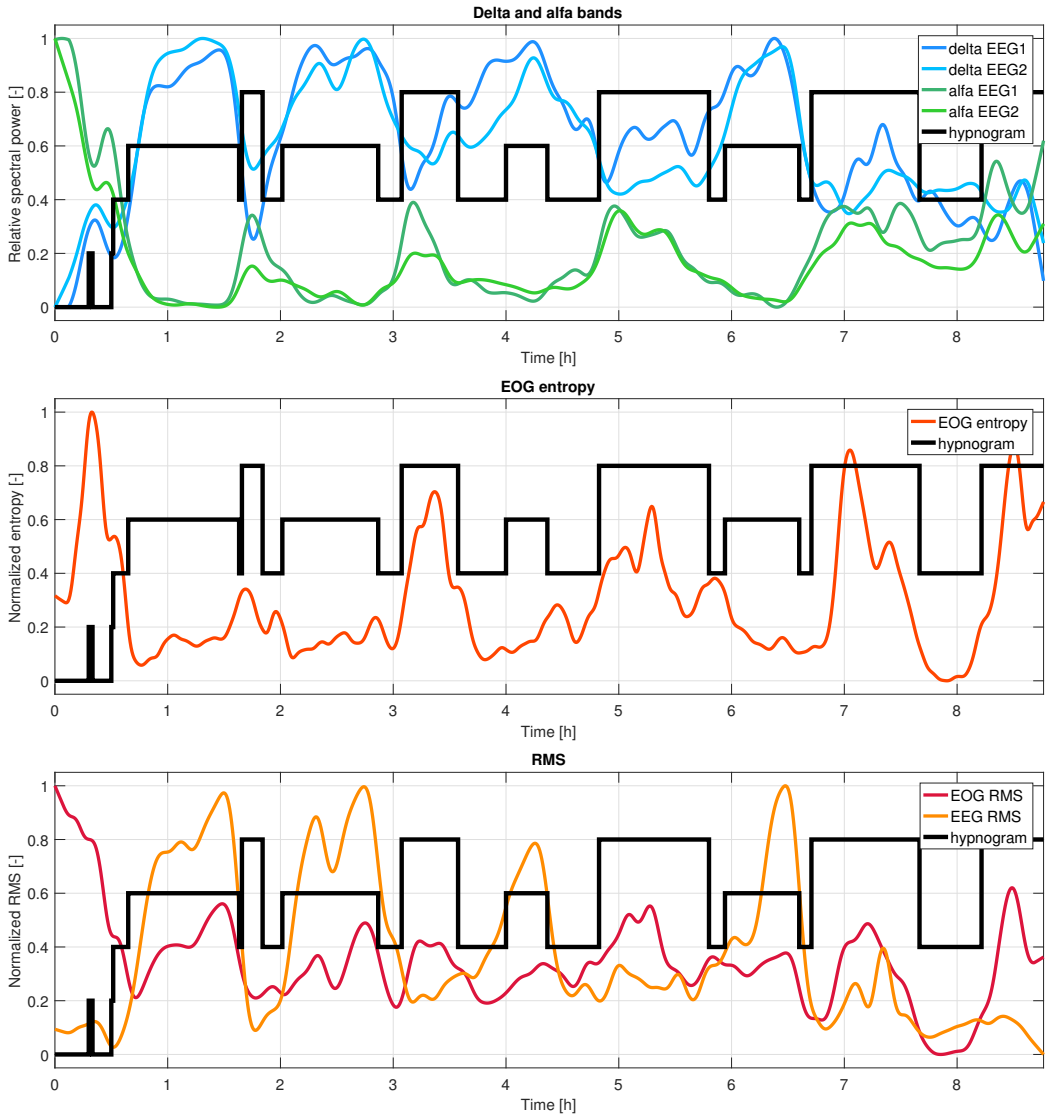
number	channel	type	No pathology	Insomnia	Narcolepsy	NFLE	PLM	RBD
1	EOG	*zerocross*	0,11	0,10	0,15	0,02	0,06	0,09
2	EEG1	*zerocross*	0,16	0,10	0,50	0,10	0,16	0,20
3	EEG2	*zerocross*	0,11	0,18	0,53	0,12	0,16	0,25
4	CHIN	*zerocross*	0,06	0,17	0,22	0,03	0,08	0,04
5	RLEG	*zerocross*	0,15	0,22	0,14	0,03	0,09	0,09
6	LLEG	*zerocross*	0,06	0,20	0,19	0,03	0,07	0,08
7	EOG	*entropy*	0,07	0,07	0,44	0,02	0,07	0,10
8	EEG1	*entropy*	0,10	0,11	0,17	0,01	0,08	0,02
9	EEG2	*entropy*	0,13	0,01	0,06	0,01	0,03	0,02
10	CHIN	*entropy*	0,04	0,13	0,15	0,03	0,05	0,05
11	RLEG	*entropy*	0,09	0,21	0,17	0,01	0,06	0,09
12	LLEG	*entropy*	0,05	0,04	0,14	0,00	0,06	0,11
13	EOG	*variance*	0,06	0,07	0,33	0,00	0,03	0,08
14	EEG1	*variance*	0,12	0,17	0,26	0,01	0,06	0,05
15	EEG2	*variance*	0,15	0,02	0,09	0,01	0,02	0,03
16	CHIN	*variance*	0,05	0,07	0,13	0,02	0,05	0,02
17	RLEG	*variance*	0,05	0,09	0,11	0,00	0,01	0,07
18	LLEG	*variance*	0,04	0,02	0,14	0,00	0,03	0,10
19	EOG	*RMS*	0,07	0,08	0,34	0,01	0,06	0,08
20	EEG1	*RMS*	0,17	0,21	0,35	0,02	0,09	0,07
21	EEG2	*RMS*	0,18	0,10	0,20	0,02	0,06	0,07
22	CHIN	*RMS*	0,08	0,12	0,20	0,03	0,09	0,07
23	RLEG	*RMS*	0,04	0,21	0,20	0,01	0,04	0,12
24	LLEG	*RMS*	0,08	0,12	0,19	0,01	0,03	0,11
25	EOG	*peak2peak*	0,08	0,09	0,42	0,01	0,09	0,08
26	EEG1	*peak2peak*	0,18	0,24	0,39	0,02	0,10	0,09
27	EEG2	*peak2peak*	0,18	0,04	0,20	0,03	0,04	0,08
28	CHIN	*peak2peak*	0,10	0,19	0,20	0,03	0,10	0,07
29	RLEG	*peak2peak*	0,08	0,13	0,25	0,02	0,06	0,09
30	LLEG	*peak2peak*	0,08	0,15	0,24	0,02	0,04	0,08
31	EOG	*skewness*	0,05	0,06	0,12	0,01	0,09	0,01
32	EEG1	*skewness*	0,09	0,11	0,42	0,04	0,12	0,12
33	EEG2	*skewness*	0,07	0,04	0,05	0,01	0,04	0,09
34	CHIN	*skewness*	0,05	0,05	0,05	0,01	0,05	0,04
35	RLEG	*skewness*	0,06	0,05	0,08	0,02	0,03	0,02
36	LLEG	*skewness*	0,07	0,05	0,14	0,01	0,04	0,03
37	HR	*mean*	0,12	0,14	0,22	0,03	0,11	0,07
38	EEG1	*delta*	0,15	0,17	0,35	0,05	0,12	0,10
39	EEG1	*theta*	0,12	0,11	0,28	0,03	0,06	0,08
40	EEG1	*alfa*	0,10	0,15	0,35	0,06	0,10	0,14
41	EEG1	*beta*	0,15	0,17	0,21	0,03	0,07	0,09
42	EEG2	*delta*	0,08	0,15	0,28	0,07	0,08	0,14
43	EEG2	*theta*	0,07	0,18	0,14	0,05	0,13	0,09
44	EEG2	*alfa*	0,09	0,11	0,39	0,08	0,10	0,19
45	EEG2	*beta*	0,10	0,12	0,23	0,05	0,10	0,12
46	EOG	*0.1 - 2 Hz*	0,06	0,15	0,31	0,04	0,06	0,06
47	EOG	*2 - 6 Hz*	0,04	0,12	0,29	0,03	0,04	0,07
48	EOG	*6 - 8 Hz*	0,06	0,08	0,25	0,02	0,06	0,08
49	EOG	*8 - 10 Hz*	0,06	0,08	0,16	0,01	0,06	0,07
50	EOG	*10 - 12 Hz*	0,04	0,20	0,25	0,02	0,06	0,05
51	EOG	*12 - 14 Hz*	0,03	0,18	0,20	0,02	0,06	0,05
52	CHIN	*10 - 17 Hz*	0,06	0,08	0,15	0,02	0,10	0,04
53	CHIN	*17 - 30 Hz*	0,10	0,11	0,16	0,02	0,07	0,08
54	CHIN	*30 - 47 Hz*	0,11	0,15	0,15	0,03	0,13	0,05
55	CHIN	*53 - 74 Hz*	0,10	0,19	0,25	0,03	0,12	0,05
56	CHIN	*76 - 110 Hz*	0,09	0,19	0,16	0,03	0,09	0,04
57	RLEG	*10 - 22 Hz*	0,13	0,19	0,17	0,02	0,08	0,05
58	RLEG	*22 - 40 Hz*	0,06	0,15	0,14	0,01	0,07	0,03
59	RLEG	*40 - 47 Hz*	0,09	0,14	0,17	0,02	0,09	0,05
60	RLEG	*53 - 100 Hz*	0,09	0,11	0,23	0,02	0,09	0,06
61	LLEG	*10 - 22 Hz*	0,10	0,31	0,12	0,02	0,09	0,03
62	LLEG	*22 - 40 Hz*	0,10	0,21	0,23	0,01	0,08	0,02
63	LLEG	*40 - 47 Hz*	0,10	0,17	0,09	0,01	0,07	0,02
64	LLEG	*53 - 100 Hz*	0,14	0,18	0,16	0,01	0,10	0,02

