Sleep, Rapid Eye Movement, and Alertness in Patients with Amyotrophic Lateral Sclerosis

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Summary

The aim of this dissertation was to investigate sleep architecture, rapid eye movement, and alertness in patients diagnosed with amyotrophic lateral sclerosis (ALS) at different stages of the disease including subjective and objective measures of sleep quality. Amyotrophic lateral sclerosis and other types of neurological diseases lead to mild to severe sleep disturbances resulting from direct and indirect factors due to the progression of the disease. First, 10 patients at varying stages of amyotrophic lateral sclerosis, some artificially ventilated and fed, were polysomnographically recorded over the course of three nights as well as for daytime sleepiness during the day by EEG-based Multiple Sleep Latency Tests (MSLT) and Maintenance of Wakefulness Tests (MWT). Subjective sleep quality and sleepiness were assessed by means of questionnaires. In the second study, polysomnographic electrooculogram (EOG) recordings served as the basis for the analysis of rapid eye movements (REM) to evaluate the possible preservation of involuntary extraocular eye movement muscles during REM sleep. The third study was aimed at investigating alertness/information processing in 14 ALS patients and matched healthy controls using auditory and visually evoked P300 EEG potentials over the course of four time points during the day. First, ALS patients demonstrated reduced sleep efficiency, significantly prolonged stage 1 sleep and decreased REM sleep. Six of ten ALS patients displayed mild daytime sleepiness (MSLT), but all had normal scores for daytime wakefulness as measured with the MWT. These results were reflected in subjective sleep quality and daytime sleepiness findings with reported poor sleep quality with mild daytime sleepiness likely caused by nocturnal motor symptoms and nocturia as the most prominent factors. Second, it was demonstrated that function of extraocular motor neurons significantly decline over the course of the progression of amyotrophic lateral sclerosis reflected by significant deterioration in REM components amplitude, density and duration. Finally, no significant differences between ALS patients and healthy controls could be found, but a different time pattern in alertness over the course of the day became apparent in patients with amyotrophic lateral sclerosis for auditory P300.

Zusammenfassung

Ziel der vorliegenden Dissertation war es, die Schlafarchitektur, die schnellen Augenbewegungen im Schlaf (REM; rapid eye movement) und die Aufmerksamkeit bzw. Informationsverarbeitung in Patienten mit Amyotropher Lateraler Sklerose (ALS) zu untersuchen. Amyotrophe Laterale Sklerose und andere degenerative neurologische Erkrankungen haben meist milde bis schwere Schlafstörungen zur Folge, die auf direkte und indirekte Ursachen der Krankheit und deren Fortschreiten zurückzuführen sind. In der ersten Studie wurden Schlafmessungen bei zehn Patienten in verschiedenen Stadien von Amyotropher Lateraler Sklerose in drei Nächten durchgeführt und Tagesschläfrigkeit objektiv mittels EEG-basierten multiplen Schlaflatenzmessungen und Tests zur Aufrechterhaltung der Schlaflosigkeit während des Tages erfasst. Subjektive Schlafqualität und Tagesschläfrigkeit wurde mit Fragebögen erhoben. In der zweiten Studie dienten polysomnographische EOG (Elektrookulogramm) Messungen als Grundlage zur Analyse der schnellen Augenbewegungen im Schlaf, um eine mögliche Erhaltung der unwillkürlichen extraokulären Muskelbewegungen der Augen im REM Schlaf zu evaluieren. Die dritte Studie im Rahmen dieser Dissertation war darauf ausgerichtet, die Aufmerksamkeit und Informationsverarbeitung bei 14 ALS Patienten und einer gesunden Kontrollgruppe mit auditorisch und visuell evozierten P300 EEG Potentialen zu vier verschiedenen Tageszeitpunkten zu untersuchen. Die Ergebnisse der ersten Untersuchung zeigten, dass die Schlafeffizienz in ALS Patienten signifikant herabgesetzt ist, eine Verlängerung des Schlafstadiums I stattfindet und eine verkürzte REM Schlafphase zu finden ist. Mehr als die Hälfte der ALS Patienten leiden unter milder Tagesschläfrigkeit, während keiner der TeilnehmerIinnen Schwierigkeiten hatten im Laufe des Tages wach zu bleiben. Diese Ergebnisse spiegelten sich auch in den Resultaten der subjektiven Erfassung von Schlafqualität und Tagesschläfrigkeit wider mit berichteter schlechter Schlafqualität und mild ausgeprägter Schläfrigkeit während des Tages. Die Hauptursache könnte in dem häufig berichteten Auftreten von motorischen Symptomen und Blasenschwäche während der Nacht liegen. Im zweiten Teil der Dissertation konnte erfolgreich nachgewiesen werden, dass sich die Funktion der extraokulären Motoneuronen signifikant mit dem Fortschreiten der Krankheit verschlechtert, welches sich in der signifikanten Verminderung der REM Komponenten von Amplitude, Dichte und Dauer zeigte. Zuletzt wurde ein verändertes zeitliches Muster in der Aufmerksamkeit für die auditorisch evozierte P300 bei ALS Patienten gefunden, obwohl sich ALS Patienten und Gesunde nicht grundsätzlich unterscheiden.

Table of Contents

SLEEP, RAPID EYE MOVEMENT AND ALERTNESS IN PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS

Sleep, Rapid Eye Movement and Alertness in Patients with Amyotrophic Lateral Sclerosis

1 Amyotrophic Lateral Sclerosis (ALS)

1.1 Epidemiology, Classification, and Pathogenesis

Amyotrophic lateral sclerosis (ALS) is a devastating degenerative neurological disease with uncertain pathogenesis. ALS is generally known as an upper and lower motor neuron disease without affecting sensory pathways leading to complete motor paralysis.

The term amyotrophic lateral sclerosis derives from
A = loss
myo = muscle
trophic = state of nutrition
lateral = at the side (of the spinal cord)
sclerosis = hardened (lateral spinal cord)

"Lateral sclerosis" because glia cells, which grow into the spinal cord lead to the impression of sclerotic tissue. The loss of central neurons in the motor cortex, connecting the brain to the anterior horn of the spinal cord, is also followed by growth of glia cells.

First described by Jean Martin Charcot in 1869, the incidence of ALS worldwide is about 1.4 - 2.4/100,000 (Chancellor & Warlow, 1992) with age-specific incidence peak occurring between 55 and 75 years of age. The prevalence is estimated for about 6/100000 with males being usually more affected than females (ratio about 1.6:1). There are areas with a higher than average prevalence of diseases similar to ALS. One particular region of interest for epidemiologists has been the Pacific rim (e.g. Guam). The role of methylaminoalanine in these areas has drawn particular attention. Inhabitants of the Pacific Island of Guam, the Chamorro population, include the flour made of the seeds of the cycad Cycas cirinalis (a tropical plant) into their diet, and was thought to be a toxic agent and a risk factor for amyotrophic lateral sclerosis (Naganska & Matyja et al., 2011).

5–10% of patients have a proven family history for amyotrophic lateral sclerosis. These usually show an autosomal-dominant pattern of inheritance. Of these, approximately 1 in 10 is linked to a mutation in the superoxide dismutase (SOD1) enzyme (Bowling et al., 1993). Autosomal-recessive forms have been reported in highly consanguineous populations in North Africa (Figlewicz & Orrell, 2003).

The cause of ALS is widely unknown. There exist four major hypotheses that try to explain which factors contribute to the generation of amyotrophic lateral sclerosis:

a) oxidative damage
b) axonal strangulation from neurofilamentous disorganization
c) toxicity arising from intracellular aggregates and/or failure of protein folding or degradation
d) excitotoxicity from aberrant handling of glutamate, especially arising from missplicing of a glutamate transporter mRNA (Cleveland, 1999)
e) enteroviral hypothesis: viruses (non-lytic) and apoptosis interplay are speculated to play an important role in neurodegeneration in sporadic amyotrophic lateral sclerosis (Ravits, 2005)
f) recently a genetical protein defect has been found to be present in all patients (Yahia, 2011).

Animal models of ALS revealed that lesions of motoneurons occur long before clinical symptoms are manifest. When patients notice clinical symptoms, 50 % of the peripheral motoneurons are already degenerated. This has led to the conclusion that degeneration actually starts years before the onset of the actual illness (Mitchell & Borasio, 2007).

1.2 Clinical Features and Symptoms

Clinical features of amyotrophic lateral sclerosis are mainly representative of the progressive loss/degeneration of motor neurons at all levels. Physical signs of this disease are representative for both upper and lower motor neuron degeneration.

While progressive motor paralysis as a result of degenerations of upper and lower motoneurons is the most pre-eminent symptom of ALS, other neurons of the central nervous system are not spared either (Martin & Chang, 2012; Agosta et al., 2009).

ALS has an insidious and fatal course that leads to variably progressing loss of motor function and finally to death from respiratory failure (Norris, 1992) with 50% of patients dying within 3 years of onset. The symptoms present at the onset of amytrophic lateral sclerosis can be categorised relative to their originating neurological region:

- bulbar
- cervical
- lumbar (see terminology below).

The disease leads to loss of muscle tissue due to degeneration of the peripheral motoneurons. Cell bodies of the peripheral motoneurons in the anterior horn of the spinal cord as well as their axons extending to the neuromuscular junctions degenerate. Consequently, patients experience muscle weakness and rigidity of the entire skeletal muscular system.

Additionally, central motoneurons, selected motor nuclei of the brain stem and the Betz cells of the motor cortex are involved in the degeneration process, leading to tetra-plegia and in the end-stage to collapse of trunk and respiratory muscles. Over the course of the disease patients experience increasing respiratory muscle weakness, which may be already present at diagnosis (Tsara et al., 2010). As a result patients die from respiration insufficiency commonly linked with pneumonia (Borasio, 1996; Ludolph, Meyer, Riepe, & Völkel, 1998). Patients do not die because the disease process is particularly malignant or rapidly progressive, but due to the location of the damage. In case respiration is spared, patients can live considerably well for a long period of time (Munsat, 1992).

About 25% of cases are ***"bulbar-onset" patients***. At first these patients recognise slurring of speech (dysarthria), e.g. difficulty in pronunciation, and/or difficulty in swallowing (dysphagia), and can stand for the degeneration in the lower and/or upper motor neurons. Bulbar palsy is connected with facial weakness and difficulties of the palatal reflex showing as fasciculations and weakness of the tongue. Ultimately patients lose the ability to speak and are unable to protect their airway when swallowing. Early bulbar symptoms indicate a rapid progression with an unfavourable prognosis. This means, the later bulbar muscles are involved, the better is the prognosis (Borasio, 1996).

Around 15-45% of patients experience ***"pseudo-bulbar affect"*** which is characterised by emotional lability, e.g. unintentional laughing or crying. This can be ascribed to degeneration of upper motor neurons which leads to exaggeration of motor expressions of emotion**.**

"Cervical-onset" amyotrophic lateral sclerosis starts in the upper limbs, with uni- or bilateral symptoms. Tasks involving shoulder abduction (e.g. hair washing, combing) can prove challenging as is the use of fine motoric skills. Arms and hands can be especially debilitated with frequent fasciculations and acute reflexes.

"Lumbar onset" signifies degeneration of the anterior-horn cells of the lumbosacral enlargement which gives attachment to the nerves supplying the lower limbs. This is associated with symptoms of the lower motor neuron circuit and weakness in the legs. Patients are experiencing difficulties in walking with a tendency to trip or climbing stairs (Mitchell and Borasio, 2007). To be diagnosed with ALS, patients must show symptoms of both upper and lower motor neuron degeneration that cannot be attributed to other causes.

Table 1.2: Overview of ALS related symptoms (in Mitchell and Borasio, 2007)

Direct **(due to motor neuronal degeneration)**	• Weakness and atrophy • Fasciculations and muscle cramps • Spasticity • Dysarthria (poor articulation) • Dysphagia (difficulty in swallowing) • Dyspnoea (shortness of breath) • Emotional lability
Indirect **(as a result of primary symptoms)**	• Psychological distress • Disturbed sleep • Constipation • Drooling • Mucous secretions • Symptoms of chronic hypoventilation • Pain

Amyotrophic lateral sclerosis may be accompanied by disturbances in other structures of the nervous system, i.e. not only the motor nervous system is involved.

Mulder et al. (1983) found abnormal detection thresholds for cutaneous sensation in 18% of patients tested. Shefner et al. (1991) showed that the minimum sensory conduction velocity was slowed in the sural nerve in 9 of 18 patients with ALS. Jamal et al. (1985) found thermal sensory abnormalities in up to 80% of the cases. Behnia and Kelly (1991) found that the action potential amplitude in sensory nerves was reduced in a small proportion of their patients.

Ludolph and colleagues (1987) found reduced perception of vibration in 35% of the investigated ALS patients. In the same study it is reported that the function of the ascending spinal sensory pathways is disturbed in 70% of the cases.

These studies suggest that the sporadic as well as familial forms of amyotrophic lateral sclerosis consist of a multi-system disorder where the majority of the pathological process involves the nervous system, rather than sole motor system degeneration.

1.3 Diagnostic Criteria and Clinical Rating Scales

The El Escorial diagnostic criteria for amyotrophic lateral sclerosis were formulated in the late 1980s and have subsequently been revised (World Federation of Neurology Research Group on Motor Neuron Diseases, 1998). Table 1.3 shows the essential features of the revised criteria.

Table 1.3: Summary of revised El Escorial criteria (in Mitchell and Borasio, 2007)

Definite	Lower and upper motor neuron signs in three regions
Probable	Lower and upper motor neuron signs in two regions
Probable with laboratory support	Lower and upper motor neuron signs in one region with EMG evidence of acute denervation in two or more limbs
Possible	Lower and upper motor neuron signs in one region
Suspected	Lower or upper motor neuron signs only in one or more regions
All categories need evidence of disease progression and absence of sensory signs not explicable on the basis of co-morbidity.	

These criteria provide a structured approach to assess patients for amyotrophic lateral sclerosis. This enables a higher objectivity in clinical practice and supports clinical studies. There are several functional rating scales in use that have been developed over the past three decades. These are namely the Norris scale (Hillel and Miller, 1989), the Appel amyotrophic lateral sclerosis rating scale (Appel et al., 1987), and the Amyotrophic Lateral Sclerosis-Functional Rating scale (ALSFR_R) in its revised form (Cedarbaum et al., 1999), currently the most commonly used scale in the clinical setting.

1.4 Treatment and Therapeutic Intervention in ALS

The classical therapeutic intervention in ALS concentrates on the clinical and functional problems. Physicians and relatives focus primarily on physical needs of the patients. No cure has yet been found for ALS. Until now only one drug treatment has been approved for this disease, Riluzole (Rilutek) (Riviere et al., 1998). This drug is thought to slow down the progress of degeneration in motor neurons with decreasing the release of glutamate when glutamate transporters are activated (Noh et al., 2000). The positive effect ofRiluzole in prolonging the life of patients with ALS has been reported in two randomised, double-blind, placebo-controlled trials and may better serve patients with a bulbar onset (Bensimon et al., 1994; Lacomblet et al., 1996). This compound additionally extends the time before a patient needs ventilatory support.

With disease progression respiratory muscles weaken, particularly the diaphragm, and lead to respiratory insufficiency and increasing aspiration problems. Failure of ventilation is reported to be the most common cause of death in ALS (Newsom-Davis et al., 2001). The presence of sleep disordered breathing has been thoroughly proven in ALS (Kimura et al., 1999; Gay et al., 1991; Ferguson et al., 1996).

ALS affects night-time sleep two-fold. Firstly, sleep architecture can be disrupted due to cerebral neurodegeneration and secondly, due to increased paralysis with its consequences for moving, swallowing, and breathing. Sleep irregularities in breathing are common in ALS and were shown to be uncorrelated with daytime respiratory status (Tsara and Kaimakamis, 2010). Initial symptoms of oxygen deficiency are sleep disruption, restlessness, headache in the morning, fatigue during the day, concentration problems, and loss of appetite.

Sleep disruption may be further exacerbated by muscle cramps, problems in swallowing, and restricted mobility (Hetta and Jansson, 1997). Especially ALS patients with bulbar involvement may experience such sleep disturbance with a probability up to 44% (Aboussouan et al., 1999). Patients can be supported by domiciliary mechanical ventilation for several hours during day and overnight night. This improves respiration and has been shown to increase survival rate in patients with ALS (Bach, 1995; Pinto et al., 1995, 1999).

Sleep problems not only affect patients, but also their partners. Kiely and McNicholas (1997) presented a short questionnaire with nine items to bed partners of patients having been on CPAP treatment (continuous positive airway pressure) between two to twelve months. Results could show that quality of life of bed partners improved and improvement was even greater than that of the affected partner.

There are two common types of mechanical ventilation for home use: non-invasive ventilation (NIV) with a mask and invasive ventilation by tracheostoma. With non-invasive and invasive ventilation these symptoms can be efficiently treated and thus, quality of life significantly increased (Lule et al., 2009). Patients should be made aware of the different techniques of home mechanical ventilation and they must know that artificial ventilation does not stop the progression of the disease and that they finally might experience a total locked-in syndrome.

Other treatments for ALS patients try to help to alleviate the symptoms of their disease and increase their quality of life under these circumstances. The advised approach to facilitate good care would be offered by a multidisciplinary team of health care professionals. These can include specialists such as physicians, physical and speech therapists, nutritionists, social workers, and home care nurses. To keep patients as comfortable and mobile, these teams can develop a plan of medical and physical interventions also offering the provision of special equipment.

Patients experience their inevitable physical decline with a fully conscious mind. Therefore, the necessity of psychological intervention is essential which is pointed out in a study of McDonald and colleagues (1994). It was examined how psychological well-being influenced the course of the disease. Psychological well-being was defined as low level of such factors as depression, hopelessness, and perceived stress. Patients with psychological well-being had a 9.41 times lower risk of dying than those with psychological distress.

Rabkin and her colleagues (2005) assessed the prevalence of depressive symptoms and disorders in patients in late-stage amyotrophic lateral sclerosis. They conducted semi-structured clinical interviews with ALS patients and their caregivers on a monthly basis until the decision for or against tracheotomy were inevitable to be made. Interestingly, at the beginning of this study 81% of patients had no depressive disorder, only 10% had minor depression and 9% of patients had been diagnosed with major depression.

Protective factors like e.g. spiritual beliefs, spouse as care partner, financial situation were identified but did not determine who were depressed or not and depression does not generally increase toward death.

The physical and emotional challenges generating from this disease not only impact the patients' health and well-being, but also that of their carers. The physical demands on the patient grow disproportionately on the carer (Jenkinson, 2000). Their study highlighted that carers display a lower health status compared with the general population and places greater emotional demands upon carers in direct proportion with the increase of adverse emotional reactions of their patients. As a consequence, treatment aimed to reduce the burden of this disease in patients will result in less strain, better physical health and well-being in their devoted carers.

2 Sleep

It has been said that "… more has been learned about sleep in the past 60 years than in the preceding 6,000" (Hobson, 1989, p. 1).

Hans Berger (1930) pioneered in recording electrical activity of the human brain in 1928. This measurement demonstrated that there actually were differences in electrical rhythms when subjects were awake or asleep. This development of electroencephalography (EEG) and the experiments of Moruzzi and Magoun (1949) during the first half of the last century paved the way for a new approach to sleep research. They investigated the role of the brain stem reticular formation in the transition from sleep to wakefulness in cats. Lesions of the brain stem reticular formation resulted in behavioural stupor and continuous EEG pattern similar to sleep. They concluded that, although brain stem reticular activation can be increased through collaterals of the specific sensory systems, direct input of sensory pathways does not keep the forebrain awake, but tonic activity in the pathways from the brain stem reticular formation to the cortex.

The next substantial landmark was contributed by Kleitman, Aserinsky, and Dement in 1953. They discovered that the slow waves of sleep are periodically interrupted by periods of a low voltage EEG akin to that of waking and were accompanied by rapid eye movements. The differentiation of NREM (non rapid eye movement) and REM (rapid eye movement) sleep was instated. The discovery of REM sleep put the general assumption that not much of interest happens during sleep to rest.

Once methods for investigating human sleep were established with polysomnography, basic research on sleep exploded and the different phases of "normal" sleep became apparent.

