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Jussi Virkkala

Automatic Sleep Stage Classification Using Electro-oculography

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Automatic Sleep Stage Classification Using Electro-oculography

Thesis for the degree of Doctor of Philosophy to be presented with due permission for public examination and criticism in Tietotalo Building, Auditorium TB222, at Tampere University of Technology, on the 20th of May 2009, at 12 noon.

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"Very little can be said about sleep that has not been said already", Nathaniel Kleitman 1963

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Abstract

In this thesis automatic sleep stage classification was developed and evaluated. The method was based on signals recorded by electro-oculography electrodes. Monitoring sleep is important for the diagnosis of sleep disorders. Altered sleep is related to obesity and diabetes, and loss of sleep may lead to daytime sleepiness which in turn may cause accidents. Standard sleep stage measurement requires the application of multiple electrodes by trained professionals. Signals are then classified visually in a time-consuming and subjective process. Many automatic sleep classification methods also exist. Some methods work with self-applicable, usually forehead, electrodes. However, the use of standard sleep electro-oculography electrode placement enables the recording of frontal EEG, EMG and EOG using a single electrode pair.

Nearly 300 sleep recordings were used to develop automatic methods for separating wakefulness and sleep stages during intentional night-time sleep and during unintentional daytime sleep through maintenance of wakefulness tests (MWT). Signals detected using only standard electro-oculography electrodes were used for automatic sleep stage classification. The signals were recorded both with and without the mastoid reference electrode. Results were also compared with activity-based methods, and for reference, we also recorded EEG and submental EMG tonus. Reference sleep stage scoring was carried out visually according to the Rechtschaffen and Kales standard. Reasonable sleep stage information could be obtained using self-applicable electro-oculography electrodes combined with automatic analysis.

This developed self-applicable automatic sleep staging system would make large scale ambulatory sleep studies plausible for screening sleep disorders and investigating the relationship between irregular sleep and health.

Keywords: sleep, electro-oculography, sleep stage, automatic, classification

Tiivistelmä

Tässä väitöstyössä kehitettiin automaattinen unen luokittelija, joka perustuu silmänliike-elektrodeista mitattaviin signaaleihin. Unen arviointi on tärkeätä esimerkiksi unihäiriöiden diagnosoinnissa. Muutokset unen pituudessa ja laadussa liittyvät myös liikalihavuuteen ja diabetekseen. Vähentynyt uni voi aiheuttaa päiväväsymystä, josta voi seurata muun muassa tapaturmia. Perinteinen unilaboratoriossa tehtävä uniluokitus vaatii koulutetun henkilökunnan asentamia useita elektrodeja sekä visuaalista analysointia. Prosessi on työläs ja uniluokitus on altis henkilöistä riippuville vaihteluille. Unen automaattista analysointia ja luokittelua on tutkittu paljon. Jotkut menetelmät perustuvat käyttäjän itsensä kiinnittämiin elektrodeihin. Nämä menetelmät perustuvat yleensä otsalle asetettaviin elektrodeihin. Kuitenkin käyttämällä unirekisteröinneissä tyypillisiä kertakäyttöisiä silmänliike-elektrodeja voidaan samoilla elektrodeilla mitata frontaalista aivosähkökäyrää, kasvojen alueen lihasaktiviteettia sekä silmänliikkeitä.

Analysoimalla lähes 300 unirekisteröintiä kehitettiin unen automaattinen luokittelija unirekisteröinteihin sekä päiväaikaisiin vireystesteihin. Kehitetty automaattinen uniluokittelija perustuu ainoastaan silmänliike-elektrodeista mitattuihin signaaleihin. Signaalit olivat joko unipolaarisia tai bipolaarisia laskettuina tai mitattuina. Tuloksia verrattiin myös kiihtyvyysantureiden signaaleihin. Vertailuluokitus perustui Rechtschaffen and Kales standardin mukaiseen visuaaliseen analyysiin useammasta signaalista. Silmänliike-elektrodeilla ja automaattisella analyysilla saavutettiin kohtuullinen tulos verrattuna visuaaliseen vertailuluokitukseen.

Kehitetty käyttäjän itsensä käytettävissä oleva automaattinen järjestelmä mahdollistaa laajat kenttämittaukset unihäiriöiden seulontaan ja esimerkiksi tutkimukset epäsäännöllisen unen ja terveyden välisistä vuorovaikutuksista.

Avainsanat: uni, elektro-okulografia, uniluokitus, automaattinen, luokittelu

Preface

I want to express my gratitude to my supervisor Alpo Värri, Dr.Tech., Adjunct Professor and instructor Joel Hasan, M.D., Ph.D., Adjunct Professor for endless support. It is due to Joel Hasan and Sari-Leena Himanen, M.D., Ph.D., Adjunct Professor that I am hoping to be a sleep researcher. I wish to thank pre-examiners of this thesis: Martti Juhola, Ph.D., Professor and Periklis Ktonas, Ph.D., Professor Emeritus for their work.

Recordings were carried out at Sleep Laboratory, Finnish Institute of Occupational Health, Helsinki, Finland. I want to thank especially Kiti Müller, M.D., Ph.D., Adjunct Professor and Mikko Härmä, M.D., Ph.D., Adjunct Professor for providing stimulating work environment for the last ten years. I wish to thank all the nurses and sleep technicians I have worked with in Helsinki and in Tampere especially Riitta Velin, Susan Pihl and Nina Lapveteläinen. They are the only ones who really know what goes on in a sleep lab. Eero Huupponen, Dr.Tech. and Eus Van Someren, Ph.D., Adjunct Professor are thanked for their contribution to this thesis.

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I want to thank my parents Touko and Toini for encouragement. My dearest gratitude goes to my wife Maarit who has organized all the practical things in our family for the last twenty years. I also sincerely hope that our son Jesse will sooner or later show me how things should have been carried out.

Jussi Virkkala, Neuroupdate.com 14.4.2009

CONTENTS

List of original publications

This thesis is based on the following publications (I-VI), which are referred to in the text by their Roman numerals. The articles are reprinted with the permission of the copyright holders. This thesis also includes some unpublished work and work published in abstract format.

I. Virkkala J, Hasan J, Värri A, Himanen S-L, Müller K. Automatic detection of slow wave sleep using two channel electro-oculography. Journal of neuroscience methods, 2007, 160: 171-177.

II. Virkkala J, Hasan J, Värri A, Himanen S-L, Härmä M. The use of two-channel electro-oculography in automatic detection of unintentional sleep onset. Journal of neuroscience methods, 2007, 163: 137-144.

III. Virkkala J, Hasan J, Värri A, Himanen S-L, Müller K. Automatic sleep stage classification using two-channel electro-oculography. Journal of neuroscience methods, 2007, 166: 109-115.

IV. Virkkala J, Hasan J, Värri A, Huupponen E, Himanen S-L, Müller K. Reducing the effects of electrocardiographic artifacts on electro-oculography in automatic sleep analysis. Conf Proc IEEE Eng Med Biol Soc, 2007, 590-593.

V. Virkkala J, Hasan J, Velin R, Himanen S-L, Värri A, Van Someren EJW. Automatic sleep detection using activity and facial electrodes. Conf Proc IEEE Eng Med Biol Soc. 2008, 1639-1642.

VI. Virkkala J, Velin R, Himanen S-L, Värri A, Müller K, Hasan J. Automatic sleep stage classification using two facial electrodes. Conf Proc IEEE Eng Med Biol Soc. 2008, 1643-1646.

Author's contribution

Author participated in the technical aspects of data collection in all publications (I-VI). Author solely developed custom algorithms and software and performed all data analyses. Visual sleep stage analyses in all studies were carried out by Susan Pihl (SP), Riitta Velin (RV), and Nina Lapveteläinen (LP). Author wrote the papers with close collaboration with co-authors Joel Hasan, Alpo Värri, Kiti Müller, Sari-Leena Himanen, Mikko Härmä, Riitta Velin, Eus Van Someren and Eero Huupponen. Language editing of original publications were carried out by Hanna Liikala, Päivi Roland and Alice Lehtinen.

List of abbreviations

A1	Left earlobe electrode
A2	Right earlobe electrode
AASM	American Academy of Sleep Medicine (www.aasmnet.org).
AC	Alternating current
AHI	Apnoea-hypopnoea index
ASDA	American Sleep Disorders Association, currently named AASM.
C3	Left central EEG electrode
C4	Right central EEG electrode
DC	Direct current
DFT	Discrete Fourier transform
E1	EOG electrode 1 cm below the left outer canthus of the left eye. In alternative configuration 1 cm below and 1 cm lateral to the outer canthus.
E2	EOG electrode 1 cm above the right outer canthus of the right eye. In alternative configuration 1 cm below and 1 cm lateral to the outer canthus.
ECG	Electrocardiography
EEG	Electroencephalography
EM	Eye movement
EMD	Eye movement density
EMG	Electromyography
EOG	Electro-oculography

EOG L	EOG electrode slightly lateral and 1 cm above the left outer canthus of the left eye
EOG R	EOG electrode slightly lateral and 1 cm below the right outer canthus of the right eye
FN	False negative
FP	False positive
IDFT	Inverse discrete Fourier transform
KC	K complex
M1	Left mastoid electrode
M2	Right mastoid electrode
MSLT	Multiple Sleep Latency Test
MT	Movement time
MWT	Maintenance of Wakefulness Test
N1	Stage 1
N2	Stage 2
N3	Stage 3
NREM	non-REM
NSWS	non-SWS
PPV	Positive predictive value
PSG	Polysomnography
R	Stage REM
R&K	Rechtschaffen and Kales
REM	Rapid eye movement

S1	Stage 1
S2	Stage 2
S3	Stage 3
S4	Stage 4
SEM	Slow eye movement
SREM	Stage REM
SWA	Slow wave (0.5-4.5 Hz) activity of EEG
SWS	Slow wave sleep, S3+S4, N3
TN	True negative
TP	True positive
W	Wakefulness

List of definitions, modified mainly from (Iber et al., 2007)

Alpha rhythm: Train of sinusoidal 8-13 Hz EEG activity recorded over the occipital region with eye closure, attenuating with eye opening.

Beta rhythm: An EEG rhythm consisting of 13-30 Hz activity.

Delta rhythm: An EEG rhythm consisting of 1-4 Hz activity.

K complex: A well-delineated negative sharp wave in EEG immediately followed by a positive component with total duration at least 0.5 s. Usually maximal in amplitude over the frontal regions.

Low amplitude, mixed frequency activity: Low amplitude, predominantly 4-7 Hz EEG activity.

Low chin EMG tonus: Baseline EMG activity in the chin derivation not higher than in any other sleep stage and usually at the lowest level of the entire recording.

Major body movement: Movement and muscle artefact obscuring the EEG for more than half an epoch to the extent that sleep stage cannot be determined.

Positive predictive value: The proportion of subjects with positive test results who are correctly classified.

Rapid eye movements: Conjugate, irregular, sharply peaked eye movement-related EOG deflections with an initial deflection usually lasting <500 ms. REMs are characteristic of stage R sleep.

Sensitivity: Probability of correctly predicting a positive example, TP/(TP+FN).

Sleep onset: The start of the first epoch scored as any stage other than W (In most subjects this will usually be the first epoch of stage N1).

Sleep spindle: A train of distinct waves with frequency 11-16 Hz (most commonly 12-14 Hz) with a duration at least 0.5 s.

Slow eye movement: Conjugate, reasonably regular, sinusoidal eye movements with an initial EOG deflection usually lasting >500 ms.

Slow waves. EEG waves of frequency 0.5 Hz-2 Hz and peak-to-peak amplitude >75 μV, measured over the frontal regions.

Specificity: Probability of correctly predicting a negative example, TN/(TN+FP). Same as sensitivity of the negative category.

Theta rhythm: An EEG rhythm consisting of 4-8 Hz activity.

Transient muscle activity: Short irregular bursts of EMG activity usually with duration <0.25 seconds superimposed on low EMG tonus. The activity may be seen in the chin or anterior tibial EMG derivations, as well as in EEG or EOG derivations, the latter indicating activity of cranial nerve innervated muscles. The activity is maximal in association with rapid eye movements.

Vertex sharp waves (V waves): Sharply contoured waves with duration <0.5 seconds maximal over the central region and distinguishable from the background activity.

1 Introduction

Sleep covers about one third of our life. Sleep is a period of consolidation and recovery. Aristotle wrote almost 2500 years ago in "On Sleep and Sleeplessness" that sleep regulation is related to heat produced by the body. Since this, however, why we sleep has been reviewed by several authors (Cirelli and Tononi, 2008; Mignot, 2008). Sleep has been postulated as important for energy conservation, for facilitating learning, for memory, and for restoration of biosynthesis. During sleep our memories are strengthened (Stickgold and Walker, 2007), motor performance improves (Hill et al., 2008), and more generally, synaptic connections are downscaled (Tononi and Cirelli, 2003, 2006). Sleep is also related to metabolic function and obesity (Knutson et al., 2007; Knutson and Van Cauter, 2008). Fragmented and short sleep increases the susceptibility to the common cold (Cohen et al., 2009). Sleep loss affects public health (Balkin et al., 2008) and various aspects of cognition (Durmer and Dinges, 2005), such as vigilant attention (Lim and Dinges, 2008). Sleep disorders or sleep restriction can result in sleepiness and may lead to unintentional sleep onset, possibly causing accidents (Philip and Åkerstedt, 2006). Altered sleep/wake patterns affect performance in neuropsychological tests, and in simulated work (Åkerstedt, 2007). The recording of sleep stages is important for the clinical diagnosis and treatment of sleep disorders (Carskadon and Rechtschaffen, 2005; Matheson et al., 2007). Sleep stage information is important per se and is also used for calculating, e.g., respiratory disturbance indexes in different sleep stages.

Traditionally sleep is monitored using polysomnography with EEG, EOG and EMG electrodes and various other sensors (Penzel and Conradt, 2000; Hauri et al., 2002). Sleep stage is classified (scored) visually using central EEG, EOG and EMG (Rechtschaffen and Kales, 1968). Measurements are usually taken in an attended sleep laboratory. The limiting aspects of ambulatory polysomnography are scalp EEG electrodes, and the manual scoring of the recordings. Manual sleep scoring is a time-consuming and a subjective process, thus there is a demand for easily applied automatic methods which could be used in clinical and experimental ambulatory studies and, for instance, for studying the role of sleep duration and quality in the ethiology of metabolic disorders (Knutson et al., 2007). Scalp EEG electrode placement is more complicated (performed by trained sleep technicians) than the use of self-adhesive disposable

electrodes. Placement of electrodes outside the hairline would enable the use of self-adhesive disposable electrodes, which could be a self-applicable task (Ehlert et al., 1998; Poree et al., 2006).

In this thesis signals detected using standard electro-oculography electrodes were used for automatic sleep stage classification. The signals used were referential (I-III), and calculated or recorded as bipolar (IV-VI). Automatic analysis was developed to classify electro-oculography signals into epochs of wakefulness and different sleep stages. Algorithms are simple with only few assumptions. We also compared the results with activity-based methods (V). Reference sleep stage scoring was carried out visually according to the Rechtschaffen and Kales standards (Rechtschaffen and Kales, 1968).

The use of a developed, possibly self-applicable automated sleep system would make large (field) sleep studies plausible for screening sleep disorders, doing sleep related phenotyping (Viola et al., 2007; De Gennaro et al., 2008), studying individual differences in neuronal correlates of sleep, and investigating relationships between (irregular) sleep and health.

2 Objectives of the study

Objectives of the study were to develop and validate algorithms for automatic sleep analysis. Analysis was focused on the use of signals detected using the standard electro-oculography electrodes. Placement of these electrodes could be a self-applicable task. Although the scope of the study was limited to sleep stage classification, the developed methods can be used also for non-epoch based sleep analysis. Other physiological signals, for instance, heart rate, respiration and airflow during sleep were not studied.

The aim of the study I was to develop and to validate an automatic method to detect slow wave sleep (SWS) based on two-channel electro-oculography. The goal was to achieve 90% agreement in separation of NSWS and SWS epochs.

The aim of the study II was to develop and to validate the automatic detection of unintentional sleep epochs during Maintenance of Wakefulness Test (MWT). The aim was also to develop a new slow eye movement (SEM) detection algorithm for the task. The goal was to achieve 90% agreement in separation of wakefulness and sleep epochs.

The aim of the study III was to extend the work of studies I and II to all sleep stages. The goal was to achieve 70% agreement in separation of wakefulness, S1, SREM, S2 and SWS epochs using two-channel electro-oculography.

The aim of the study IV was to study the reduction of QRS artefacts on single-channel EOG. The goal was to improve the results of automatic sleep detection with QRS artefact reduction.

The aim of the study V was to develop and validate single-channel sleep and wakefulness separation based on single-channel EOG and to compare it with activity-based methods. The goal was to have greater specificity with single-channel EOG sleep detection compared with the activity-based methods.

The aim of the study VI was to extend the single-channel EOG algorithm for the separation of wakefulness, SREM, S1/S2 and SWS. The goal was to achieve 70% agreement. Aim was also to validate a low weight single-channel EOG device for sleep stage estimation.

3 Review of literature

3.1 Sleep

Scientific interest in the phenomenon of sleep has a long history. Before neurophysiologic measurements sleep depth was measured behaviourally (Weber and Burgmair, In press). Using data from 211 nights Michelson confirmed earlier reports that sleep depth (measured as arousal threshold) reached its maximum about one hour after falling asleep. During the night there were as many as four other sleep depth minima and maxima before lowest sleep depth in the morning. Low arousal (deep sleep) was later related to 0.5-3 Hz large brain waves (Blake and Gerard, 1937). Effects of sleep deprivation were measured on numerous outcomes including memory, heart rate and urine analysis by Patrick and Gilbert (Patrick and Gilbert, 1896). One of first structured neurophysiologic sleep recordings were carried out by Loomis et al. in 1930's (Loomis et al., 1935, 1937). In Figure 1 a sleep recording is shown. Much of the early work was described in Nathaniel Kleitman's book (Kleitman, 1963). This book "Sleep and Wakefulness" contains 4337 references dated before 1963. Earlier references can be found from Manacéïne book "Sleep: Its physiology, pathology, hygiene, and psychology " (Manacéïne, 1897). Discovery of REM sleep was recently summarized by Gottesmann (Gottesmann, 2009).

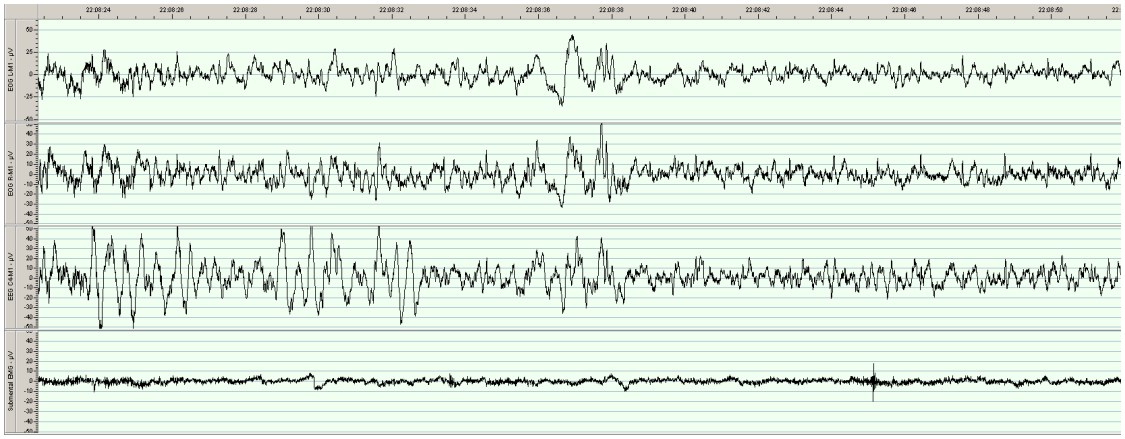

Figure 1. A sleep recording demonstrating two EOG traces (EOG L-M1, EOG R-M1), one central EEG (EEG C4-M1) and submental EMG during S2. K complex appear in the middle. Horizontal axis is 30 s. Vertical axes are between -50 µV and 50 µV. Data is from subject 213 from study III.