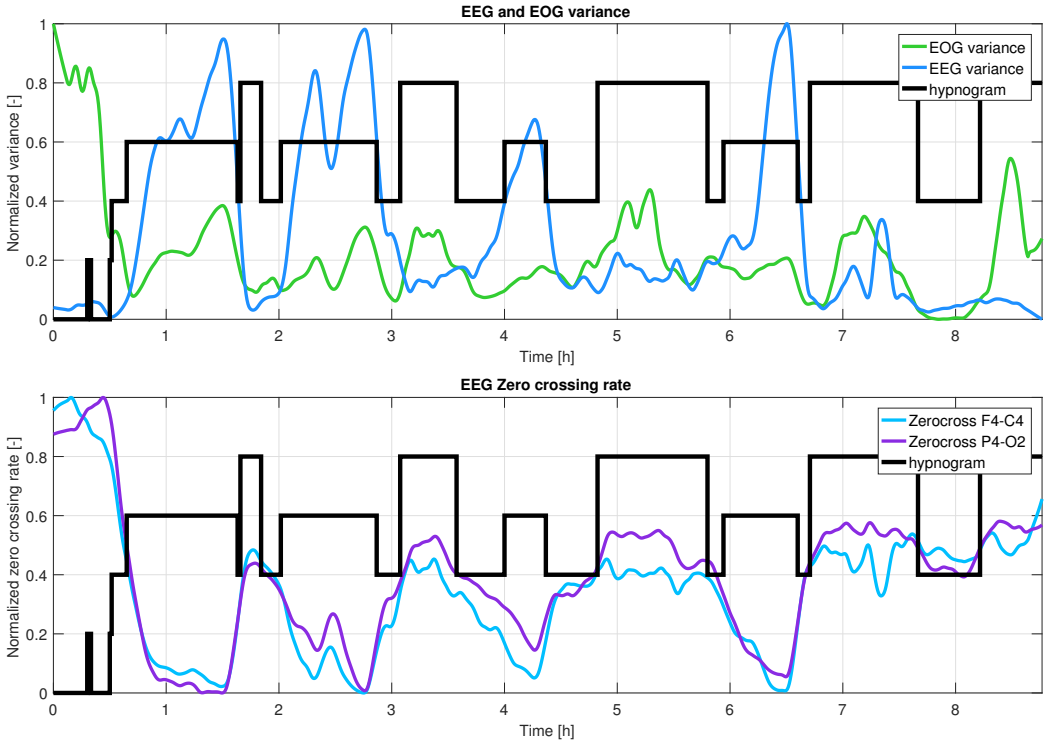
Table 9.1: Values of mutual information between the referential scoring and set of attributes