2.1 Basics of Sleep-Cycle

Normal sleep is composed of recurring succession of discernable stages. Two separate states of sleep have been defined based on physiologic measures that are detected with using Electroencephalography (EEG), Electrooculography (EOG) and Electromyography (EMG). These measurements comprised are termed polysomnography (Rechtschaffen and Kales, 1968) and discern the following two main sleep states: non-rapid eye movement (NREM) and rapid eye movement (REM) sleep.

Table 2.1: An Overview of Sleep Stages

Sleep Stage	Brain Waves		Common Characteristics
	Frequency (Hz)	Type	
1 N R E M	4 - 8	α, θ	• transition between sleep and wakefulness • gradual change from alpha waves to theta waves. • onset of sleep stage 1 is associated with potential sudden twitches and jerks
2 N R E M	8 - 16	θ, spindles, k-complexes	• Characterised by *sleep spindles* (12 to 16 Hz) and • *k-complexes*, followed by a burst of spindles • only lasts a few minutes • muscular activity lowers and conscious awareness of external environment disappears • occupies 45 to 55% of total sleep
3 N R E M	2 - 4	δ, θ	• delta waves (0.5 to 4 Hz) make up 20 to 50% of brain waves • functions primarily as a transition into stage 4
4 N R E M	0.5 - 2	δ, θ	• defined by more than 50% of delta activity; the rest is comprised of theta activity • deepest sleep stage before REM sleep
R E M (paradoxical sleep)	> 12	β	• occupies 20-25% of total sleep, lasting about 90-110 min • periodic bursts of rapid eye movements (REMs) and muscle atonia • increased heart rate • most vivid dreaming during this stage

According to Rechtschaffen and Kales (1968) NREM sleep is categorised into four sleep stages (see Table 2.1). The classification from 1-4 reflects the increase in depth of sleep over the course of one sleep cycle. The deeper sleep, the more dominant high-voltage, low-frequency ('synchronised') EEG wave activity becomes. Such low-frequency waves are predominant in the deepest stages of NREM sleep (3 and 4 NREM, also termed slow-wave sleep) (Pace & Schott, 2002).

In 2007, stages 3 and 4NREM were combined to stage 3NREM for all of deep stages of NREM by the American Academy of Sleep Medicine (AASM) (Schulz, 2008). At the time of this change in terminology data analysis in this dissertation has already been completed based on the previous standardization (Rechtschaffen and Kales, 1968), hence this standardization still applies to this thesis.

Stage 2NREM is characterized by sleep spindles and K-complexes, as well as a slow (<1Hz) oscillation. During NREM sleep the muscles are relaxed and a normal person wakes up quite easily then. Typically one makes a major postural adjustment approximately once every 20 min in this sleep stage. Figure 2.1.a demonstrates the typical waveforms of the different sleep stages.

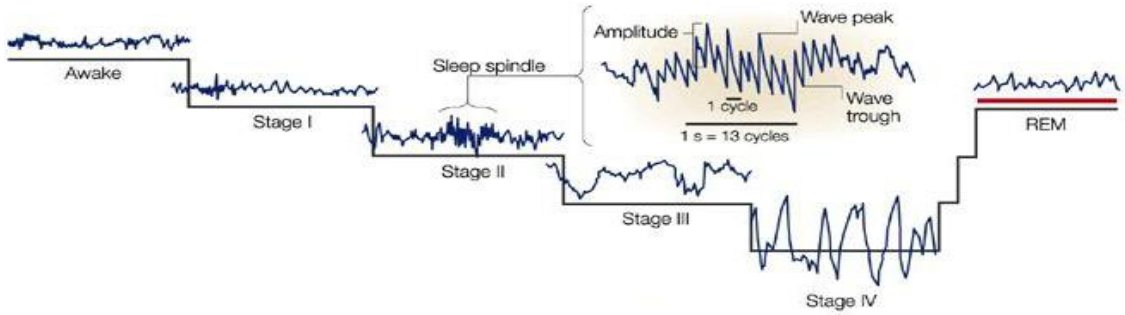


Figure 2.1.a: Characteristic waveforms of sleep stages (from Pace-Schott & Hobson, 2002, p. 600, panel a)

REM sleep (also termed paradoxical or 'desynchronised' sleep, see Table 2.1) is characterized by the following: During REM sleep the brain's neurons display a wake-like and 'activated' (high-frequency, low-amplitude, or 'desynchronised' sleep) activity in the EEG comparable to waking, hence the reason for calling this sleep stage paradoxical sleep (Pace & Schott, 2002). Further, in this stage singles and bursts of rapid eye movements (REMs) occur and EMG findings show that a very low muscle tone (atonia) prevails (Aserinsky & Kleitman, 1953). Subjects are not easily aroused during REM, but spontaneous awakenings are occurring most frequently in this stage.

The five stages of NREM and REM sleep occur cyclically and are repeated in each of the four to five cycles that arise in each night of an adult human's sleep. The first cycle, which ends after the completion of the first REM stage, usually last for 90-110 minutes. Each subsequent cycle lasts longer, in the beginning of the night REM stage is still quite short but extends toward the morning hours. The first REM period usually occurs about 70-90 min after sleep onset (Mc Carley, 2007). REM duration increases within each cycle (Fig. 2.1.b: red lines).

In the first half of the night, NREM sleep is predominant and occupies an overly large amount of time, especially in the first cycle. Then the REM epoch is still short. In sleep stage NREM1 the arousal threshold is generally lower and higher in sleep stage 3NREM (Carskadon & Dement, 1994). During the early night sleep cycle NREM reaches its greatest depth at sleep stage 3 and 4NREM (a) Fig. 2.1.b). Later in the night, NREM sleep becomes shallow and only reaches sleep stage 3NREM (c) during the 2nd half of the night. Figure 2.1.b illustrates an ideal progression of these changes over the course of a night's sleep.

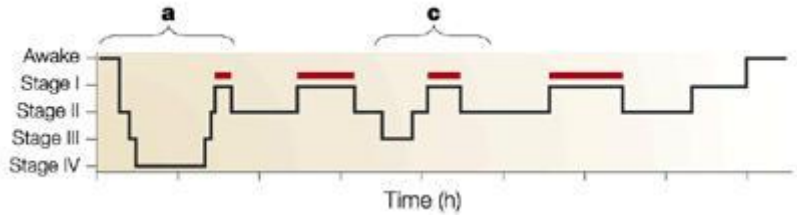


Figure 2.1.b: Hypnogram (from Pace-Schott & Hobson, 2002, p. 600, panel b)

During their first weeks of life the human newborn spends about 60% sleeping, of which REM sleep comprises half of their total sleep time (McLaughlin Crabtree & Williams, 2009). REM sleep decreases with age: 50% of the total sleep of a newborn to only 25% by 10 years of age (Kelly, 1991).

The percentage of REM sleep declines over the first ten years of childhood to adult level which is about 20% of total sleep time (McCarley, 2007). The predominance of REM sleep in children is important in stimulating nervous system growth and development.

In newborns NREM sleep with delta waves occurs only minimally but increases over the first years of life, reaching a maximum at about age 10 declining again in post-mature age (McCarley, 2008). Feinberg and his colleagues (1990) investigated the time course of delta activity over the first 30 years in humans. They found that his reduction in delta activity is similar to time course of the frontal cortex metabolic activity and synaptic density (as measured by positron emission tomography (PET). The reduction in these factors is interpreted as a trimming of redundant cortical synapses. This in turn should allow for greater specialisation enabling cognitive maturation. This may suggest that differentiation of sleep can be seen as a function of brain differentiation.

2.2 Functions of Sleep

Sleep has a restorative function not only for the body but particularly for the mind. It is not just a passive phenomenon or the absence of waking: rather it is "a special activity of the brain, controlled by elaborate and precise mechanisms" (Hobson, 1989, p. 1).

Sleep has likely evolved for primeval function. Over time sleep's original purpose was broadened and more and more functions were adopted as organisms have evolved. For one, sleep has a restorative value, conserves energy and for two, helps to consolidate recent learning. Whole brain energy metabolism is reduced by 25-30% in NREM sleep compared to the waking in both monkeys (Nakamura et al., 1983) and humans (Boyle et al., 1994).

Ramm and Smith (1990) studied protein synthesis in rats during NREM sleep, waking and REM sleep. They observed a positive significant correlation between cerebral protein synthesis and NREM sleep. Nakanashi et al. (1997) reported widely distributed increases in rates of cerebral protein synthesis in naturally occurring deep sleep (NREM 3-4) in comparison to light sleep (NREM 1-2) in adult rhesus monkeys. These findings support the hypothesis that deep sleep has restorative function. Based on the observation that deep sleep increases during recovery from sleep deprivation, it has also been suggested that it reverses the effects of prolonged wakefulness (Borbely, 1982).

It has been demonstrated that sleep deprivation has a detrimental effect on immune modulation and metabolism. Zager et al. (2007) deprived rats of REM sleep for 24 hours. Rats were blood tested and results in sleep deprived subjects showed a 20% decrease in white blood cell count showing a significant reduction in immune resistance, compared to a control group.

It could not be shown yet if sleep duration plays a role in somatic growth. Jenni et al. (2007) investigated this question of interest by recording growth, height and weight in 305 children over a time of nine years. They could not find that sleep duration had an effect on their somatic growth. On the other hand, it could be shown that NREM sleep does affect growth hormone levels in grown men. Van Cauter, Leproult and Plat (2000) demonstrated that men with a high percentage of NREM (average 24%) also had a significantly higher secretion of growth hormones than participants with a low percentage of NREM (average 9%). As sleep is a global state and manifests at every level of biological organization, genetic and intracellular mechanisms are involved as well as central neuronal systems which control autonomic functions, movement, behavior and cognition.

Over the last decade a series of studies have investigated the role sleep plays in memory. Research was able to provide substantiated proof supporting the importance of sleep in memory processing dependent on sleep (Walker & Stickgold, 2006).

These studies aimed specifically to assess the role of sleep in memory encoding, consolidation, and reconsolidation. They could confirm this newly formed hypothesis of sleep contributing importantly to processes of memory consolidation and brain plasticity (Kalia, 2006). Since memory consolidation requires sleep and inhibitors of protein synthesis block long-term memory (Agranoff, 1981), it is possible that cerebral protein synthesis in deep sleep is related to consolidation of memory.

The specific role of REM sleep in the consolidation of memory though, is still not clear. Its ontogenic pattern roughly goes parallel to cerebral myelinisation and it has been claimed that REM sleep becomes vital only in the critical stages of development of the central nervous system (Roffwarg, 1966).

In animal experiments it has been conclusively proven that REM sleep is imperative for consolidation of recent learning and memory (Bloch, 1979; in Bloch 1995). In humans, studies investigating sleep and memory have mainly focussed on learning tasks concentrating on declarative memory encoding. The results of these studies were inconclusive (Walker & Stickgold, 2006). As one of the first to investigate the subject, De Koninck et al. (1989) sleep recorded ten students before and after a six-week language course. They could show a significant correlation between successful learning and an increase in the percentage of REM sleep pre- to post-training course. They concluded that REM sleep may constitute an important factor in memory consolidation.

Several studies have been conducted to investigate the function of NREM sleep stages in memory consolidation of declarative memory tasks (Gais & Born, 2004; Gais et al., 2002) and procedural memory (Karni et al., 1994; Atienza et al., 2002; 2004; Stickgold et al., 2000c).

While the results on procedural memory and its reliance on sleep are quite persistent, the role of NREM sleep in memory consolidation of declarative learning content is still contradictory (Walker & Stickgold, 2006). Gais and his colleagues (2002) presented their subjects with a declarative learning task of 336 unrelated word pairs right before sleep onset in the 2nd and 3rd night of sleep recording. They found an increase in sleep spindle density characteristic for 2NREM sleep stage for the learning task compared to a nonlearning cognitive task.

Gais et al. (2004) tried to verify the hypothesis of the correlation between low cholinergic tone during NREM sleep and memory consolidation. Acetylcholin is thought to be the quintessential transmitter for smooth conduct in the declarative memory system dependent on the hippocampus.Two memory tasks (non-declarative: mirror tracing task; declarative: word-pair associates task) were presented to be learned 30 min before sleep onset. The experimental group was injected with physostigmine enhancing their central cholinergic tone during NREM rich sleep. As a result declarative memory consolidation was impaired in the experimental group and confirmed the above mentioned hypothesis.

For the dependence of procedural memory on sleep, on the other hand, research findings have been consistent and proved to be robust across visual, auditory, and motor systems (Walker & Stickgold, 2006).

Karni et al. (1994) could show that learning on a visual texture discrimination task shows significant improvement after a night of sleep. Atienza et al. (2002 and 2004) could report that auditory memory consolidation was dependent not only on time but also on sleep. This was reflected by changes in brain evoked response potentials (ERPs). Interestingly, sleep deprivation following training did not hinder performance but ERPs, normally occurring with the shift of attention to relevant stimuli, did not after one night of sleep deprivation post training.

Walker et al. (2002a) have shown that a night of sleep can result in significant higher speed and accuracy performance on a sequential finger-tapping task, while a corresponding amount of time during waking showed no significance. Furthermore, learning gains over one night of sleep were correlated with the amount of stage 2 NREM sleep.

Behavioural studies in humans could convincingly demonstrate that sleep plays a critical role in memory consolidation post-training. Except one sleep stage, namely stage 1NREM sleep, all other NREM sleep stages have been successfully connected to aspects of this consolidation. Memory consolidation and reconsolidation seem to be a reflection of several processes such as on the molecular, cellular and systems level. They transform still volatile memory representations into more stable ones where they are then available for later reactivation and/or recall. These processes appear to be a persisting series of biologic adjustments that increase the efficiency and incorporation of stored memories over time (Stickgold, 2005).

The duration and intensity of sleep are regulated through a process known best as sleep homeostasis (see below). The best index of the intensity of sleep is slow wave activity which is seen in NREM sleep. It has been shown that sleep in the first half of the night, when NREM is dominant, hippocampus-dependent declarative memory is increased (McEwen, 2006). Wagner (2005) showed that this is associated with low cortisol levels and low muscle tone.

Sleep in the second half of the night, when REM sleep is prevalent, has been found to be associated with amygdala-dependent emotional memory. This finding has been substantiated by a recent study which used functional nuclear magnetic resonance imaging. Takashima and his colleagues (2006) investigated the process by which short term memories are transferred to and consolidated in the neocortex and how this affects neural correlates when memories are being retrieved. Their findings lead to the conclusion that the cortisol rise, naturally occurring during the second half of the night when REM sleep dominates, helps to prevent an overshoot in emotional memory formation.

The use of functional nuclear magnetic resonance tomography could also demonstrate that motor memory improves after a night of sleep following a period of intensive training. This can be seen through an increased activation of the right primary cortex, medial prefrontal lobe, hippocampus and the left cerebellum (Walker & Stickgold, 2005). These findings were correlated to more accurate and faster key-press movements. With observed decreases in activity in the frontal and parietal cortex, and temporal lobe, this was interpreted as needing less conscious monitoring when spatial skills were applied. These results carry implications for learning a wide variety of real life skills and for rehabilitation after stroke or brain trauma (Walker and Stickgold, 2006). When sleep is deprived, it not only impairs our capability to learn, to restore our health but our day-to-day functioning and quality of life.

2.3 Basic Models of Sleepiness

Sleepiness is our subjective experience of sleep deprivation, but was firstly objectified by Borbély (1982). He developed a two-process model of sleep regulation which postulated a basic model of sleepiness that is still broadly referred to. The model delineates the processes involved in the regulation of waking and sleeping and defines that sleepiness arises from the combined action of two components (See Fig. 2.3):

- Homeostatic Process S
- Circadian Process C

'Process S' dependent on the balance of sleep and wakefulness increases during wakefulness and decreases during sleep. 'Process C' keeps the two tresholds in balance determining onset and discontinuation of one sleep episode (Daan et al., 1984).

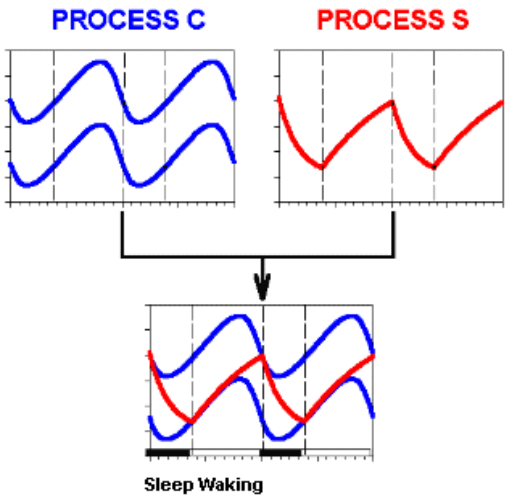


Figure 2.3: Schematic representation of the 2-process model of sleep regulation (adapted from Daan, Beersma, & Borbely, 1984)

It has been empirically confirmed that the homeostatic and circadian components are generated by separate brain mechanisms and neurotransmitter systems and that both of them influence sleep and vigilance states.

As to ***'Process S'***, recent evidence points to adenosine, a neurotransmitter with extra-cellular levels coupled to metabolism on the cellular level as one modulator in the homeostatic sleep response (McCarley & Sinton, 2008). During wakefulness accumulating adenosine is inhibiting noncholinergic and cholinergic neurons in the basal forebrain, part of the ascending activating system (AAS) (McCarley, 2007). Adenosine as the mediator of sleepiness increases after prolonged wakefulness and slowly decreases in recovery sleep.

The second factor, ***'Process C'***, is circadian, which varies with a 24-h periodicity and is independent of the amount of preceding sleep or wakefulness (Mc Carley & Sinton, 2008). The suprachiasmatic nucleus (SCN) is the pacemaker for the circadian rhythm. Through inhibiting projections to the ascending activating system (AAS) SCN regulates the circadian influence. The discharge activity of cells in the suprachiasmatic nucleus is dependent on the circadian rhythm (Inouye and Kawamura, 1979; cited from McCarley & Sinton, 2008).

Both processes, circadian and homeostatic, regulate the need for sleep and counterbalance alertness and sleepiness. Empirical support for this basic model has been obtained in several studies: subjective performance and physiological measures of sleepiness have been shown to be sensitive to time of day as well as sleep deprivation, reflecting circadian and homeostatic effects, respectively (Casagrande et al., 1997; Babkoff et al., 1991; Dijk et al., 1990).

Originally it was proposed that process S and C are two independent processes, where S is oscillating between two thresholds modulated by the circadian rhythm. An alternative construct suggests that sleepiness results from the continuous interaction of the two components. Thereby it can be represented as a single process (Achermann and Borbély, 1994). A criticism to the proposed models concerns the exclusive emphasis on the sleep drive. Strong indications of a pivotal role of arousal or a wake drive on the likelihood of falling asleep are available. Whether somebody will fall asleep, feel sleepy, experience vigilance problems or show physiological signs of sleepiness appears to depend not only on sleep need or sleep drive, but additionally on arousal level or wake drive.

Edgar et al. (1993) was the first to propose the idea of two opponent processes in sleep-wake regulation and can be summarised as followed: Sleep propensity depends on the relative strength of two mutually inhibiting drives, the wake and the sleep drives. The sleep drive consists of the C and S components of the two-process model; the wake drive is composed of chronobiological factors, e.g. circadian rhythm, as well as of environmental factors like posture and physical activity (Bonnet and Arand, 1997).

The relative pre-eminence of the wake or the sleep drive will cause wakefulness or sleep, respectively. Johns (1998) incorporated this line of thought in his four-process model of sleep and wakefulness and stressed the importance of environmental contributors, such as soporific circumstances of a situation, to the wake drive which was largely ignored previously. Further in the text, sleep need or sleep requirement are used as synonyms for the sleep drive; the wake drive is called arousal and the tendency to fall asleep is referred to as sleep propensity.

A study of Bonnet and Arand (1998) empirically supports the existence of the sleep drive and an arousal component of sleepiness. Sleep drive was manipulated through partial and total sleep deprivation and arousal by physical activity.

Both factors independently influenced the ability to stay awake (Maintenance of wakefulness test (MWT)) and the tendency to fall asleep (Multiple sleep latency test (MSLT)). The effect of physical activity, the arousal effect, was even stronger than the sleep deprivation effect.

Sleepiness or sleep propensity can be defined as consisting of two independent factors, an arousal and a sleep component. The sleep propensity of a particular person can be presented as the result of the person's position on a continuum ranging from hypo-arousal to hyper-arousal and on a second, independent, continuum indicating the level of sleep need. It implies that a high level of sleepiness can reflect a high sleep drive, a low arousal level or their combination.