3.1.1 Sleepiness and sleep onset

Sleepiness is a problem reported by 10–25% of the population (Roehr et al., 2005). Excessive sleepiness is defined as sleepiness that occurs at a time when the individual is usually expected to be awake and alert (Littner et al., 2005). Opposite to sleepiness usually alertness is considered. Fatigue has a broader meaning. Sleepiness may result in involuntary sleep onset. During extended wakefulness the increase in slow EEG frequencies is noted (Finelli et al., 2000; Cajochen et al., 2002). Although EEG power is modulated by state and sleep pressure, basic topographic features appear to be state-independent (Tinguely et al., 2006). During sleep onset (S2) 1-7 Hz and 14-15 Hz ranges linearly increased and 18-28 Hz range decreased (De Gennaro et al., 2001). In Figure 2 an example of recording after sleep onset is shown.

Visual sleep onset scoring is a manual process requiring central scalp EEG electrode, two EOG electrodes and an EMG electrode (Rechtschaffen and Kales, 1968). In contrast to long 30 s epochs shorter epochs have been used to classify drowsiness and sleep onset. Early literature was reviewed by Häkkinen (Häkkinen, 1972). Shorter fixed epoch durations have been used (Kiymik et al., 2004) or isolated micro sleep events (Tirunahari et al., 2003). Hori et al. have developed scoring with more stages defining the sleep onset (Tanaka et al., 1996, 1997). In addition to more stages also epoch lengths can be adaptive (Värri et al., 1992; Hasan et al., 1993; Hirvonen et al., 1997; Himanen, 2000).

Number of fast saccades decrease while sleepy defined by EEG (Hyoki et al., 1998) and saccade velocities decrease during partial and total sleep deprivation (Russo et al., 2003; Rowland et al., 2005). Oculomotor system in sleep-wake transitions has been reviewed by Henn and co-workers (Henn et al., 1984). Blink durations increase while sleepy (Caffier et al., 2003, 2005; Åkerstedt et al., 2005). Lid closure speed is also affected (Schleicher et al., 2008). The transition from wakefulness to sleep is characterized by a progressive decrease of saccades and blinks and by an appearance of slow eye movements (De Gennaro et al., 2005). Electroencephalography (EEG) and electro-oculography (EOG) changes in drowsiness have been reviewed by Santamaria and Chiappa (Santamaria and Chiappa, 1987) and the process of falling asleep has been reviewed by Ogilvie (Ogilvie, 2001). The importance of slow eye movements in sleepiness and in sleep onset is well known (Hori, 1982; Santamaria and Chiappa, 1987; Åkerstedt et al., 1987; Åkerstedt and Gillberg, 1990; Hasan, 1996).

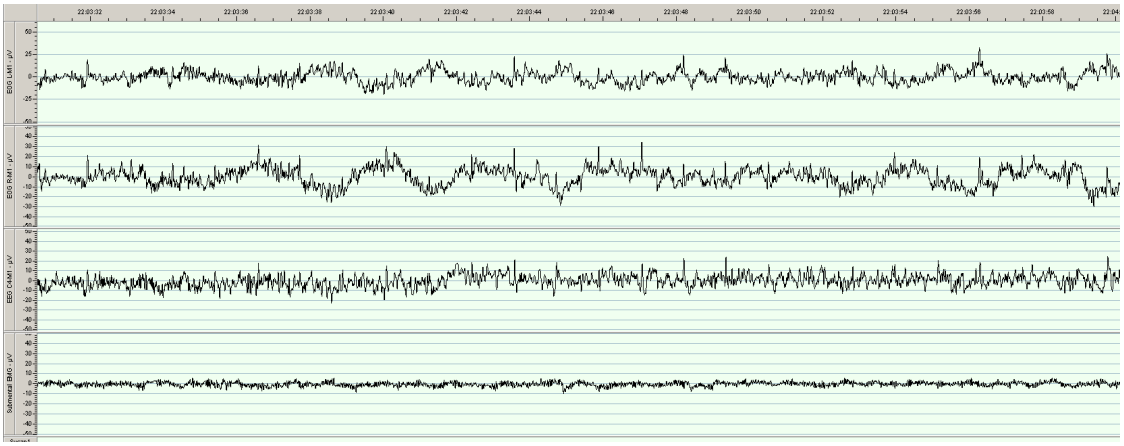

Figure 2. Example of a sleep onset recording demonstrating two EOG traces, one central EEG and submental EMG during the first S1 epoch. Slow eye movements appear in first half of the epoch. Horizontal axis is 30 s. Vertical axes are between -50 µV and 50 µV. Data is from subject 213 from study III.

Instead of using EEG and EOG sleepiness can be measured with other techniques. One is pupillography, measurement of spontaneous pupil size fluctuations in darkness (Merritt et al., 2004). Autonomic changes appear during sleep onset period (Shinar et al., 2006) and, for instance, heart rate has been used as indicator of sleepiness (Chua et al., 2008).

3.1.2 NREM sleep

Sleep is electrophysiologically separated into non-REM (NREM) and REM (rapid eye movement) sleep. NREM is separated into light sleep S1, S2 (N1, N2) and deep sleep S3, S4 (N3). Deep sleep is called also slow wave sleep (SWS). Sleep stage S2 (N2) is characterized by sleep spindles and K complexes (KC). Abbreviations W, MT, S1, S2, S3, S4, SREM are from the old standard (Rechtschaffen and Kales, 1968) and W, N1, N2, N3, R are from the new standard (Iber et al., 2007). In Figure 3 an example of recordings during SWS is shown.

An increase of NREM sleep, especially SWS, has been associated with recovery from sleep deprivation (Borbély and Achermann, 2005). During NREM sleep, cortical neurons are depolarized and fire tonically as in quiet wakefulness, but these depolarized upstates are interrupted by short, hyperpolarized downstates when neurons remain silent (Steriade et al., 1993; Sanchez-Vives and McCormick, 2000).

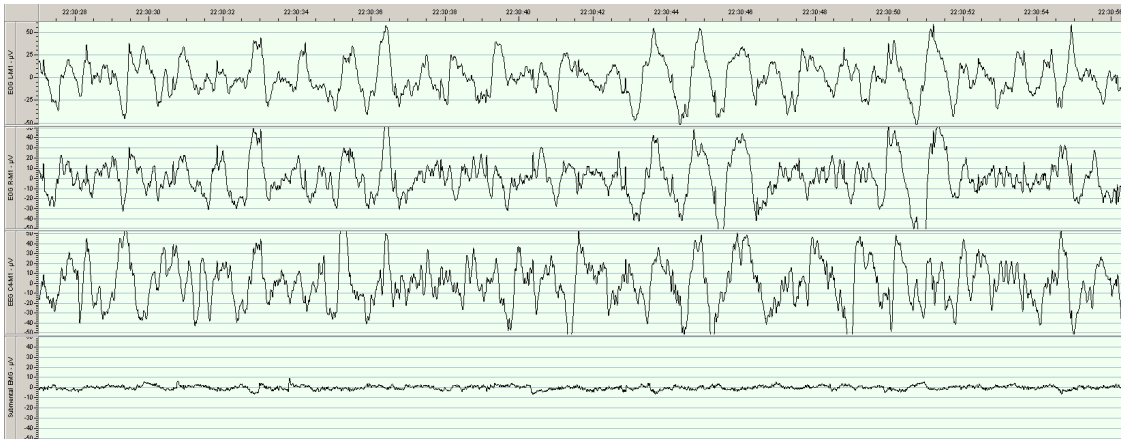

Figure 3. Example of SWS sleep recording demonstrating two EOG traces, one central EEG and submental EMG during SWS. Large slow waves appear in EOG and in EEG traces. Horizontal axis is 30 s. Vertical axes are between -50 µV and 50 µV. Data is from subject 213 from study III.

Slow wave sleep (SWS) part of NREM sleep is one of the key markers of sleep regulation (Borbély and Achermann, 2005). Already in 1962 it was demonstrated that prolonged wakefulness resulted in an increase in the proportion of slow wave sleep during the following recovery sleep (Berger and Oswald, 1962). Usually instead of visually scored slow wave sleep (SWS) spectral delta (0.5-4.5 Hz) power of EEG is used. This is called slow wave activity (SWA). Changes in SWS and SWA have been verified in different experimental paradigms (Borbely et al., 1981). After total sleep deprivation recovery sleep demonstrates an increase in the amount of SWS (Berger and Oswald, 1962; Borbely et al., 1981; Jay et al., 2007).

Apprehension of a difficult next working day (Kecklund and Åkerstedt, 2004) and sleep apnoea (Himanen et al., 2004) has been associated with a decreased amount of slow wave sleep and slow wave segments. Experimental reduction of slow wave sleep has been linked with an increased risk of diabetes by Tasali et al. (Dijk, 2008; Tasali et al., 2008). The increase of slow wave activity is greatest in frontal electrodes after sleep deprivation (Cajochen et al., 1999). Frontal slow wave activity also separates apnoea patients from control subjects (Himanen et al., 2004; Huupponen et al., 2005). It has been recently suggested by Brandenberger et al. that slow wave sleep offers a “self controlled” quiet moment of observation for assessing heart rate variability (Brandenberger et al., 2005). Slow wave sleep has been considered an indicator of brain maturation process (Feinberg et al., 2006). Usually slow wave sleep is considered

important for memory consolidation (Backhaus et al., 2007; Stickgold and Walker, 2007) but also different results have been obtained (Genzel et al., 2009).

3.1.3 REM sleep

Already 140 years ago (1868) dreams were tentatively associated with twitching of the eyelids and somatic muscles during sleep by Griesinger (Pedersen et al., 2008). Dewar appears to have been the first to record eye movements using electrical means (Dewar, 1877). He noticed "electrical variation due to the involuntary movements of the eye-ball". Most early measurements assumed that the recorded potentials were action-potentials from the ocular muscles (Jacobson, 1930). Mowrer et al. concluded that the recorded activity is due to corneo-retinal potential (Mowrer et al., 1936). However, it was not until 1953 that Aserinsky & Kleitman (Aserinsky and Kleitman, 1953, 1955) identified rapid eye movements (REM) during sleep. In Figure 4 an example of recording during SREM is shown.

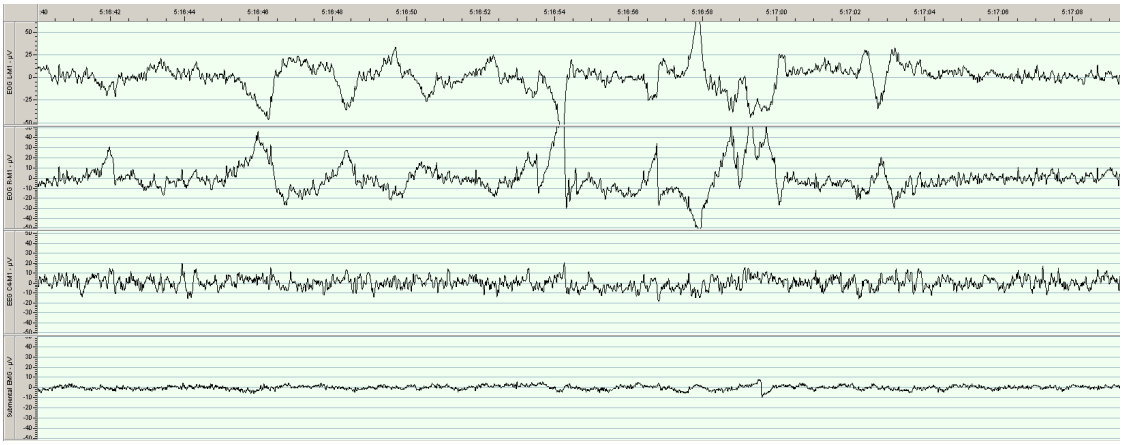

Figure 4. Example sleep recording demonstrating two EOG traces, one central EEG and submental EMG during SREM with rapid eye movements. Horizontal axis is 30 s. Vertical axes are between -50 µV and 50 µV. The data are from subject 213 from study III.

There has been a growing interest in analysing eye movements during sleep since the work by Aserinsky and Kleitman (Aserinsky and Kleitman, 1953, 1955). Rapid eye movement (REM) density (EMD) and REM sleep has been associated with sleep need since 1969 (Aserinsky, 1969). Aserinsky found that REM density approaches maximum after 7-10 hours of sleep. Eye movement density decrease during recovery sleep from sleep deprivation (Feinberg et al., 1987). Using within-subjects study with various sleep

restrictions Lucidi et al. found that decrease in REM density parallels an increase in SWS (Lucidi et al., 1996). De Gennaro et al. also found similar results (De Gennaro et al., 2000a). Eye movement density is higher in REM sleep periods followed by awakenings than in REM sleep periods followed by NREM sleep (Barbato et al., 1994). These findings do not apply to old subjects (Ficca et al., 2004). Density of eye movements is highest 5-10 minutes after the onset of REM sleep period followed by significant decline 10 min later (Aserinsky, 1971). Eye movement density has around two-minute periodicity (Ktonas et al., 2003). Recently lower amount of REM sleep, REM density and REM activity (total of REM) has been correlated with overweight in children and adolescents (Liu et al., 2008).

The proportion of vertical eye movements has also been related to the intensity of REM sleep processes (Feinberg et al., 1969). They used two recording configurations: H with electrodes placed at the outer canthus of each eye referenced to joined bilateral mastoid and VH with same EOG electrodes referenced to forehead electrode placed just above the nasion. They found that when recording also vertical eye (VH) movements the EM activity during SREM was about one third greater in young adults (19-36 years). No difference was found for aged (65-87 years) subjects.

Eyes have been noted to be upward and outwards during sleep as discussed by Aserinsky and Kleitman (Aserinsky and Kleitman, 1955). Jabocs et al. measured eye movement in eight normal subjects using DC electro-oculogram (Jacobs et al., 1971). Electrodes were placed lateral to each eyes and above and below right eye. Experimenter also observed directly the corneal bulge beneath the closed eyelids. Eyes remained at upward position 55% to 85% of S2, S3, S4 time. During SREM onset eyes moved downward. During SREM eye movements were 5% to 15% horizontal, 25% to 35% vertical and 55% to 65% oblique (with vertical tendency). Vertical eye movements predominated during the first REM sleep period. Eye movement patterns in REM sleep were further studied by Hansotia et al. (Hansotia et al., 1990). He noticed that there was a tendency for the eyes to move between the two opposite lateral positions.

Escudero and Marquez-Ruiz have recently characterized similar binocular eye movements during sleep in cats using scleral search-coil technique (Escudero and Marquez-Ruiz, 2008; Marquez-Ruiz and Escudero, 2008). This technique allows measurement of binocular eye movements and rotations without artefacts from neuronal activity which is problematic with EOG based eye movement recording. They found

both tonic and phasic eye movement patterns during sleep. During NREM sleep there was divergence and elevation of visual axis and eye movements were unconjugated (Escudero and Marquez-Ruiz, 2008). During REM sleep there was a convergence and downward rotation of visual axis. During REM sleep all vertical rapid eye movements were always upward.

3.2 Visual sleep stage analysis

Quantitative visual sleep analysis can be event or sleep stage epoch marking and counting. Events can be sleep spindles, K complexes or eye movements. Sleep staging is a data reduction procedure where 30 s of EEG, EOG and EMG signals are classified into one discrete sleep stage. With visual analysis this data reduction is needed to provide consistent, quantitative and practical sleep structure information. Recording of the sleep stage is important for the clinical diagnosis and treatment of sleep disorders (Carskadon and Rechtschaffen, 2005; Matheson et al., 2007). In the standard approach, sleep is visually segmented into epochs of wakefulness (W), movement time (MT), sleep stages SREM, S1, S2, S3 and S4 based on features of EEG, EOG and EMG (Rechtschaffen and Kales, 1968). An example hypnogram demonstrating sleep stages during night is shown in Figure 5. The main information used is the appearance and quantity (density) of certain features within epochs. Standard sleep scoring is a time consuming manual process requiring central scalp EEG electrode, two EOG electrodes and an EMG electrode pair (Rechtschaffen and Kales, 1968). Recently update for scoring was developed (Iber et al., 2007; Silber et al., 2007). Beside sleep staging the polysomnography contains simultaneous recording of multiple sleep parameters. These are e.g. respiration, cardiac activity and limb movements (Penzel and Conradt, 2000; Hauri et al., 2002; Matheson et al., 2007). These recordings are part of the clinical assessment of sleep disorder as described in the International Classification of Sleep Disorders manual (American Academy of Sleep Medicine, 2005).

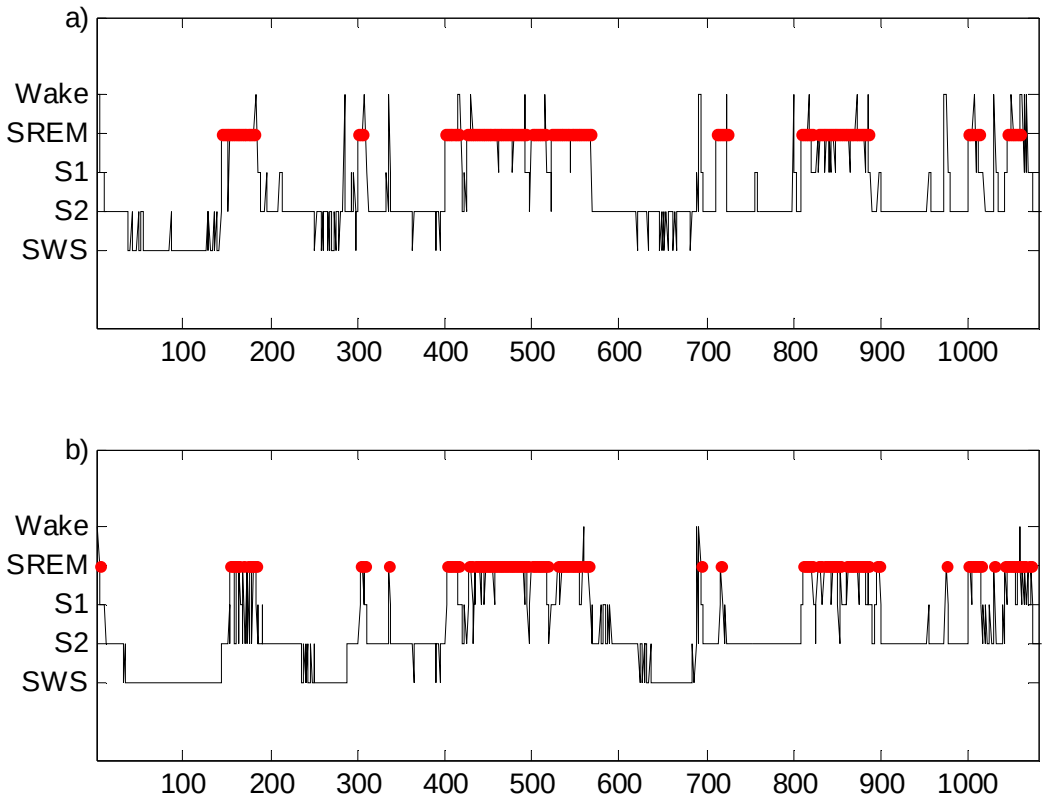

Figure 5. Example hypnograms demonstrating sleep stages as a function of time. Visual scoring a) and automatic EOG based scoring b). Horizontal axis is 30 s epochs number from 22:00 to 07:00. Agreement was 72% with Cohen's Kappa 0.58. The data are from subject 213 from study III.

As described by Schulz (Schulz, 2008) visual sleep staging has evolved three times. First step included work mainly by Loomis in 1930's (Loomis et al., 1937). Loomis categorized sleep into stages A-E. Second step was the discovery of rapid eye movement by Aserinsky and Kleitman (Aserinsky and Kleitman, 1953, 1955). This led to addition of new sleep stage with low voltage EEG and rapid eye movements (Dement and Kleitman, 1957a, b). With the addition of information about muscle tonus first discovered by Michel Jouvet and by Dement (Dement, 1958) in cats and later in humans (Berger, 1961), the new rules were standardized by committee led by Rechtschaffen and Kales in 1968 (Rechtschaffen and Kales, 1968).

3.2.1 Rechtschaffen and Kales scoring manual 1968

According to Rechtschaffen and Kales (R&K) standard criteria sleep is segmented into wakefulness, movement time (MT) and sleep stages SREM, S1, S2, S3 and S4 based on

features of EEG, EOG and EMG (Rechtschaffen and Kales, 1968). Sleep stages were defined as W (wakefulness), MT (movement time), S1, S2, S3, S4 or SREM.