9.5 Attribute visualization examples

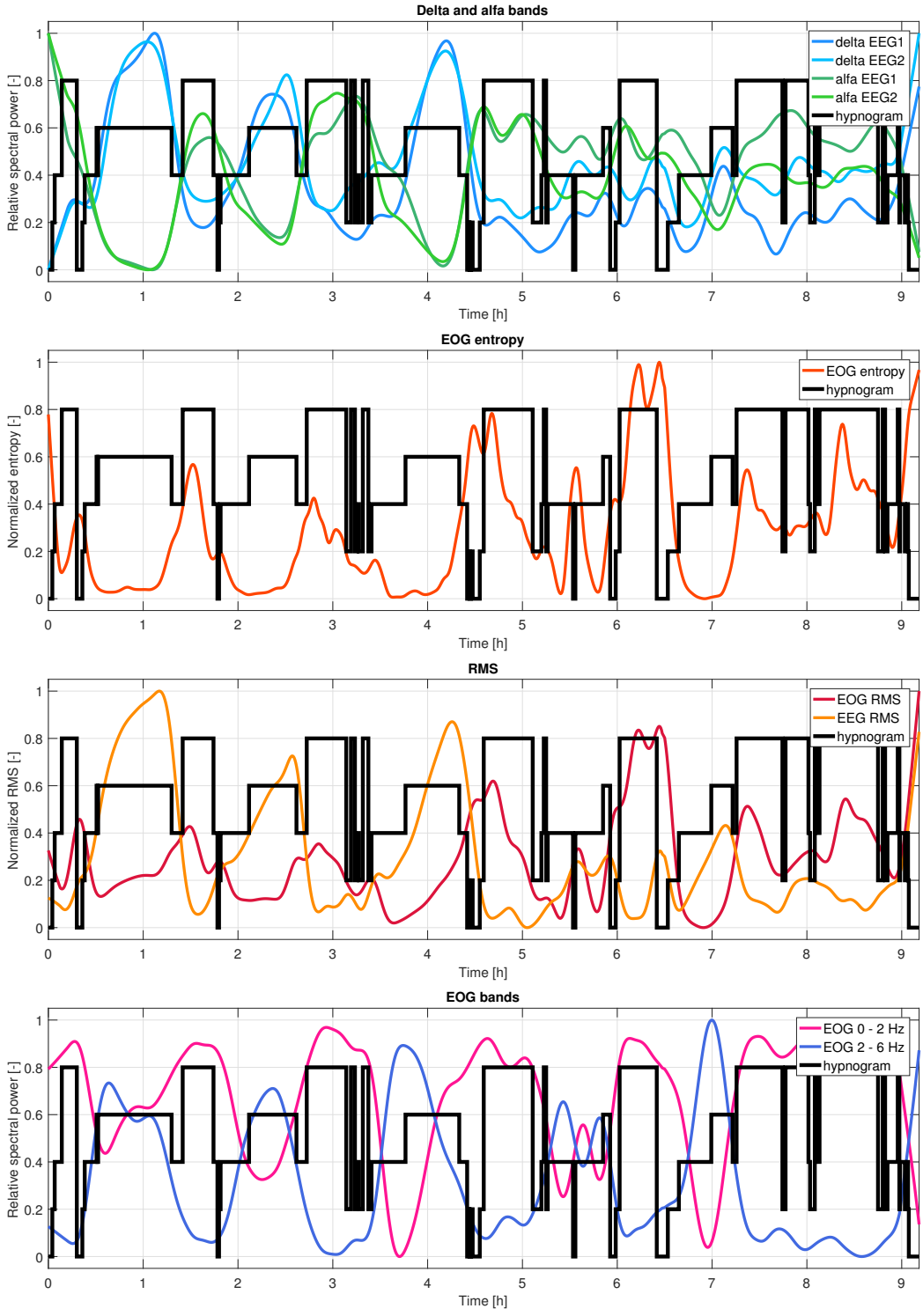
This section contains figures showing the selected attributes plotted against the referential scoring. The attributes were smoothed prior to the plotting (the same smoothed set used for the mutual information computation was the base for the following plots).