This supports the idea of the existence of different states of sleepiness, instead of a single unitary phenomenon of varying degrees (Cluydts et al., 2002).

2.3.1 Assessment of Sleepiness

Measuring sleepiness is a complex task. Multiple conceptual frameworks of sleepiness and different putative underlying mechanisms gave rise to many different operationalisations. As a consequence, a lot of assessment tools have been developed over the years. The tools I chose for my dissertation were:

1. Self-evaluation of sleepiness by rating scales
2. Direct electrophysiological measures

Using self-evaluation of sleepiness by rating scales is the most economical way to measure excessive sleepiness (hyper somnolence), but it encounters some drawbacks inherent to self-report measures, such as unintended bias and purposeful falsification.

These assessment tools can be divided into two categories: simple self-report of the experienced level of sleepiness and the assessment of a more global level of sleepiness on the basis of the estimated sleep propensity in various daily-life situations. Scales from the first category can be used to follow short-term changes in sleepiness, in other words to assess "state" sleepiness. The second category of tests gives an indication of a subject's global level of sleepiness (Cluydts et al., 2002).

The ***Stanford Sleepiness Scale (SSS)*** (Akerstedt and Gillberg, 1990) and the ***Epworth Sleepiness Scale (ESS)*** (Johns, 1991) are the most common subjective tests of sleepiness. The SSS was introduced in 1972 and consists of a checklist of adjectives that are used to describe the subject's sleepiness at that moment. However, its reliability in chronically sleepy patients is uncertain (Dement et al., 1978; Roth et al., 1980).

The ESS is the most commonly used subjective test for the assessment of sleepiness. First described in 1991, it requires rating of the tendency to fall asleep in eight common situations and is not influenced by variations in sleepiness during the day or between days (Johns, 1991). The validity of the ESS as a measure of "trait" sleepiness (i.e. a general level of daytime sleepiness, seen as a stable individual characteristic) is further supported by its satisfactory test-retest reliability five months apart (Johns, 1992). Subjective tests are thought to be particularly sensitive to other factors such as motivation, recall bias, education level, and fatigue rather than simply the propensity to fall asleep. Despite the minor short comings of some of the test instruments, over the years they have proven to be the most commonly used and most reliable tests available at this point in time.

Only through the new implementation of the electroencephalogram (EEG), it was discovered that the sleep state was associated with changes in the EEG that seperated it from wakefulness (Blake and Gerard, 1937). A system for describing sleep architecture based on the changes in EEG waveforms was developed by Rechtschaffen and Kales (1968). This system made the quantification of sleep stages possible and assessment of sleep latency, formulated as the time from lights out to the onset of sleep.

The ***Multiple Sleep Latency Test (MSLT)*** method was first formalized in 1977 to assess sleepiness in young subjects with no sleep related problems in sleep deprivation experiments (Carskadon and Dement, 1977; 1979). Six volunteers (age 18-21) were deprived of sleep for two consecutive. During daytime subjects were put in bed every two hours and asked to try to fall asleep. Each recording was concluded after 20 min if the subject was not successful in falling asleep. If falling asleep was successful, the subject was awakened after the first two epochs (30 sec per epoch) of stage 1 NREM sleep and the test terminated to prevent interference with the procedure of sleep deprivation. Sleep latency was accounted for from lights off to the first minute of stage 1 NREM sleep. The degree of sleep deprivation and sleep latency significantly correlated and validated sleep latency as a biologically based measure of sleepiness (Arand et al., 2004).

The key concept of the MSLT is that of sleepiness as a physiological need for sleep. Hence, an increased tendency to fall asleep reflects greater sleepiness. The procedure requires subjects to lie down in a quiet darkened room and not to resist falling asleep. Sleep latency is determined by standard electrophysiological means and is defined as the elapsed time from lights-out to the first epoch of any sleep stage. If sleep does not occur, the test is discontinued after 20 min. The important outcome variable is the mean sleep onset latency and the number of REM onset trials.

It has been shown to be sensitive to factors that increase sleepiness, such as acute and chronic partial and total sleep deprivation (Carskadon and Dement, 1982), sleep disruption, circadian rhythm, hypnotic and alcohol intake, narcolepsy, obstructive sleep apnea (Thorpy, 1992) and idiopathic hypersomnia (Chervin et al., 1995). Additionally, studies have shown that MSLT is sensitive to state as well as trait levels of the central nervous system arousal (Bonnet and Arand, 2000; cited from Arand et al., 2004). For these reasons, the MSLT was chosen to assess daytime sleepiness in ALS patients.

The methodology of the ***Maintenance of Wakefulness Test (MWT)*** resembles that of the MSLT, except that subjects are instructed to attempt to stay awake sitting in a dark room (Mitler et al., 1982) for 20 min without taking extraordinary measures, such as mental or physical activity, to remain awake. It results in a test score that corresponds better than the MSLT with the main problem of sleepy patients, namely resist sleep in monotonous circumstances (Sangal et al., 1992). Until now there does not exist a direct biological measure to assess wakefulness. Therefore, this phenomenon is assessed indirectly through the incapability or delayed tendency for falling asleep by the MSLT (Arand et al., 2004). The latency on the MWT decreases with sleep deprivation (Härmä et al., 1998) and artificial sleep fragmentation in normal subjects (Martin et al., 1996).

In general, the MWT is able to discriminate between highly increased levels of sleepiness, while it has problems in discriminating lower levels of sleepiness. The MSLT comparatively is better at showing differences among people who are more alert (Cluydts et al., 2002). Thus, both measures tap into different constructs (wakefulness vs. sleepiness); for this reason both measures were applied to assess wakefulness and sleepiness in ALS patients.

Another technique to measure sleepiness has been shown in the late components of cerebral evoked potentials, especially for the auditory system. They are altered in the drowsy state in healthy subjects and have lower amplitude in narcoleptics in comparison with healthy subjects (Broughton, 1982). Sangal et al. (1999) demonstrated that prolonged auditory and visual P300 latencies were found in narcolepsy patients as compared with healthy subjects. Evoked potentials, namely the P300, were used in this dissertation as a physiological measure to address daytime alertness and information processing in ALS patients (please see study III).

2.4 Neurophysiology of Sleep

Sleep is a global state and the development of more advanced methods in quantitative electrophysiology resulted in enhanced processing of human EEG signals. This enabled the revelation of how broad the involvement of cortical and sub-cortical systems actually is. Neuroimaging, on the other hand, helped to specify the ongoing changes in activity in those regions.

There are several essential brain regions which execute specific functions in sleep at different levels, e.g. circadian rhythm, dreaming, control of NREM sleep rhythms, memory consolidation, control of the REM-NREM cycle or sleep onset (Fig. 2.4, see below).

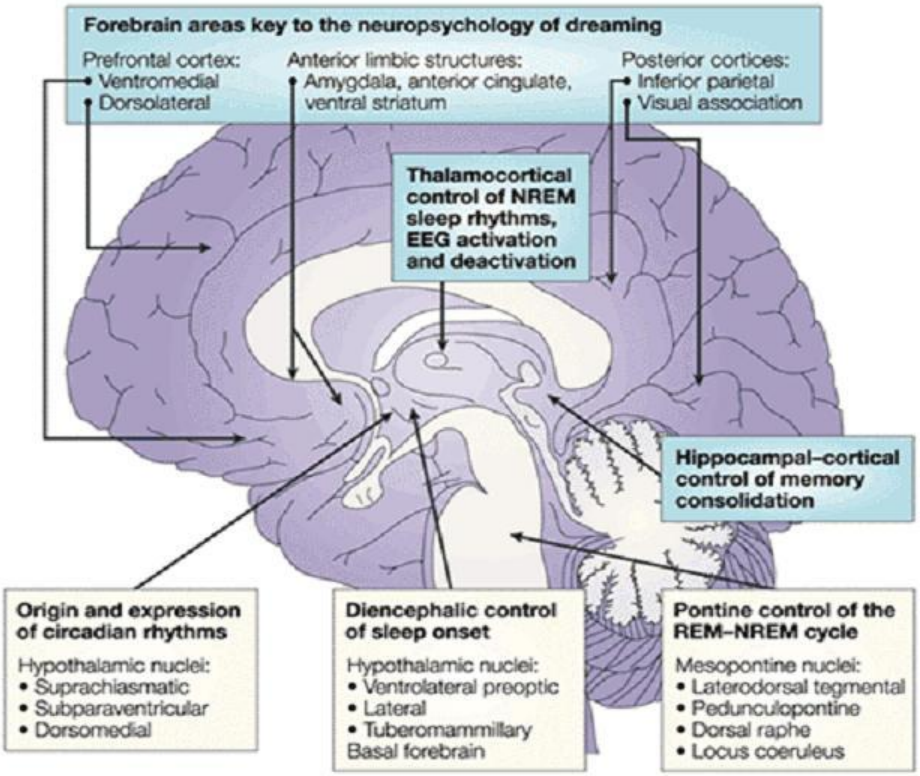


Figure 2.4: Brain regions of interest in the neurobiology of sleep
(in Pace-Schott & Hobson, 2002, p. 592, Fig. 1a)

2.4.1 Circadian Rhythm

There have been recognized two basic mechanisms – a homeostatic mechanism and a circadian mechanism. As stated above (see 2.3), the homeostatic process dictates that a certain amount of sleep duration needs to be obtained over a short term and that current needs depend on the individual's immediate history of sleep and wakefulness. When sleep is deprived, it causes a so-called 'rebound' effect. The individual compensates for lost sleep in sleeping longer and with more intensity reflected in a higher amount of NREM sleep (slow waves).

The circadian rhythm is of approximate daily periodicity, a roughly 24-hour cycle in the biochemical, physiological or behavioral processes of living beings, including plants, animals, fungi and cyan bacteria. As defined by Cassuto (1972), the term "circadian" originates from the Latin word "circa*",* which means "approximate", and *"dies"* meaning "day" respectively a 24-hour period. Circadian rhythms are mostly associated with sleep, but there is a variety of other processes influenced by the circadian clock such as adjustment of body temperature, secretion of hormones and digestion (Harmer et al., 2001). Circadian rhythms are usually controlled by a combination environmental factors and internal factors. Ambient light as well as temperature cycle on a daily basis, yet light is still the most important external factor (Harmer et al., 2001).

The molecular circadian clock is genetically controlled and synchronously expressed collectively and individually by all of the approximately 20,000 cells of the mammalian *suprachiasmatic nucleus (SCN)*. The SCN is located bilaterally in the *anterior hypothalamus,* just above the optic chiasm. This proximity to the optic nerve explains its reaction to light. The SCN is housing the 'master clock' mechanism, responsible for the daily light-dark cycle setting the 24-hour-rhythm for all other organism's physiological rhythms. This in part is done by the SCN by controlling molecularly related peripheral cellular oscillators exerting local control over physiological rhythms at locations closer to the expression of these rhythms (Pace-Schott et al., 2002).

The study of Ralph and his colleagues (1990) definitely showed that the SCN of the anterior hypothalamus holds the mammalian circadian pacemaker. They transplanted the SCN of hamsters that had normal circadian rhythms into hamsters with mutant rhythms (Pace-Schott & Hobson, 2002). This restored normal periodicity in the implanted hamsters where mutant-to-normal transplantation had the opposite effect. Additionally, loss of input from the SCN causes a loss of sleep consolidation (Dijk et al., 1997).

Most of SCN neurons project to the dorso-medial hypothalamus, which in turn projects to the ventro-lateral preoptic area; to a collection of hypothalamic endocrine cells that secrete hypocretin, corticotrophin-releasing hormone, thyrotropin-releasing hormone, and gonadotrophin-releasing hormone; and to autonomic neurons that project to the brain stem and spinal cord autonomic (sympathetic and parasympathetic) nuclei.

These interconnections of areas involved in the regulation of sleep are addressed in this chapter to enable an understanding of the changes in sleep and daytime sleepiness in patients with amyotrophic lateral sclerosis resulting from motor degeneration over the course of the disease.

2.4.2 Diencephalic Control of Sleep Onset

The transition from wake to sleep is anything but straightforward. The alertness-mediating neurons in the midbrain, thalamus, and cerebral cortex slow down during sleep but do not instantly discontinue firing. These millions of neurons change their output in a smoothly graded manner across states. The sleep latency period, defined as the time from start of the polysomnographic recording and actual sleep onset, is mostly indicated by the first appearance of sleep spindles or K-complexes (NREM 2) (Merica & Fortune, 2004). This often entails a drifting in and out of NREM 1 and wake. The occurrence of NREM 1 characterises a period of gradual change operating at every level of biological organisation where arousal is continuously abated until definite sleep is established.

The role of the hypothalamus in the regulation of sleep and wake states has been recognised 1930 (Merica & Fortune, 2004). Von Economo (1930) deduced the existence of specific centres in the brain for the regulation of sleep and wakefulness, but only in recent years Sherin and his colleagues (1996) identified a population of neurons promoting sleep in the *ventrolateral preoptic (VLPO)* area of the *hypothalamus* (Saper et al., 2001). The axons from the VLPO innervate the cell bodies and proximal dendrites of the *tuberomammillary nucleus* and less intensely the dorsal and median *raphé nuclei* and the *locus coeruleus*. The axons from the VLPO terminate in the cholinergic *basal forebrain* (Saper et al., 2001); pedunculopontine tegmental and laterodorsal tegmental nuclei groups. Almost 80% of VLPO neurons contain the glutamic acid decarboxylase enzyme that synthesizes γ-aminobutyric acid (GABA) as well as the peptide galanin (Sherin et al., 1998) and are active during sleep.

Two major nuclei have been identified: One located in the VLPO promotes NREM sleep receiving circadian output from the *suprachiasmatic nucleus (SCN)* and the *dorsomedial hypothalamic nucleus (DMH)*. The other is located dorsal and medial to the VLPO and was found to be closely linked to REM sleep (Lu et al., 2000; 2002).

2.4.3 Thalamocortical control of NREM sleep

When the change from waking to NREM sleep is realised, the thalamocortical input is switched off (Muzur et al.2002). The majority of neurons in the ascending activating systems of brainstem and diencephalon, relay nuclei of the thalamus, and the neocortex display decreased firing. The input from several activating areas responsible for waking and attention have to diminish, for thalamocortically induced NREM to begin. That includes noradrenergic neurons in the *locus coeruleus*, serotonergic projections from the *dorsal raphe nucleus*, histaminergic neurons from the *tuberomammilary nucleus*, orexinergic neurons from the *lateral hypothalamus*, and cholinergic neurons from the *basal forebrain* and the *mesopontine tegmentum* (Pace-Schott and Hobson, 2002).

The hypothalamus takes on a regulatory role influencing the state of activation of thalamocortical systems as well as synchronising the latter with adrenergic-cholinergic centres of REM and NREM. Each of the systems of thalamus, hypothalamus and pontine brainstem are able to innervate the cortex.

The ascending reticular activating system (ARAS), composed of regions in the rostral reticular formation, projects to the forebrain through two pathways. Both are important for the sleep-wake cycles. Dorsally, one pathway, originating mainly in the rostral pons and caudal midbrain, ascends through the lateral hypothalamus to the basal forebrain and projects through several thalamic nuclei to the cortex. Neurons in the pons and midbrain fire during wakefulness and reduce firing during NREM sleep. Ventrally, the other pathway ascends through the lateral hypothalamus and terminates on neurons in the medial septum and the diagonal band. These are areas consisting of neurons projecting to the cortex. This pathway starts in the *locus coeruleus* and the *dorsal raphe nuclei*. Locus coeruleus is a nucleus of the brainstem that is the main supplier of noradrenalin to the brain. Dorsal raphe nucleus, on the other hand, comprises a large cluster of serotonin-containing neurons and supplies serotonin to the *forebrain* and other *brainstem* nuclei. These neurons will fire during wakefulness and stop during REM sleep.

As the cycle continues through the sleep stages, the brain undergoes exciting changes in neurochemistry. In waking noradrenergic and serotonergic systems (locus coeruleus and nucleus raphe) are active while the cholinergic influence (acetylcholine release in the thalamus) is markedly less active but not repressed entirely. During REM sleep both aminergic systems are completely inhibited and cholinergic systems become dominant.

2.4.4 Brain Areas controlling REM sleep

The discovery of REM sleep (Kleitman, Aserinsky and Dement, 1953) in humans led to animal experiments to investigate the mechanism of its regulation. Experimental transection studies of the spinal cord in cats and in human patients with spinal injury showed that the spinal cord is not involved in the brainstem signs specific for REM sleep. These findings suggested that REM sleep is generated in the brainstem (Jouvet, 1962). Further studies followed to investigate which sites in the brainstem could be responsible for the regulation of REM sleep. Various pontine nuclei were damaged to examine their effect.

Some reported that the nucleus pontis oralis is responsible for the regulation of paradoxical sleep (Jouvet, 1962), others identified nucleus pontis caudalis (Carli et al., 1965). Later, Roussel and his colleagues (1976) found *locus coeruleus* to be significant for the generation of REM sleep.

Another area considered as crucial is the pons (Siegel, 1989). Vanni-Mercier et al. (1991) micro-injected carbachol into the medio-dorsal pontine tegmentum in seven cats. This induced an increase in REM episodes with short latencies of less than five minutes, although not in cats transected at the pre-bulbar level. This led to the conclusion that the pons alone is insufficient to generate REM sleep, but needs the support of the medulla and cholinergic input to reach this state of sleep.

The new technique to record single neuron activity led to better insight into how pontine nuclei interact at the neuronal level and their importance for REM sleep physiology. Those studies found neurons in the pontine reticular formation that stop or decrease their firing during paradoxical sleep (Chu et al., 1973) and were termed REM-OFF neurons. Those neurons that increase their firing during REM sleep were termed REM-ON neurons (McCarley & Hobson, 1971). The interplay of these neurons determines the generation of REM sleep and its regulation.

2.5 Sleep Relevant Disorders in Amyotrophic Lateral Sclerosis

Although amyotrophic lateral sclerosis has been linked already in 1979 with disturbances of sleep architecture and with sleep disordered breathing by Minz and his colleagues, only recently a better and more plenary approach was taken to assess sleep behaviour in amyotrophic lateral sclerosis.

The described abnormalities of sleep architecture in ALS have included increased sleep latency, persistence of EMG activity during REM sleep and slow wave sleep, increased REM sleep latency, and longer and more frequent awakenings. Other studies document a reduction in total sleep time (refers to the total sleep period minus time spent awake during the sleep period), shortened 2NREM and decreased REM latency, prolonged 1NREM periods, fasciculations in anterior tibial muscles, equally represented in all stages, and more frequent arousals and stage changes per hour (Minz et al., 1979; Ferguson et al., 1996; Hopkins et al., 1996; Gay et al., 1991; Sonka et al., 2004).

A variety of factors like depression, difficulty in handling secretions, fasciculations, cramps and orthopnea may contribute to these disruptions; sleep disordered breathing may be just an additional determinant. For instance, 83% of patients in the Ferguson study (1996) suffered from orthopnea which portends significant diaphragmatic muscle weakness. In stage REM, ventilation has to be maintained only from the respiratory intercostals and accessory muscles to the diaphragm. In consequence REM sleep reduction is linked with impaired ventilation in REM sleep because of diaphragm insufficiency. Patients with diaphragmatic dysfunction from neuromuscular disease would be primarily sensitive to respiratory events as a result, especially during REM sleep.

The degeneration of corticospinal tract, brainstem and spinal motor neurons is the main characteristic of degeneration in amyotrophic lateral sclerosis (ALS). But in the last decade data from neuroimaging (Kew et al., 1993a, Pioro et al., 1994; Abrahams et al., 1996; Lloyd et al., 2000; Ellis et al., 2001; Turner et al., 2004; Thivard et al., 2007; Van der Graaff et al., 2011) and neuropathology (Maekawa et al., 2004) were reported which show that widespread cortical lesions in ALS involve also important areas for sleep regulation such as hypothalamus, thalamus, and brainstem (Saper et al., 2005). The most relevant studies will be summarized below.

Several neuroimaging techniques have shown potential for the assessment of the extent or presence of cortical pathology, magnetic resonance imaging (MRI), positron emission tomography (PET) and transcranial magnetic stimulation.