Slow waves are visually defined as waves of 2 Hz or slower which have amplitudes greater than 75µV from peak-to-peak (Rechtschaffen and Kales, 1968). An epoch is defined as stage 3 (S3) if at least 20% of epoch time is slow waves and stage 4 (S4) if more than 50% of epoch time is slow waves. Stages S3 and S4 together are called slow wave sleep (SWS). Amplitudes should be measured from C4-M1 or C3-M2 channel according to standard. Any epoch not fulfilling the S3 or S4 criteria is a candidate for another sleep stage.

The sleep stage 1 (S1) is defined as relatively low voltage, mixed-frequency EEG with a prominence of activity in the 2–7 Hz range. Vertex sharp waves, occasionally as high as 200 µV, may appear and S1 is also characterized by slow eye movements. When alpha activity is less than 50% of the epoch, and a relatively low voltage, mixed-frequency activity, is at least 50% of the epoch, then the epoch is scored as stage 1 (S1). Any clear K complexes (KC) or spindles indicate sleep stage 2 (S2) (Rechtschaffen and Kales, 1968). Less than 3 minute interval between K complexes and/or spindles without indication of movement arousal or pronounced increase of muscle tonus is scored S2. Such intervals of at least 3 minutes are scored as S1. SREM is relatively low voltage, mixed frequency EEG in conjunction with episodic REMs and low amplitude EMG. There are detailed rules especially for the onset and offset of SREM. Basically SREM period is extended to both directions beyond the rapid eye movements until muscle tonus is increased or spindles appear.

3.2.2 American Academy of Sleep Medicine scoring manual 2007

There has been criticism against the Rechtschaffen and Kales scoring system (Himanen, 2000; Himanen and Hasan, 2000; Schulz, 2008). Various supplements have been suggested e.g. clearer definitions of waveforms (Hori et al., 2001; Rodenbeck et al., 2006). After almost 40 years the standard visual sleep scoring manual was recently revised (Iber et al., 2007; Silber et al., 2007). Technical background article about the technical changes was described by Penzel et al. (Penzel et al., 2007). The scoring manual also includes guidelines for measuring e.g. respiration, cardiac activity and periodic limb movements (Iber et al., 2007). Quinonez has reviewed the new scoring rules (Quinonez, 2008a, b). Main changes included additional frontal and occipital EEG

electrodes, combination of S3 and S4 into single SWS stage called N3 and simpler rules.

Beside new stage names there are some clear differences between R&K 1968 and AASM 2007 scoring manuals. In R&K scoring is always based on C4/A1 or C3/A2, in AASM frontal F3-M1 or F3-M2 channels are used for N3 scoring. In R&K slow eye movements cannot define the onset of S1 and in AASM SEM can define N1 in subjects without alpha rhythm. Stage N2 can end to arousal without an increase in muscle tonus. In R&K no spindles or K complexes were allowed during SREM. In AASM there is no 3 minute rule of maximum N2 duration without spindles or K complexes as in R&K. This rule removal has been suggested earlier (Hasan, 1983). Quantitative differences between scoring systems has been evaluated by Moser et al. (Moser et al., 2009). It was found that the new scoring increases the amount of light sleep (+3%) and deep sleep (+2%) and decreases the amount of S2 (-5%). Interestingly effects on stage REM were age dependent. Interrater reliability of the new sleep scoring is higher in all other except stages S2/N2 (Danker-Hopfe et al., 2009).

3.3 Electro-oculography

3.3.1 Measurement

The eye has a standing electrical potential called the corneo-fundal potential. This potential is lower in darkness (Arden and Constable, 2006). Similarly the magnetic field of blinks is lower in darkness (Antervo et al., 1985). Electro-oculography has clinical use to measure function of outer retina and retinal pigment epithelium (RPE) (Arden and Constable, 2006).

Most measurements are AC coupled. Thus absolute potentials cannot be measured, only changes in potentials. The DC recording is problematic. Skin potential gives large DC components (Picton and Hillyard, 1972). Necessary requisition for DC measurement is nonpolarizable Ag/AgCl electrode and skin preparation. Tursky and O'Connell have compared the AC and DC eye movement recording (Tursky and O'Connell, 1966). More detailed discussion about the effects of AC recording see review by Boukadoum and Ktonas (Boukadoum and Ktonas, 1986). Too high high pass filter cut-off reduces the detection of overshoot as described by Brown (Brown et al., 2006). The effects of

time constant for slow eye movements have been studied by Hiroshige (Hiroshige, 1998). He concluded that time constant of longer than 3 s should be used.

There are beside EOG also other techniques to measure eye movements. Miles photographed reflected light from cornea during sleep onset (Miles, 1929). With eyes open video-oculography (VOG) is the most common. Scleral search coils is considered the most accurate method to record eye movements (Van der Geest and Frens, 2002). With coils measurement of eye movements is possible during eye closures and also rotational movements can be measured. Mechanical sensors have been placed on eyelid (Messin et al., 1975; Kayed et al., 1979; Mamelak and Hobson, 1989). Reflected infrared light from an open or closed eye has been used to measure eye movements in infants (Harper et al., 1976). There are video based methods looking at the closed eyelids (Hsieh et al., 2007; Hsieh et al., 2008). Video monitoring has been recently used also inside MRI scanner (Hong et al., In press).

3.3.2 Electrode placement

Early sleep studies had variable EOG electrode configurations. Loomis et al. used one referential electrode "above and left of left eye" (Loomis et al., 1937). Aserinsky and Kleitman used two bipolar channels of one eye (Aserinsky and Kleitman, 1953). Hord combined four electrodes (inner and outer canthi of the eyes) into single bipolar channel to increase the common mode rejection of EEG (Hord, 1975). This setup has drawbacks in automatic analysis (Hasan, 1983). Wells et al. used only two electrodes for single-channel bipolar measurement (Wells et al., 1977). They stated that "flexibility in electrode placement: positioning above and below the centerline of the eye may be alternated for each electrode". This could minimize skin irritation in sleep recordings over many consecutive nights. Toth placed electrodes on the eyelid to record eye movements without any clear contamination from EEG activity (Toth, 1970).

In standard manual (Rechtschaffen and Kales, 1968) electro-oculography electrode positions are recommended as: "electrode approximately 1 cm above and slightly lateral to the outer canthus of one eye and a reference electrode on either homolateral ear lobe or mastoid. On the second eye movement channel are recorded the potentials from an electrode 1 cm below and slightly lateral to the outer canthus of the eye referred to the contralateral ear or mastoid, i.e. both eyes are referred to the same ear or mastoid electrode" (Rechtschaffen and Kales, 1968). In figure 1-1 (Figure 6) of the standard

manual left earlobe (A1) is shown as a reference electrode but in later examples (Figure 1-9 to Figure 1-34 in manual) right earlobe (A2) is indicated.

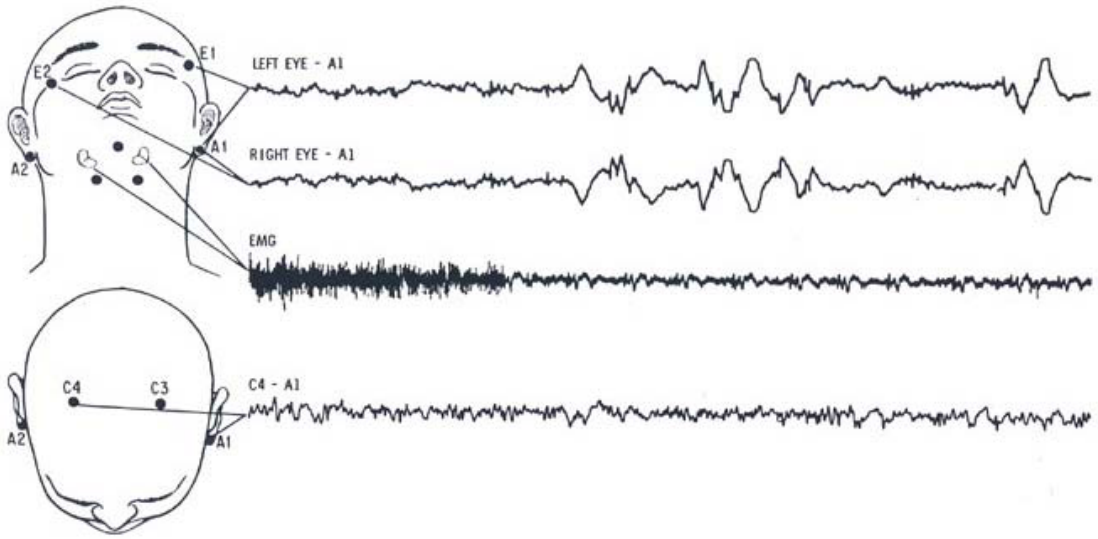

Figure 6. Standard electrode placement according to Rechtschaffen and Kales (Rechtschaffen and Kales, 1968). Reprinted with permission from (Kryger et al., 2005).

Limitations of used electrode configuration were already noticed within the manual: "some oblique eye movements can result in relatively flat traces". Various other configurations have been used. Quite common is to use contralateral reference electrodes for left and right EOG electrodes to maximize the signal amplitude for both EOGs and equalize the amplitudes of deflections for conjugate eye movements (Hilbert and Naitoh, 1972; Carskadon and Rechtschaffen, 2005). Setup also enables one EOG signal in case of one faulty reference electrode. Ipsilateral mastoid has also been used as reference by Agarwal et al. (Agarwal et al., 2005).

Häkkinen et al. compared different electrode positions for recording saccades and blinks during wakefulness (Häkkinen et al., 1993). Electrode positions are at the outer canthus and 1 cm below left eye (P18) and 1 cm above right eye (P8) referenced to the left mastoid (M1) produced the largest and most symmetrical deflections of blinks and saccadic movements. The electrode P8 is placed over the eyebrow. This configuration was also used in SIESTA project (Klosch et al., 2001). Placing the electrodes too close to eyes can cause discomfort and usually electrodes are not placed over the eyebrow. In new manual (Iber et al., 2007; Silber et al., 2007) this configuration was recommended

with the exception of using M2 instead of M1. Electrodes are labelled as E1-M2 for left and E2-M2 for right.

Alternative EOG derivation in new manual is electrodes 1 cm below and 1 cm lateral to the outer canthus of the eyes with Fpz as a reference. This E1-Fpz, E2-Fpz has been used by Hauri et al. (Hauri et al., 2002). Essentially same configuration for vectonystagmography was first suggested by Padovan and Pansini 1972 (Padovan and Pansini, 1972). This has been used for automatic analysis (Degler et al., 1975) and for artefact rejection (Schlögl et al., 2007). Similar configuration, placing the electrodes at outer canthus and referenced to a forehead electrode, has been used by Feinberg et al. (Feinberg et al., 1969). In order to reduce the amount of EEG recorded other configurations have also been suggested (Hord, 1975; Hyoki et al., 1998; Leinonen et al., 2003).

Time constants shorter than 0.3 s (0.5 Hz) are not recommended in the old manual (Rechtschaffen and Kales, 1968). In new manual (Iber et al., 2007; Silber et al., 2007) high pass filter setting for EOG was lowered to 0.3 Hz. The relationship between time constant *tc* and high pass (first order analog filter with capacitance *C* and resistance *R*) filter cut off *fc* is the following

$$tc = {}^{1}\!\!\diagup\!\!{}_{2\pi fc} = RC \tag{1}$$

$$a(t) = a(0)e^{-t/tc} \tag{2}$$

Thus after time *tc* fixed DC signal is reduced to 0.37 of original amplitude (-3 dB amplitude is 10^(-3/20)=0.71 from maximum). Analog high pass filter with capacitance *C* and resistor *R* can be presented as the following recursive digital filter

$$\alpha = {}^{RC}\!\!\diagup\!\!{}_{RC+dt} \tag{3}$$

$$y(t) = \alpha\left[y(t-dt) + x(t) - x(t-dt)\right] \tag{4}$$

Embla A10 (Embla, Broomfield, CO, USA) has a digital high pass filter with a linear phase. Effect of 0.5 Hz filter and 0.5 Hz zero phase filter is shown in Figure 7. In the new standard analog type filters are recommended (Iber et al., 2007).

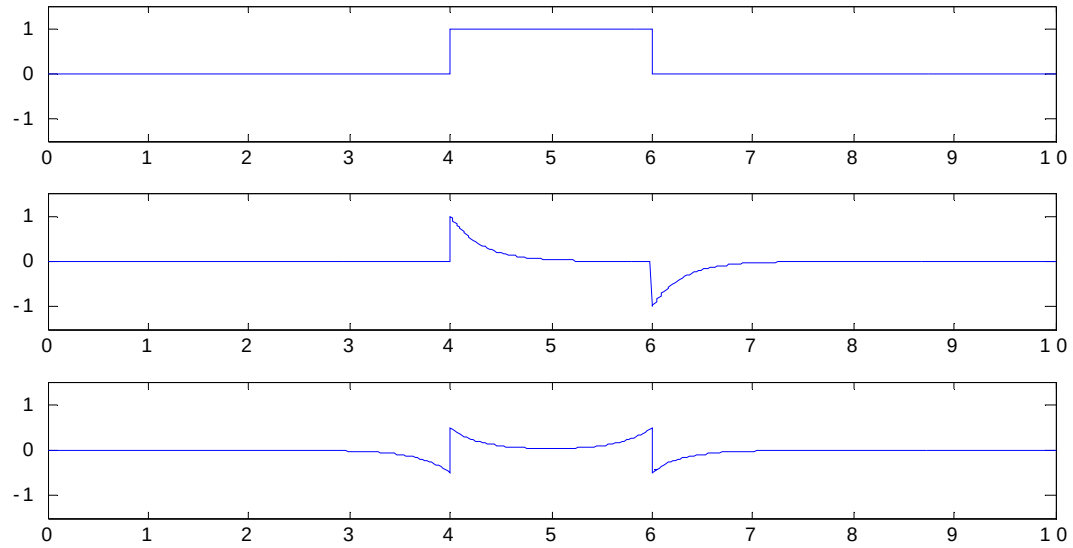

Figure 7. On top 2 s calibration signal, in middle the effect of 0.5 Hz high pass filter, in bottom the effect of 0.5 Hz high pass zero phase filter obtained by refiltering the reversed filtered signal. Due to double filtering this filter has steeper frequency response. Horizontal axis is 10 seconds.

3.3.3 Blinks and eyelid closures

During blinks the moving eyelid over the positively charged cornea alters the electrical field around the globe and is responsible for the recorded potentials (Matsuo et al., 1975). Blinks can be recorded as positive peaks on electrode positions superior to eyes, e.g. on forehead, Figure 8. Magnetic signal resulting from blinks is also consistent with this (Antervo et al., 1985). The Bell's phenomenon, upward eye rotation, seems to apply only to slow or forced blinks (Iwasaki et al., 2005). Blinks suppress neuronal processing of retinal information (Bristow et al., 2005).

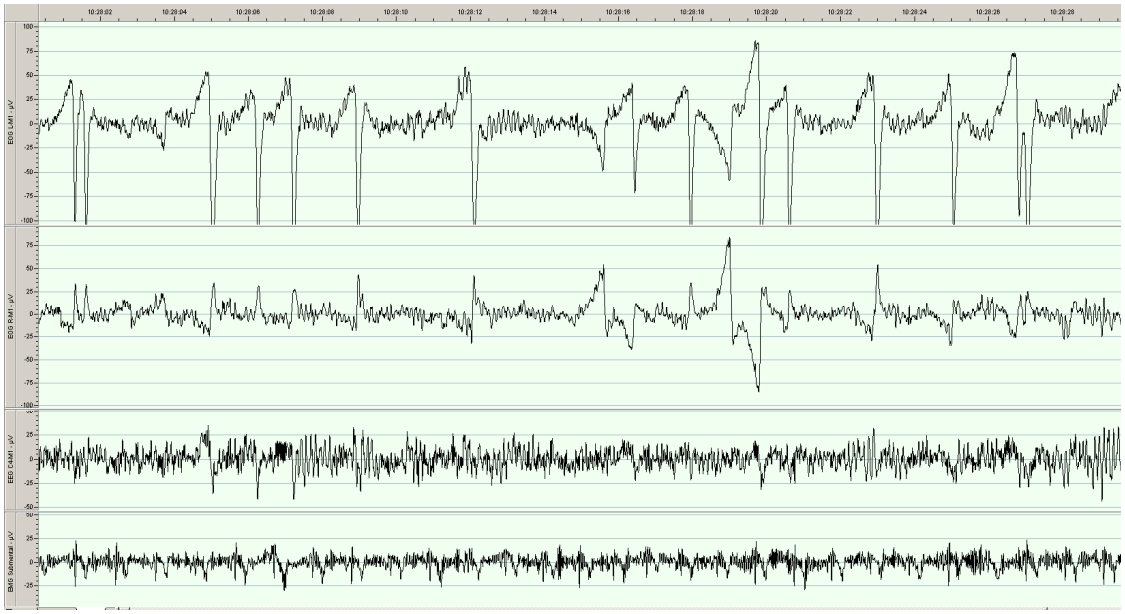

Figure 8. Example recording demonstrating blinks during wakefulness. Two EOG traces (first EOG L-M1), one central EEG, and submental EMG during wakefulness. Vertical axes are between -100 µV and 100 µV for EOG and between -50 µV and 50 µV for EEG and EMG. Horizontal axis is 30 s. Positive is downward as in every figure. The data are from subject 33 from study II.

Blink durations are indicators of fatigue (Schleicher et al., 2008). The used algorithm searched eye movements with velocity >30°/s and blinks were detected as upward "saccade" followed by a downward "saccade". Overlong blinks with a delay of more than 100 ms between full closure and reopening are difficult to distinguish from an upward gaze followed by a downward gaze. Related to subjective and video based defined fatigue most sensitive parameters were blink duration, lid reopening, blink interval and standardised lid closure speed (Schleicher et al., 2008). De Gennaro et al. measured spontaneous blinks during Multiple Sleep Latency Test (MSLT) (De Gennaro et al., 2005). Spontaneous blinks were identified on the vertical channel using a velocity plus a duration criterion: peaking within 50–100 ms and with a duration <400 ms with triangular shape (Santamaria and Chiappa, 1987). These blinks while eyes closed are called mini-blinks and are best detected with movement sensor on eyelid (Santamaria and Chiappa, 1987). Recently dry electrodes have enabled the use of EOG e.g. in helmets (Kim et al., 2009). With reference electrode on the jaw they noticed also changes in blink waveform.

Visually measured blinks during driving were longer while sleepy. Sleepiness was measured by maintenance of wakefulness test (MWT) (Häkkänen et al., 1999). After treating apnoea the improvement of MWT was correlated with the decrease of blink duration. The partial eye closure, the proportion of time that the eyes of a subject are >80% closed using video (PERCLOS), has been found to be a sensitive drowsiness indicator (Wierwille et al., 1994; Wierwille and Ellsworth, 1994; Dinges and Grace, 1998; Dinges et al., 1998). Blink durations have also been measured using reflected amount of infrared (Caffier et al., 2003, 2005). Johns et al. have used multiple eyelid parameters, e.g. amplitude-velocity ratios (AVR) of eyelids closing and reopening to develop index for drowsiness (Johns et al., 2007). Most typically EOG is used to measure blink durations (Åkerstedt et al., 2005; Jammes et al., 2008; Shuyan and Gangtie, 2009). Typically the signal is first low pass filtered and differentiated for velocity. Velocity profiles are used to define the onset and the offset of the blinks.

3.3.4 Slow eye movements

Already in 1929 Miles (Miles, 1929) observed the importance of eye movements in the transition between wakefulness and sleep: "The contrast between alertness and drowsiness is most evident in the behaviour of the eyes". There was also reference to slow eye movements: "These horizontal eye movements which we have found to occur also at the very onset of sleep resemble pursuit movements when the eye is closely following some object like a slow swinging pendulum.". In standard sleep stage scoring (Rechtschaffen and Kales, 1968) slow eye movements do not define sleep onset but are related to sleep onset: "Stage 1, especially following wakefulness, is characterized by the presence of slow eye movements, each of several seconds duration, which are usually most prominent during the early portions of the stage". In the new scoring manual (Iber et al., 2007; Silber et al., 2007) slow eye movements (SEM) can be used to define sleep onset for subjects who do not generate alpha rhythm. They are defined as "conjugate, reasonably regular, sinusoidal eye movements with an initial deflection usually lasting >500 ms".