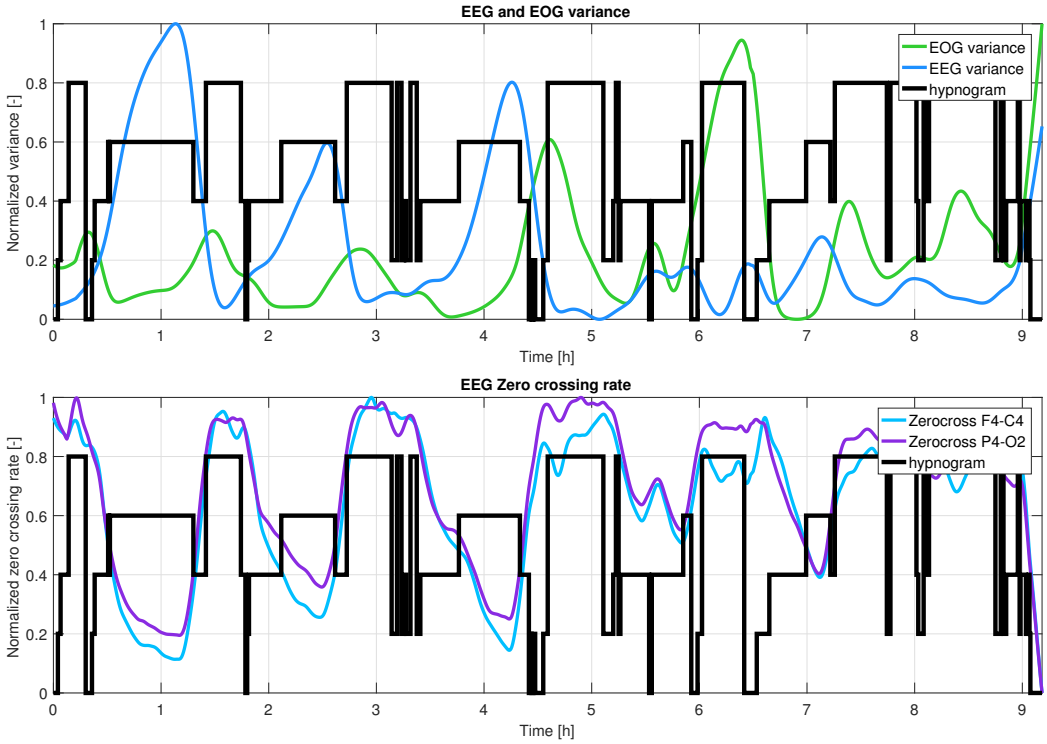
9.5.1 Healthy subject




EEG and EOG variance
EOG variance
EEG variance
hypnogram
Normalized variance [-]
Time [h]
EEG Zero crossing rate
Zerocross F4-C4
Zerocross P4-O2
hypnogram
Normalized zero crossing rate [-]
Time [h]

9.5.2 Patient with narcolepsy




EEG and EOG variance
EOG variance
EEG variance
hypnogram
Normalized variance [-]
Time [h]
EEG Zero crossing rate
Zerocross F4-C4
Zerocross P4-O2
hypnogram
Normalized zero crossing rate [-]
Time [h]

9.6 Classification potential

Below, there are figures showing the dependency of parameters C (number of clusters generated in the phase of training set selection) and X (a factor influencing the final number of segments used for training). Examples of only two disorder groups are shown.

As expected, the classification accuracy increases along with the factors C and X.

Section 9.6.1 presents examples of the classification task applied on single recordings. Both C and X parameters are always stated in the respective table, as well as the count of segments presented to the physician for manual scoring, and subsequently used as a training set.

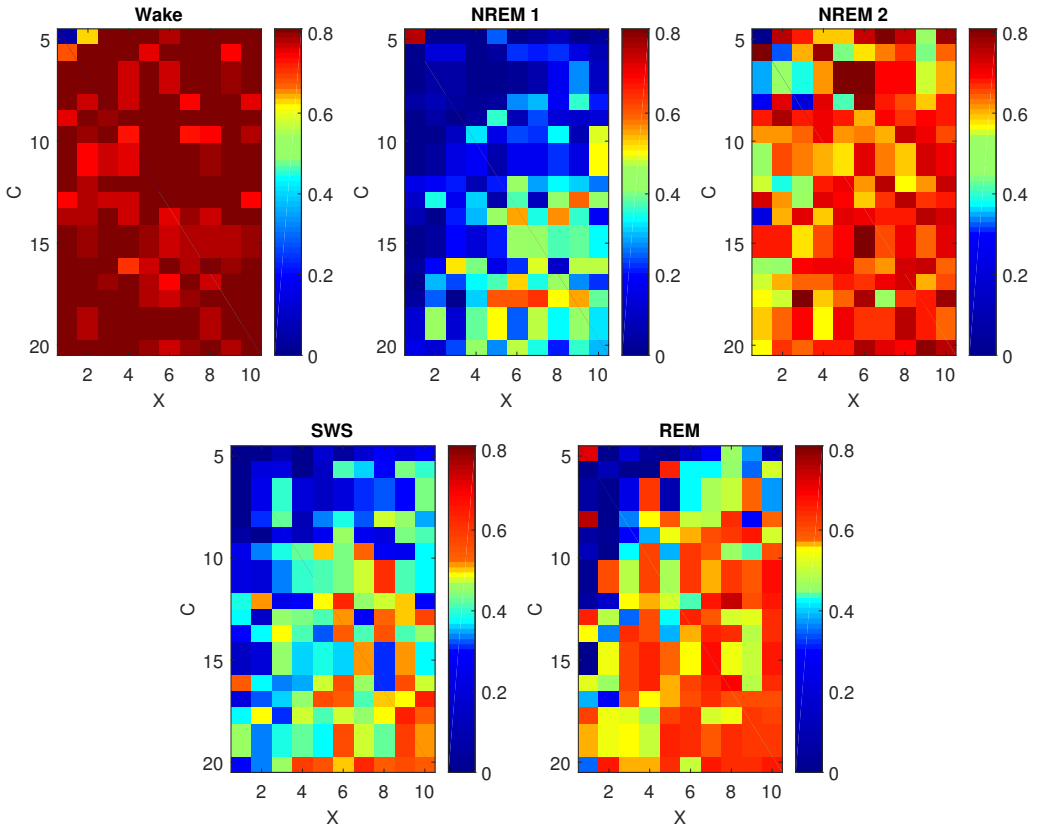


Figure 9.23: Insomnia group, classification accuracy (True positive rate)