In 1993, Kew and his group incorporated positron emission tomography to compare regional cerebral blood flow (rCBF) in twelve patients with amyotrophic lateral sclerosis (ALS) to six age-matched controls. ALS patients, scanned during movements of a joystick with their right hand and at rest, showed a significantly reduced rCBF at rest compared to controls in the primary sensorimotor cortex, the lateral pre-motor cortex, the supplementary motor area and the *anterior cingulate cortex* (ACC). It is suggested that the reduced rCBF at rest might reflect a combination of neuronal loss in all areas of the cortex projecting through the *pyramidal tract* (Kew et al., 1993a).

Several studies have questioned the view that ALS is a disorder restricted to the motor system but ultimately this view was found wrong. A dysfunction of the *extramotor cortex* and in particular the *prefrontal cortex* has been identified (Ludolph et al., 1992; Abrahams et al., 1996) with more evidence to come in the following years of research in this area facilitating newly developed technologies and approaches.

In the PET study of Lloyd et al. (2000) they sought to extend these observations using the benzodiazepine $GABA_A$ marker [^{11}C] flumazenil. This approach constituted the possibility to detect both extra-motor and motor dysfunction in amyotrophic lateral sclerosis as $GABA_A$ receptors are broadly distributed in the cerebral cortex as well as on pyramidal cells and inter-neurons. The 17 patients with amyotrophic lateral sclerosis showed significantly decreased regional flumazenil volumes of distributions in the *prefrontal cortex* (area 9 and 10, bilateral), *parietal cortex* (area 7, bilateral), visual association cortex (area 18, bilateral) and left motor/pre-motor cortex.

In a volumetric analysis of cerebral grey and white matter on MRI Ellis et al. (2001) tried to quantify pathologic changes in 16 ALS patients (with equally lumbar- and bulbar-onset) and eight healthy controls. By comparing the sum of ALS patients with the control group, they found a bilateral shortage in grey matter volume in *Brodman areas 8, 9 and 10*. They could also reveal a decrease in the volume of white matter in ALS patients with bulbar-onset. This encompassed areas spreading bilaterally from the *precentral gyrus* to the *internal capsule* and *brainstem*. The precentral gyri remained intact. The reported loss of grey matter in the frontal regions of ALS patients, independent of bulbar- or lumbar onset, suggests that amyotrophic lateral sclerosis is a multi-system disorder.

Microglial cell activation has been suggested in the course of the disease of several neurodegenerative disorders. There are reports of inflammatory mechanisms where microglial cells may play a central role in initiating cell death or survival, especially in ALS (McGeer and McGeer, 1998; 2002; cited from Turner et al., 2004). There are also some imminent hypotheses about selective motoneuronal cell death where microglia may have a fundamental role (Tortarolo et al., 2003; Raoul et al., 2002; cited from Turner et al., 2004).

In a morphometric study Maekawa and his colleagues (2004) tried to quantify the loss of SMI-32-IR pyramidal neurons and GABAergic interneurons in the primary motor cortex (Brodman area 4) and in two of the extra-motor cortical areas, in particular the dorsolateral prefrontal cortex (DLPC; Brodman area 9) and the anterior cingulated cortex (ACC; Brodman area 24c). They used SMI-32, which is a mouse monoclonal antibody against a non-phosphorylated form of neurofilament protein, as it stains pyramidal neurons (and Betz cells) as well as motor neurons. They analysed human post-mortem brain tissue samples of 13 cases diagnosed with amyotrophic lateral sclerosis (ALS) and eight control subjects without previous history of neurological or psychiatric disease. They found a significant reduction of about 25% in the density of SMI-32-immunoreactive pyramidal neurons within cortical layer V in the *primary motor cortex*, the *DLPC* and *ACC* compared with controls.

Turner et al. (2004) used [^{11}C](R)-PK11195 PET to measure the presence and spatial distribution of microglial activation in the brain of ten ALS patients and matching 14 normal controls. [^{11}C](R)-PK11195 is a ligand for the peripheral benzodiazepine binding site (PBBS) expressed by activated microglia. The PBBS can be found in many organs except for the healthy brain. The authors found increased binding in the *motor cortex* ($p=0.003$), *pons* ($p=0.004$), *DLPC* ($p=0.01$) and the *thalamus* ($p=0.005$). Results showed a significant correlation between benzodiazepine binding in the motor cortex and clinical upper motor neuron signs.

Thivard et al. (2007) investigated the extent of cortical and subcortical lesions in 15 patients with definite (n=9) and probable (n=6) sporadic ALS and a control group of 25 volunteers. They used whole brain voxel based DTI (diffusor tension imaging) and voxel based morphometry (VBM) in combination to study mean diffusivity (MD) and fractional anisotropy (FA) to assess morphological changes in grey and white matter. Further extent of lesions was correlated to the degree of motor disability appraised with the revised ALS Functional Rating Scale (ALSFRS-R) (Cedarbaum et al., 1999).

There was no correlation found between ALSFRS-R score and MD abnormalities, but grey matter volume was found to be decreased bilaterally in the hippocampal formations, temporal isthmus, thalamus, in the inferior frontal and precentral gyrus.

In figure 2.5 below the areas of impairment are highlighted as described in the studies above.

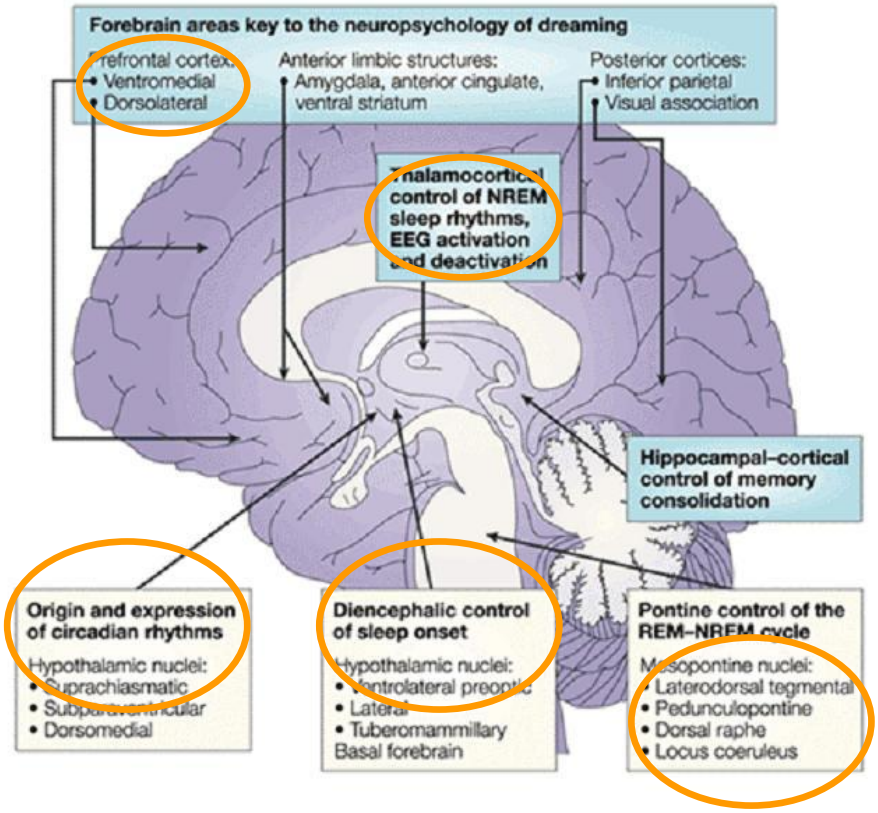


Figure 2.5: Highlighted: Impaired brain regions in ALS involved in sleep (modified from Pace-Schott and Hobson, 2002, p. 392, Fig. 1a)

These findings clearly state that cerebral pathology is widespread and particularly involves many areas important for sleep regulation and generation such as prefrontal cortex, hypothalamus, thalamus, and brainstem.

3 Questions

Study I - Sleep Architecture in Patients with Amyotrophic Lateral Sclerosis

In previous studies sleep in ALS patients was mainly investigated with respect to the impact of ventilation (e.g., Ferguson et al, 1996; Sonka et al., 2004). Results on sleep architecture were mostly reported as secondary findings. In my first study, I aimed to receive a detailed and critical appraisal of sleep architecture in ALS with emphasis on sleep quality, subjective and objective sleepiness measures, and a detailed dissection of polysomnographic elements of sleep in this degenerative motoneuronal disease. With data reported in this study, I aimed at (1) further elucidating changes in sleep architecture in ALS patients during all stages of the disease and (2) assessing related daytime wakefulness and sleepiness.

I specifically included patients in later stages of the disease, which renders our study different from those reported in the literature. Moreover, I assessed both night-time sleep and daytime sleepiness/wakefulness on the subjective and physiological level.

On the basis of previous findings I hypothesised

(1) More fragmented sleep, reduced sleep efficiency, reduced 3 and 4NREM sleep (sleep stages 3 and 4) and reduced REM sleep in ALS patients as compared to age-matched normative data from healthy subjects. Further,
(2) Due to reduced sleep efficiency I predicted increased daytime sleepiness and reduced daytime wakefulness in ALS patients as compared to normative data.
(3) I assumed that the physiological results would be positively correlated with the subjective data such that reduced sleep efficiency would be related to subjectively experienced reduced sleep quality and more symptoms of depression.
(4) Finally, I predicted that objective and subjective measures of sleep quality would deteriorate as the disease progresses.

4 Methods and Materials

4.1 Patients

Subjects, who participated in the sleep study between September 2005 and February 2007 were 10 ALS patients (7 men and 3 women, between 40 and 77 years of age, mean age 58.09; s ±11.21) (Table 4.1).

Table 4.1: Participants in Sleep Study

Patient	Age	Sex	CPAP	PEG	Diagnosis	ALSFRS-R
A	**42**	**Male**	**No**	**No**	**2003**	**28**
B	**40**	**Male**	**Yes**	**Yes**	**1998**	**2**
C	**58**	**Female**	**No**	**No**	**2001**	**13**
D	**70**	**Male**	**Yes**	**No**	**1996**	**25**
E	**50**	**Female**	**Yes**	**No**	**2002**	**9**
F	**51**	**Male**	**No**	**No**	**2003**	**36**
G	**56**	**Male**	**Yes**	**Yes**	**1999**	**10**
H	**73**	**Male**	**No**	**No**	**2002**	**32**
I	**67**	**Female**	**No**	**No**	**2006**	**24**
J	**65**	**Male**	**No**	**No**	**2005**	**30**

ALSFRS-R= The ALS Functional Rating Scale revised is a tool for the assessment of Severity of ALS (12 questions "0 worst to 48 best"); CPAP = Continuous positive airway pressure; PEG = Percutaneous endoscopic gastrostomy feeding tubes

4.1.1 Patient Details

Over the course of this study a total of ten patients were investigated.

Male patient **A,** aged 42, former engineer, was diagnosed with amyotrophic lateral sclerosis in summer 2003. At the time he was still having difficulty in coping with his diagnosis. The ALS started with lumbar symptoms which quickly led to the use of a wheel chair and showed some signs of weakness of hands and arms. **A** was able to breathe without artificial ventilation and swallow fluids. A's main complaint were fasciculation and muscle cramps.

Male patient **B,** aged 40, had been diagnosed with amyotrophic lateral sclerosis (ALS) for 7 years. **B** worked in the family business of agricultural machinery. He formerly was a passionate

biker and loved extended trips to exotic places. At the time of the study he had just started to be artificially fed but was still able to consume normal food when cut into little pieces. At the time of the study he had been using artificial ventilation (CPAP; continuous positive airway pressure) overnight for two years. His motor abilities were reduced to head and facial muscle movement. Although almost completely paralyzed, **B** was still interested in working in the family business and in current affairs. Together with his wife and two children he enjoyed a busy social life. He lived with his family and parents in their house, but needed 24-hour care. (Deceased April, 2010†).

Female patient **C,** aged 59, was diagnosed with amyotrophic lateral sclerosis in May 2001. The ALS started with lumbar symptoms and was accompanied by almost total loss of speech in 2004. This didn't impair her ability to eat normally, though with help by feeding. She can sit with help but is paralyzed with no use of arms and legs. She has no artificial ventilation overnight. **C** has extremely positive personality and happy family (two daughters) and social life. She has drop-in home care twice a day while she is being taken care of by her husband the rest of the time. **C** enjoys reading and music very much and uses a reading device for books.

Male patient **D,** aged 70, received his diagnosis of amyotrophic lateral sclerosis in summer of 1996. He lives now in his retirement home together with his wife. Due to the very slow progression of the disease in his case, he still was able to use a walker and only sometimes took advantage of his wheelchair as his legs were impaired while his arms were still fully functional. A speech therapist came by twice a week and a physiotherapist was attended once a week. Artificial ventilation was not only used overnight during sleep but also sometimes applied in the afternoons if shortness of breath occured. His brother had died of amyotrophic lateral sclerosis 2 years prior to this study and was the main incentive to participate. **D** and his wife lead a calm but happy life together with frequent visits of their grandchildren.

Female patient **E**, aged 50, was diagnosed with ALS in December 2002 with distally accentuated tetraparesis, dysphagia, dysarthria, and microcytic anemia. **E** used a walker and at the time of the study she was at the edge of losing her speech. She lives alone in her apartment with a caretaker coming every day. She is very interested in current events and reading is one of her most favorite pastimes. Although she reported increasing shortness of breath, she was not on overnight artificial ventilation (CPAP) at the time of the study.

Male patient **F,** aged 51, a former maintenance supervisor at the local school, has been diagnosed with the disease since 2003. He has slight tetraparesis in his legs. Speech, breathing and swallowing are not yet affected. **F** lives together in his house with his wife and adolescent daughter. He is trying to stay physically active on a daily basis and undergoes daily massages (Jin Shin Jyutsu; Japanese healing technique aiming at the energy system of the body).

Male patient **G,** aged 56, retired, had been diagnosed with amyotrophic lateral sclerosis (ALS) in 1999. He used an electric wheelchair and had overnight artificial ventilation (CPAP). He had problems with swallowing and was artificially fed. His speech was still intact at the time of study. **G** and his family have a very good social life and his children/grandchildren visit the family at least three times a week.

Male patient **H,** aged 73, retired, was diagnosed with ALS (amyotrophic lateral sclerosis) in 2002. His disease was very slow in progression and he was still very mobile but occasionally was using a walking stick. Previous to diagnosis of ALS he suffered from five strokelets. **H** reported that he already had had sleeping problems for 3 – 4 years prior to the study with cramps in the left hand (fasciculations). His breathing and swallowing were not impaired yet through the disease at the time of assessment.

Female patient **I,** aged 67, retired, had received her diagnosis of ALS just six months before her participation in the study (10/2006). Walking was possible only with her walker. Swallowing and breathing were not affected yet, but she displayed weakness in both of her hands and impaired fine motor skills. Patient **I** lives together with her husband in a nice house in the country. Her favorite pastime was needlework which she regreted not being able to perform anymore.

Male patient **J,** aged 65, retired, had been diagnosed with amyotrophic lateral sclerosis in 2005. He had milder paresis in his arms and legs; he still coul walk independently with the help of

his walker. Breathing, swallowing and speaking were not disturbed. He lives at home with his wife who also takes care of him. At the time **J** was still very active and went for slow walks with his wife (walker) and visits his daughter and friends.

All subjects who participated in this study gave informed consent for the study (see Appendix 16.4), which had been reviewed and approved by the Ethical Review Board of the Medical Faculty of the University of Tübingen, Germany. The inclusion and exclusion criteria are listed below:

Recruitment Criteria

Inclusion Criteria for ALS-patients

- Diagnosis of definite ALS with El Escorial Criteria by a neurologist
- Sustained ability for communication, e.g. patients must have residual muscle control for the possibility of „Yes/No"-communication

Exclusion Criteria for ALS-patients

- Psychiatric disorder (depression, anxiety etc.)
- Psychotropic drugs
- Heavy caffeine, alcohol or drug intake
- Dementia

One patient was not included in the study because of diagnosis of depression.

Meeting of criteria was ensured after medical consultation with treating physician and interviews with patients preceding their approval for participation.

All ALS-patients were recruited through the following clinics:

ALS outpatient clinic, Department of Neurology, University Hospital, Ulm

We were able to recruit ALS patients through the cooperation with Prof. A. C. Ludolph at the University Hospital in Ulm, Policlinic for Neurology. This was be supported by Dr. A. Kurt in the ALS outpatient clinic.

Department of Neurology, University Hospital, Tübingen

In cooperation with the sleep laboratory, Clinic for Neurology and the Hertie-Institute for clinical brain research, University of Tübingen.

4.2 Questionnaires

A set of sleep questionnaires and measures of psychological well-being was administered in the presence of either the investigator or a caregiver within two sessions. One session took place at the patients' home, the second in the sleep laboratory after the first night of polysomnography. These questionnaires are important for evaluation and interpretation of physiological results. Additionally this information gives a subjective measurement on quality of sleep, arousal and well-being during the day (day time sleepiness, fatigue) which will be correlated to progression of the disease (e.g., ALS-FRS) and physiological parameters (e.g., REM):

4.2.1 Self- and Third-Party-Evaluation of Sleep Quality

a. **Epworth Sleepiness Scale (ESS) (Johns, 1994).** The ESS is a self-administered questionnaire with eight items. Subjects are asked to rate on a four point Likert-type scale their likelihood of dozing in each of eight distinct situations that are often encountered in daily life. The ESS score is the sum of scores from the eight items and can vary from 0 to 24. It provides a measurement of the participant's average sleep propensity in daily life (please see appendix, 16.6 ff, C and F).

b. **Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1988).** The PSQI consists of 19 self-evaluative questions and five items for third-party evaluation and retrospectively records the frequency of sleep disrupting events, estimate of sleep quality, sleep latency, sleep medication intake as well as daytime sleepiness over the last four weeks. The summary score can vary from 0 to 21. The cut-off-score of 5 is able to distinguish "good sleepers" (below 5) from "poor sleepers" (above 5) reflecting the poor overall quality of sleep. This questionnaire was applied because of the benefit of a third-party rating and gives a very detailed overview of sleep related complaints.

c. **Questionnaire about Chronotype (D-MEQ) (Griefahn et al., 2001).** The D-MEQ is the German translation of the Morningness-Eveningness Questionnaire (MEQ, Horne & Östberg, 1976) and is used to identify the subjective circadian phase (chronotype). It is able to discriminate moderate or definitive 'evening-type' from the different 'morning-types', respectively, and the neutral type. This questionnaire was conducted to identify if patients with amyotrophic lateral sclerosis belong to a certain chronotype group (see appendix 16.6 ff, G).

d. **Parkinson`s disease sleep scale (PDSS) (Chaudhuri et al., 2002).** The PDSS is a visual analogue scale addressing 15 commonly reported symptoms of sleep disturbance and allows sensitive differentiation of specific factors contributing to sleep disruption. Items of the PDSS address overall quality of night's sleep (item 1), sleep onset and maintenance insomnia (items 2 and 3), nocturnal restlessness (item 4 and 5), nocturnal psychosis (items 6 and 7), nocturia (i.e. urination at night, especially when excessive) (items 8 and 9), nocturnal motor symptoms (items 10-13), sleep refreshment (item 14), and daytime dozing (item 15). The severity of symptom for each item ranges from 0 (symptom severe and always experienced) to 10 (symptom free). The maximum accumulative score for the PDSS is 150 (free of symptoms). The PDSS was used as especially motor symptoms of amyotrophic lateral sclerosis are similar to Parkinson's disease (please see appendix 16.6 ff, D).

e. **Tübingen Sleep Questionnaire (Clinic for Neurology, Tübingen).** This questionnaire is part of standard evaluation before polysomnographic recording at the department of Neurology, University Hospital in Tübingen and was therefore included in this study. This battery of questionnaires (standardized interview) assesses several areas of interest for sleep evaluation, e.g. 'falling asleep', 'parasomnia', 'waking up', 'sleepiness', 'cataplexy', or 'varia'. In this study, only areas of interest were included in the result section (please see appendix 16.6 ff, F).

4.2.2 Measures of Depression

f. **ALS – Depression – Inventory (ADI) (Kübler et al., 2005).** The ADI-12 measures depressive symptoms in severely paralyzed patients taking into account the specific situation of increasing physical impairment.

g. **Beck's Depression Inventory (BDI) (Beck et al., 1965).** The Beck Depression Inventory is a self-report scale that measures the severity of depressive symptoms, if present.