Santamaria and Chiappa defined slow eye movements as 0.25 Hz pendular, horizontal eye movement and were seen in all subject and in 51% as the first sign of drowsiness (Santamaria and Chiappa, 1987). Torsvall and Åkerstedt have defined slow eye movements on the horizontal EOG channel to have a duration of 1 second or longer and at least 100 μV in amplitude (Torsvall and Åkerstedt, 1988). Instead of calculating the

number of SEMs they calculated the proportion of the epoch occupied by such activity. De Gennaro et al. added velocity criterion <50°/s and minimum amplitude 3° (De Gennaro et al., 2000b).

Slow eye movements can also be measured using a movement sensor on the eyelid (Santamaria and Chiappa, 1987; Atienza et al., 2004). This Nightcap system uses an adhesive-backed, 25 mm x 7 mm piezoelectric film attached to the upper eyelid. An eyelid movement (ELM) was automatically identified whenever the output of the piezoelectric film, filtered between 3 and 20 Hz, exceeded 10 mV during a 250 ms epoch. A low ELM count correlated with a high SEM count (Atienza et al., 2004). Slow eye movements have been indicated to be sensitive for sleep deprivation only when eyes are closed (Marzano et al., 2007). Sometimes SEMs have been measured using vertical EOG channel (Torsvall and Åkerstedt, 1987). This likely reflects slow eye closures.

Fabbri et al. (Fabbri et al., In press) have defined slow eye movements by the following criteria

1. slow sinusoidal excursion (0.2–0.6 Hz) lasting more than one second
2. amplitude between 20 and 200 μV
3. binocular synchrony with opposed-phase detections in the two EOG channels
4. onsets of the right and left eye movements occur within 300 ms of one another;
5. movements begin and end at near-zero velocity
6. absence of artefacts (such as blinks, EEG/EMG artefacts)

Porte had almost same criteria for slow eye movements (Porte, 2004). Värri et al. developed hybrid median filter for detection and separation of different eye movements (Värri, 1992; Värri et al., 1995; Värri et al., 1996). The algorithm used two-channel EOG data. EOG data was preprocessed with weighted median hybrid (WFMH) filter. Filter length was 220 ms. By subtracting the output from original signal high pass version of the original signal was obtained. It was used for blink detection. After low pass filters the running correlation was calculated using different windows for blinks,

saccades and SEMs (Värri et al., 1996). The correlation was transformed and used as multiplier. Running sum based symmetry index was also used as a multiplier. For SEM detection also maximum derivative was used. System provided continuous estimates of saccades, blinks and slow eye movements. Correlation coefficient is defined as

$$\rho_{X,Y} = \frac{\operatorname{cov}(X,Y)}{\sigma_X \sigma_Y} = \frac{E[(X-\mu_X)(Y-\mu_Y)]}{\sigma_X \sigma_Y} = \frac{E(XY)-E(X)E(Y)}{\sqrt{E(X^2)-E^2(X)}\sqrt{E(Y^2)-E^2(Y)}} \qquad (5)$$

Sample (Pearson) correlation coefficient can be formulated as

$$r_{x,y} = \frac{\sum x_i y_i - n\bar{x}\bar{y}}{(n-1)s_x s_y} = \frac{n\sum x_i y_i - \sum x_i \sum y_i}{\sqrt{n\sum x_i^2 - (\sum x_i)^2}\sqrt{n\sum y_i^2 - (\sum y_i)^2}} \qquad (6)$$

The square of correlation coefficient is the fraction of the variance in *y* that is accounted for by a linear fit of *x(i)* to *y(i)*.

Chang et al. used half-wave period, leading slope threshold, an amplitude threshold and central EEG background check (Chang et al., 1990). Hiroshige used linear regression (Hiroshige, 1999). Regression line was fitted every 20 ms using 400 ms window. Rising point of SEM was defined as the first appearance of absolute velocities ≥25 °/s and a peak point as the first appearance absolute velocities of ≤10 °/s. The degrees are not related to visual angle but to the angle of the regression line. The inter-peak interval had to be at least 750 ms and interval between rising point and peak at least 500 ms. During S1 on average two slow eye movements were detected every epoch with mean amplitude of 140 µV and 1800 ms peak time (Hiroshige, 1999).

Suzuki et al. used template matching to detect SEM and REM (Suzuki et al., 2001). Various templates of the altered sine waves were used and degree of similarity was calculated. If the duration of best fit template was more than 250 ms then the EOG wave was considered as a SEM. They concluded that SEM detection was similar but the template matching overestimated REM during S1/S2 and linear regression by Hiroshige (Hiroshige, 1999) underestimated REM during S1/S2 when compared to visual analysis (Suzuki et al., 2001).

Recently Magosso et al. developed wavelet based method for SEM detection (Magosso et al., 2007). They used power in different wavelet bands in 16 s window to define SEM. They validated the system also during 24h recordings (Magosso et al., 2007). In a

follow up study they found high correlation with standard sleep onset (Fabbri et al., In press). Automatic analysis was based on single calculated bipolar channel (Magosso et al., 2006). Frequency representation was calculated based on 10 wavelet frequencies from 32-64 Hz (E1) to 0.0625-0.125 Hz (E10). Decision was based on weighted sum E7-E10 divided by a weighted sum of E3-E5 (2-16 Hz) and E7-E10 (0.0625-0.5 Hz). Based on weights (Magosso et al., 2006) most important in this algorithm seems 0.25-0.5 Hz as indicator of SEM and frequencies 2-8 Hz as indicator of non SEM.

During wakefulness slow eye movement like smooth pursuits can be measured. Unlike saccades, smooth pursuit eye movements are not under voluntary control and their initiation generally requires a moving visual target (Deckert, 1964; Berryhill et al., 2006). They are not as clear indicators of sleepiness as, for instance, the velocities of saccades (Porcu et al., 1998). Interestingly drowsy people could extrapolate the smooth pursuit movement up to 17 s without visual stimulus (de'Sperati and Santandrea, 2005).

3.3.5 Saccades and saccade detection

For saccade detection there are many automatic detection systems as they are frequently measured also during daytime. Various cognitive aspects can be probed with eye movements, for instance, attention (Duc et al., 2008). Automatic systems exist for the analysis waking saccades (Jäntti, 1982; Juhola et al., 1985). Here mainly electro-oculography based methods are discussed during sleep recordings.

Early systems used analog circuits to detect eye movement synchrony (Minard and Krausman, 1971; Ktonas and Smith, 1978). System developed by Okuma et al. was used for waking subjects during REM sleep for dream reporting (Okuma et al., 1970). The system filtered EOG 0.3-2 Hz. Using vector configuration of Padovan and Pansini (Padovan and Pansini, 1972) Degler et al. separated also direction of eye movements (Degler et al., 1975). Goldberg and Beiber developed a system using filtered EOG 0.3-2.5 Hz to detect REM (Goldberg and Beiber, 1979). Extensive discussion about effect of electrode montage and filtering was carried out by Boukadoum and Ktonas (Boukadoum and Ktonas, 1986).

With digital technology Gopal and Haddad developed system based on slope and amplitude (Gopal and Haddad, 1981). Matched filtering was studied by Hatzilabrou et al. (Hatzilabrou et al., 1994). Tsuji et al. used wavelet transformation (Tsuji et al., 2000). Tan et al. used period-amplitude (PA) and FFT analysis to count the number of

EMs during SREM (Tan et al., 2001). REMs were visually scored as number of 2 s segment with EM with amplitude >25μV. Automatic analysis was based on integrated amplitude of waves 0.3-2 Hz.

Takashashi and Atsumi analyzed horizontal EOG (Takahashi and Atsumi, 1997). Data was averaged with 88 ms window and differentiated to detect onset and offset of saccades. Amplitude, duration and slope of saccades had to be >30 μV, <500 ms and >250 μV/s respectively. Doman et al. used 8 Hz low pass (Doman et al., 1995). Agarwal et al. used two-channel EOG referenced to ipsilateral mastoids (Agarwal et al., 2005). Signals were filtered with 4th order Butterworth 1-5 Hz. Following steps were used in analysis

1. Instantaneous product of traces at least 10 $(\mu V)^2$. Local maximum if no higher peak in 1 s time window
2. Maximum absolute amplitude of left or right EOG below 500 μV.
3. Correlation coefficient below -0.2.
4. Calculation of negative instantaneous product. Values >120 $(\mu V)^2$ provided identical sensitivity and specificity of 80%.
5. Calculation of deflection angles using 0.2 s of data on the left and on the right side of peak. Deflection angle had to change at least 45º for both left and right or at least 30º of one and at least 60º for another.

Manual scoring of REM (minimum time between events 0.5 s) was compared to automatic detection. Sensitivity was defined as correct detections divided by manual count. Specificity was defined as correct detections divided by automatic count. Overall sensitivity and specificity of system were 67% and 78%.

3.3.6 Eye movements as artefact signal

In EEG and MEG studies eye and eyelid movements are usually considered as artefacts (Anderer et al., 1999; Fatourechi et al., 2007). There are three main approaches to handle these artefacts: to exclude periods of eye movements and blinks, or to use regression or independent component analysis to separate them from EEG activity.

Regression based methods have been most popular (Croft and Barry, 2000; Croft et al., 2005; Schlögl et al., 2007).

Biophysical model explaining effect of eye movements on EEG has been developed (Elbert et al., 1985). Principal component analysis (PCA) has been used by Lins et al. (Lins et al., 1993). A promising new approach is the use of a gaze tracker to monitor eye movement and calculate the resulting electrical artefact on EEG (Kierkels et al., 2006) or on MEG (Hironaga et al., 2004). Using the model Kierkels et al. (Kierkels et al., 2007) compared different correction methods. Independent component analysis was compared with a regression based method also by Hoffman and Falkenstein (Hoffmann and Falkenstein, 2008) indicating the superiority of independent component analysis.

From ocular motoneurons another artefact signal is called "presaccadic spike potential" (Thickbroom and Mastaglia, 1985). This is also called "saccade spike" (Jäntti et al., 1983). This was first described by Blinn (Blinn, 1955). This anterior negative peak appears before saccade start with latencies being shorter for medially oriented (adducting) saccades. These spikes can be noticed as gamma band activity in EEG (Yuval-Greenberg et al., 2008).

3.4 Automatic sleep analysis

In all sleep analysis some features are estimated from measured physiological signals during sleep. There are mainly two different ways of developing automatic sleep analysis: 1) one can imitate human sleep scoring or 2) one can try to develop other types of measures to characterize the sleep processes (Hasan, 1983). If the goal is sleep staging then the calculated features are used to derive sleep stage. Sleep analysis can be divided into following steps (Penzel and Conradt, 2000)

1. Removal of artefacts (e.g. ECG, EOG, movement, respiration)
2. Feature detection and waveform recognition (e.g. delta, theta, alpha, sigma, beta, spindles, K complexes, vertex wave, SEM, REM)
3. Classification rule (e.g. neural networks, adaptive segmentation, fuzzy logic)
4. Sleep stage epochs or self clustering. Alternatively non epoch based analysis, for instance, continuous sleep plots

Very soon after the first automatic EEG analysis (Burch, 1959) the same methods were applied also to sleep recordings. Agnew et al. used the system developed by Drohocki to plot EEG integrated amplitude during the night (Agnew et al., 1967). Highest values were obtained during S3 and S4. Smith et al. used bandpass filters to detect the rhythmical waveforms (Smith et al., 1969). Frost developed portable (one cubic feet) analog sleep detector using one channel EEG and one channel EOG (Frost, 1970). System used EEG filtered 0.7-13 Hz amplitude and period to generate continuous sleep depth curve which was thresholded to sleep stages. There were three amplitude levels 100%, 20% and 1%. The 100% corresponded to the only highest amplitudes detected during wakefulness. Only the 100% peaks were combined with periods. Periods were detected when 1% and 20% thresholds were crossed in a sequence. Lowest curve values were with low period and high count of high peaks. Filtered 2-3 Hz EOG amplitude was an indicator of SREM if EEG indicated stage S1. Many systems used period-amplitude analysis (Itil et al., 1969; Roessler et al., 1970). Review of analog, hybrid and early digital automatic sleep analysis systems was carried out by Hasan (Hasan, 1983).

One of the first fully digital systems was pattern recognition system by Martin et al. (Martin et al., 1972). The EEG was low pass filtered at 28 Hz and EOG at 14 Hz. Fourier analysis on 30 s epochs was used to separate W, S1 and S2. Conjugate REMs were detected on the two EOG channels. Pattern recognition was used for delta detection. Peaks were detected as local maxima with no higher local maxima within 0.5 s. Valleys were identified as lowest points between two adjacent peaks. Peak-to-valley difference had to exceed 75μV and correlation coefficient of raw data with the fitted straight line from valley to peak had to be at least 0.75. Agreement of 82% was obtained for separating W, S1, SREM, S2, S3 and S4. This was only 7% less than inter-rater agreement.

Currently all sleep recordings are carried out in digital format. This digital process has been described by (Hasan, 1996; Penzel and Conradt, 2000; Agarwal and Gotman, 2002; Penzel et al., 2007). Review of early and later development in automatic sleep analysis has been carried out by several authors (Hasan, 1996; Agarwal and Gotman, 2001; Anderer et al., 2005). Recently two automated and semi-automated methods, Somnolyzer 24x7 (Anderer et al., 2005) and Morpheus (Pittman et al., 2004), were compared by Svetnik et al. (Svetnik et al., 2007) for analyzing clinical trial data. Automated or semi-automated sleep scoring offered alternatives to costly, time

consuming, and variable manual scoring. With the introduction of new scoring manual there have been discussions about the use and misuse of automatic methods (Schulz, 2008; Zammit, 2008). One reason for developing automatic methods is the visual scoring variability (Danker-Hopfe et al., 2004; Danker-Hopfe et al., 2009). Larsen et al. have indicated that automatic analysis of slow wave sleep could be more reproducible than visual analysis (Larsen et al., 1995).

3.4.1 Artefacts

Artefact processing of sleep EEG has been reviewed by Anderer (Anderer et al., 1999). Artefacts can be ocular artefacts from eye movements or movements of the eyelids, EMG artefacts from swallowing or body movements. Brunner et al. demonstrated that rejection of short-lasting muscle bursts significantly reduced power spectral density in all EEG frequencies (Brunner et al., 1996). Myogenic activity was detected using high frequency 26-32 Hz activity in each 4 s epochs and compared to the local 3 min average.

One artefact is the electrical conduction of ECG to EEG, EOG and EMG. Barlow and Dubinsky developed R peak reduction by averaging using non cephalic reference for EEG (Barlow and Dubinsky, 1980). Nakamura and Shibasaki used exponentially weighted average of ECG artefact on EEG using ECG R peak as trigger. This average was then subtracted from the contaminated EEG (Nakamura and Shibasaki, 1987). Larsen and Prinz used iterative least square to eliminate ECG from EEG. Points which had highest residual were excluded from next round AR fitting (Larsen and Prinz, 1991). The system was later used in sleep analysis (Prinz et al., 1994). Park et al. fitted AR model excluding the R peak data and reconstructed the data (Park et al., 1998). There are different approaches to detect QRS needed for this approach (Kohler et al., 2002). Later Park et al. used smoothed nonlinear energy operator (SNEO) to detect candidate R peaks and used periodicity criterion to detect R peaks and then used averaging to subtract the artefact from EEG (Park et al., 2002).

Also other techniques exist for eliminating artefacts from single-channel data (Teixeira et al., 2006). Especially with multichannel data blind source separation (BSS) as independent component analysis (ICA) has been used to separate different waveforms (Poree et al., 2006).

3.4.2 Features and events

There are three main uses of features in sleep staging. Either features are 1) calculated as an average over the epoch or 2) the density of features (e.g. slow waves) is calculated within an epoch or 3) discrete events (e.g. spindles, REM) are detected. Average of features has been used widely (Schaltenbrand et al., 1996; Zoubek et al., 2007; Susmakova and Krakovska, 2008). Density of slow wave activity was used as the sole criterion by Durka et al. (Durka et al., 2005). Main discrete events are spindles, K complexes, vertex waves, SEM and REM. Sleep onset epochs have been detected using only automatic SEM detection (Fabbri et al., In press).

Typically all these three types of features are used either in fixed epochs (Anderer et al., 2005) or in adaptive length epochs (Värri et al., 1992; Agarwal and Gotman, 2001). Typically the importance of each individual feature in sleep staging is not reported. Sometimes features are used as sleep plots without explicit sleep staging (Kemp, 1993; Davies et al., 1999; Flexer et al., 2005).

Early work used period-amplitude (PA) analysis (Feinberg et al., 1978). Period of either zero crossing or zero derivatives are calculated. Methods have been compared and they give similar results for <2 Hz activity (Ktonas, 1987; Geering et al., 1993; Armitage et al., 1995a; Uchida et al., 1999). Period-amplitude analysis has been used also for detection of eye movements (Tan et al., 2001). With period-amplitude analysis single waveforms can be quantified which is not possible with power spectral analysis. For instance different waveform incidences and amplitudes can result in similar power spectrum (Ktonas and Gosalia, 1981). Period-amplitude analysis (PAA) is sensitive for filtering (Ktonas, 1987) and has been mostly replaced by spectral analysis. Recently there has been new interest in waveform analysis, for instance, analysis of grouping of spindles (Mölle et al., 2002) and linking waveform characteristics of SWS to sleep pressure (Riedner et al., 2007).

Most common features are based on spectral estimates. Early work used long 16 s or 30 s spectral windows (Martin et al., 1972; Prinz et al., 1994) but currently shorter e.g. 1 s (Park et al., 2000) windows are used and averaged over the 30 s epoch. Spectral estimates are typically obtained by using discrete Fourier transform (DFT) (7). Inverse discrete Fourier transform (IDFT) can be used to obtain filtered time domain signals (8).

$$X(k) = \sum_{n=0}^{N-1} x(n) e^{-\frac{i2\pi}{N} kn} \tag{7}$$

$$x(n) = \frac{1}{N} \sum_{k=0}^{N-1} X(k) e^{\frac{i2\pi}{N} kn} \tag{8}$$

Typically *x(n)* is first windowed. Discrete Fourier Transform can be interpreted as least square fitting of sines and cosines and there is matrix presentation of transform (Smith, 2007). There exist various Fast Fourier Transform (FFT) algorithms for calculating the DFT. The most common is the Radix-2 when number of samples is equal to 2^n where *n* is integer. With modern computers the calculating of DFT of practically any sample length is not a time-consuming task. Jobert et al. have used ratio of alpha power 8-11.5 Hz divided by delta and theta power 2-8 Hz (ASI) to detect wakefulness epochs (Jobert et al., 1994). Spectral edge has been used by Huupponen et al. (Huupponen et al., 2005).

Sometimes adaptive segmentation is used. Using linear prediction errors of 2 segments Gath and Bar-On searched quasi-stationary segments (Gath and Bar-on, 1980). Värri et al. (Värri et al., 1992) used two 0.8 s sliding windows to calculate sum of absolute amplitude and sum of absolute differences (used as an estimate of frequency). Segments were decided based on weighted sum of these two features. Kaplan et al. (Kaplan et al., 2001) used change point statistics developed by Brodsky et al. (Brodsky et al., 1999). Agarwal and Gotman used following nonlinear energy operator (NLEO) to define segment borders (Agarwal and Gotman, 2001)

$$\Psi(n) = x(n-1)x(n-2) - x(n)x(n-3) \tag{9}$$

There exist also other decompositions beside DFT (Smith, 2007) e.g. wavelets or matching pursuit (MP) (Durka et al., 2001; Durka et al., 2005; Durka, 2007) first introduced by Mallat and Zhang (Mallat and Zhang, 1993). Basic idea with MP is to iteratively break up signal into a weighted sum of known functions. Sometimes filtering is used to obtain power in different bands (Anderer et al., 2005). Berthomier et al. used subject specific frequency bands (Berthomier et al., 2007). Other used features can be time domain features e.g. ones developed by Fujimori (Uchida et al., 1996), Hjorth (Hjorth, 1970) or nonlinear features (Fell et al., 1996; Susmakova and Krakovska, 2008).