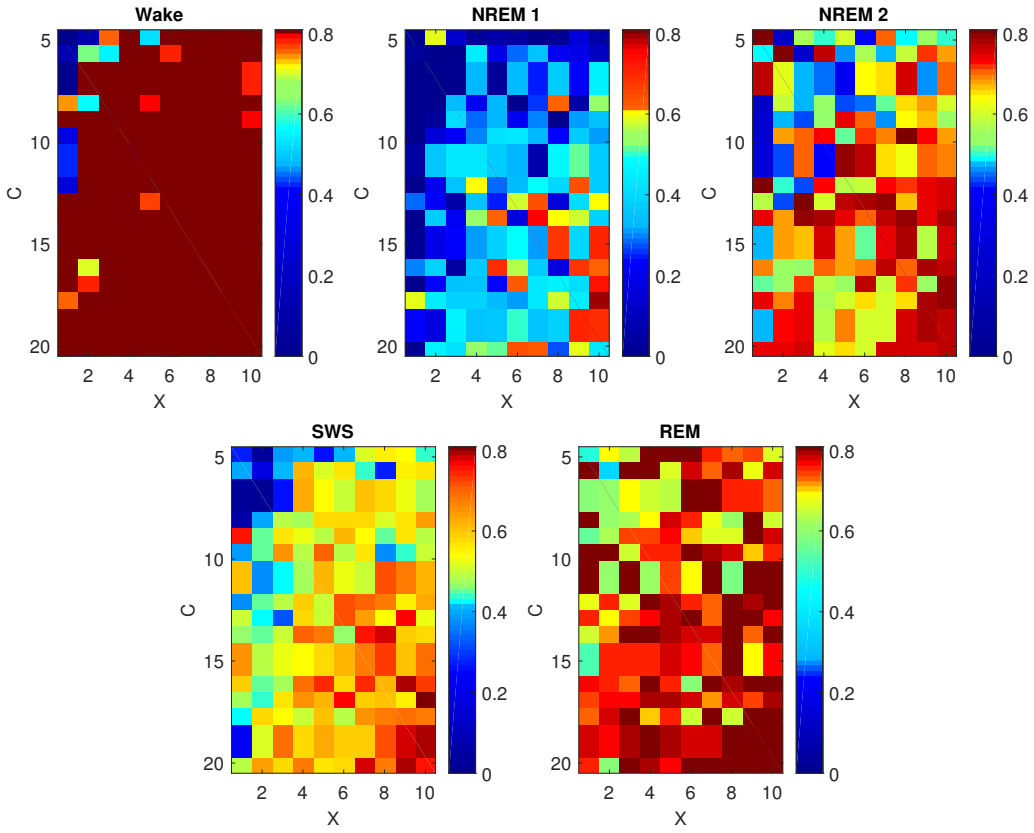


Figure 9.24: Narcolepsy group, classification accuracy (True positive rate)

9.6.1 Single recording examples

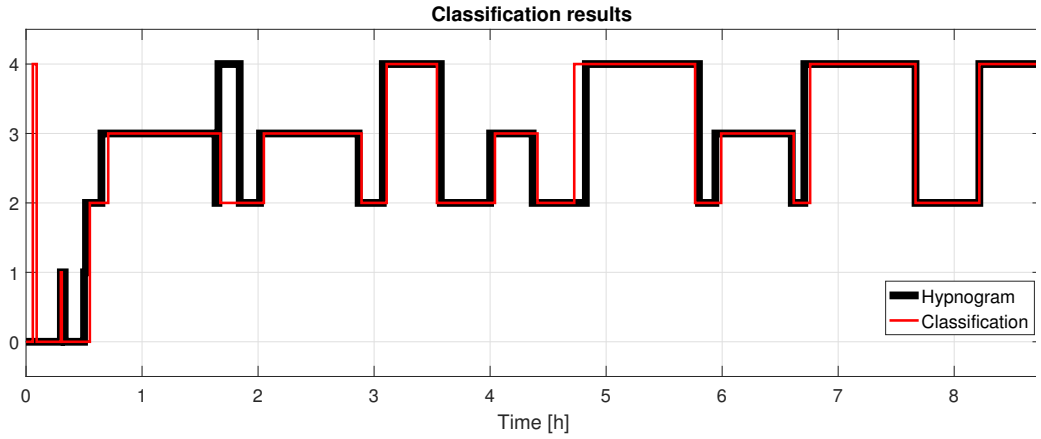


Figure 9.25: Healthy subject, classification results

	Wake	NREM 1	NREM 2	SWS	REM
Sensitivity [%]	92.86	16.67	89.14	93.59	89.50
Specificity [%]	99.09	100	92.37	97.89	97.62
Total correct classification [%]				90.50	
C				5	
X				4	
Total number of segments in the recording				1053	
Number of segments presented for manual scoring				61	

Table 9.2: Healthy subject, classification results

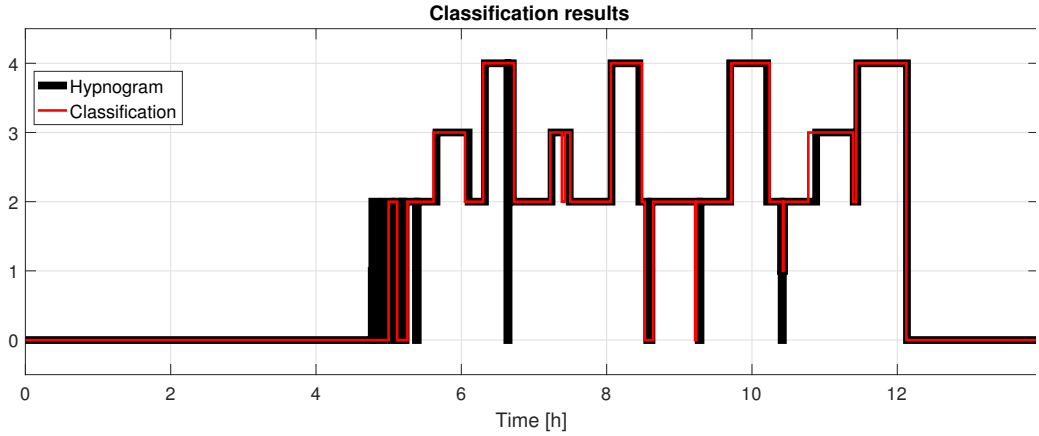


Figure 9.26: Patient with insomnia, classification results

	Wake	NREM 1	NREM 2	SWS	REM
Sensitivity [%]	98.09	20	85.49	91.72	98.71
Specificity [%]	96.18	100	97.54	98.63	98.75
Total correct classification [%]				93.97	
C				10	
X				3	
Total number of segments in the recording				1675	
Number of segments presented for manual scoring				106	