ADI was applied as it takes into account physical impairment of ALS patients which is not covered in the Beck's Depression Inventory. The BDI was also applied as it is the most commonly used self-rating instrument for assessing depressive symptoms. Although it should only be applied after a diagnosis of depression if ascertained, it is often used to categorize patients as depressed or not.

4.2.3 Results - Questionnaires

4.2.3.1 Self- and Third-Party-Evaluation of Sleep Quality

a. Epworth Sleepiness Scale (ESS)

In Table 4.2.3.1.a below each patient's score is listed. An ESS Score above 10 is considered as pathological.

Table 4.2.3.1.a: Individual ESS scores for patients A to J

Patient	Score (0-24)
A	**10**
B	**6**
C	**3**
D	**7**
E	**9**
F	**17**
G	**4**
H	**5**
I	**11**
J	**7**

30 % of patients reported severe sleepiness during daytime (A, F and I).

b. Questionnaire about Chronotype (D-MEQ)

Based on the summary scores of this questionnaire patients can be attributed to five categories of 'Definitive Evening Type' (16-30), 'Moderate Evening Type' (31-41), 'Neutral Type' (42-58), 'Moderate Morning Type' (59-69), and the 'Definitive Morning Type' (70-86).

Patients could be categorized in the following categories: Neutral Type: 4 patients (E, B, I and J); Definitive Morning Type: 2 (D, F); Moderate Morning Type: 3 (C, G and H); Definitive Evening Type: 1 patient (A), and Moderate Evening Type: 0.

Please see Table 4.2.3.1.b below:

Table 4.2.3.1.b: Individual Chronotype scores for patients A to J

Patient	Chronotype	Score (16-86)
A	**Definite Evening Type**	**29**
B	**Neutral Type**	**53**
C	**Moderate Morning Type**	**64**
D	**Definitive Morning Type**	**71**
E	**Neutral Type**	**54**
F	**Definitive Morning Type**	**70**
G	**Moderate Morning Type**	**63**
H	**Moderate Morning Type**	**64**
I	**Neutral Type**	**54**
J	**Neutral Type**	**58**

c. The Pittsburgh Sleep Quality Index (PSQI)

The Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1988) was chosen for this study as it provides a brief, but clinically useful assessment of a variety of sleep disturbances and includes not only self- but also third-party-ratings to give an index (>5 indicates 'poor sleep quality') for easy discrimination between "good" and "poor" sleepers.

The 19 self-rated questions were grouped into seven component scores, each weighted equally on a 0-3 scale. The seven component scores (subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction) were then summed to yield a global PSQI score, which has a range of 0-21. A global PSQI score >5 indicates poor sleep quality and that a subject is having severe difficulties in at least two areas, or moderate difficulties in more than three areas.

30 % of ALS patients (A, F and H) could be classified as „poor sleepers" (Score >5; see above, Table 4.2.3.1.c).

Only two patients described their subjective sleep quality as 'fairly bad', all other patients reported their quality of sleep as "fairly or very good". Seven out of ten (70%) patients complained of impaired sleep latency on a mild or moderate level resulting from early awakenings or later than usual sleep onset. 50% reported shortened sleep duration, i.e. 6-7 hours and one patient 5-6 hours on average per night, respectively.

Two patients reported impaired habitual sleep efficiency of 65-74%. Four patients reported sleep disturbances occurring 'once or twice a week', all other 'less than once a week', but all reported some degree of disruption stemming from several sources such as difficulty in breathing, pain, bad dreams, temperature regulation, and nocturia.

Except one, all patients experienced difficulty to stay awake during e.g. eating or social gatherings over the last four weeks prior to assessment at least once a week. None of the patients took sleep medication.

Individual PSQI scores are as followed:

Table 4.2.3.1.c: Individual PSQI scores for patients A to J

Patient	Subjective Sleep Quality	Sleep Latency	Sleep Duration	Habitual Sleep Efficiency	Sleep Disturbances	Use of Sleep Medication	Daytime Dysfunction	Summary Score (0-21)
A	**2**	**2**	**2**	**2**	**2**	**0**	**1**	**11**
B	**1**	**0**	**0**	**0**	**1**	**0**	**1**	**3**
C	**1**	**1**	**0**	**0**	**1**	**0**	**0**	**3**
D	**1**	**0**	**1**	**0**	**2**	**0**	**1**	**5**
E	**0**	**1**	**1**	**0**	**1**	**0**	**1**	**4**
F	**2**	**1**	**1**	**0**	**2**	**0**	**2**	**8**
G	**1**	**1**	**1**	**0**	**1**	**0**	**1**	**5**
H	**1**	**0**	**0**	**2**	**2**	**0**	**1**	**6**
I	**1**	**1**	**0**	**0**	**1**	**0**	**2**	**5**
J	**1**	**1**	**0**	**0**	**1**	**0**	**2**	**5**

Main areas of impairment were reduced subjective 'sleep quality', 'sleep disturbances', and 'daytime dysfunction', but only three out of ten patients showed pathologically reduced quality of sleep.

d. The Parkinson's disease Sleep Scale (PDSS)

A similar picture was shown by the results of the Parkinson's disease Sleep Scale (PDSS) (Chaudhuri et al., 2002). Four out of ten patients (40%; A, D, I and F) showed 'Poor overall quality of night's sleep'; only one (A) reported experiencing a late sleep onset; 5 (A, D, F, H and I) stated 'nocturnal restlessness'; just one (D) experienced 'nocturnal psychosis'; 7 patients suffer from either severe (I, D and G) or mild 'nocturia' (H, E, A and F); 5 showed 'nocturnal motor symptoms'; 7 of patients reported 'poor sleep refreshment' (A, B, D, E, F, G and J); and 3 patients (C, I and F) 'daytime dozing'.

Summary scores for each patient are listed in Table 4.2.3.1.d below:

Table 4.2.3.1.d: PDSS summary scores for patients A to J

Patient	Score (0-150)
A	**74**
B	**135**
C	**134**
D	**82**
E	**131**
F	**72**
G	**103**
H	**110**
I	**100**
J	**126**

The primary concerns patients reported were 'poor sleep refreshment' and 'severe or mild nocturia', followed by 'nocturnal restlessness' and 'nocturnal motor symptoms'. The chart below (Figure 4.2.3.1.d) demonstrates the distribution amongst patients.

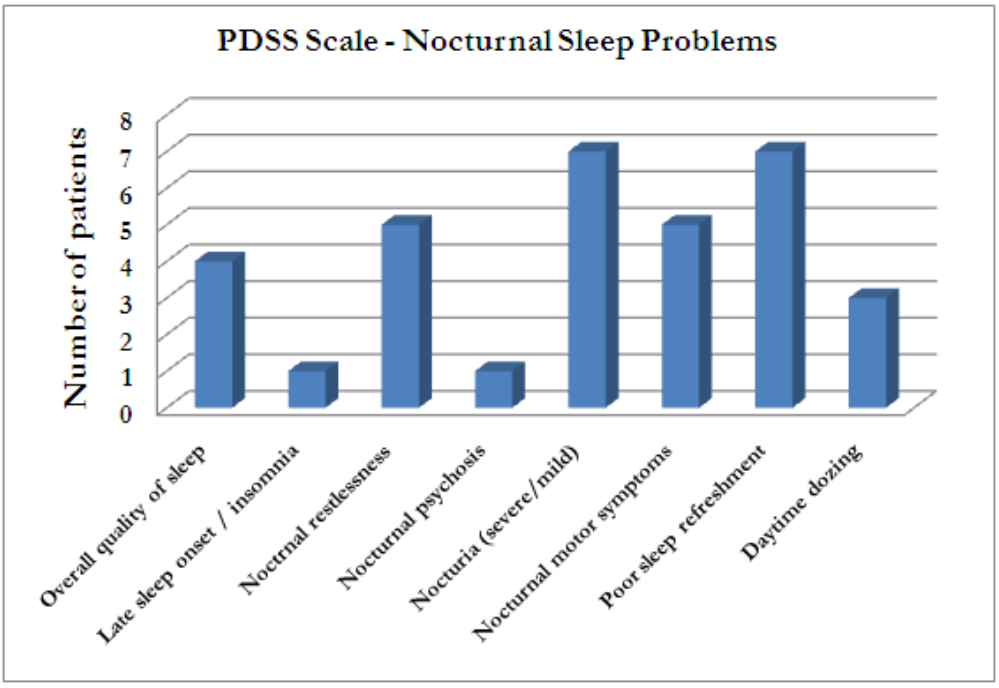


Figure 4.2.3.1.d: Distribution of PDSS results for patients A to J.

e. Tübingen Sleep Questionnaire (Clinic for Neurology, Tübingen)

Falling asleep

- 3 patients had trouble falling asleep or sleeping through the night
- 2 needed more than 30 min to fall asleep
- 7 woke up more than once during the night

Parasomnia

- 4 report leg/feet tremor when falling asleep and 30 % while sleeping
- 2 complain about muscle cramps during the night
- 3 show symptoms of Restless Legs Syndrome (RLS) or so-called pins and needles in their legs while asleep

Waking up

- 4 feel sleep-deprived

Daytime Sleepiness

- 3 complain about daytime sleepiness
- 2 report falling asleep involuntarily during the day
- only one patient describes daytime sleepiness as insurmountable
- 8 take a nap during the day

The Tübingen Sleep Questionnaire showed a similar outcome with a more detailed description of symptoms patients were suffering from, i.e. muscle cramps during the night (20%), leg/feet tremor when falling asleep (40%) and while sleeping (30%). Three out of ten patients showed self-reported symptoms of Restless Legs Syndrome (RLS) or so-called pins and needles in their legs while asleep. 'Nocturnal motor symptoms' and 'nocturnal restlessness' seem to be an important cause of sleep disturbances in amyotrophic lateral sclerosis, as it is in other neurodegenerative disorders, e.g. Parkinson's disease (Chaudhuri et al., 2002). Along with nocturia, nocturnal motor symptoms could account for waking up more than twice during the night in 50% of our patients.

Daytime Sleepiness is variably manifested by 'falling asleep' involuntarily during the day (20%) and daytime time naps (80%), although only 10% describe their daytime sleepiness as insurmountable.

4.2.3.2 Measures of Depression

a. ALS – Depression – Inventory (ADI)

Total scores can range from 12 to 48. Scores below 22 express 'no depression', 23 to 28 'mild to moderate depressive symptoms' and 30+ 'clinically relevant depression' (Hammer et al., 2008). 7 patients showed no depression (A, B, E, H, I, and J), 2 were suffering from mild depression (C and D) and only one patient exhibited clinically relevant depressive symptoms (F).

Raw scores in Table 4.2.3.2.a as listed below:

Table 4.2.3.2.a: Total ADI scores for patients A to J

Patient	Score (12- 48)	
A	**20**	**No depression**
B	**12**	**No depression**
C	**26**	**Mild to moderate depressive symptoms**
D	**26**	**Mild to moderate depressive symptoms**
E	**18**	**No depression**
F	**32**	**Clinically relevant depression**
G	**21**	**No depression**
H	**21**	**No depression**
I	**21**	**No depression**
J	**20**	**No depression**

b. Beck's Depression Inventory (BDI)

Total scores for this Depression Inventory can range from 0 to 63. Scores <10 show absence of depression, 10-16 mild symptoms of depression, 17-29 moderate symptoms, and >30 severe symptoms (Rabkin et al., 2005).

Total scores for each patient in Table 4.2.3.2.b as below:

Table 4.2.3.2.b: BDI Scores for patients A to J.

Patient	Score (0-63)	
A	**11**	**Mild symptoms of depression**
B	**0**	**No depression**
C	**10**	**Mild symptoms of depression**
D	**15**	**Mild symptoms of depression**
E	**3**	**No depression**
F	**11**	**Mild symptoms of depression**
G	**8**	**No depression**
H	**9**	**No depression**
I	**16**	**Mild symptoms of depression**
J	**9**	**No depression**

According to this assessment of depression 5/10 patients (A, C, D, F and I) showed mild symptoms of depression.

4.3 Polysomnography

4.3.1 Protocol

Patients participating in the sleep study came to the sleep laboratory by different means of transportation depending on their progression of amyotrophic lateral sclerosis. Patient B (see pictures 4.3.1 a – d below), for example, was transported by a member of staff at university and myself in the patient's, especially reconstructed, minivan with an electric hydraulic hoist. Other patients traveled to the hospital by ambulance, taxi or were brought by their relatives.

Picture 4.3.1 a : waiting for mini van

Picture 4.3.1 b: Manoeuvre of B to enter van using a joystick (yellow ball) with his chin

Picture 4.3.1 c: B on hydraulic hoist

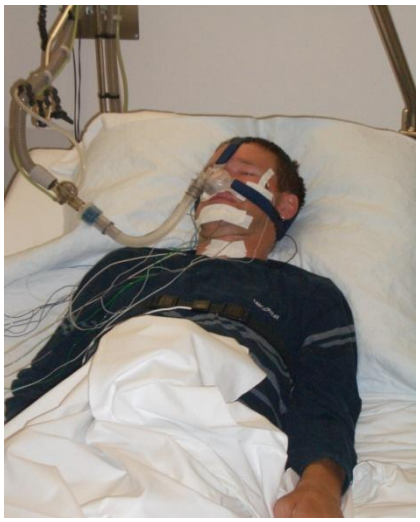
Pic. 4.3.1 d: Adjusting inside

Upon arrival each patient was checked in at the hospital registration which included presenting a full history of medical records, health insurance card for identification. All patients arrived at mid-day to provide enough time for adjusting to the new surroundings. They received three meals a day. Physical care was fully taken care of by me while e.g. heavy lifting in or out of bed was assisted by nurses on the ward.

Each patient was set up for full diagnostic polysomnography (PSG) using the complete sleep disorders screening montage for three consecutive nights (8 h recordings) in the sleep laboratory at the University Hospital of Tübingen, Department of Neurology. Data were acquired with a Neurofile NT/Nihon-Kohden digital video EEG-system with 24 channels for standard polysomnography recording. In all three nights, patients were set up by me, the researcher. Each hook-up took approximately one hour.

The following parameters were registered:

- Electroencephalography (EEG) with two electrodes over the sensorimotor cortex (C3/A2, C4/A1, O1/O2 additionally for Multiple Sleep Latency Test (MSLT) and Maintenance of Wakefulness Test (MWT), referenced to CZ, according to international standards (Rechtschaffen & Kales, 1968))
- Horizontal Electrooculogram (EOG)
- Electromyogram (EMG) (mentalis muscles and right anterior tibial muscle)
- Electrocardiogram (heart function/rate)
- Photoplethysmography (SaO2, Oxygen saturation during sleep)
- Electropneumogram (abdominal and thoracic respiration with the use of sensitive bands)
- Position of the body (movement during sleep to the left or right side) with the use of a sensitive band around the patient's waist
- Airflow at nose and mouth using thermistor sensors



Picture 4.3.1e: Patient B Set up for PSG

After completed set up of all electrodes and sensors, start of recording, indicated as "lights out", was standardized between 10:00 and 11.30 pm. During polysomnography the experimenter was continuously monitoring the physiological recording. The video recording assessing movement and body position during sleep is part of the international standard and essential to assign sleep stages accordingly. In the morning, patients were awakened at 7:30 a.m. and all sensors removed except for the sleep monitoring electrodes (C3/A2, C4/A1, and CZ).

4.3.2 Analysis

Data were analyzed with Neurofile NT Version 4.0 sleep lab module for polysomnographic analysis. PSG records were scored in 30-s epochs according to rules set by Rechtschaffen and Kales (1968).

4.3.3 Results - Polysomnography

All 10 ALS patients were measured for three consecutive nights in the sleep laboratory. The results for the initial night of recording were not included in the table below as it served the patient to get familiar with the procedure of polysomnography. Each ALS patient needed individual attention and adjustment as a result of their special needs such as optimizing sleeping position, light, temperature, air condition, medication, toilet habits including urine catheter, artificial ventilation (CPAP) etc. This helped both, experimenter and patient, to eliminate possible disturbances for the upcoming recordings. Therefore, the results for the two consecutive nights of recording which were accountable for analysis are referred to as 1st and 2nd night.

In table 4.3.3.2 below the following sleep parameters were included and significant results were highlighted in blue:

- CPAP Nocturnal ventilation during recording (Yes or No)

- ALS-FRS ALS Functioning Rating Scale (0 worst to 48 best)

- Age In years at the time of the recording

- Sleep Efficiency (%)

Total Sleep Time (TST; Duration of Sleep Stage 1-4 (=NREM1-4), and REM)/Time in Bed (TIB) * 100. I.e., Sleep Efficiency is rated as normal if >90% (30 to 45 yrs), >85% (46 to 55 yrs), and >83% (56 to 66 yrs).

- Sleep Stage changes per hour/TIB (%)

Sleep stage changes are considered as normal if below 15 %, borderline if 16-25 %, and pathological if above 26 %

- Stages in %/PTS

Amount of each sleep stage in % to Period of Total sleep (PTS)
(Sleep onset (first epoch which is not sleep stage 1 (NREM1, S1).

For interpretation of results for 1st and 2nd night (Table 4.3.3.1, next page), please refer to Table 4.3.3 below which includes sleep norms based on standardized samples of sleep laboratory Pfalzklinik, Landeck and ZI Mannheim.

Table 4.3.3: Sleep norms

Sleep Stage (SS)		Awake	S 1 (NREM 1)	S2 (NREM 2)	S3 (NREM 3)	S4 (NREM 4)	REM
Latency (min)			< 15	< 15	< 30	<40	70-110
SS-ratio (%) of PTS							
Age (yrs)	30-45	< 10	<14	<62	<4.5	<2.5	<14
	46-55	< 13	<14	<63	<3	<1.5	<11.5
	56-66	< 14	<17	<64	<2	<1	<11

Respiratory events such as apnoea were not included in the analysis because measuring of nasal flow was not tolerated by patients, specifically by those who were nocturnally ventilated.

4.3.3.1 Summarized Polysomnographic Results for All Patients

Resulting sleep parameters for 10 ALS patients for 1st and 2nd night were:

Table 4.3.3.1: Summary of results of polysomnographic analysis for ALS patients A to J

Subject	A		B		C		D		E		F		G		H		I		J	
CPAP	No		Yes		No		Yes		No		No		Yes		No		No		No	
ALS-FRS	28		2		13		25		9		36		10		32		24		30	
Age	42		40		58		70		50		51		56		73		67		65	
Night	1rst	2nd	1rst	2nd	1rst	2nd	1rst	2nd	1rst	2nd	1rst	2nd	1rst	2nd	1rst	2nd	1rst	2nd	1rst	2nd
Sleep Efficiency (TST/TIB)	79.90*	no record	62.71*	76.56*	83.33	72.19*	84.06	76.98*	89.58	75.42*	80.10*	86.67	74.06*	87.50	89.69	81.35*	79.58*	65.37*	81.46*	83.85
Stage changes per hour/TIB	25.13*	"	12.50	31.75*	34.75*	29.00*	25.88*	23.75*	18.25*	23.13*	22.63*	35.75*	16.38*	26.88*	35.75*	37.25*	41.13*	32.78	31.13*	29.00*
Stages in %/PTS																				
Awake	17.74*	"	32.63*	13.59*	13.04	21.82*	11.37	20.35*	7.40	19.68*	14.60*	10.99	21.98*	10.34	8.71	7.13	6.84	24.97*	12.48	17.45*
Stage 1	14.29*	"	11.31	22.78*	24.72*	23.96*	23.42*	26.99*	35.29*	17.41*	17.06*	29.27*	24.20*	27.19*	36.37*	28.18*	56.34*	45.38*	27.88*	39.93*
Stage 2	32.14	"	29.72	37.72	35.79	32.03	40.77	36.06	26.99	34.47	37.68	29.49	20.31	21.46	34.46	38.53	29.39	17.85	32.91	29.15
Stage 3	14.61	"	18.18	12.34	6.38	8.07	14.08	11.17	18.81	19.91	13.49	11.32	19.87	22.36	12.30	12.72	2.80*	6.38	14.00	10.01
Stage 4	4.22	"	5.94	2.37	0.91*	0.12*	5.52	0.88*	5.20	1.14*	0.33*	2.07	2.33	7.08	2.33	1.43	0.00*	0.53*	2.02	0.11
Stage REM	17.64	"	5.01*	11.98*	22.60	18.03	7.09*	6.64*	8.85*	9.44*	17.17	18.39	12.21	16.29	5.83*	12.01	4.63*	4.89*	10.81*	9.35*

CPAP=Nocturnal Ventilation, ALS-FRS=ALS Functioning-Rating-Scale, TST=„Total Sleep Time“ (Duration of S1, S2, S3, S4, REM), TIB=„Time in Bed“, PTS=„Period of Total Sleep“ (Sleep onset (first epoch which is not S1) - last awakening), *=pathological (= as compared to international standards of healthy subjects)

Polysomnographies (for detailed polysomnographies for each ALS patient per night, see appendix 16.4 ff) of ten ALS patients showed a reduced sleep efficiency in patients A, B and I for both nights, F, G, J for the 1st night and C, D, H for the 2nd night . Fragmented sleep and prolonged sleep stage 1 was found in all patients. Irrespective of nocturnal ventilation (CPAP; patient B and D), 6 out of 10 patients (B, D, E, H, I and J) showed significantly decreased amount of REM sleep. Due to fasciculations, patient H's 3rd night of polysomnography had to be aborted.