Various other patterns have been detected from sleep EEG. Olbrich and Achermann detected oscillatory patterns (Olbrich and Achermann, 2005) using technique developed by Franaszczuk and Blinowska (Franaszczuk and Blinowska, 1985). Kemp has developed model-based delta analysis (Kemp et al., 2000). Beside eye movements (discussed in previous chapters) spindles are the most important event features in sleep staging. Sleep spindles are distinct phasic feature of NREM sleep (De Gennaro and Ferrara, 2003). For spindle detection various methods have been developed (Smith et al., 1975; Schimicek et al., 1994; Huupponen et al., 2007; Malinowska et al., 2007).

3.4.3 Classification

Pattern recognition goal is either supervised or unsupervised classification (Jain et al., 2000). In sleep analysis events, epochs (fixed or unfixed duration) or recordings can be classified. Usually event classification is supervised, for instance, looking for spindles. Non epoch based unsupervised classification was carried out by Flexer et al. (Flexer et al., 2005). Agarwal et al. segmented data and did unsupervised classification on these segments. The user then gave these fixed number of classes labels to obtain R&K sleep scoring (Agarwal and Gotman, 2001). Non fixed supervised epoch classification was carried out by Värri et al. (Värri et al., 1992). Most typically single 30 s epochs are classified using a training material (supervised classification) (Anderer et al., 2005).

Neural networks have been used extensively (Schaltenbrand et al., 1996). With complex algorithms like neural networks it is important to have separate training, testing and validation data sets (Jain et al., 2000). With small sample size e.g. leave-one-out cross validation (LOOCV) can be used. With leave-one-out cross validation a classifier is trained using *(n-1)* samples and evaluated on the one remaining sample and the procedure is repeated *n* times. Fuzzy rules have been used by Jansen and Dawant (Jansen and Dawant, 1989). Bayesian approach with explicit prior sleep stage probabilities has been used by, for instance, Lacroix and Stanus (Lacroix and Stanus, 1985). Sometimes prior probabilities are varying with time (Redmond et al., 2007) or varying within NREM sleep cycles (Anderer et al., 2005). Modelling approach has been studied by Kemp et al. (Kemp et al., 1985; Kemp et al., 2000). Learning vector quantizers were used by Kubat et al. (Kubat et al., 1994).

System developed by Hasan was based on detecting epoch transitions (Hasan, 1983). Park et al. had two-stage classification (Park et al., 2000). After rule-based classification

case specific classification was used. The algorithm of Somnolyzer 24x7 has been described in details by Anderer et al. (Anderer et al., 2005). They used various power and density features and linear discriminant analysis (LDA) with a decision tree. The first step in the decision tree was S3 and S4 separation using slow wave density, theta density and alpha density.

Currently the use of support vector machine (SVM) is getting popular for any supervised classification. For introduction of SVM see (Cristianini and Shawe-Taylor, 2008). SVMs have been used with animals in several studies (Sunderam et al., 2007; Crisler et al., 2008). There exist also other techniques. Luo and Mi used conditional random field (CRF), an extension of hidden Markov Model (HMM), which models the probabilities of possible label sequences given an observation (Luo and Min, 2007).

Classification of sleep stages is different from classification used in brain computer interfaces (Besserve et al., 2007; Lotte et al., 2007) or mental fatigue classification (Shen et al., 2008). In these applications the time window is usually fixed and a single state is assumed to exist within time window. In e.g. S3 sleep stage detection it is the unknown part (at least 20%) of the epoch which is assumed to contain high amplitude slow wave activity.

3.4.4 Postprocessing and smoothing

Quite often automatic sleep stage is postprocessed to obtain closer agreement with human scoring (Baumgart-Schmitt et al., 1998; Agarwal and Gotman, 2001). Baumgart-Schmitt et al. used e.g. following rescoring rules.

(SREM,W,SREM)	->	(SREM,SREM,SREM)
(SREM,S1,SREM)	->	(SREM,SREM,SREM)
(SREM,S2,SREM)	->	(SREM,SREM,SREM)
(S2,S1,S2)	->	(S2,S2,S2)

Special rules have been used for scoring SREM epochs as S1 before the first appearance of S2. The use of smoothing and e.g. estimation based on position of epoch within the

NREM/REM sleep cycle (Anderer et al., 2005) could limit the accuracy of classification with abnormal sleep structure.

3.4.5 Accuracy of classification

There are different ways to evaluate the results of automatic sleep analysis. First step is to evaluate distribution of features in different sleep stages (Saastamoinen et al., 2007). Results can be related to e.g. medication treatment e.g. (Kemp et al., 2000; Svetnik et al., 2007). Sometimes, when there is no direct synchronization between methods, the amount of sleep stages are compared between automatic and visual analysis (Ehlert et al., 1998). Similar approach is especially used when comparing sleep apnoea indexes (Heneghan et al., 2008). Hypnograms have been correlated with continuous features using correlation coefficient (Kaartinen et al., 1996). Most common approach is to calculate concordance by creating contingency (agreement) table event by event. That is a table of counts that cross-classifies the data (Durka et al., 2005). Typically data of all subjects is included in same table. Sometimes format of tables is percentages (Anderer et al., 2005) or incomplete tables are shown (Pittman et al., 2004) which makes impossible to recalculate e.g. W/SREM/NREM agreements.

Agreement matrix for binary detection is following with true positive (*TP*), true negative (*TN*), false positive (*FP*), false negative (*FN*). Total number of epochs is *N=TN+FP+FN+TP*. In this study rows are the true polysomnograph (PSG) results and columns the results of tested automatic system.

	Detection of sleep		Detection of wakefulness	
	Test wake	Test sleep	Test wake	Test sleep
PSG wake	TN	FP	TP	FN
PSG sleep	FN	TP	FP	TN

Detection sensitivity is *TP/(TP+FN)*, specificity is *TN/(TN+FP)*, positive predictive value (PPV) is *TP/(TP+FP)* and negative predictive value (NPV) is *TN/(TN+FN)*. For more classes than two see following the example for three classes

	Matrix for W, R, N			R detection		
	W	R	N	W	R	N
PSG W	n(1,1)	n(1,2)	n(1,3)	TN	FP	TN
PSG R	n(2,1)	n(2,2)	n(2,3)	FN	TP	FN
PSG N	n(3,1)	n(3,2)	n(3,3)	TN	FP	TN

True positive for stage *i* is $TP(i) = n(i,i)$, False positive is $FP(i) = \sum_j n(j,i) - n(i,i)$ and false negative $FN(i) = \sum_j n(i,j) - n(i,i)$ and true negative $TN(i) = N - FP(i) - FN(i) - TP(i)$ where $N = \sum_{i,j} n(i,j)$.

Overall agreement of classification is proportion of diagonal elements $\sum_i n(i,i)/N$.

Cohen's Kappa is the proportion of agreement after chance agreement p_C is removed from consideration. For example, if everything is automatically scored as non SWS then recording containing 10% SWS has an agreement of 90% separating non SWS and SWS but Cohen's Kappa is 0. Using probabilities $p(i,j) = n(i,j)/N$ from agreement matrix the κ can be defined as (Cohen, 1960)

$$\kappa = \frac{p_o - p_c}{1 - p_c} \tag{10}$$

$$p_o = \sum_i p(i,i) \tag{11}$$

$$p_c = \sum_i \left[\left(\sum_j p(i,j) \right) \left(\sum_j p(j,i) \right) \right] \tag{12}$$

Cohen's Kappa values greater than 0.80 represent almost perfect agreement (Landis and Koch, 1977). Cohen's Kappa values between 0.61-0.80, 0.41-0.60, 0.21-0.40 and 0-0.20 represent substantial, moderate, fair, and slight agreement, respectively (Landis and Koch, 1977). Cohen's Kappa is well suited for comparing interrater as it makes no assumption about which observer is correct (Dyson et al., 1984). There exist also

alternatives to Cohen's Kappa (Baldi et al., 2000). One is Matthews correlation coefficient (*MCC*) based on Pearson correlation coefficient. For binary classification it is calculated as

$$MCC = \frac{TP*TN - FP*FN}{\sqrt{(TP+FN)(TP+FP)(TN+FP)(TN+FN)}} \quad (13)$$

As a comparison Cohen's Kappa for binary classification can be expressed as (Hripcsak and Heitjan, 2002) and has been used in this format by (Magosso et al., 2007)

$$\kappa = \frac{2(TP*TN - FP*FN)}{(TP+FN)(FN+TN)+(FP+TN)(TP+FP)} \quad (14)$$

Both measures are symmetric for *FN* and *FP*. For testing the null hypothesis that pattern of ratings is random the chi-square distribution with $df = (categories - 1)^2$ is used (DeVellis, 2005)

$$X^2 = \sum_{i,j} \left[\left(n(i,j) - e(i,j) \right)^2 / e(i,j) \right] \quad (15)$$

$$e(i,j) = \left(\sum_k n(i,k) \right) \left(\sum_k n(k,j) \right) / N \quad (16)$$

Number of epochs in agreement matrix element *(i,j)* is *n(i,j)* For slightly different approach see Dyson et al. (Dyson et al., 1984).

3.4.6 Analysis based on restricted number of electrodes

For large scale field measurement the use of reduced set of electrodes would be preferred together with automatic analysis. Single central EEG channel systems have been developed (Flexer et al., 2005; Berthomier et al., 2007). Some devices use also electrodes outside hairline (Ehlert et al., 1998; Poree et al., 2006) making electrode placement an easier task. Poree et al. used independent component analysis together with visual classification. With 14 subjects the agreement with two visual scorings was 67%.

Berger and Meier (Berger and Meier, 1965) combined EMG and EOG to separate wakefulness (W), slow-wave sleep (HSV) and "low-voltage, fast-wave" (LVF) sleep from wakefulness. High EMG indicated wakefulness and high EOG with low EMG

indicated LVF. In 1972 Hilbert and Naitoh used electro-oculography to automatically quantify delta activity during sleep (Hilbert and Naitoh, 1972). Using analog components they used bands 1-2 Hz for delta and 80-131 Hz for artefacts. Band 1-2 Hz was used to exclude slow eye movements. They cited an earlier paper to have visual sleep scoring based on EOG (Naitoh et al., 1971). In that paper however no mention of visual scoring using EOG was noticed. Usually EOG is used as part of the automatic sleep staging (Drewes et al., 2000). EOG is needed especially to separate S1 and SREM. Koivuluoma et al. demonstrated that eye movement together with delta activity can be used for automatic sleep staging (Koivuluoma et al., 2000).

Lapinlampi and Himanen used frontopolar Fp2-A1 with EOG and EMG for visual scoring with ten subjects and EOG and EMG for visual scoring with four subjects (Lapinlampi and Himanen, 2004). Higher percentage of SWS and lower percentage of S2 was obtained when compared to visual scoring based on central EEG, EOG and EMG. This difference was not noted with apnoea patients. Eskelinen et al. later used Fp1-A2 with EOG and EMG to notice that nasal continuous positive airway pressure (nCPAP) treatment of apnoea patients increased the amount of visually scored SWS based on frontopolar Fp1-A2 but not based on C3-A2 (Eskelinen et al., 2007).

When awake, healthy subjects blink about 10 to 25 times in a minute (Barbato et al., 2000). Leinonen et al. used blinks to separate wakefulness and sleep (Leinonen et al., 2003). They placed one electrode at the eyebrow center of left eye and another electrode 1 cm below and lateral of the same eye. This provided about the same amplitude of blinks but attenuated slow waves during sleep (Leinonen et al., 2003). The blinks were detected using FIR median hybrid filtering developed for this purpose by Värri et al. (Värri et al., 1992; Värri et al., 1996). Filter length was 220 ms and blinks are attenuated by this filtering and saccades and slow eye movements were less attenuated. Subtracting the filtered signal from the original resulted in a signal with blinks enhanced. From this trace blinks were detected using amplitude and duration criteria (Leinonen et al., 2003).

Dyson et al. used one frontopolar EEG electrode together with EOG and EMG to visually score sleep (Dyson et al., 1984). With two scorers Cohen's Kappa values 0.87 and 0.86 were obtained between standard EEG and frontopolar EEG scoring. Werth and Borbely used two-channel EOG together with EMG for visual scoring (Werth and Borbely, 1995). EOG electrodes were placed 1 cm lateral and 3.5 cm vertically up from left outer canthus and 3.5 cm vertically down from right outer canthus with A2

reference. Using EOG for visual scoring resulted in a higher amount of S4 and a lower amount of S2. They also performed quantitative EEG analysis on EOG electrodes using 4 s epochs. Artefact rejection was based on variance of two EOG traces sum divided by variance of two EOG traces difference. If this ratio was below 1 then the epoch was not used for analysis. Typical time course of SWA activity was noted but frequencies above 2 Hz were attenuated and typical changes in the spindle frequency range were not evident using this E1-A2.

Monitoring anaesthesia depth is usually accomplished using facial electrodes (Walsh et al., 2008). Single-channel data is used for anaesthesia depth (Viertiö-Oja et al., 2004). Same electrodes and analysis have been used for correlating with sleep stages (Mahon et al., 2008) and also for sleep staging (Toppila et al., 2008). Average correlation between sleep stages obtained by entropy and by manual scoring was 57% and inter-rater agreement was 75%.

Activity signals of an eyelid and a hand have been combined with EMG by Kayed et al. for wake, NREM, and REM sleep separation (Kayed et al., 1979). Wakefulness has dense eye and body movements with high-level EMG. NREM sleep has absence of eye and body movements and low-level EMG. REM sleep has excessive number of eye movements, few body movements and low-level tonic EMG with phasic components. The activity of eyelid and head without any other signals is used in Nightcap device developed by Mamelak and Hobson (Mamelak and Hobson, 1989). This device has been used extensively (Ajilore et al., 1995; Cantero et al., 2002; Atienza et al., 2004).

3.4.7 Analysis based on body and limb movements

Monitoring movements has been an important part of sleep recordings for long time (Loomis et al., 1937). Usually sensors were placed on springs of bed mattress (Aserinsky and Kleitman, 1953). Body movements are also recognized as artefacts on EEG (Dement and Kleitman, 1957a). Non contact methods e.g. ultrasonic (Peacock and Williams, 1962; Levitt, 1966) or radar (Fox et al., 2007; Chazal et al., 2008) have been used. In standard sleep scoring body movements are described by the increase of muscle activity and do not necessary involve the substantial spatial displacement of the body (Rechtschaffen and Kales, 1968). Typically automatic analysis systems using EEG, EOG and EMG do not use movement information per se. Exception is the system developed by Hasan (Hasan, 1983) where static charge sensitive bed (SCSB) was used

as a feature together with EEG, EOG and EMG. With animals the addition of movement sensor analysis has improved the sleep-wake and behaviour discrimination (Sunderam et al., 2007).

The most commonly applied unobtrusive sleep monitoring method is actigraphy, the measurement of body limb movements. Wrist is the usual placement of activity sensors (Kripke et al., 1978). First studies used visual scoring of activity data (Mullaney et al., 1980) and tendency of activity monitors to overestimate sleep was noted. Actigraphy is currently clinically accepted method for studying sleep patterns in normal, healthy adult populations and in circadian sleep disorders (Morgenthaler et al., 2007).

One of first automatic wrist activity analyses was one by Webster et al. (Webster et al., 1982). They used experimental device with 240 Hz sampling rate and 2 s epoch lengths. Weighted (7 weights) sum was formed using maximal 2 s epoch values in current, preceding 4 minutes and following 2 minute epochs. Also additional rules were developed e.g. after at least 4 min scored wake, the first period of 1 min scored sleep is rescored wake. They also noted that if data was represented with 4 bits instead of 16 bits no change in agreement occurred. The method was later applied to a commercial actigraphy by Cole et al. (Cole et al., 1992) and reconfirming the importance of maximum activity value. Same device was also used by Sade et al. using zero crossing analysis and algorithm was based on e.g. standard deviation of prior 2 minutes and following 9 minutes (Sadeh et al., 1989). They later studied the use dominant and non-dominant wrist and concluded that twin-wrist actigraphy enables identification of some artefacts (Sadeh et al., 1994).

Kushida et al. evaluated the weighted sum of 9 epochs of 30 s (Kushida et al., 2001). Lötjönen et al. studied online actigraph with logistic regression based sleep estimation (Lötjönen et al., 2003). Logistic regression has also been used by Sazonov et al. in infants (Sazonov et al., 2004). Hedner et al. developed system to detect periodicity in activity data related to sleep apnoea (Hedner et al., 2004). This periodicity was thus taken as indicator of sleep. Usually actigraphs have low specificity for sleep detection (Paquet et al., 2007; Sitnick et al., 2008).

There are also unobtrusive alternatives for monitoring body movement during sleep. Static charge sensitive bed (SCSB) has been used to record body movements during sleep (Alihanka and Vaahtoranta, 1979). The sensor is sensitive enough for detecting

ballistogram (BCG) and respiratory rate and respiratory amplitude (Alihanka et al., 1981). Ballistocardiography generally is relatively old technique to measure cardiac activity (Rubenstein, 1952). Hasan and Alihanka used SCSB to separate SREM and NREM sleep based on number of short (<5 s) body movements in a 17 min time window (Hasan and Alihanka, 1980). If the number of movements was greater than or equal to three SREM was decided. Mean agreement with 10 subjects was 75% (range 63%-90%). No wake detection was used. Salmi and Leinonen applied SCSB for Wake, NREM and SREM detection. They used the number of short <15 s movements inside 3 min window and compared it to the number of movements in the whole record (Salmi and Leinonen, 1986). Jansen and Shakar extended the work for all sleep stages (Jansen and Shankar, 1993). Kaartinen et al. used SCSB with autonomic activity index (AAI) to separate wakefulness, NREM and SREM (Kaartinen et al., 1996).

Activity monitors are used also during daytime. E.g. physical activity can be assessed with accelerometers (Plasqui and Westerterp, 2007). Combining day time physical activity and night time physical inactivity has been informative (Paavilainen et al., 2005). Sensors can also separate different daily activities (Mathie et al., 2004; Pärkkä et al., 2006; Ermes et al., 2008; Godfrey et al., 2008). This dual use of unobtrusive activity sensors suggests their wider use to monitor sleep and daily activity.

4 Subjects and Methods

4.1 Subjects

In studies I-IV and study VI training and testing data sets subjects were from a large study described by Härmä et al. (Härmä et al., 2002). The local ethics committee approved this cross-sectional, population-based random sample study. Total of 139 professional train drivers and 138 railway traffic controllers were studied. Subjects were recorded for a single night followed by four up to 40 min Maintenance of Wakefulness Test (MWT) sessions the following day. Twelve subjects were excluded (resulting in 265 subjects) due to acute sickness or technical problems during polysomnography recordings.

In study I total number of subjects was 265. In study II 228 subjects were used as MWT scoring was carried out by a different technologist for some subjects and those were left out. In study III it was noted that two subjects of study I, one in the training and one in the validation group, had EOG electrode artefacts (flat EOG and ECG on EOG) for the whole night and were excluded from study III analyses. Description of subjects in study III is in Table 1. Same data sets are also used for reanalysis of study I. Description of subjects in study II is in Table 2. Apnoea-hypopnoea index (AHI) was based on evaluation of static charge sensitive bed (SCSB) and thermistor signals.

Table 1. Number of subjects, age, number of 30 s epochs and sleep parameters in the training and validation group in study III. In original study I there were additional two subjects. Groups are also training and testing groups of study VI.

	Subjects (males)	Age mean (range)	Epochs	Wake (%)	SREM (%)	S1 (%)	S2 (%)	SWS (%)	AHI (SD) h^{-1}
Training	132 (117)	43 (26-61)	134744	16.0 %	17.0 %	12.6 %	41.9 %	12.5 %	8.3 (12.4)
Validation	131 (119)	43 (28-60)	134889	15.9 %	17.8 %	12.1 %	42.0 %	12.2 %	5.8 (12.1)

AHI data of five training and one validation subject was unavailable

Table 2. Number of subjects, age, number of 30 s epochs and sleep parameters in the training and validation group in study II.