Table 9.3: Patient with insomnia, classification results

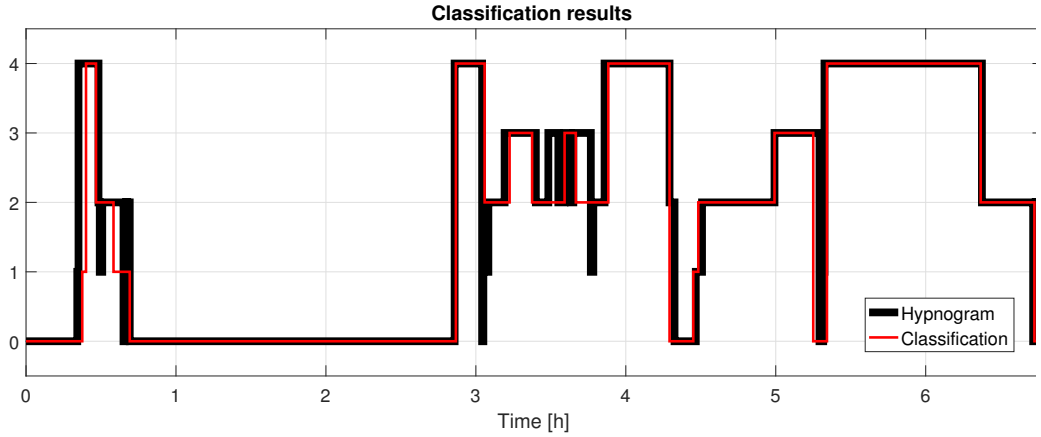


Figure 9.27: Patient with narcolepsy, classification results

	Wake	NREM 1	NREM 2	SWS	REM
Sensitivity [%]	98.46	23.53	86.4	63.64	93.06
Specificity [%]	95.10	97.99	93.19	99.73	99.67
Total correct classification [%]				89.20	
C				10	
X				4	
Total number of segments in the recording				815	
Number of segments presented for manual scoring				82	

Table 9.4: Patient with narcolepsy, classification results

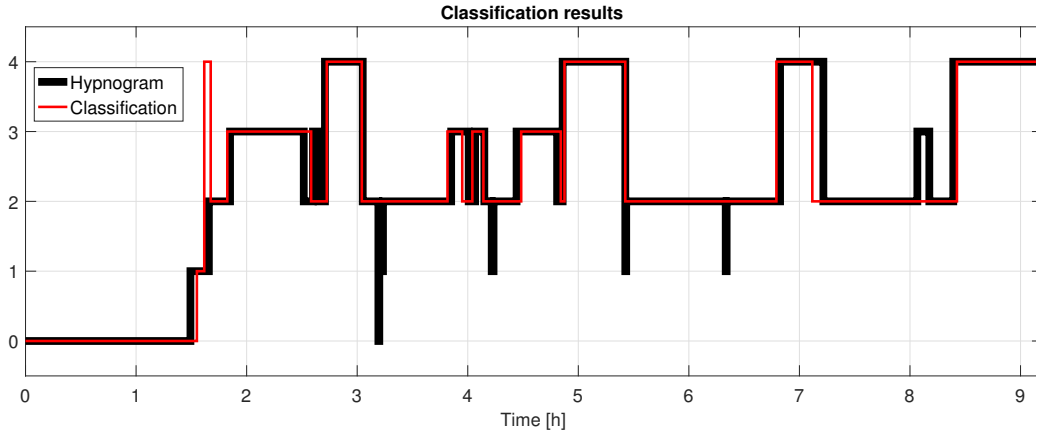


Figure 9.28: Patient with nocturnal frontal lobe epilepsy, classification results

	Wake	NREM 1	NREM 2	SWS	REM
Sensitivity [%]	98.89	28.57	94.06	81.39	91.67
Specificity [%]	99.24	100	90.22	97.64	98.59
Total correct classification [%]				90.68	
C				6	
X				5	
Total number of segments in the recording				1105	
Number of segments presented for manual scoring				52	