4.4 Assessment of Daytime Sleepiness

4.4.1 Protocol

After the first night of overnight-sleep recording (8 hour recording) tests for objective assessment of daytime sleepiness were conducted during the day. Excessive sleepiness is defined as sleepiness occurring in a situation when an individual would be expected to be awake and alert. The most common causes of sleepiness include partial sleep deprivation, fragmented sleep and medication effects. Patients were advised to abstain from caffeine in the evenings and mornings of each sleep recording, and during the daytime assessments (MSLT, MWT) decaffeinated beverages were provided.

Multiple Sleep Latency Test (MSLT). The MSLT measures sleep tendency in the absence of alerting factors. It is based on the assumption that physiological sleepiness reduces sleep latency. The inclination to fall asleep should increase as physiological sleepiness increases (Carskadon and Dement, 1986). Hence, objective daytime sleepiness was assessed with the Multiple Sleep Latency Test (MSLT) at 10:00 am, 12:00 pm, 14:00 pm and 16:00 pm. Patients were asked to fall asleep within a 20 min time span. All trials were performed in the same bedroom using a simplified montage (C3/A2, C4/A1, O1/A2, O2/A1, EMG, and EOG). Each patient's sleep latency was calculated as the time from "lights out" to the first epoch of stage 1 sleep or any single epoch of another sleep stage.

Maintenance of Wakefulness Test (MWT). The MWT measures the ability to stay awake under soporific conditions for a defined period of time (Mitler et al., 1982). It is based on the assumption that the ability to stay awake at will is more important to know in some instances than the inclination to fall asleep (Arand et al., 2004). Here subjects are instructed to stay awake during a time period of 20 min without any alerting factors in the environment. The MWT was conducted at 10:30 am, 12:30 pm, 14:30 pm and 16:30 pm.

The advantage of this test is a test score corresponding better to attentional abilities of patients with daytime sleepiness than the MSLT, because it requires resisting falling asleep under monotonous circumstances. The MSLT is more sensitive to factors increasing daytime sleepiness like acute, chronic or complete sleep disorders. All trials were performed in the same bedroom using a simplified montage (C3/A2, C4/A1, O1/A2, O2/A1, EMG, and EOG). Each patient's maintenance of wakefulness was calculated as the time from "lights off" to the first epoch of stage 1 NREM sleep or a single epoch (30 sec) of another sleep stage.

4.4.2 Results – Daytime Sleepiness

4.4.2.1 Multiple Sleep Latency Test

The ASDA (American Sleep Disorder Association and Sleep Research Society, 1992) stated the following associations between severity of sleepiness and average sleep latencies: >15 min = normal, 10 – 15 min = mild sleepiness, 5 – 10 min = moderate sleepiness, and <5 min = severe sleepiness.

Table 4.4.2.1: MSLT results for 4 time points for ALS patients A to J.

Patient	10 am	12 pm	2 pm	4 pm	Mean Sleep Latency (in min)
A	**14 min**	**9 min**	**20 min**	**20 min**	**normal (15.75)**
B	**8 min**	**12 min**	**20 min**	**6 min**	**mild (11.50)**
C	**12 min**	**7 min**	**20 min**	**10 min**	**mild (12.25)**
D	**15 min**	**20 min**	**6 min**	**10 min**	**mild (12.75)**
E	**20 min**	**10 min**	**20 min**	**20 min**	**normal (17.50)**
F	**20 min**	**13 min**	**11 min**	**11 min**	**mild (13.75)**
G	**20 min**	**20 min**	**20 min**	**13 min**	**normal (18.25)**
H	**9 min**	**10 min**	**8 min**	**15 min**	**mild (10.50)**
I	**5 min**	**20 min**	**20 min**	**20 min**	**normal (16.25)**
J	**11 min**	**14 min**	**17 min**	**8 min**	**mild (12.50)**

As seen in table 4.4.2.1 above, 6 of 10 ALS patients experienced mild daytime sleepiness, patients A, E, G and I were within the normal range.

4.4.2.2 Maintenance of Wakefulness Test

Same norms apply as for MSLT apply (see 4.4.2.1).

Table 4.4.2.2: MWT results for four time points for ALS patients A to J

Patient	10 am	12 pm	2 pm	4 pm	Mean Sleep Latency (in min)
A	20 min	20 min	14 min	20 min	normal (18.5)
B	20 min	20 min	20 min	20 min	normal (20.0)
C	14 min	20 min	20 min	12 min	normal (16.5)
D	20 min	13 min	17 min	20 min	normal (17.5)
E	20 min	20 min	20 min	20 min	normal (20.0)
F	20 min	20 min	20 min	20 min	normal (20.0)
G	20 min	20 min	20 min	20 min	normal (20.0)
H	20 min	20 min	20 min	20 min	normal (20.0)
I	20 min	20 min	20 min	20 min	normal (20.0)
J	20 min	20 min	20 min	20 min	normal (20.0)

None of the patients had difficulties in staying awake in the Maintenance of Wakefulness Test.

4.4.2.3 Correlation of Subjective and Objective Sleep Parameters with Progression of ALS

Three of 10 ALS patients reported severe sleepiness during daytime. (ESS Score>10; Table 4.4.2.3.1). Sleepiness during daytime was neither related to the degree of depressive symptoms (BDI) (r-.49, p>.05) (nor to the degree of physical impairment (ALS-FRS) (r=.37, p>.05).

Six of 10 Patients experienced mild daytime sleepiness as measured with the MSLT and all were within the normal range with regards to daytime wakefulness as measured with the MWT.

Table 4.4.2.3.1: Results of objective (MSLT, MWT), subjective daytime sleepiness (ESS), subjective sleep quality (PSQI, PDSS) for 10 ALS patients. Numbers in bold indicate values outside the "normal" range.

Patient	A	B	C	D	E	F	G	H	I	J
MSLT	15.75	**11.50**	**12.25**	**12.75**	17.50	**13.75**	18.25	**10.50**	16.25	**12.50**
MWT	18.50	20.00	16.50	17.50	20.00	20.00	20.00	20.00	20.00	20.00
ESS	**10**	6	3	7	9	**17**	4	5	**11**	7
PSQI	**11**	3	3	5	4	**8**	5	**6**	5	5
PDSS	**74**	135	134	**82**	131	**72**	103	110	100	126

MSLT and MWT (=Mean sleep latency in min); ESS (>10 pathological); PSQI (>5) poor sleepers); PDSS (150 = free of symptoms)

According to the results of the PSQI, three patients were classified as 'poor sleepers' (see Table 4.4.2.3.1). Poor sleep quality was experienced due to reduced subjective 'sleep quality', increased 'sleep disturbances', and 'daytime dysfunction'. Seven patients complained of impaired sleep latency on a mild or moderate level resulting from early awakenings or later than usual sleep onset. Five patients reported shortened sleep duration of 6-7 hrs and one of the 5-6 hrs on average per night.

Two patients reported impaired habitual sleep efficiency of 65-74%. Four reported sleep disturbances of more than 'once or twice a week', all others 'less than once a week'. All patients reported some degree of disruption stemming from sources such as difficulty in breathing, pain, bad dreams, temperature regulation, or nocturia. PSQI scores were unrelated to depressive symptoms and strongly related to ALS-FRS-R scores (r=.80, p<.01; corrected for two correlations), indicating an inverse relationship between sleep quality and physical impairment (See Table 4.4.2.3.2).

Table 4.4.2.3.2: Spearman correlation (N=10) for relation between ALSFRS-R scores, subjective daytime sleepiness (ESS), subjective sleep quality (PSQI; PDSS), depression (ADI; BDI)

Measures	1	2	3	4	5	6	7	M	SD	Range
1. Sleep Efficiency	-	**.66***	.09	**.**51	-.29	.25	-.10	80.65	4.98	72.5-85.55
2. ALSFRS-R		-	.37	**.80****	**-.65***	.52	.53	20.9	11.50	2-36
3. ESS			-	.52	**-.64***	.03	.49	7.9	4.09	3-17
4. PSQI				-	**-.86****	.29	.48	5.5	2.42	3-11
5. PDSS					-	-.53	**-.73***	106.7	24.64	2-135
6. ADI						-	**.65***	21.7	5.36	12-32
7. BDI							-	9.20	4.85	0-16

The PDSS yielded a similar picture. The primary concerns patients reported were 'poor sleep refreshment' and 'severe or mild nocturia', followed by 'nocturnal restlessness' and 'nocturnal motor symptoms'. Figure 4.2.3.1.d provides an overview to what extent patients experienced sleep disturbances. Sleep quality measured with the PDSS was highly negatively correlated with symptoms of depression (r=-.73, , p<.01) and with ALSFRS-R scores (r=-.65, p<.05, corrected for two correlations), indicating that less sleep related concerns were associated with less symptoms of depression and a higher degree of physical impairment (See Table 4.4.2.3.2).

5 Discussion Study I

To my knowledge, this study represents the first empirical on sleep architecture in patients with definite and later stage amyotrophic lateral sclerosis taking into account night- and daytime polysomnographic measures of sleep and daytime sleepiness and subjective measures thereof. Amyotrophic lateral sclerosis has not been shown (see 2.5 ff) to directly impact sleep-relevant areas of the brain, but it is probable that indirect effects of this disease result in sleep disruption too. The main finding of this study is that qualitative and quantitative sleep data confirmed ALS patients' complaints about poor quality of sleep.

All patients presented with a significantly decreased level of sleep efficiency in one or both nights of recording. This was reflected by shortened Total Sleep Time which is in line with findings from Ferguson et al. (1996) and other studies not designed to investigate sleep macrostructure in ALS, but have mainly focussed on respiratory function (Bourke et al., 2001; Pinto et al., 1999).

As Sonka and colleagues (2004), we found significantly longer waking periods after sleep onset compared to sleep norms in almost all (9/10) patients. Fragmented sleep was frequently present. Sleep fragmentation can be due to several reasons such as worsened mobility, increased salivation, swallowing problems and muscle cramps. Additionally, several disease-related symptoms, such as restless legs and fasciculations, can disturb both initiation and maintenance of sleep.

Previous findings of prolonged stage 1NREM sleep (Ferguson et al., 1996; Sonka et al., 2004) could be confirmed for all patients. In 6/10 ALS patients significantly shortened stage REM sleep was found. During REM sleep, the only active inspiratory muscle is the diaphragm, normally the 'prime mover' (agonist) of inspiration during wakefulness. Diaphragmatic weakness may result in hypoventilation and this problem is likely heightened by a loss of accessory respiratory muscle function during REM sleep. Ferguson and colleagues (1996) reported 4/14 patients (28%) with ALS and bulbar symptoms to have sleep-disordered breathing, and Minz et al. (1979)3/12 (25%) with sleep-related respiratory dysfunction. Importantly, Arnulf et al. (2005) reported that REM sleep reduction was connected with impaired ventilation in REM sleep.

In my study, 3 patients were nocturnally ventilated (CPAP) to prevent episodes of hypoventilation. Despite nocturnal ventilation 2/3 of these patients showed a significantly reduced amount of REM sleep in both nights of recording. A more thorough individual adaption of nocturnal ventilation may thus improve sleep architecture and quality of sleep.

Impaired respiration in ALS might not be the sole cause for the significant decrease in REM sleep. Interestingly, reduction of REM sleep was not correlated with the progression of the disease (ALSFRS-R) nor age. This might show that impairment of brain areas involved in sleep control are not following a certain pattern of degeneration, but might reflect a diffuse process which would need to be further investigated with neuroimaging techniques individually for each patient prior to sleep recording. This would enable to clarify the amount of involvement of brain stem degeneration in the decrease in the amount of REM sleep compared to respiratory impairment. Degeneration of brain areas involved in REM sleep generation such as thalamus and brainstem (Abrahams et al., 1996; Lloyd et al., 2000; Turner et al., 2004, 2005; Maekawa et al., 2004; Thivard et al., 2007; Van der Graaff et al., 2011) could also account for REM sleep reduction. Indeed, preliminary analysis of REM sleep periods in our sample indicated reduced REM density, amplitude and duration (see chapter 9).

Confirming my first hypothesis, polysomnographic sleep recording confirmed ALS patients' complaints about poor quality of sleep, a significantly decreased level of sleep efficiency (in one or both nights of recording), reduced REM and prolonged 1NREM sleep. High and significant correlation between sleep efficiency and physical impairment confirmed reduced sleep efficiency as the disease progresses (LoCoco et al., 2011).

In line with these objective measures patients' subjective ratings of the PSQI indicated impaired sleep latency or early awakenings, or both, reduced sleep duration and sleep disturbances more than twice a week. Objective sleep efficiency was not correlated to the degree of physical impairment (ns) or depression (ns). While sleep quality, as measured with the PSQI, was unrelated to depressive symptoms, subjective sleep quality, as assessed with the PDSS, was related to fewer symptoms of depression. The PDSS assesses sleep related symptoms in a more differentiated manner as compared to the PSQI which may account for the different results. Both measures of sleep quality were highly correlated to the degree of physical impairment such that the more impaired the higher the subjectively reported quality of sleep.

Over a period of six months 4/10 patients consistently felt sleep deprived. Although almost all patients (9/10) reported "daytime dysfunction" in the PSQI, only 3/10 experienced persistent "daytime sleepiness" or "daytime dozing" (as assessed with the ESS, and PDSS). Although 8/10 patients napped regularly in the afternoon, only 1/10 patients found daytime sleepiness insurmountable. "Daytime dysfunction" is assessed with two items (items 8 and 9 of the PSQI). Item 9 is not aiming at daytime sleepiness but assesses motivational aspects (e.g. 'enthusiasm to get things done'). This might suggest that daytime sleepiness is not the only factor leading to daytime dysfunction in amyotrophic lateral sclerosis, but also reduced motive force.

Despite these results which indicate reduced sleep efficiency and quality, all patients were within the norm with regards to daytime wakefulness as measured with the Maintenance of Wakefulness Test which is supposed to take into account attentional capacities during the day. However, six patients experienced mild daytime sleepiness as measured with the Multiple Sleep Latency Test, confirming that these two measures indeed tap into different aspects of daytime alertness and underlining that both have to be recorded for a complete picture of sleep and wakefulness architecture in patients with ALS.

Interestingly and in contrast to hypotheses 3 and 4, objective (sleep efficiency) and subjective measures (PSQI and PDSS) were dissociated: as sleep objectively deteriorated, it was increasingly appreciated by patients. Subjectively measured sleep quality increased with progress of the disease while the physiological sleep efficiency decreased. Correlation between PSQI and sleep efficiency was $r=.51$ but did not reach the level of significance ($p=.13$). If I may speculate that this correlation may render significant in a larger sample it would underline the discrepancy between subjectively and objectively measured sleep quality, as higher scores of subjective sleep quality were related to lower scores of objective sleep efficiency. One explanation could be that fasciculation and muscle cramps, a direct consequence of muscle denervation, are less frequent in later stages of the disease. Thus, albeit patients experience less sleep efficiency as the disease progresses, they may not feel so severely affected. I further speculate, as waking experience becomes more and more difficult and painful in the course of the disease, sleep may – even objectively poor – become subjectively highly welcome and comforting. Thus, objective sleep efficiency may not be a good index of sleep quality, because subjectivity is so strongly influenced by the general context.

These results seriously question the notion that objective assessment of sleep by means of PSG would provide a full picture of sleep quality. Instead subjective measures have to be included as they may not only be clinically counter-intuitive but also opposite to the physiological data.

My results are in contrast to those of LoCoco and his colleagues (2011). The main differences between our studies are the larger and less affected sample (for subjective reports) and fewer night-time recordings (one night only), sleep quality was lower in more depressed and more impaired patients. Thus, these results may only appear if patients in later stages of the disease are includeed.

As other studies on sleep architecture in ALS, our study suffers from a small sample which reduces the generalizability of our results. However, our sample included patients in all stages, i.e., also in later stages of the disease, and thus, renders data collection extremely effortful for the experimenter and the patients alike. Moreover, our patients were not hospitalised, meaning they came to the hospital only to take part in our study. This may have introduced a selection bias and we were likely presented here data of a relatively well functioning sample, which is supported by the reduction of sleep problems with progression of the disease.

Sleep problems are also a symptom of depression. The general assumption is that depressive symptoms go hand in hand with increased physical disability and worsen as death approaches, but research findings on depression in amyotrophic lateral sclerosis are particularly inconsistent. Rabkin and colleagues (2000) evaluated 56 ALS patients conducting the Structured Clinical Interview for the Diagnostic and Statistical Manual for Mental Disorders (4th ed.; DSM-IV) to find that 88% of the patients had no diagnosis, 10% could be diagnosed with minor depression and only 2% with major depression. Depressive symptoms did not increase over time, when patients were reassessed after about 5 months.

In a longitudinal study (Rabkin et al., 2005), five years later, the same group found that 9% of patients (N=80) with late-stage ALS had major depression and 10% symptoms consistent with minor depression. Massman et al. (1996) reported depression not to be a conspicuous concomitant phenomenon, whereas Ganzini et al. (1998) published similar results to Rabkin et al. (2000).

Some studies found a lower prevalence of depression in ALS patients (Goldstein et al., 2002; Trail et al., 2003), while other studies reported a higher rates (Hogg et al., 1994; Lou et al., 2003). It is essential to accurately diagnose depression as 'psychological well-being' is an important factor for progression of amyotrophic lateral sclerosis. McDonald and colleagues (1994) found a 9.4 times higher risk of mortality in ALS patients who suffered from depression than in those with a good level of psychological well-being.

We used two different means of questionnaires to assess depressive symptoms in our patient group. The ALS Depression Inventory (ADI) (Kübler et al., 2005) which was especially developed for patients with ALS and takes into account the specific situation of increasing physical impairment during the progression of this disease. Two out of ten patients displayed 'mild to moderate depressive symptoms', only one patient suffered from 'clinically relevant depression' with a fairly high ALSFRS-R score (36) reflecting a very high functional stage of amyotrophic lateral sclerosis (ALSFRS-R scores ranging from 13 to 36). Patients with low ALSFRS-R score (ranging from 2-10) showed no signs of depression according to this inventory and ADI was not related to progression of the disease.

In line with these findings were the resulting depression scores from the Beck Depression Inventory-Revised (BDI-II) (Beck et al., 1996) commonly used for appraisal of depression in a clinical setting. According to this inventory, 50% of patients displayed 'mild symptoms of depression', where the other half did not show depressive symptoms. Again, no correlation between depressive symptoms and ALSFRS-R scores was found. In this patient group, depressive symptoms only showed in early or mid-stage ALS. This supports the finding of Rabkin et al. (2005) that major depression in late-stage ALS is rare (<10%), and although depressive symptoms do occur during the progression of the disease, that risk of depression is not inevitably heightened with approach of death. Acceptance of illness was found to be related to the severity of disease (Hogg et al., 1994).

Interestingly, poor quality of sleep (PDSS) was related to the occurrence of depressive symptoms. As sleep quality is worse in the early stages of ALS we conclude that depressive symptoms might be related to emotionally, behavorially and cognitively processing the diagnosis of ALS and dealing with the onset of physical symptoms. This result shows that patients are able to sustain psychological well-being in mid- to late stages of the disease.

Subjective and Objective Daytime Sleepiness

To my knowledge, this is the first study the Multiple Sleep Latency Test (MSLT), Maintenance of Wakefulness Test (MWT), and Epworth Sleepiness Scale (ESS) were incorporated in parallel to quantify excessive daytime sleepiness in patients with amyotrophic lateral sclerosis. Excessive daytime sleepiness is an important symptom in other neurodegenerative diseases such as multiple-system atrophy, progressive supranuclear palsy, dementia with Lewy bodies, and Parkinson's disease (Arnulf, 2005).