	Subjects (males)	Age mean (range)	Epochs	Wake (%)	SREM (%)	S1 (%)	S2 (%)	SWS (%)	AHI (SD) h^{-1}
Training	114 (105)	43 (28-60)	33235	96.7 %	0.0 %	3.2 %	0.2 %	0.0 %	7.8 (11.8)
Validation	114 (99)	42 (26-57)	33480	96.6 %	0.0 %	3.2 %	0.2 %	0.0 %	6.2 (13.7)

AHI data of four training and four validation subject was unavailable

In studies I and III polysomnographic recordings were sorted by the amount of visually scored slow wave sleep (SWS). From the sorted list, entries with an odd order number were assigned to the training group and entries with even order number were assigned to the validation group. In study II recordings were sorted by the amount of visually scored sleep. From the sorted list, entries with an odd order number were assigned to the training group and entries with even order number were assigned to the validation group. Subjects in study IV were identical to subjects in validation data set of studies I and III who were scored twice for inter-rater agreement, Table 3. In study V and VI validation data sets 16 subjects (3 males, 13 females, and age 24-52 year) were laboratory personnel and acquaintances.

Table 3. Number of subjects, age, number of 30 s epochs and sleep parameters in study IV.

Subjects (males)	Age mean (range)	Epochs	Wake (%)	SREM (%)	S1 (%)	S2 (%)	SWS (%)	AHI (SD) h^{-1}
14 (13)	43 (36-50)	14738	11.9 %	18.8 %	10.9 %	46.4 %	12.0 %	3.3 (3.1)

4.2 Recording equipment

The recording equipment in studies I-IV and VI testing and training data set included a digital 16-channel Embla A10 (Flaga, Reyakjavik, Iceland) with a sampling rate of 200 Hz and a bandwidth of 0.5–90 Hz. Two different Somnologica versions were used for recording with identical dynamical range of ±7.8 mV and filter settings 0.5-90 Hz for EEG, EOG and EMG.

In studies V and VI validation data set custom modified Alive Heart Rate Monitor (Alive Technologies, Arundel, Australia) was used. The monitor includes a triaxial accelerometer with 8 bit Analog-to-digital converter (ADC) and ±2.7 g range. The bandwidth is 0-20 Hz and the sampling rate is 75 Hz. The monitor also includes an ECG input with 8 bit ADC, a range of ±2.6 mV and a bandwidth of 0.5-90 Hz with sampling rate of 300 Hz. We used a version modified by the manufacturer to obtain a higher gain. The resulting range of ±260 μV allowed the EOG use. In studies V and VI validation data set visual scoring was based only on EOG. Equipment used for this was Embla Titanium (Embla, Broomfield, USA) recorder with a sampling rate of 256 Hz and a bandwidth of 0.15-127 Hz. Visual scoring using EOG was validated in a separate study

(Virkkala et al., 2008) using Embla N7000 (Embla, Broomfield, USA) with sampling rate of 200 Hz and bandwidth 0.3-90 Hz.

4.3 Reference scoring

Visual scoring was based on the old standard (Rechtschaffen and Kales, 1968). Scoring was carried out based on recorded EOG L-M1, EOG R-M1, C4-M1, C3-M2, O2-M1, O1-M2 and submental EMG. Scoring was carried out according to standard R&K criteria (Rechtschaffen and Kales, 1968) by an experienced sleep technologist. The standard EOG locations, EOG Left (EOG L) slightly lateral and 1 cm up from the outer canthus and EOG Right (EOG R) slightly lateral and 1 cm down from the outer canthus referenced to left mastoid M1, were used (Rechtschaffen and Kales, 1968). A ground electrode was placed on forehead.

In studies V and VI validation data set the visual scoring was based only on EOG. This approach was validated in a study which has been published only in abstract format (Virkkala et al., 2008). That separate validation study contained eleven sleep recordings (females, age 20-54 years). In all studies the analyzed visual sleep stage scoring were carried out by a single sleep technician. For studies V and VI validation data set the sleep technician (RV) was different from other studies (SP).

4.4 Software

Analysis in original articles I-VI was based on using several softwares. Commercial Somnologica 2 and 3 softwares (Embla, Broomfield, CO, USA) were used for recording and reviewing the data. Recorded data were stored with 2 byte resolution as *ebm* files (Embla - File format description, Version 4.0, 1997, Embla). Custom developed Visual C++ 6.0 (Microsoft, Redmond, WA, USA) Somnologica Plugin was used to create traces of visually scored hypnograms. Features were calculated with custom developed Visual Basic 6 (Microsoft, Redmond, WA, USA) program. This program uses Intel Signal Processing Library 4.5 (Intel, Santa Clara, CA, USA) for calculating e.g. DFT and IDFT. Features were saved in ASCII file with 8 byte double resolution. These ASCII files were combined into 2 byte binary files with custom Visual Studio Net 2003 and 2005 (Microsoft, Redmond, WA, USA) software. These files were further analyzed with Matlab 7 (Mathworks, Natick, MA, USA). In this section all analysis were

recalculated using only Matlab 7 based analysis using 4 byte single resolution without any other software. Different resolution of variables resulted in slight differences. All analysis were based on 2 s segmented with 75% overlap (segments were processed every 0.5 s).

4.5 Artefact analysis

In all analysis high 18-30 Hz beta power in EOG was used as an indicator of wakefulness. Beta band 18–30 Hz was chosen in study I because Merica et al. have shown that lower 15–18 Hz are specific to NREM sleep and upper 18–30 Hz to REM sleep (Merica and Fortune, 2005). This band does not contain any significant amount of spindle activity. Usually high frequencies e.g. 26-32 Hz are used as an indicator of muscle activity (Brunner et al., 1996). In study IV indirect measure of mean frequency was used.

With two-channel electro-oculography (I, II, III) correlation coefficient separated synchronous EEG activity from the EOG activity. In study VI eye movements were separated from NREM sleep activity based on amplitude.

For ECG artefact removal in study IV segments were filtered 10-30 Hz. Maximum absolute peak was located as a candidate of QRS artefact and two additional peaks were detected if there were at least 665 ms between peaks (heart rate <90 bpm). Five time points (25 ms) around peaks were excluded before estimating spectral components.

4.6 Features

There were three main features: 18-30 Hz EOG beta power, 0.5-6 Hz filtered peak-to-peak EOG amplitude and 0.5-6 Hz correlation coefficient between the EOG electrodes. Beta power and peak-to-peak amplitudes were calculated from the difference EOG L-R. Segments with synchronous EEG activity and with low beta values were counted during each epoch. In studies II, III also alpha power of EOG L-M1 was used as an indicator of wakefulness and 1.5-6 Hz peak-to-peak amplitude and 1.5-6 Hz correlation coefficient were used for S1 detection. Correlation coefficient is quite often used as a feature for EOG detection (Drewes et al., 2000). In study III SREM was separated from S1 using the largest eye movements (correlation coefficient<-0.50) during a 30 s. This feature

affected 3 adjacent epochs. Description of the algorithm data flow and basic analysis steps are shown in Figure 9. In study IV mean frequency within 2 s segments was used.

The difference between the correlation coefficient of the 1–6 Hz band and the correlation coefficient of the 0.5–6 Hz band was used as an indicator of slow eye movements (SEM). If eye movements recorded by EOG are restricted to the 0.5 Hz band and have an opposite phase, this difference is close to 1, and if in addition there is synchronous low amplitude activity in the 1–6 Hz band, the difference is close to 2. This slow eye-movement feature is amplitude independent in noise-free measurements.

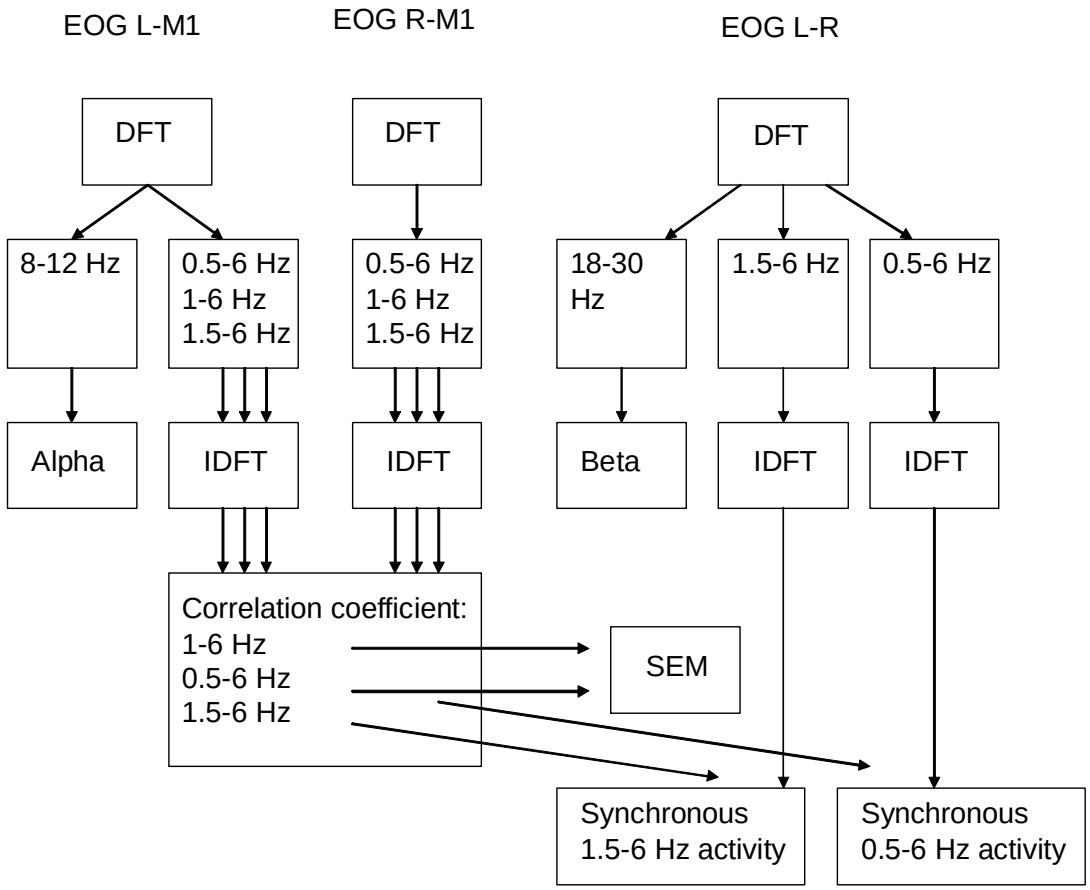

Figure 9. Description of the algorithm data flow and basic analysis steps. DFT indicates the discrete Fourier transform and IDFT the inverse discrete Fourier transform. Alpha power is obtained by summing the 8–12 Hz bins of the DFT of EOG L-M1. Beta power is obtained by summing the 18–30 Hz bins of DFT of EOG L–R. Synchronized activity is calculated in 0.5–6 Hz and in 1.5–6 Hz bands. The diagram represent the study III. In study I only beta and synchronous 0.5-6 Hz activity were used. In study II synchronous 0.5-6 Hz activity was not used. In studies

4.7 Classification

In studies I, IV and V a single binary decision was made based on the density (number) of accepted 2 s segments during a 30 s epoch. As segments were overlapped 75% there were 60 segments in each 30 s epoch. In study I accepted segments were synchronous delta activity with low beta for SWS detection. In study IV accepted segments were low mean frequency for sleep detection. In study V accepted segments were ones with low beta power. The decision tree used in study III is shown in Figure 10 and decision tree used in study VI is shown in Figure 11.

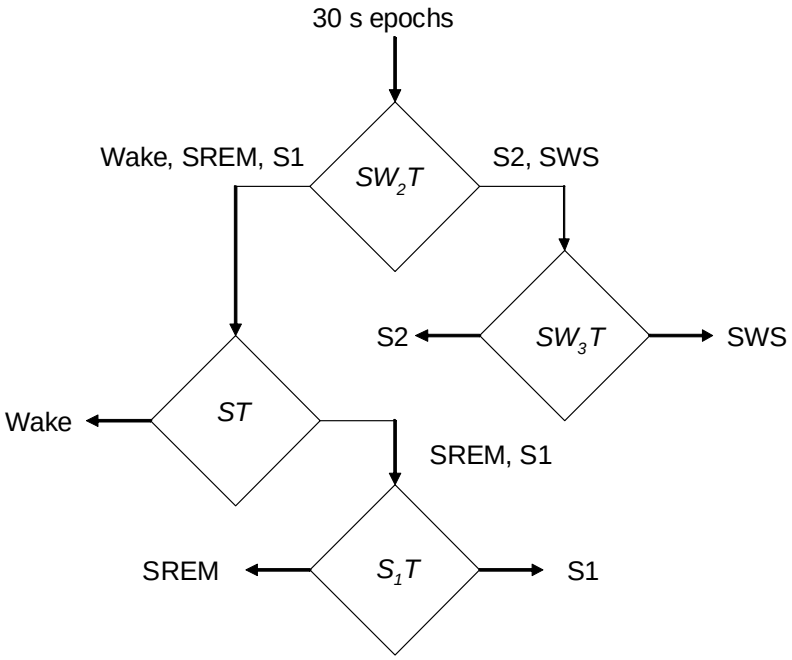

Figure 10. Decision tree used in study III. Four binary decisions rules SW_2T, SW_3T, ST and S_1T were used to separate S2, SWS, wakefulness, SREM and S1.

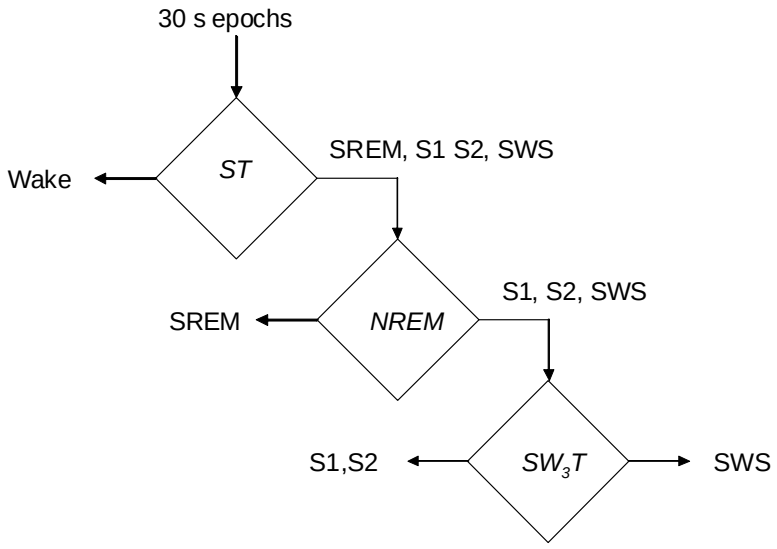

Figure 11. Decision tree used in study VI. Three binary decisions rules *ST*, *NREM*, and SW_3T were used.

In each binary decision Cohen's Kappa was maximized using the data of the training groups. In study I a range of combination of variables was tested. In other studies gradient search algorithm was used, e.g. with 3 parameters 27 (3^3) different combinations around initial values were tried (with 4 parameters 3^4=81 combinations) and one with the highest Cohen's Kappa was used as new initial value. Process was repeated until maximum Kappa was found.

5 Results

5.1 Reliability of reference scoring

For studies I and III a subset of 14 subjects were visually scored by two technologists (SP, NL) to obtain inter-rater agreement. Those 14 subjects were every 10th of the validation group sorted by the amount of slow wave sleep. Agreement matrix for separation of W, SREM, S1, S2 and SWS is in Table 4. Agreement percentage was 82% and Cohen's Kappa was 0.75. Recalculated agreement for NSWS and SWS separation is in Table 5. Agreement percentage was 95% and Cohen's Kappa was 0.70. Although high agreement was obtained the second scorer (NL) scored more S1 and S2 than the first one (SP) and less Wake and SWS.

Table 4. Agreement matrix, agreement percentage, sums, sensitivity, positive predictive value (PPV), and Cohen's Kappa for inter-rater agreement in study III. Rows are by first scorer (SP) and columns by second scorer (NL).

Inter-rater							
	Wake	SREM	S1	S2	SWS	Sum	Sensitivity
Wake	**1274**	65	387	21	2	1749	72.8%
SREM	4	**2532**	136	103	0	2775	91.2%
S1	92	219	**1050**	242	1	1604	65.5%
S2	27	82	428	**6163**	145	6845	90.0%
SWS	3	1	6	656	**1099**	1765	62.3%
Sum	1400	2899	2007	7185	1247	14738	
PPV	91.0%	87.3%	52.3%	85.8%	88.1%		
Agreement							82.2%
Cohen's Kappa							0.75

Table 5. Agreement matrix, agreement percentage, sums, sensitivity, positive predictive value (PPV), and Cohen's Kappa for inter-rater agreement in study I. Rows are by first scorer (SP) and columns by second scorer (NL).

Inter-rater				
	NSWS	SWS	Sum	Sensitivity
NSWS	**12825**	148	12973	98.9%
SWS	666	**1099**	1765	62.3%
Sum	13491	1247	14738	
PPV	95.1%	88.1%		
Agreement				94.5%
Cohen's Kappa				0.70

For study II similarly every tenth recording of sorted validation data set were rescored by an another technologist (RV). Agreement matrix is in Table 6.

Table 6. Agreement matrix, agreement percentage, sums, sensitivity, positive predictive value (PPV), and Cohen's Kappa for inter-rater agreement in study II. Rows are by first scorer (SP) and columns by second scorer (RV).

Inter-rater				
	Wake	S1,S2	Sum	Sensitivity
Wake	**3253**	4	3257	99.9%
S1,S2	16	**76**	92	82.6%
Sum	3269	80	**3349**	
PPV	99.5%	95.0%		
Agreement				99.4%
Cohen's Kappa				0.88

In studies V and VI validation data set visual scoring was based only on two-channel EOG. This was validated in a study published in abstract format (Virkkala et al., 2008). Eleven sleep recordings (females, age 20-54 years) were visually scored four times by two experienced sleep technicians (RV and NL). Besides repeated standard visual sleep scoring, visual sleep scoring was conducted twice based on two electro-oculography channels only (EOG Right-M1, EOG Left-M1). This scoring with a reduced set of electrodes was carried out using standard criteria with reduced alpha, spindle and EMG activity visible on traces. In all analysis S3 and S4 were combined to SWS. Agreement matrix between standard R&K and EOG scoring is in Table 7 for technologist RV. This visual scoring has overall epoch-by-epoch agreement of 87% and Cohen's Kappa of

0.81. As a comparison intra-rater R&K scoring by same sleep technologist (RV) is in Table 8 and inter-rater (RV, NL) R&K scoring is in Table 9.

Table 7. Agreement matrix, agreement percentage, sums, sensitivity, positive predictive value (PPV), and Cohen's Kappa for visual EOG scoring. Rows are standard R&K scoring and columns are visual EOG scoring by same technologist (RV).

EOG scoring							
	Wake	SREM	S1	S2	SWS	Sum	Sensitivity
Wake	**853**	6	91	14	1	965	88.4%
SREM	2	**2256**	36	28	0	2322	97.2%
S1	133	95	**550**	111	4	893	61.6%
S2	30	123	245	**4542**	129	5069	89.6%
SWS	0	0	0	365	**973**	1338	72.7%
Sum	1018	2480	922	5060	1107	10587	
PPV	83.8%	91.0%	59.7%	89.8%	87.9%		
Agreement							86.7%
Cohen's Kappa							0.81

Table 8. Agreement matrix, agreement percentage, sums, sensitivity, positive predictive value (PPV), and Cohen's Kappa for intrarater R&K scoring. Rows are second scoring and columns first scoring by same sleep technologist (RV).

Intra-rater							
	Wake	SREM	S1	S2	SWS	Sum	Sensitivity
Wake	**915**	2	44	4	0	965	94.8%
SREM	1	**2274**	31	16	0	2322	97.9%
S1	56	72	**710**	55	0	893	79.5%
S2	2	74	157	**4701**	135	5069	92.7%
SWS	0	0	0	85	**1253**	1338	93.6%
Sum	974	2422	942	4861	1388	10587	
PPV	93.9%	93.9%	75.4%	96.7%	90.3%		
Agreement							93.1%
Cohen's Kappa							0.90

Table 9. Agreement matrix, agreement percentage, sums, sensitivity, positive predictive value (PPV), and Cohen's Kappa for inter-rater R&K scoring. Rows are by first scorer (RV) and columns by second scorer (NL).