Table 9.5: Patient with nocturnal frontal lobe epilepsy, classification results

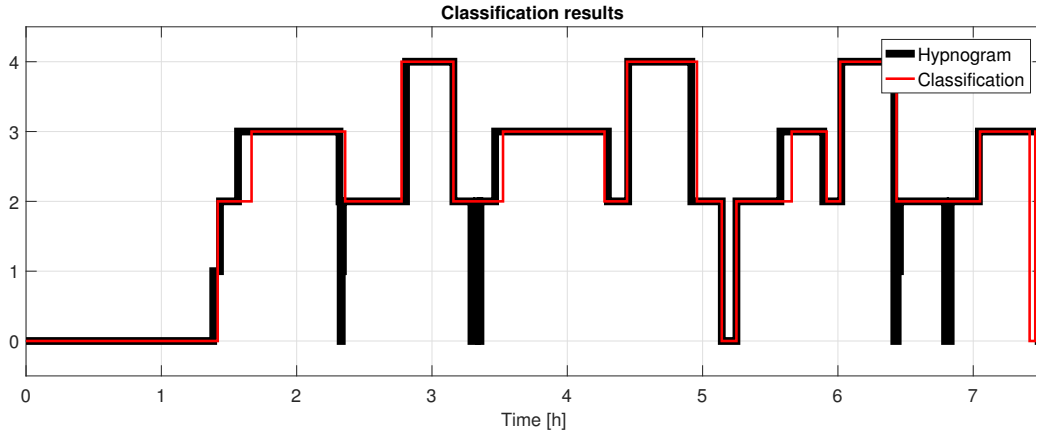


Figure 9.29: Patient with periodic limb movements, classification results

	Wake	NREM 1	NREM 2	SWS	REM
Sensitivity [%]	92.46	0	93.68	86.48	100
Specificity [%]	98.72	100	92.27	98.71	98.29
Total correct classification [%]				91.25	
C				8	
X				3	
Total number of segments in the recording				903	
Number of segments presented for manual scoring				67	

Table 9.6: Patient with periodic limb movements, classification results

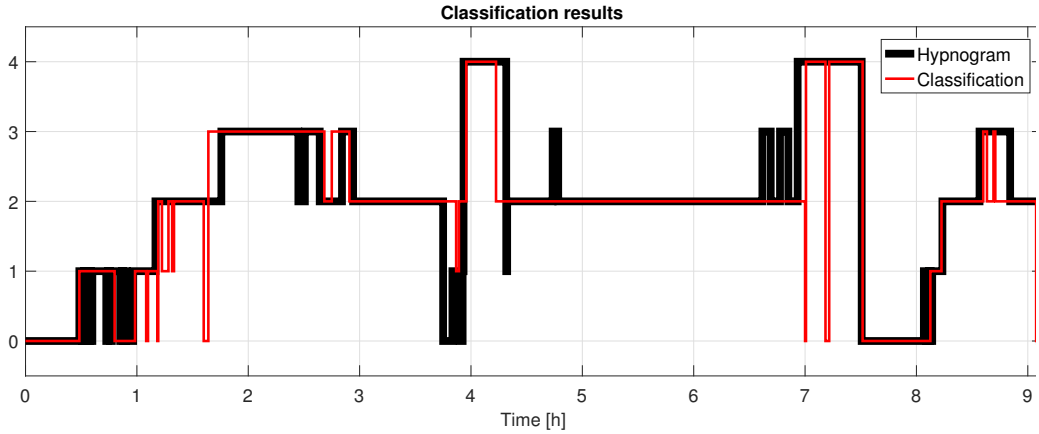


Figure 9.30: Patient with REM behavior disorder, classification results

	Wake	NREM 1	NREM 2	SWS	REM
Sensitivity [%]	83.14	70.73	89.64	67.26	76.52
Specificity [%]	96.65	97.44	81.75	96.02	99.89
Total correct classification [%]				82.40	
C				10	
X				1	
Total number of segments in the recording				1097	
Number of segments presented for manual scoring				100	

Table 9.7: Patient with REM behavior disorder, classification results

Part III

Discussion and conclusion

During the process of researching the sleep medicine topics and writing this thesis, it has been proven that polysomnography is, indeed, a very complex and broad interdisciplinary field. However, the current research efforts are still divided into discrete departments that do not favor the necessary interdisciplinary approach.

The main underlying problems have been emphasized, especially the increasing need for general awareness for sleep related health issues, which is directly linked to essential demands for improvements in sleep diagnostics technology. Firstly, a complete visual inspection of the nocturnal polysomnography is time consuming and expensive. Secondly, inter-expert variability in visual sleep scoring is an acknowledged limitation often producing subjective and unreliable results.

For the reasons above, feature extraction was implemented as an essential pre-processing step to achieve data reduction and to mine other informative measures for automatic sleep staging. This phase might already be very useful in clinical practice, before implementing any automatic classifier. Simply having a channel displaying a trend of an extracted feature can significantly reduce the time needed for visual scoring performed by a physician. For example (see 9.5.1), seeing directly the "time-development" of EEG spectral bands power or entropy measures could result in the sleep-expert being able to determine the most probable sleep stage right away without searching for characteristic graphoelements that are often lost in noisy signals. By inspecting the raw time series, some patterns in biological signals, are, simply put, hidden to the human eye.

The next phase covered the classification process and aims to develop an automatic method being able to score the PSG recording.

There were few limitations that had to be dealt with. Firstly, it would be highly desirable, if the provided recordings had been scored visually by two independent experts, ideally form two different sleep centers. The mentioned inter-scorer variability is not only limiting in real-life clinical situations when a physician is possibly evaluating the sleep quality based on subjective and potentially faulty scoring, but it also affects the results reported using automatic methods, and hampers the development and research. Often, even the benchmark against which methods under development are compared in each study shows inter-study variability too.

During the feature extraction for following classification task, unfortunately, only a limited number of PSG channels could be used within this thesis. Useful additional information could have been provided by being able to exploit respiratory signals, including breathing effort, air flow or oxygen blood saturation. These signals were, however, present only in few original recordings, therefore choosing them as a mandatory signal source for features extraction would have significantly reduced the final dataset size, that had to be consistent in both the number and the type of leads. Inclusion of even more physiological signal sources, for example blood pressure or body temperature, would most likely improve the results.

One of the pitfalls of the current efforts in automatic sleep staging software development is the requirement for clean data and an "ideal and standardized" environment for the signal acquisition. That is, however, very far away from real-situation possibilities. In real clinical setup, the conditions can never be ideal, and the medical operators or the patients themselves can influence the examination procedure only to a very limited extent. The final dataset used for analysis in this thesis was a subset of manually selected recordings having relatively higher quality compared to others. In other words, the "virtual simulated" conditions were much more ideal than they would have ever been in practice. Yet, the results were still not perfect and the strong dependency on the number of artifacts or signal-to-noise ratio in general, was very self-evident.