The Epworth Sleepiness Scale (Johns, 1994) was used because of its ability to measure a global level of daytime sleepiness independent of short-term variations in sleepiness with the time of the day and its high test-retest reliability of five months (George et al., 1997). Only 30 % of patients reported severe sleepiness during daytime. Interestingly, all three patients were still at an early stage of their disease with high ALSFRS-R scores (24 to 36), but this result was not related to progression of their disease. Patients with comparable ALSFRS-R scores did not report pathological levels of sleepiness.

This might be due to the fact that the accuracy of the Epworth Sleepiness Scale (ESS) is contingent on the awareness of subjects of their falling asleep. Reyner and Horne (1998) validated this assumption in finding that a fifth of their participants distinctly underestimated their risk of dosing off. Another contributing factor might be social desirability and/or lack of objectivity (Van Ert et al., 1999). Van Ert and his colleagues correlated ESS scores with resulting objective electrophysiological measures of the Multiple Sleep Latency Test (MSLT). In their study ESS scores only correlated with MSLT measures when a significant other completed the questionnaire, not when participants themselves answered it. In our study ESS was not correlated with MSLT measures. Reason could be relayed to the fact that questionnaires were answered by patients themselves and not their carers or relatives. On the other hand, it is important to point out that such discrepancies are to be expected, considering that 'sleepiness' is not at all a unitary construct.

Sleepiness is a complex phenomenon and is currently assessed by different operationalisations that reflect different theoretical frameworks of sleepiness. Sleep drive, as an example, seems to be important for the MSLT while the MWT appears to mainly measure the strength of the arousal system. ESS seems to be well suited to indicate a general level of sleepiness which could be interpreted as a "trait" rather than "state" sleepiness which is better reflected by the Stanford Sleepiness Scale (Hoddes et al., 1973), a good instrument to appraise acute changes of sleepiness (Cluydts et al., 2002).

The Multiple Sleep Latency Test (MSLT) is seen as the golden standard for assessing daytime sleepiness (Carskadon et al., 1986) and MSLT sleep latencies, i.e. time until sleep onset, vary with the time of day, in answer to sleep deprivation (Thorpy, 1992). 60% of our patient group (6/10) showed mild daytime sleepiness with an average sleep latency ranging from 10 to 12.5 minutes where patients are sitting/lying in bed in a quiet dimly lit room. Interestingly, the results of the Maintenance of Wakefulness Test (MWT) showed that ALS patients had no difficulties in staying awake under the same soporific circumstances. This might be due to the fact that the two tests assess different abilities or types of sleepiness (Sangal et al., 1992). Johns (1998) argued that there are different kinds of sleepiness. Situational sleep propensities, as he termed them, are dependent on the specific situation and subject.

The MSLT and MWT are significantly correlated (Sangal et al., 1992; 1997), but only about 20-25 % of variance is shared in these tests. In this study, MSLT and MWT were not correlated. The Epworth Sleepiness Scale (ESS), on the other hand, measures eight different situational sleep propensities; an average score of the habitual tendency to doze or stay awake in situations reflecting activities of daily life (Johns, 2000), while MSLT and MWT can only each capture one situational sleep propensity. This might explain the difference to the ESS result. Generally speaking, results on daytime sleepiness reflect a high resilience of patients with amyotrophic lateral sclerosis in the light of the many sleep disrupting circumstances they have to confront due to the disease.

To conclude, despite the above mentioned caveats of this study, my data contribute to the evidence that sleep is already disrupted in early stages of the disease and thus, night-time sleep should not only be monitored with regards to respiratory function. To optimise palliative care in patients with ALS, also daytime sleepiness and wakefulness should be assessed and both physiological recordings should be completed by subjective measures.

Subjective measures of sleep quality and daytime sleepiness help to specify individual concerns and sleep related problems and may thus, facilitate and improve intervention. As reported previously (Matuz et al., 2010) depressive symptoms seriously hamper coping with the disease and as shown with the present study, are also related to quality of sleep and should thus, be routinely assessed and rigorously treated! Taking into account sleep architecture, daytime alertness, and subjective measures thereof may support patients in coping with the disease and as a result improve their quality of life.

6 Rapid Eye Movements in Patients with Amyotrophic Lateral Sclerosis

6.1 Introduction

For a long time it has been assumed that the ability to generate voluntary saccades, pursuit and convergence eye movements (Cohen & Caroscio, 1983) stays intact in patients with tamyotrophic lateral sclerosis. Several studies though demonstrated that the oculomotor system, too, is affected by the neurodegenerative process in this disease (Jacobs et al., 1981; Leveille et al., 1982; Cohen and Caroscio, 1983; Palmowski et al., 1995; Liu et al., 2011;).

Recentstudies suggest a preservation of some oculomotor muscles, i.e. involuntary controlled extraocular motor neurons (Mosier et al., 2000; Haenggeli et al., 2002; Angenstein et al., 2004).

The aim of this study was to investigate the possible preservation of extraocular eye movement muscles in patients with amyotrophic lateral sclerosis during REM sleep.

6.2 Rapid Eye Movement sleep

Derbyshire et al. (1936) were very likely the first to identify peripheral and central criteria of REM sleep while studying the influence of hypnotics on the electroencephalography (EEG) in cats. They observed occasional groups of cortical large waves during sleep, bigger than those in waking state, while at other times there were only small rapid waves comparable to those during waking. Eye movements, as such, were first recorded by Jacobson (1930) during waking. Finally, Aserinsky and Kleitman (1953) were the first to really identify REM sleep. They described "rapid, jerky and binocularly symmetrical movements" (p. 273) occurring at regular intervals during the night.

In healthy humans, REM sleep is characterised by the absence of activity in the antigravity muscles (atonia), presence of relatively low voltage cortical EEG, and last but not least, regular bursts of rapid eye movements. Those rapid eye movement bursts often go hand in hand with changes in respiration. For further reference on the characteristics and a detailed description of REM sleep, please see 2.1ff and 2.4.4ff of this dissertation.

6.3 Generation of Rapid Eye Movements

Rapid eye movements (REMs) are a core feature of REM sleep or also so-called paradoxical sleep, but their origin and functional implication is still unsatisfactorily understood.

Dement and Kleitman (1957) described eye movements as binocularly synchronous during REM sleep and similar to waking fixational eye movements with similar velocities in all directions. Muscle tone of the extra-ocular muscles was found to be at its minimum level during NREM or slow wave sleep while certain muscles became completely atonic (Michel et al., 1972). In REM sleep muscle tone returns and presents similar to that observed in waking. Rapid eye movements during REM sleep consist mainly of horizontal saccades triggered by the abducens nuclei. The paramedical pontine reticular formation, the peri-abducens region and the praepositus hypoglossi nuclei project to the abducens nuclei. They are the pre-oculomotor structures involved in the generation of rapid eye movements (REMs) during REM sleep. The generation of rapid eye movements transpires in the pontine reticular formation and is closely linked to ponto-geniculo-occipital (PGO) waves in the cat (Mouret et al., 1963).

In animal models, rapid eye movements appear to be preceded by ponto-geniculo-occipital (PGO) waves as an early sign of REM sleep. REM comprises two very distinct tonic and phasic states, with the latter manifested by bursts of spontaneous PGO activity. Those waves occur during transition from slow wave to REM sleep or during paradoxical sleep itself (Datta, 1999a) and normally can be recorded throughout the brain but pre-eminently in the pons, thalamus, and occiput (Steriade, 1992).

Peigneux and his colleagues (2001) tested their hypothesis that PGO waves were also present in humans by means of positron emission tomography (PET) and regional cerebral blood flow (rCBF). They were searching for cerebral areas where local neuronal activity was more correlated to REM density during REM sleep than during waking. They found REM counts and rCBF to be significantly correlated in the *anterior cingulate cortex* during REM sleep and to be more closely related to regional cerebral activity in the *primary occipital cortex* and the *right lateral geniculate* body. These results support their hypothesis that mechanisms similar to those of PGO waves take place in humans during REM sleep.

6.4 REM Density and Sleep Deprivation

Since the discovery of rapid eye movement or REM sleep, different theoretical explanations have been suggested to interpret the occurrence of rapid eye movements (REMs), which are one of the core features of REM sleep.

Aserinsky et al. (1973) investigated the time course of REM density and found that the amount of REMs increased when sleep was extended beyond its normal duration. Subsequently, Aserinsky could confirm his hypothesis that REM density could be considered as an index of sleep need/depth. Feinberg et al. (1980) were able to confirm this negative correlation with their finding that REM density is indeed reduced after total sleep deprivation.

In the following years a few studies followed to explore how partial sleep deprivation might affect eye movement density. Travis and his colleagues (1991) deprived eleven young adults of the terminal four hours of sleep followed by a night of recovery sleep. The duration of REM sleep in the recovery night was not affected by this partial sleep deprivation. But despite the loss of REM, eye movement density was significantly decreased in the night of recovery sleep. This finding, together with a previous study by Feinberg et al. (1988), where sleep was limited to 100 min (from 23.30 h to 01.10 h), demonstrated that REM density was more vulnerable to total rather than partial sleep deprivation.

Barbato and his group (1994) found, when REM periods ended in wakefulness, REM density was higher than in those periods that did end in extended sleep. Consequently, they too came to the conclusion that a higher REM density was an indication of reduced sleep pressure.

In 1996, Lucidi et al. (1996) approached the subject in question in a gradual sleep restriction paradigm with six healthy male participants. Each participant was polygraphically studied in five experimental nights with sleep reduction schedules divided into slight (sleep reduced to 3, 4 h per night), medium (5 h) and strong reduction (6, 7 h; respectively) by delaying sleep onset time but keeping the same wake up time for all participants, each followed by a recovery night. Comparing the distribution of REM densities occurring in baseline nights and recovery nights, they found that their results were consistent with data indicating that sleep deprivation decreases rapid eye movement density during REM sleep in subsequent recovery nights. This decrease showed to be directly in proportion to the amount of sleep loss. However, De Gennaro et al. (2000) found that the decrease in REM density was not actually due to changes in prior sleep duration, but was correlated with slow wave sleep (SWS) rebound.

6.5 Degeneration of Eye Movements in ALS

In the end stage of amyotrophic lateral sclerosis voluntary eye movements are barely possible and signs of this impairment are already detectable in the early stages of the disease.

Jacobs et al. (1981) found impaired pursuit eye movements in 11 out of 18 patients (61%) with amyotrophic lateral sclerosis using electrooculography (EOG), where in nine patients these where obvious by visual inspection only, as well as by EOG. In a longitudinal study, Palmowski and his colleagues (1995) provided further evidence of oculomotor impairment in ALS patients early on, e.g. prior to respiratory failure. Although two out of eight patients showed progressively pathologic EOG, three showed intermittent impairment and three gradual changes in their EOG, their findings represented a trend and further investigation with a bigger cohort was suggested.

The core feature of amyotrophic lateral sclerosis is the progressive degeneration of selective motoneuron populations, but it is still unclear why some groups of motor neurons are more vulnerable than others. Although the ocular motor nuclei seem to be spared and impaired oculomotor mobility is not a typical trait of ALS, anomalies of the oculomotor system in ALS patients have been found (Leveille et al., 1982; Palmowski et al., 1995; Averbuch-Heller et al., 1998). Especially ALS patients on long-term respiratory support are prone to develop oculomotor disturbances (Ahmadi et al., 2010).

Zang et al. (2004) used magnetic resonance imaging (MRI) to investigate neurodegeneration in a widely used animal model of familial human ALS, the superoxide dismutase (SOD) 1 $^{G93A\ G1H}$ transgenic mouse. The results of their T2-weighted MRI imaging showed pathology in nucleus ambiguous, facial and motor trigeminal nucleus in these mice. In a histological study by Nimchinsky et al. (2000) similar findings were reported in that the facial but not the oculomotor or hypoglossal nuclei did degenerate. This group reported a 48% neuronal loss in the facial nucleus, compared to a 50% loss in Zang's study. Haenggeli and his colleague Kato (2002) reported selective motoneuron loss depending on the stage of the disease and upon the mouse model they investigated. In these mice (wobbler, pmn, and SOD1 G93A) they found a consistent decline with progression of the disease in the facial nucleus, whereas the hypoglossal and oculomotor nuclei were less affected, especially in the SOD1 G93A mouse.

Several theories, such as excitotoxic, free radical-mediated, and autoimmune mechanisms, have been proposed to explain the cause of this selective vulnerability (Shaw et al., 2000). Those mechanisms have one characteristic in common, an increase in intracellular calcium. Motoneurons degenerating in amyotrophic lateral sclerosis show a significantly reduced expression of calcium-binding proteins, e.g. calbindin-D_{28k} and parvalbumin (Ince et al., 1993; Alexianu et al., 1994; in Roy et al., 1998).

In a study with mice, Mosier and his colleagues (2000) found that extraocular motor neurons, i.e. not voluntarily controlled ocular motoneurons, seem to show a resistance to the progressive dysfunction and degeneration in amyotrophic lateral sclerosis. The motor neurons innervating the extraocular muscles are found in the oculomotor (III), trochlear (IV) and abducens (VI) cranial nerve nuclei and commands come from different regions of the brainstem, i.e. pons, medulla, and the rostral midbrain (Sparks, 2002). For some reason, degeneration of these involuntary motoneurons seems to be prevented by a different calcium metabolism.

In extraocular motoneurons the elevation in calcium concentration is prevented by calcium binding proteins (calbindin-D_{28k}, parvalbumin) which subsequently seem to prevent these cells from degeneration and death. Reiner et al. (1995) found that 85-100% of the oculomotor, trochlear, and abducens motoneurons contained parvalbumin, while trigeminal, facial, ambiguous, and hypoglossal motoneurons only held 20-30%. In their study with monkeys results pointed toward the possibility that the pathogenetic process in sporadic amyotrophic lateral sclerosis is caused by a cytosolic Ca^{2+} excess and hypothesized that the presence of parvalbumin could be a protective factor against degeneration of above mentioned motoneurons.

In 2011 Liu and colleagues investigated the impact of amyotrophic lateral sclerosis on extraocular muscles (EOMs). They analysed the composition of laminin isoform in the basement membranes in EOMs and limb muscles from human donors with ALS. The same group had presented a study demonstrating EOMs of terminal ALS donors being affected by the disease (Ahmadi et al, 2010). This was true in familial forms of ALS as well as sporadic cases, not dependent on whether it was a bulbar or spinal disease onset. In 2011 they collected muscle samples from ALS donors at autopsy, from transgenic mice who were overexpressing human superoxide dismutase type I mutations (D90A or G93A), and an age matched control group. The muscle samples were analysed by means of immunohistochemistry using antibodies against certain laminin chains. Neuromuscular junctions were identified with α-bungarotoxin. Their study could show that ALS has a marked impact on EOMs in comparison with limb muscles.

The current study raised the question of how to assess the degeneration in extraocular motoneurons in patients with amyotrophic lateral sclerosis non-invasively. A study by Seelke et al. (2005) presented the solution to this challenge.

Seelke and his colleagues investigated rapid eye movements (REMs) and their relationship with extraocular muscle activity in infant rats using the invasive electrooculography (EOG) and electromyography (EMG). The finding essential to solving our problem was a significant correlation between extraocular muscle twitches and rapid eye movements that developed over the first two post-natal weeks in infant rats. In matured rats, twitches of the extraocular muscles showed increasinging correlation with rapid eye movements that are comparable to those detected in human adults incorporating standard EOG techniques.

In the light of controversial results in terms of the preservation of extraocular motoneurons in ALS patients and based on Seelke's report of the causal relationship between extraocular muscle activity and rapid eye movements, recording of rapid eye movements during sleep presented itself as a mediate non-invasive way to investigate the degenerative process of extraocular muscle activity in amyotrophic lateral sclerosis. This way a residual muscular channel might be found that could possibly be exploited for communication in these patients when all voluntary muscular control is lost.

7 Questions

Rapid Eye Movement Sleep in Patients with Amyotrophic Lateral Sclerosis

With the data reported in the next chapter the following questions were addressed:

1. Are extraocular motor neurons resistant to the progressive dysfunction and degeneration in patients with amyotrophic lateral sclerosis?
2. Is REM amplitude negatively correlated to the progression of the disease (ALSFRS-R score)?
3. Is REM density positively correlated with the progression of the disease (ALSFRS-R score)?
4. Is REM asynchrony negatively correlated to the progression of the disease (ALSFRS-R score)?
5. Does a correlation between REM duration and ALSFRS-R exist?

8 Method and Materials

8.1 Participants

Subjects, who were included in this part of the sleep study from September 2005 till February 2007 were nine ALS patients (6 men and 3 women, between 40 and 73 years old, mean 58.8 age; s=10.8) (Table 8.1). These patients were in for three consecutive nights: one adaptation (1rst night) and two recording nights (2nd and 3rd night) used for analysis. For details on data collection see protocol of polysomnography in study I (p. 47 ff).

Table 8.1: Participants in REM study

Patient	Age	Sex	ALSFRS-R	Time since Diagnosis (months)
A	Not included in analysis as didn't conclude 3rd night of sleep recordings.			
B	**40**	**Male**	**2**	**56**
C	**58**	**Female**	**13**	**73**
D	**70**	**Male**	**25**	**139**
E	**50**	**Female**	**9**	**28**
F	**51**	**Male**	**36**	**45**
G	**56**	**Male**	**10**	**36**
H	**73**	**Male**	**32**	**57**
I	**67**	**Female**	**24**	**7**
J	**65**	**Male**	**30**	**13**

ALSFRS-R=The ALS Functioning Rating Scale revised is a tool for the assessment of severity of ALS (12 questions "0 worst to 48 best")

All subjects who participated in this study gave informed consent for the study, which had been reviewed and approved by the Ethical Review Board of the Medical Faculty, University of Tübingen. After being informed about the study, patients or their legal representatives signed informed consent.

8.2 Analysis of Rapid Eye Movement

Data were analyzed with Neurofile NT Version 4.0 sleep lab module for polysomnographic analysis. The inclusion criterion was that the recordings included left and right EOG channels (horizontal) and REM periods. Polysomnographic (PSG) records were scored in 30-s epochs according to standard criteria set by Rechtschaffen and Kales (1968) prior to analysis of rapid eye movements. Polysomnographic EOG data from 10 patients from study I were investigated in this study

Any deflection of the pen equivalent to an eye movement greater than 3° and separated from another deflection by more than 200 ms was considered to be an independent complete left or right eye movement. This rule was used to score horizontal rapid eye movements to the left and right. Subsequently, REM epochs were displayed in 5 sec windows on screen for visual scoring.

EOG was scored (marked manually as can be seen in Figure 8.2 with vertical lines) visually by two different reviewers. Blinks (eye movements of low amplitude that didn't fit criteria for REM) and other artifacts, e.g. muscular artifacts, were excluded by visual inspection. In order to exclude low amplitude artifacts but to include rapid eye movements (REMs) with an obscured component on one channel, REMs with amplitudes lower than 50 μV on left and right recording were rejected. Rapid eye movements with asynchrony (see definition above Figure 8.2.a) above 100 ms were rejected, respectively. Subsequent close REMs lasting less than 50 ms were discarded.

A representation of manual REM scoring can be seen in Figure 8.2 below:

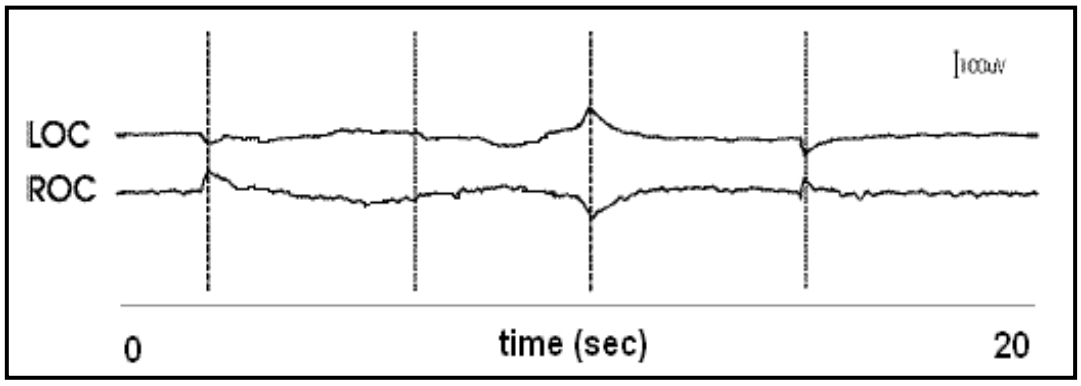


Figure 8.2: REM scoring (LOC=Left Oculogram; ROC=Right Oculogram)

All artifact-free eye movements were manually counted for each occurring REM cycle and duration of each cycle was counted in 30 sec epochs. Results see Table 8.2 below.