Inter-rater							
	Wake	SREM	S1	S2	SWS	Sum	Sensitivity
Wake	**799**	3	131	30	2	965	82.8%
SREM	1	**2238**	47	36	0	2322	96.4%
S1	49	79	**628**	137	0	893	70.3%
S2	6	56	122	**4756**	129	5069	93.8%
SWS	0	0	0	189	**1149**	1338	85.9%
Sum	855	2376	928	5148	1280	10587	
PPV	93.5%	94.2%	67.7%	92.4%	89.8%		
Agreement							90.4%
Cohen's Kappa							0.86

Inter-rater agreement and Cohen's Kappa were higher (0.86 vs. 0.75) than obtained in study III (Table 4). This is probably due to having scorings from three different technologists. Pair (SP, NL) data is in Table 4 and pair (RV, NL) data is in Table 9. Also technologist SP and NL have not worked together. This result indicates subjective nature of visual scoring.

5.2 Slow wave sleep epoch detection

In study I there were two subjects, one in training and one in validation group, who had a flat EOG trace. Those subjects are excluded in all analyses here. Peak-to-peak amplitudes and correlation coefficient of 0.5-6 Hz band of training data are shown in different sleep stages in Figure 12. Values larger than 1000 µV were clipped before calculation for keeping the figure informative. In Figure 13 beta and alpha powers are shown. Values larger than 100 (μV^2 /Hz) were clipped before calculation for keeping the figure informative. In Figure 14, SEM feature, difference between correlation coefficients between 0.5-6 Hz and 1-6 Hz, are shown in different sleep stages.

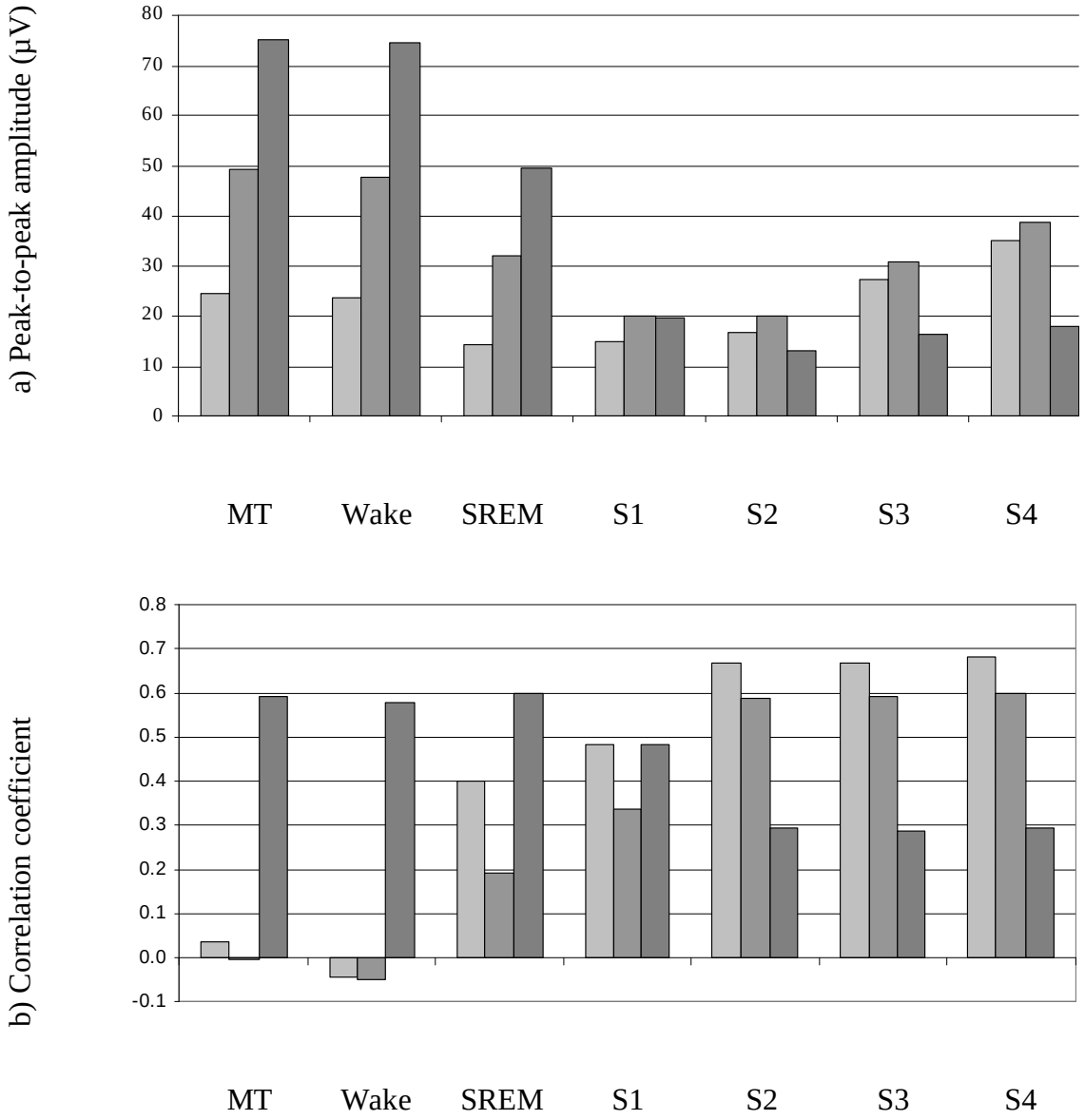

Figure 12. (a) Median, mean and standard deviation of 0.5–6 Hz EOG L-R amplitude in different sleep stages; (b) median, mean and standard deviation of 0.5–6 Hz EOG L-M1, EOG R-M1 correlation coefficient in different sleep stages. In both parts (a) and (b) median is represented by light gray, mean by medium gray and standard deviation by dark gray

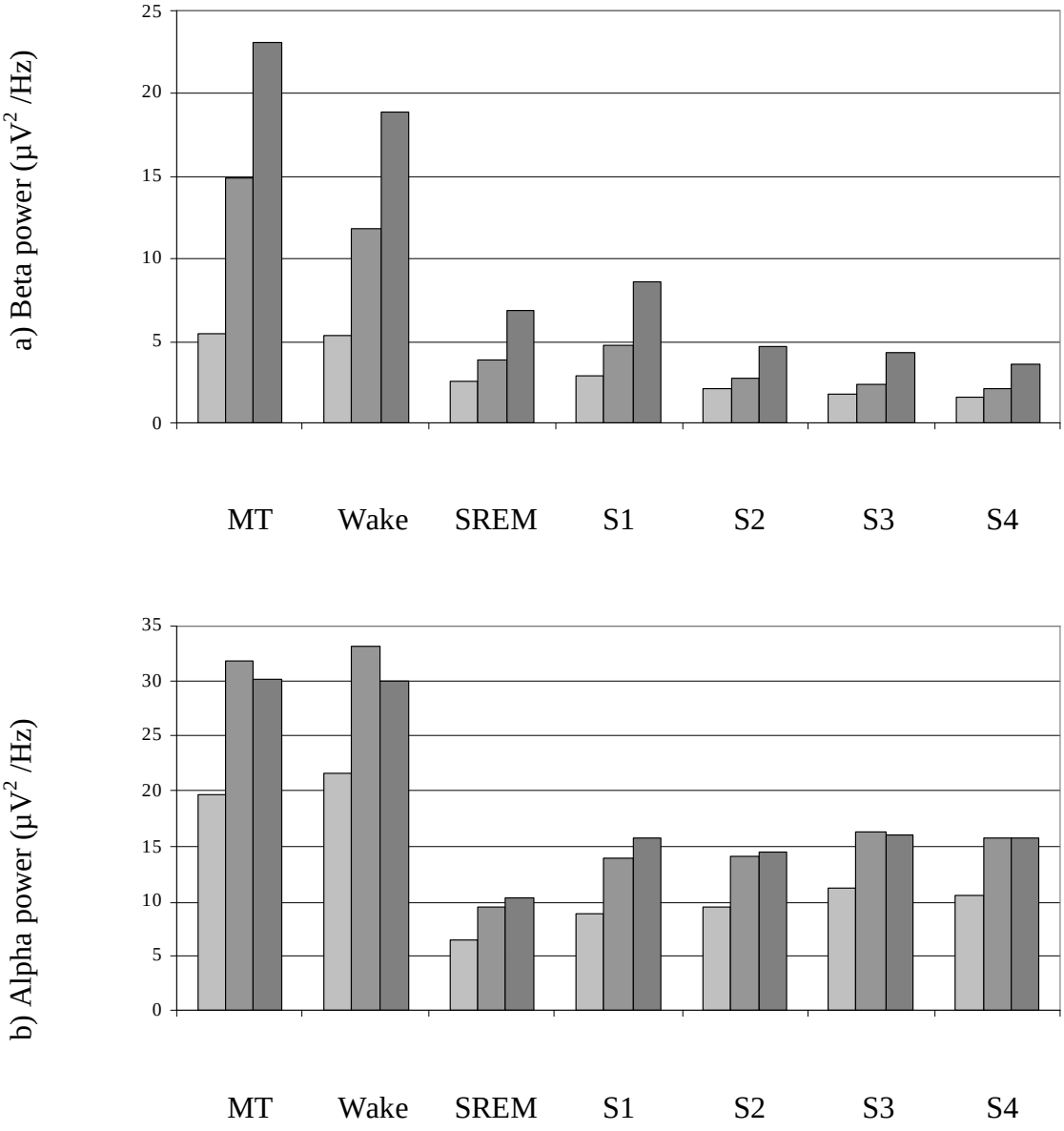

Figure 13. (a) Median, mean and standard deviation of 18–30 Hz EOG L-R beta if different sleep stages; (b) median, mean and standard deviation of 8-12 Hz alpha power of EOG L-M1 in different sleep stages. In both parts (a) and (b) median is represented by light gray, mean by medium gray and standard deviation by dark gray.

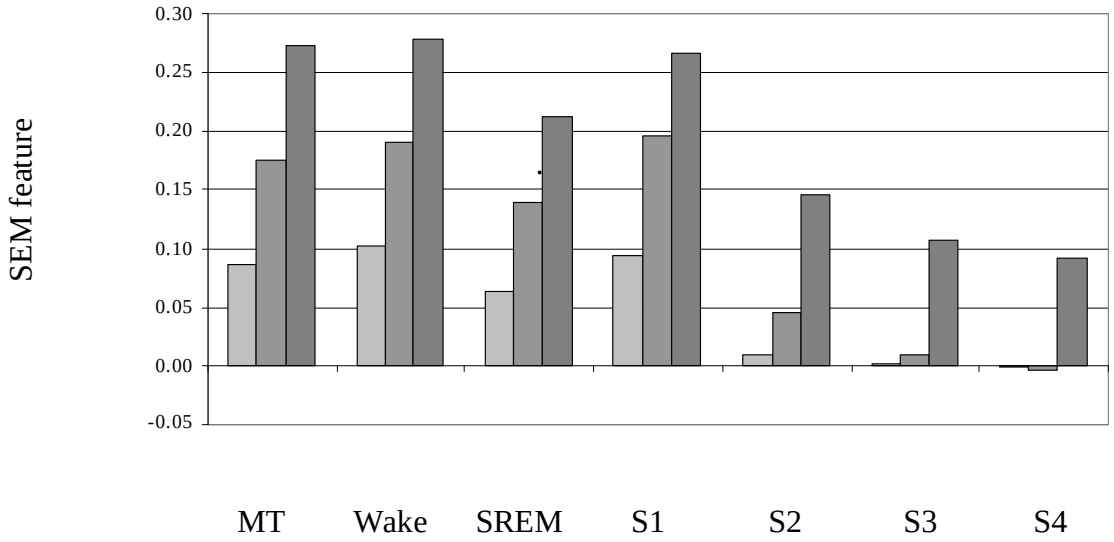

Figure 14. Median, mean and standard deviation of SEM feature in different sleep stages. Median is represented by light gray, mean by medium gray and standard deviation by dark gray

By using 0.5-6 Hz amplitude, correlation coefficient and 18-30 Hz beta power the agreement for separation of SWS from NSWS was 93.9% with Cohen's Kappa 0.728 in training data set. Optimal parameters were >33 μV, >0.2 and <6 (μV^2 /Hz). This was obtained with fixed density of at least 20%. If the density was adjustable parameter then results were 94.1% and 0.733 with parameters >31 μV, >0, <6 (μV^2 /Hz) and >27%. For validation data set agreement matrix with fixed density is shown in Table 10.

Table 10. Agreement matrix, agreement percentage, sums, sensitivity, positive predictive value (PPV), and Cohen's Kappa for validation data set in study I Rows are by visual analysis and columns by automatic EOG analysis.

Validation data set				
	NSWS	SWS	Sum	Sensitivity
NSWS	**113394**	5038	118432	95.7%
SWS	4014	**12441**	16455	75.6%
Sum	117408	17479	134887	
PPV	96.6%	71.2%		
Agreement				93.3%
Cohen's Kappa				0.70

5.3 Epoch detection of unintentional sleep

In study II sleep stage scoring during Maintenance of Wakefulness Test (MWT) was developed. Beside synchronous 1.5-6 Hz activity and beta power also slow eye movement (SEM) feature and alpha activity were used. Features of training data are shown in Figure 15. With fixed density criterion of >50% agreement matrix in training data set is in Table 11 and in validation data set in Table 12.

Table 11. Agreement matrix, agreement percentage, sums, sensitivity, positive predictive value (PPV), and Cohen's Kappa in study II training data set. Rows are by visual scoring and columns by automatic EOG method.

Training data set				
	Wake	S1,S2	Sum	Sensitivity
Wake	**31752**	369	32121	98.9%
S1,S2	382	**732**	1114	65.7%
Sum	32134	1101	33235	
PPV	98.8%	66.5%		
Agreement				97.7%
Cohen's Kappa				0.65

Table 12. Agreement matrix, agreement percentage, sums, sensitivity, positive predictive value (PPV), and Cohen's Kappa in study II validation data set. Rows are by visual scoring and columns by automatic EOG method.

Validation data set				
	Wake	S1,S2	Sum	Sensitivity
Wake	**31899**	451	32350	98.6%
S1,S2	321	**809**	1130	71.6%
Sum	32220	1260	33480	
PPV	99.0%	64.2%		
Agreement				97.7%
Cohen's Kappa				0.67

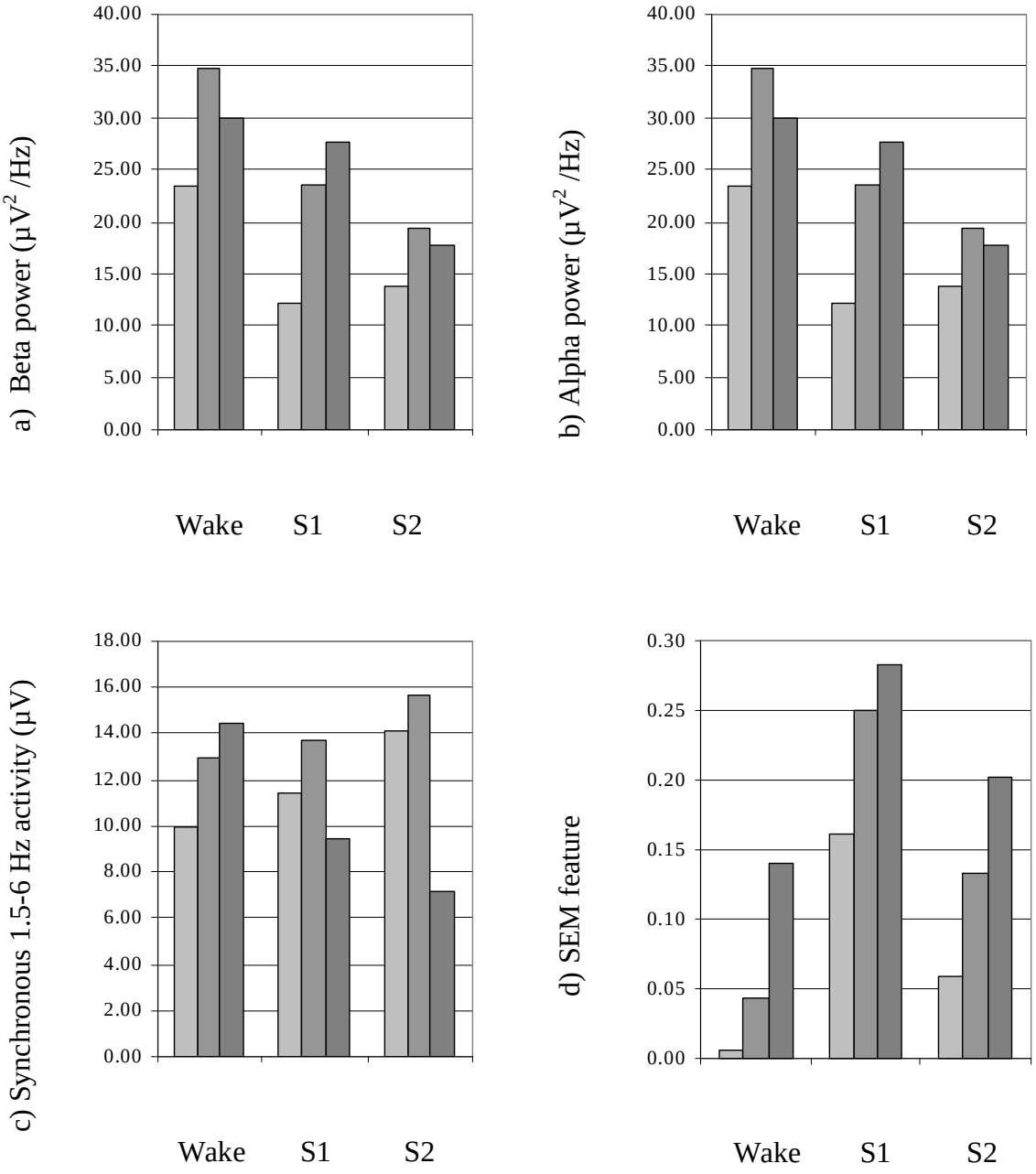

Figure 15. (a) Median, mean and standard deviation of beta power in different sleep stages; (b) median, mean and standard deviation of alpha power in different sleep stages; (c) median, mean and standard deviation of synchronous 1.5-6 Hz peak-to-peak in different sleep stages (d) median, mean and standard deviation of SEM feature in different sleep stages. In all parts (a), (b), (c) and (d) median is represented by light gray, mean by medium gray and standard deviation by dark gray.

5.4 Sleep stage detection

In study III separation of wake, SREM, S1, S2 and SWS was developed and evaluated. Decision tree was described in Figure 10. Agreement and Cohen's Kappa in training data set is in Table 13 and in validation data set in Table 14. Those tables are based on results without smoothing and without individual alpha threshold. An example of hypnogram is presented in Figure 5.

Table 13. Agreement matrix, agreement percentage, sums, sensitivity, positive predictive value (PPV), and Cohen's Kappa for automatic sleep stage detection in study III in training data set. Rows are by human scorer and columns by automatic method.

Training data set							
	Wake	SREM	S1	S2	SWS	Sum	Sensitivity
Wake	**16136**	3208	1558	658	43	21603	74.7%
SREM	1720	**16543**	2261	2337	9	22870	72.3%
S1	2261	3661	**6749**	4322	40	17033	39.6%
S2	968	927	5722	**44974**	3795	56386	79.8%
SWS	90	19	89	3652	**13002**	16852	77.2%
Sum	21175	24358	16379	55943	16889	134744	
PPV	76.2%	67.9%	41.2%	80.4%	77.0%		
Agreement							72.3%
Cohen's Kappa							0.63

Table 14. Agreement matrix, agreement percentage, sums, sensitivity, positive predictive value (PPV), and Cohen's Kappa for automatic sleep stage detection in study III in testing data set. Rows are by human scorer and columns by automatic method.