The final aim of this work was to come up with an approach, which could be applicable in clinical practice and comprehensible for physicians, rather than explore the broad spectrum of advanced classification models. Many issues surrounding a general classification approach for sleep staging have been thought through.

When trying to apply the Naive-Bayes classifier in a simulated clinical situation, the tricky part was the fact it used prior probabilities of each target class. In other words, it creates its final decision based on, among others, the probability of a particular sleep stage occurrence in general.

During the training phase, it should simply find out that stage NREM 1 is the least common, while NREM 2 the most frequent. Then, in the prediction phase, if there is a situation where the model cannot make a decision for one particular epoch based solely on its descriptive features, it will classify it as stage NREM 2, because NREM 2, in general, occurs more often than NREM 1. This creates an issue worth discussion - how to apply the Naive Bayes classifier on real clinical problems? In the very beginning of the Chapter 9, pie charts describing the sleep stages relative distribution for different groups of sleep disorders were presented. It is obvious, that these prior probabilities (sleep stages proportions) are quite different for distinct pathologies. Therefore, if we were to use a Bayesian classifier to score a new recording in a clinical setup, we would need to state the expected occurrences of each sleep stage. That would, however, require the prior knowledge of a correct diagnosis, which is logically impossible, since the PSG examination was scheduled in order to find that diagnosis.

The core of the underlying problem, however, does not manifest only in case of Bayesian classifier applicability. The resulting boxplots for particular features in respect to a target class (sleep stage) also revealed differences across different sleep disorders group. [1] In other words, typical REM stage values of attribute A in a healthy subject are no longer characteristic for a patient suffering from REM behavior sleep disorder. This fact will definitely affect all classifiers, not just the

[1] The statistical significance of these differences was not tested in this thesis, however, based on subjective observation and knowledge obtained from literature review, they were assumed to be significant enough to mind the respective consequences.

Naive Bayes. One task that should be performed in the future, therefore, is to find out which descriptive features remain characteristic for one sleep stage, no matter what condition the subject might suffer from.

In general, there are few possible solutions for using an automatic classifier in clinical practice.

1. To have different classifiers designed for specific pathologies. A doctor would then choose the classifier designated for scoring the recordings associated with the diagnosis estimate/guess. If needed, more classifiers could produce different scorings (with distinct diagnosis assumptions) and the physician could decide for the best one afterwards.
2. Develop a robust classifier working only with features that are reliably consistent throughout all possible pathologies and a healthy state too. These features, however, still need to be defined, and due to the variability of pathophysiological processes causing various neurological disorders, which are still not fully understood, it remains a question whether this universal set of features will ever be found.
3. Semi-automatic methods where a physician performs scoring only of selected segments, and the system classifies the rest. Another important question, although, arises. How will the physician know which segments and how many of them he or she should score. There are several requirements that should be met in order to get fair results.

    - At least N segments for each sleep stage present in the night recording need to be manually scored and given to the classifier. But, in general, not all sleep stages need to be present in the recording. The physicians can then find themselves in an extreme situation where they have to go over all signal to verify that some stage was not present in the signal after all. This could be overcome using unsupervised clustering methods which have the potential to segment the signal into clusters where epochs are mutually similar. However, many of these algorithms need to know the initial number of target clusters. Which is, again, something the doctor does not know in advance.
    - Depending on the classifier type that will be used to perform the classification task, the number of manually scored segments for each class should be proportional to the respective class occurrence, since not all classifiers work with balanced training sets. This, again, could be solved with the use of clustering algorithms. The bigger the found cluster is, the more segments belonging to this cluster would be presented to the expert for manual scoring.

The third approach was also the one, that this thesis have tried to demonstrate and verify its potential. The signal epochs were divided into C clusters using the

k-means algorithm (where C needed to be higher than the expected number of clusters/sleep stages) and then the proportional count of each cluster representatives was presented to the expert scorer for manual classification. It is clear, that many clusters could have represented the same class and the higher the C, the more time consuming the process for the physician would be. The limit case of this approach is C equal to the number of epochs in the signal, which corresponds to the situation of conventional manual scoring.

Another huge advantage of the described approach to semi-automatic detection is the fact, that the classification model is built each time from scratch to fit the data currently being analyzed in the best possible way. Usually the detection models built on one dataset are not reliable enough, and fail when presented with new data. Due to the enormous variability of physiological biosignals, this issue is very hard to overcome.

This approach seemed to worked relatively well, however, these are just initial observations and assumptions. The values of parameters C and X still needed to be specified manually, and not always the higher values led to better results. However, as can be seen in respective figures and tables for each example in 9.6.1, the predicted hypnograms were very close to the reference scored manually by the physician. Considering that this output required the physician to score only about 4 - 10% of the recording, the tradeoff between classification accuracy and saved time might still be useable enough in many clinical applications.

Nevertheless, the most useful method might turn out to be the one that provides the most reliable starting point for any sleep staging software, whether it will be based on a semi-automatic procedure, or fully automatized.

Appendices

Appendix A

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DIPLOMA THESIS ASSIGNMENT

Student: Bc. Jana C h á b e r o v á

Study programme: Biomedical Engineering and Informatics

Specialisation: Biomedical Engineering

Title of Diploma Thesis: Analysis of Sleep Polysomnography Data Using Advanced Signal Processing Algorithms

Guidelines:

The goal of the present thesis is to find a set of polysomnographic variables (features) with high correlation to clinical parameters of sleep and sleep stages. The use of these features will potentially simplify the visual evaluation of polysomnographic examination by medical personnel.

Outline:

1. Do a research on the topic of long-term PSG-recordings and their use and importance in the clinical practice.
2. Download a public sleep PSG database with an available expert scoring.
3. Design and implement a set of descriptive features suitable for distinguishing between sleep stages or other clinical parameters.
4. Validate the proposed solution on real clinical data and verify the classification potential of extracted features.
5. Present the obtained results in a form of tables, graphs or figures.

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