Testing data set							
	Wake	SREM	S1	S2	SWS	Sum	Sensitivity
Wake	**15949**	3174	1458	738	60	21379	74.6%
SREM	1844	**16965**	2488	2705	19	24021	70.6%
S1	2329	3446	**6104**	4514	44	16437	37.1%
S2	1913	920	5248	**44225**	4289	56595	78.1%
SWS	356	14	50	3735	**12300**	16455	74.7%
Sum	22391	24519	15348	55917	16712	134887	
PPV	71.2%	69.2%	39.8%	79.1%	73.6%		
Agreement							70.8%
Cohen's Kappa							0.61

5.5 Single-channel electro-oculography analysis

In studies V and VI single bipolar EOG channel was used. Decision tree used in study VI was described in Figure 11. Three binary decisions rules ST, NREM, and SW_3T were used. With training data from study I single-channel agreement was 74% with Cohen's Kappa 0.58, Table 15. With testing data agreement was 73% with Cohen's Kappa 0.58, Table 16.

Table 15. Agreement matrix, agreement percentage, sums, sensitivity, positive predictive value (PPV), and Cohen's Kappa in study VI training data set with individual beta threshold. Rows are by visual scoring and columns by automatic single-channel EOG method.

Training data set with individual beta						
	Wake	SREM	S1/S2	SWS	Sum	Sensitivity
Wake	**14147**	2673	4600	183	21603	65.5%
SREM	2604	**14136**	6080	50	22870	61.8%
S1/S2	4436	5048	**59824**	4111	73419	81.5%
SWS	302	663	3860	**12027**	16852	71.4%
Sum	21489	22520	74364	16371	134744	
PPV	65.8%	62.8%	80.4%	73.5%		
Agreement						74.3%
Cohen's Kappa						0.58

Table 16. Agreement matrix, agreement percentage, sums, sensitivity, positive predictive value (PPV), and Cohen's Kappa in study VI testing data set with individual beta threshold. Rows are by visual scoring and columns by automatic single-channel EOG method.

Testing data set with individual beta						
	Wake	SREM	S1/S2	SWS	Sum	Sensitivity
Wake	**14532**	2335	3887	625	21379	68.0%
SREM	2416	**14537**	7014	54	24021	60.5%
S1/S2	5004	4475	**58540**	5013	73032	80.2%
SWS	384	724	3990	**11357**	16455	69.0%
Sum	22336	22071	73431	17049	134887	
PPV	65.1%	65.9%	79.7%	66.6%		
Agreement						73.4%
Cohen's Kappa						0.58

In validation data set, leave-one-out cross validation (LOOCV) was carried out using separate 15 subjects data, Table 17. Those recordings were carried out at subjects home.

Table 17. Agreement matrix, agreement percentage, sums, sensitivity, positive predictive value (PPV), and Cohen's Kappa in study VI for validation data set with individual beta threshold. Rows are by visual EOG scoring and columns by automatic EOG method.

Validation data set with individual beta						
	Wake	SREM	S1/S2	SWS	Sum	Sensitivity
Wake	**815**	136	117	49	1117	73.0%
SREM	70	**1777**	980	29	2856	62.2%
S1/S2	454	586	**5619**	472	7131	78.8%
SWS	19	80	410	**1562**	2071	75.4%
Sum	1358	2579	7126	2112	13175	
PPV	60.0%	68.9%	78.9%	74.0%		
Agreement						74.2%
Cohen's Kappa						0.59

5.6 Use of activity signal in sleep detection

In study V activity sensors, Table 19, were used for binary wakefulness and sleep separation in addition to beta power, Table 18, described in the previous chapter.

Table 18. Agreement matrix, agreement percentage, sums, sensitivity, positive predictive value (PPV), and Cohen's Kappa for EOG in study V, recalculated from Table 17. Rows are by visual EOG scoring and columns by automatic method.

Single channel EOG				
	Wake	Sleep	Sum	Sensitivity
Wake	**815**	302	1117	73.0%
Sleep	543	**11515**	12058	95.5%
Sum	1358	11817	13175	
PPV	60.0%	97.4%		
Agreement				93.6%
Cohen's Kappa				0.62

Table 19. Agreement matrix, agreement percentage, sums, sensitivity, positive predictive value (PPV), and Cohen's Kappa for Alive activity at wrist in study V. Rows are by visual EOG scoring and columns by automatic method.

Alive at wirst				
	Wake	Sleep	Sum	Sensitivity
Wake	**409**	708	1117	36.6%
Sleep	268	**11790**	12058	97.8%
Sum	677	12498	13175	
PPV	60.4%	94.3%		
Agreement				92.6%
Cohen's Kappa				0.42

6 Discussion

In study I Cohen's Kappa between the visual and the new developed automatic scoring in separating non-SWS and SWS was substantial (0.70) with epoch-by-epoch agreement of 93%. Slow waves were estimated in 2 s overlapped segments. Wide 0.5–6 Hz band containing delta and theta was used for better eye movement separation. Alpha band was excluded as it would increase correlation coefficient. Although slow wave period is defined as less than 2 Hz or slower in the standard criteria (Rechtschaffen and Kales, 1968), human scoring is likely to take into account faster waves superimposed on slow oscillations (Hori et al., 2001). The developed method could be used for slow wave sleep deprivation by providing alerting stimulus when slow wave sleep is detected. Also effects of awakening from slow wave sleep, producing sleep inertia affecting performance could be studied (Tassi and Muzet, 2000). Durka et al. have developed a single-channel SWS detection based on matching pursuit (Durka et al., 2005). Using central EEG they obtained total concordance 81%, Kappa coefficient 0.59 in separating NSWS, S3 and S4. The advantage of the developed automatic method is that it could be applied during online recordings using only two EOG, one mastoid and one ground electrode.

For recordings during Maintenance of Wakefulness Test (MWT) epoch by epoch agreement and Cohen's Kappa between the visual and the new automatic scoring system was substantial 98% (0.67). There are not many methods for automatic analysis of sleep epochs during daytime sleep. Recently Multiple sleep latency test (MSLT) was analysed automatically using slow eye movement detection (Fabbri et al., In press). Aim of the study II was not to develop methods specific to MWT or to evaluate sleepiness but to detect unintentional sleep onset epochs in general.

With two-channel electro-oculography Cohen's Kappa between the visual and two-channel EOG based automatic scoring in separating 30 s epochs of wakefulness, SREM, S1, S2 and SWS epochs was substantial 0.62 with epoch by epoch agreement of 72%. This is slightly worse than automatic methods using EEG, EOG and EMG (Anderer et al., 2005). With single-channel electro-oculography total agreement (and Cohen's Kappa) for separating wake, SREM, S1/S2 and SWS in the training data set was 74% (0.59), in the testing data set 73% (0.59) and in the validation data set 74% (0.59). Self-

applicable electro-oculography with only two facial electrodes was found to provide reasonable sleep stage information.

In this thesis Discrete Fourier Transform (DFT) was used for calculating beta power and for filtering. Some Fast Fourier Transform (FFT) algorithms need 2^n samples but DFT can be calculated using any sample lengths. Results are expected to be practically identical when changing sampling rates to, e.g. 100 Hz, 128 or 256 Hz. With FFT identical results can be obtained only if sampling rate ratios are 2^n, where n is integer. Alternative choice for filtering would be a more conventional finite impulse response (FIR) or an infinite impulse response (IIR) filter. We chose DFT/IDFT because forward transform is needed for beta power calculation and DFT/IDFT resulted in less choice of parameters. Increases in computational requirements are not an issue with current computers.

In all studies (I-VI) movement time (MT) epochs were labelled as W. In old rules this was a separate stage (Rechtschaffen and Kales, 1968). According to new rules (Iber et al., 2007) major body movement with any alpha activity or preceded or followed by W is scored as W. Otherwise major body movement is scored as the following sleep epoch. In future this logic will be included into the system. Although the recordings are from the first night in the laboratory, we believe this does not reduce the reliability of this methodological validation. The methods are for detecting sleep stages and any effects of the first night are small compared to interindividual variation. Subjects were working people, not patients or subjects screened out of any sleep disturbances. Mean AHI was between 5 and 10 events/h, Table 1. With patients having more sleep disturbances results are likely worse. Also inter-rater agreement is likely worse with sleep apnoea (Danker-Hopfe et al., 2004).

Having a method suitable for large scale sleep measurements would be beneficial for developing sleep models. Conceptual model of sleep regulation was proposed by Feinberg (Feinberg, 1974). Using data from 105 normal subjects, age between 4 and 96, he reported sleep cycle data and pointed out the importance of slow wave sleep. There have been various other models describing sleep homeostasis and circadian rhythmicity as reviewed by Borbely and Achermann (Borbély and Achermann, 2005). Most widely used is the two process model (Borbely, 1982). Mathematical formulation of the two process model was carried out by Daan et al. (Daan et al., 1984). Usually homeostatic (S) and circadian (C) process are thought to be additive with some exceptions (Bes et

al., 2009). The marker for homeostatic process during sleep has been slow wave (0.5-4.5 Hz) activity of EEG (SWA) (Achermann et al., 1993; Achermann, 2004). Also lower (<1 Hz) frequencies of EEG are changing during sleep (Church et al., 1975; Achermann and Borbely, 1997). Recently it has been demonstrated using naps that also these low frequencies demonstrate homeostatic behaviour although the values are easily saturated (Campbell et al., 2006). As slow wave sleep was separated with great accuracy in this thesis the developed methods could be used to study sleep regulation in a large number of subjects in home environment.

There has been great interest in the possibility to use self-adhesive electrodes to be placed below hair-line to obtain sleep stage scoring without the need of central electrodes (Dyson et al., 1984; Werth and Borbely, 1995; Lapinlampi and Himanen, 2004; Poree et al., 2006). The developed automatic methods can be used to detect sleep stages with four (two EOG, mastoid reference and a ground) easily applied disposable self-adhesive electrodes in contrast to normally used central EEG electrodes, EOG and submental EMG (Rechtschaffen and Kales, 1968; Anderer et al., 2005). Central electrodes C3, C4 need to be placed by an experienced sleep technologist and require more time than placing standard EOG electrodes (can be carried out after short training). Any easier alternatives to full polysomnograph could be then combined with e.g. portable monitors which are commonly used for the screening of sleep apnoea (Collop et al., 2007; Collop, 2008).

There are also other alternatives for measuring sleep in home for multiple nights. Beside actigraphy also cardiorespiratory signals have been used been used for sleep stage detection. Heart rate has been used for sleep staging since 1973 (Welch and Richardson, 1973). Harper et al. used cardiorespiratory signals for automatic classification of sleep stages in infants (Harper et al., 1987). Main features were respiratory rate variability and heart rate. Three stage agreement was 85%, with only cardiac measures 82% and with only respiratory measures 80%. Redmond et al. studied the use of ECG and respiration in sleep apnoea patients (Redmond and Heneghan, 2006) and normals subjects (Redmond et al., 2007). Peripheral arterial tonometry (PAT) has been used with actigraphy for the separation of wakefulness and sleep (Hedner et al., 2004), SREM (Lavie et al., 2000) and for light and deep sleep separation (Bresler et al., 2008). Usually these alternative methods only separate wakefulness and sleep or wakefulness, NREM and REM sleep. Methods are also sensitive to medication affecting the autonomic

nervous system. With relation to these other screening methods based on e.g. heart rate, oximetry, and cardiorespiratory systems the developed technique is complementary enabling, e.g. calculation of the heart rate variability during slow wave sleep (Brandenberger et al., 2005).

Detailed epoch transition rules of (Rechtschaffen and Kales, 1968) were not applied. Simplicity of the used rules is likely making the system robust. More advanced rules and classification could improve the results. Although not studied, it is reasonable to assume that similar agreement results could be obtained against the new rules (Iber et al., 2007). Based on new rules e.g. slow eye movements can define the N1 sleep stage. Using more frontal electrodes F4-M1 for slow wave sleep scoring is likely more correlated with slow waves detected using EOG electrodes. According to the new rules it is also possible to score delta using electro-oculography channel E1-Fpz. Amplitude parameters were fixed across subjects. Beta and alpha power thresholds were subject specific based on automated procedure.

In a large study Redline et al. using ambulatory sleep recordings obtained an artefact free EOG, at least 6 hours, in 87% of recordings. For the EEG the same number was 65% (Redline et al., 1998). This indicates that EOG recording is feasible in field studies. Usually EOG signals are used only as part of automated sleep stage analysis. The use of standard sleep electro-oculography placement enables to record frontal EEG, EMG and EOG using a single electrode pair. As eye movements can be unconjugated during sleep there are limitations to what can be measured with two electrodes. There are some cases when eye movements during NREM sleep are affected by medication (Armitage et al., 1995b) which may limit the use of EOG in sleep staging. On the other hand, with similar medication eyelid movements have been used to monitor sleep under medication and recovery (Silvestri et al., 2001). Eye movement density also correlates with sleep depth (Feinberg et al., 1987) and the addition of this feature could enhance the developed system.

Although there is criticism against epoch based sleep staging (Hasan, 1996; Himanen, 2000; Schulz, 2008) it is widely used and serves as a basis for more advanced NREM sleep analysis e.g. slow wave activity (SWA). In rare cases (e.g. narcolepsy) there can also exist state dissociation: elements of one state being intruded inappropriately into another (Mahowald and Schenck, 2005). But usually at least wake, NREM and REM sleep can be regarded as discrete stages. The aim of the study was not to replace clinical

polysomnography but provide some alternatives to be used instead of actigraphy and ambulatory polysomnography. In the future, events within NREM and REM sleep could be detected. For instance, calculating SWA during NREM sleep and eye movement density (EMD) during REM sleep. Waveform characteristics of SWS have been linked to sleep pressure (Riedner et al., 2007) and perhaps this could be detected using frontal electro-oculography electrodes. During REM sleep it is reasonable to assume that phasic and tonic parts could be separated using only EOG information. Total amount of eye movements (EM) during REM sleep was correlated with overweight in children and adolescents by Liu et al. (Liu et al., 2008). Low amount of slow wave sleep has been associated with high body-mass index (BMI) in older men (Rao et al., 2009).

The amount of visible spindles is reduced when using EOG electrodes and in this study no spindle or sigma activity was used in any analysis. Some alpha activity was detected using a mastoid reference. If reference electrode would be more central then more alpha and sigma activity would be detected. It remains also to be studied if other important sleep phenomena, like arousals (Bonnet et al., 1992) or cyclic alternating pattern (Terzano et al., 2002), could be detected using only EOG electrodes.

Most portable sleep devices do not enable diagnosis of non-breathing related sleep disorders. In the future the developed method combined with currently used cardiorespiratory recorders could be used for home screening of sleep disorders. It could also be used for monitoring sleep disturbances related to e.g. stress and shift work. Especially large-scale longitudinal studies could benefit from this easily applied and automatic estimation of sleep stages. Since the most part of the current thesis recordings were carried out in a laboratory environment, the use and feasibility of electro-oculography in sleep stage detection in ambulatory recordings remains to be studied. It remains to be seen how well the subjects manage to place the electrodes to correct positions if they do it themselves and how this affects the automatic scoring.

7 Summary and Conclusions

Sleep is an important aspect of our health. In this thesis a large number of recordings were used to develop self-applicable automatic methods for sleep staging. In addition, preliminary results were obtained with a single-channel portable device. Used electrodes were facial electro-oculography (EOG) electrodes recordable both with and without a mastoid reference. Subjects themselves can apply these electrodes. The reference method was a standard visual sleep stage scoring based on EEG, EOG and EMG electrodes. We also studied QRS artefact reduction and compared a single-channel EOG analysis to activity-based methods.

The classification algorithms used in this thesis were simple. There were very few assumptions. Using EOG L-M1, EOG R-M1 for correlation coefficient and EOG L-R for amplitude in the SWS detection assumes that slow wave sleep can be detected as a synchronous frontal EEG activity with amplitude difference between EOG L-M1 and EOG R-M1. This measure is by no means perfect. Some eye movements are not separated and there can be phase differences in e.g. theta and delta resulting in negative correlation coefficient in absence of eye movements. With a single-channel EOG analysis the eye movements during SREM were assumed to be largest by peak-to-peak amplitude. Slow wave sleep (SWS) activity was assumed to be second largest. In all studies large beta (18-30 Hz) power was taken as an indicator of wakefulness. Counting the density of features within a 30 s epoch was used as the main criterion for classification. This density approach was also applied to the activity data. For stage REM longer (90 s) time windows were used and simple smoothing was evaluated.

Slow wave sleep (SWS) detection algorithm based on two-channel electro-oculography was developed in study I. Cohen's Kappa between the visual and the new developed automatic scoring in separating non-SWS and SWS was substantial (0.70), with an epoch-by-epoch agreement of 93%. SWS epoch detection sensitivity was 75% and specificity was 96%. We also estimated the total amount of slow waves, called slow wave time (SWT). The advantage of the automatic method is that it could be applied during online recordings using only four disposable self-adhesive electrodes (two EOG, one mastoid reference and one ground).

New slow eye movement (SEM) detection algorithm was developed in study II and applied to the detection of unintentional sleep epochs during the Maintenance of Wakefulness Test (MWT). Alpha activity was also detected using a mastoid reference electrode. Cohen's Kappa between the visual and the new automatic scoring system in separating wakefulness and sleep was substantial (0.67) with an epoch by epoch agreement of 98%. The sleep epoch detection sensitivity was 71% and specificity was 99%.

The work of studies I and II were extended to all sleep stages in study III with the addition of individualized alpha threshold. The extension included the detection of REM sleep. Cohen's Kappa between the visual and the developed new automatic EOG-based scoring in separating 30 s wakefulness, SREM, S1, S2 and SWS epochs was a substantial 0.62 with an epoch by epoch agreement of 72%. With automatic subject specific alpha thresholds for offline applications results improved to 0.63 and 73%

In study IV reduction of QRS artefacts on single-channel EOG was evaluated using mean frequency based sleep detection. When QRS peaks were automatically excluded from the least square (LS) estimation the agreement and Cohen's Kappa increased respectively from 89% to 90% and from 0.44 to 0.50 when compared to the traditional spectral estimation

In study V, we compared single-channel EOG sleep detection to two activity-based methods using activity sensors placed in two different locations. With standard actigraphy (Actiwatch placed at the left wrist) sleep detection specificity and sensitivity were 42% and 95%. With two self-applied EOG electrodes combined with automatic sleep detection analysis, specificity and sensitivity were 72% and 96%. The results confirm low specificity of actigraphic sleep estimates, and demonstrate that the novel single-channel EOG method provides a substantial improvement in specificity

In study VI, we extended single-channel algorithm for separation of Wake, SREM, S1/S2 and SWS. Algorithm was also tested using a low weight single-channel EOG recorder. In separating the four stages the total agreement (and Cohen's Kappa) in the training data set was 74% (0.59), in the testing data set 73% (0.59) and in the validation data set 74% (0.59). Self-applicable electro-oculography with only two facial electrodes was found to provide reasonable sleep stage information.

In summary, by using standard self-applicable EOG electrodes in automatic analysis, we achieved reasonable sleep stage classification. This developed method could enable large scale field studies for the objective monitoring of sleep.

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9 Original publications

This thesis is based on the following publications (I-VI), which are referred to in the text by their Roman numerals. The articles are reprinted with the permission of the copyright holders. This work also includes some unpublished work and work published in abstract format.

I. Virkkala J, Hasan J, Värri A, Himanen S-L, Müller K. Automatic detection of slow wave sleep using two channel electro-oculography. Journal of neuroscience methods, 2007, 160: 171-177.

II. Virkkala J, Hasan J, Värri A, Himanen S-L, Härmä M. The use of two-channel electro-oculography in automatic detection of unintentional sleep onset. Journal of neuroscience methods, 2007, 163: 137-144.

III. Virkkala J, Hasan J, Värri A, Himanen S-L, Müller K. Automatic sleep stage classification using two-channel electro-oculography. Journal of neuroscience methods, 2007, 166: 109-115.

IV. Virkkala J, Hasan J, Värri A, Huupponen E, Himanen S-L, Müller K. Reducing the effects of electrocardiographic artifacts on electro-oculography in automatic sleep analysis. Conf Proc IEEE Eng Med Biol Soc, 2007, 590-593.

V. Virkkala J, Hasan J, Velin R, Himanen S-L, Värri A, Van Someren EJW. Automatic sleep detection using activity and facial electrodes. Conf Proc IEEE Eng Med Biol Soc. 2008, 1639-1642.

VI. Virkkala J, Velin R, Himanen S-L, Värri A, Müller K, Hasan J. Automatic sleep stage classification using two facial electrodes. Conf Proc IEEE Eng Med Biol Soc. 2008, 1643-1646.