Table 8.2: Amount of REMs and Epochs per cycle/patient for two nights

Patient	Night	REM cycles /night	Amount of REMs (Rapid Eye Movements) /Cycle					Epochs (30 sec) /REM cycle				
			1	*2*	*3*	*4*	*5*	*1*	*2*	*3*	*4*	*5*
B	**1**	**3**	28	0	14	-	-	32	3	5	-	-
	2	**5**	20	19	19	4	157	16	14	13	4	54
C	**1**	**2**	385	204	-	-	-	94	104	-	-	-
	2	**2**	142	521	-	-	-	49	102	-	-	-
D	**1**	**3**	124	521	2	-	-	27	35	2	-	-
	2	**3**	57	20	315	-	-	7	9	45	-	-
E	**1**	**5**	26	92	42	31	154	13	18	14	5	29
	2	**4**	13	198	112	84	-	14	30	21	18	-
F	**1**	**5**	202	78	498	301	117	31	16	45	49	13
	2	**5**	233	47	367	302	426	27	12	39	41	48
G	**1**	**3**	355	131	270	-	-	51	19	40	-	-
	2	**5**	8	91	15	297	38	18	31	8	73	15
H	**1**	**4**	0	81	136	47	-	11	15	26	9	-
	2	**4**	67	152	299	186	-	17	19	40	23	-
I	**1**	**4**	8	130	12	47	-	2	20	2	13	-
	2	**2**	17	163	-	-	-	4	43	-	-	-
J	**1**	**4**	119	465	71	32	-	18	54	13	9	-
	2	**4**	131	86	121	4	-	29	26	23	4	-

In young and middle aged human sleep, the amount of NREM-REM sleep cycles can vary between 2 and 7, and the frequency has been found to be normally distributed across individuals (Merica & Gaillard, 1985; adapted from Le Bon et al., 2002). The defining features of rapid eye movements examined with respect to the progression of the disease were amplitude, duration (ms), density, and asynchrony (ms) of each identified rapid eye movement.

All features were assessed by two independent reviewers. Please refer to Figure 8.2 a below for a schematic description of below measures explained as follows:

A **Mean REM Amplitude** (see Figure 8.2.a: marked blue) was calculated as the difference between peak amplitude and onset amplitude at the preceding change of slope at the start of each rapid eye movement.

B **Mean REM Duration** (see Figure 8.2.a: marked red) in this study was determined as time between starting point (change of slope) and peak of eye movement. These parameters (A and B) were computed independently for left and right eye.

C **Mean REM Density** was expressed as the number of eye movements per minute of REM sleep. (Wichniak et al., 2002; method C is being sensitive to the amount of rapid eye movements).

D **Mean REM Asynchronicity** (see Fig. 8.2.a: grey bar) was calculated as time between peaks of left and right rapid eye movement. Asynchronicity of eye movements is the non- synchronous occurrence of left and right peak eye movement.

Amplitude and duration for left and right eye movements were averaged.

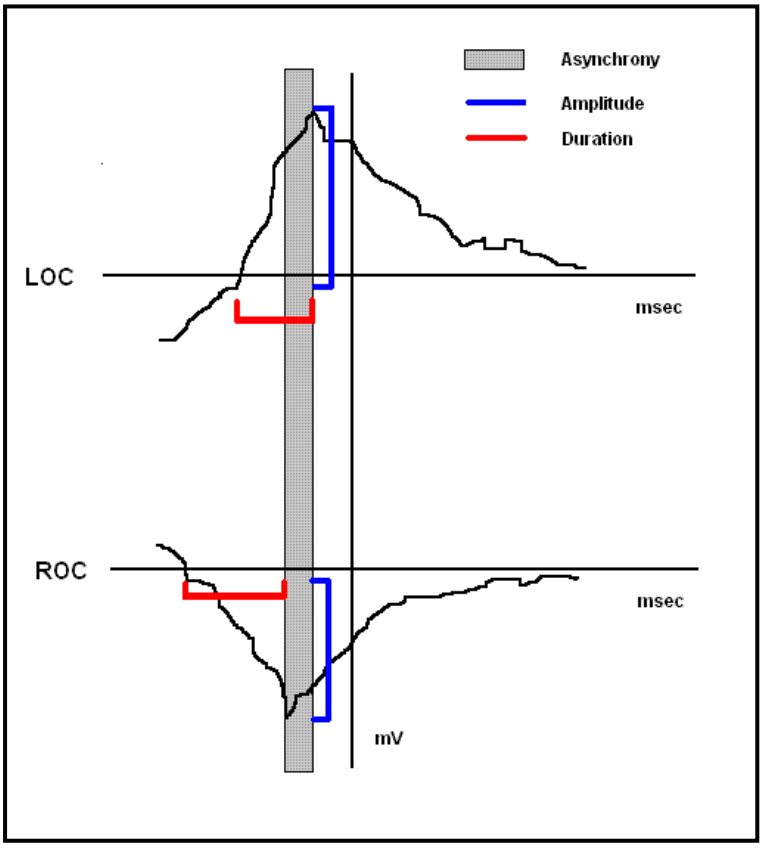


Figure 8.2.a: Schematic description of REM measures (LOC=Left Outer Canthus; ROC=Right Outer Canthus)

Individual means and standard deviations of REM density, REM asynchrony, REM amplitudes, REM duration, and ALSFRS-R score for each patient per night are reported in table 8.2.a below:

Table 8.2.a: Results of REM assessment and ALSFRS-R for all patients per night

Patient	ALS FRS-R	Night	REM Density Mean (SD)	REM Asynchronicity Mean (SD)	REM Amplitude (μV) Mean (SD)	REM Duration Mean (SD)
B	32	1	2.100 (2.865)	0.025 (0.020)	131.350 (73.625)	6.838 (0.403)
		2	4.337 (1.507)	0.016 (0.017)	122.574 (68.729)	2.181 (3.562)
C	24	1	5.950 (3.018)	0.019 (0.020)	120.220 (57.574)	7.589 (1.984)
		2	8.782 (3.197)	0.020 (0.021)	150.181 (85.563)	3.234 (1.620)
D	2	1	20.219 (14.415)	0.017 (0.017)	136.695 (73.600)	6.144 (4.410)
		2	12.853 (6.283)	0.019 (0.019)	154.861 (89.704)	6.928 (5.061)
E	13	1	8.835 (3.502)	0.023 (0.022)	134.061 (69.240)	0.725 (5.324)
		2	9.807 (4.876)	0.021 (0.021)	123.323 (61.281)	6.085 (3.285)
F	30	1	15.533 (4.967)	0.018 (0.019)	184.155 (115.906)	10.542 (5.736)
		2	16.467 (4.806)	0.015 (0.020)	187.560 (115.920)	16.112 (4.627)
G	25	1	13.746 (0.216)	0.021 (0.022)	106.030 (48.350)	1.973 (0.218)
		2	6.193 (2.680)	0.022 (0.023)	89.584 (39.577)	0.637 (1.121)
H	9	1	8.656 (0.200)	0.014 (0.014)	173.858 (106.653)	17.100 (5.901)
		2	14.222 (3.950)	0.009 (0.010)	185.990 (122.134)	19.055 (2.213)
I	36	1	10.649 (2.867)	0.029 (0.024)	168.361 (80.869)	3.931 (6.749)
		2	7.660 (0.650)	0.021 (0.017)	170.520 (81.807)	9.929 (3.958)
J	10	1	14.617 (4.234)	0.022 (0.021)	129.814 (64.056)	5.447 (1.651)
		2	8.342 (3.728)	0.027 (0.025)	123.658 (101.701)	8.948 (6.862)

8.3 Results - Rapid Eye Movements

We examined the relationship between ALRSFRS-R scores as the indicator for the physical impairment and stage of the disease with the main features of rapid eye movements such as mean amount of rapid eye movements for each patient (mean amount of REMs), mean REM density, mean REM asynchrony, mean REM amplitudes, and mean REM duration, for all nine patients using Spearman's correlation, as can be seen in Table 8.3 below:

Table 8.3: Correlation results for REM features and ALSFRS-R

		ALSFRS-R	Age	Time since Diagnosis	Mean Amount of REMs	Mean REM Density	Mean Asyn-chrony	Mean Amplitude	Mean REM Duration
ALSFRS-R	Spearman	**1**	**.600***	.083	.383	**.583****	-.267	**.833****	**-.800****
	Sig. (1-tailed)		**.044**	.416	.154	**.050**	.244	**.003**	**.005**
Age	Spearman	**.600***	**1**	.200	-.033	.317	-.050	.533	-.467
	Sig. (1-tailed)	**.044**		.303	.466	.203	.449	.070	.103
Time since Diagnosis	Spearman	.083	.200	**1**	.283	-.167	**-.733***	.167	-.267
	Sig. (1-tailed)	.416	.303		.230	.334	**.012**	.334	.244
Mean amount of REMs	Spearman	.383	-.033	.283	**1**	.367	-.033	.183	-.383
	Sig. (1-tailed)	.154	.466	.230		.166	.466	.318	.154
Mean REM Density	Spearman	**.583****	.317	-.167	.367	**1**	.283	.433	-.517
	Sig. (1-tailed)	**.050**	.203	.334	.166		.230	.122	.077
Mean Asynchrony	Spearman	-.267	-.050	**-.733***	-.033	.283	**1**	-.267	.383
	Sig. (1-tailed)	.244	.449	**.012**	.466	.230		.244	.154
Mean Amplitude	Spearman	**.833****	.533	.167	.183	.433	-.267	**1**	**-.583***
	Sig. (1-tailed)	**.003**	.070	.334	.318	.122	.244		**.050**
Mean Duration of REM	Spearman	**-.800****	-.467	-.267	-.383	-.517	.383	**-.583***	**1**
	Sig. (1-tailed)	**.005**	.103	.244	.154	.077	.154	**.050**	

* Correlation is significant at the 0.05 level (1-tailed) ** Correlation is significant at the 0.01 level (1-tailed)

We found that ALSFRS-R scores were significantly positive correlated with REM density (r=.583; p<.05), mean REM amplitude ((r=.833; p<.01) and significantly negative for mean duration of REM (r=-.80; p<.01). Time since diagnosis was significantly negative correlated with mean asynchrony (r=-.733; p<.05). Figures 8.3.1 to 4 depict the significant correlations:

1. REM Density and ALSFRS-R

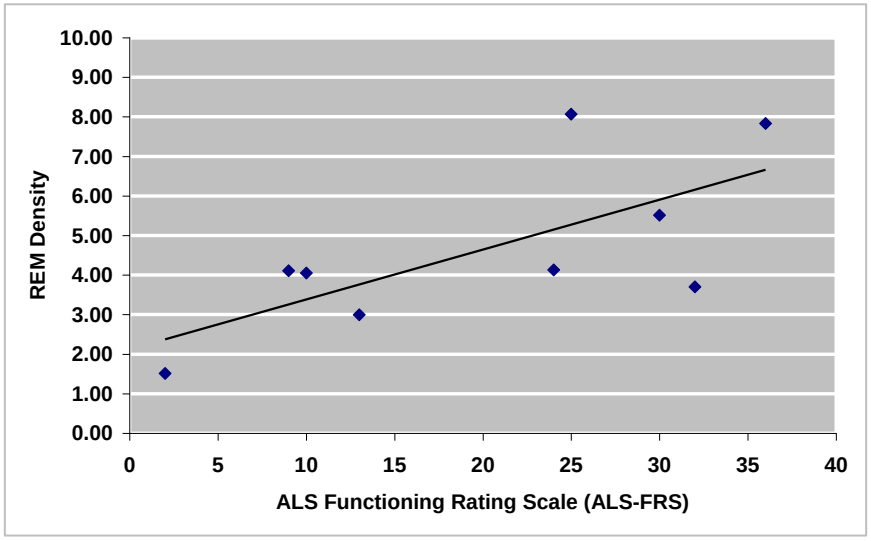


Figure 8.3.1: Correlation for REM Density and ALSFRS-R

The lower patients scored on the ALSFRS-R, the lower their REM Density (r=.583*, p=.05).

2. REM Amplitude and ALSFRS-R

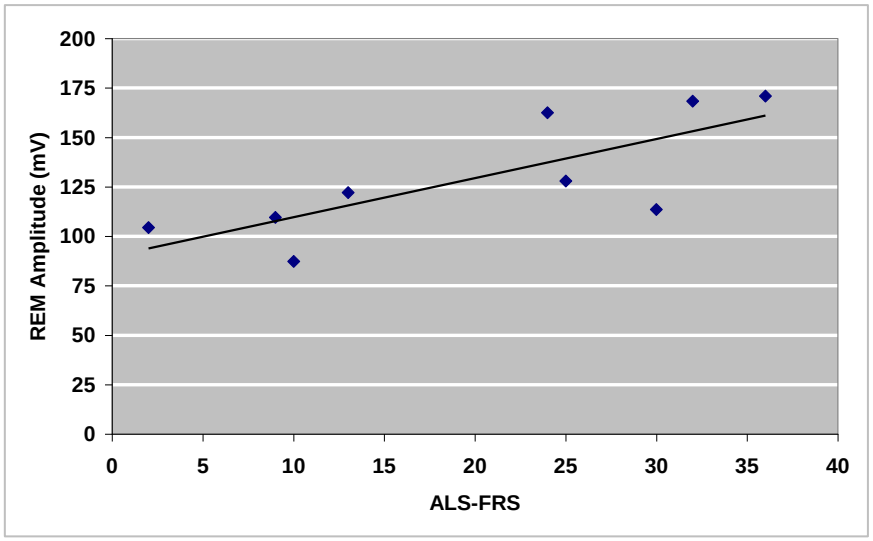


Figure 8.3.2: Correlation for REM Amplitude and ALSFRS-R

The lower patients' ALSFRS-R score, the lower their REM amplitudes (r=.833**, p=.003).

3. REM Duration and ALSFRS-R

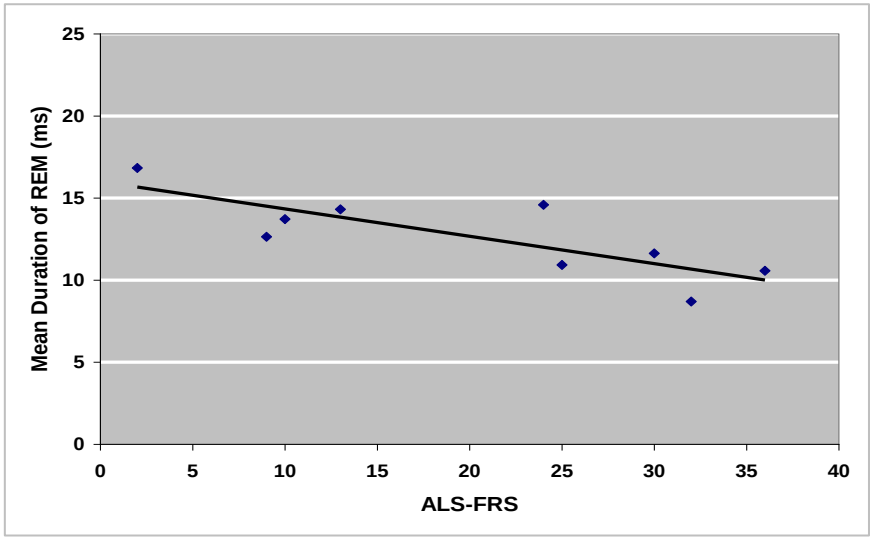


Figure 8.3.3: Correlation for REM Duration and ALSFRS-R

The lower patients scored on the ALSFRS-R, the longer the mean REM duration (r= -.800**, p=.005) for each rapid eye movement.

4. REM Asynchrony and Time since Diagnosis

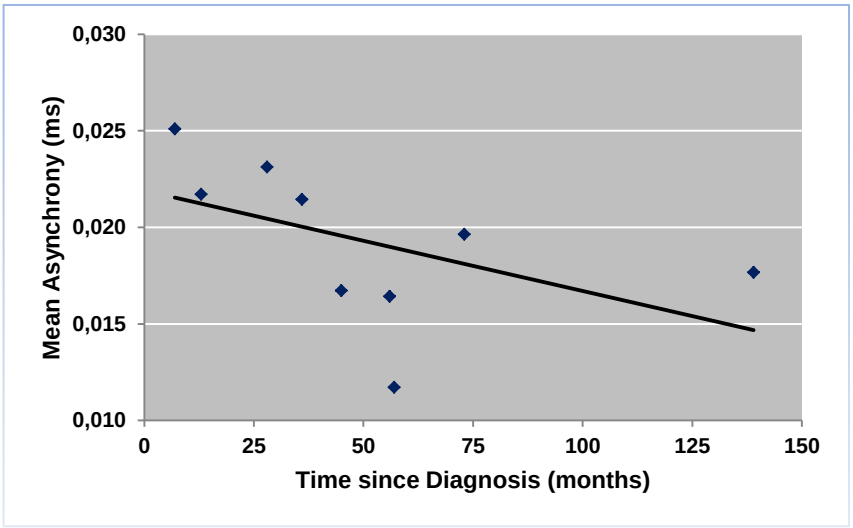


Figure 8.3.4: Correlation for REM Asynchrony and Time since Diagnosis

The shorter patients had been diagnosed with amyotrophic lateral, the higher the asynchrony between left and right rapid eye movements (r= -.733*, p=.012). Age was not correlated to rapid eye movement features, but was significantly correlated with ALSFRS-R (r=.600*, p=.044).

Visual inspection and quantitative analysis of electrooculography (EOG) during REM sleep showed that reduced rapid eye movement is significantly correlated to the progression of the disease (ALSFRS-R).

9 Discussion Study II

The findings of this study suggest that extraocular motor neurons are not resistant to the progressive degeneration of neurons in patients with amyotrophic lateral sclerosis (ALS), though in fact are significantly correlated.

Oculomotor disturbances are not a main feature of amyotrophic lateral sclerosis; mainly all skeletal muscles are impaired over the course of the disease, along with cranially innvervated muscles for speech. However, ocular motility dysfunction has been found in ALS patients in several studies (Jacobs et al., 1981; Palmowski et al., 1995; Averbuch-Heller et al., 1998). On the other hand, a study with mice (Mosier et al., 2000) suggested that extraocular motor neurons seem to be not vulnerable, and another study reported that oculomotor nuclei did not degenerate (Nimchinsky et al., 2000) over the course of amyotrophic lateral sclerosis. Chase and Morales (1990) suggested that rapid eye movement potentials (REMs) are seemingly produced by twitches of the extraocular muscles.

Feinberg et al. (1987) expressed the view that rapid eye movements constitute a non-invasive measure of higher motor centers and rapid eye movements may simply reflect intense phasic neural discharge presenting in the brain during a state of activation. The reticular formation in the brainstem has been found to be the principal area for generating rapid eye movements (REMs) Steriade, 2005).

Rapid eye movement potentials in particular, one of the characteristic signs of REM sleep, are generated by the pontine nucleus with projections to the superior colliculus and are excited through phasic firing by reticular and through vestibular cells directly inciting oculomotor neurons. The process of REM sleep generation comprises three neuronal systems (aminergic, reticular and sensorimotor) procuring rapid eye movement (REM) sleep. Particular signs of REM sleep can be evoked by stimulation of different brainstem structures. Thus, the structures responsible for the different polygraphic signs of REM sleep are well identified. Main structures in the pons responsible for rapid eye movements are raphe nuclei, locus coeruleus, peribrachial region, meso- and mediopontine tegmentum, and oculomotor (III), trochlear (IV), and abducens (VI) (Pace-Schott & Hobson, 2002).

In this study, assessment of involuntary REMs in different stages of amyotrophic lateral sclerosis showed that the more progressed ALS patients, the higher the decrease in mean amplitude and density of rapid eye movement potentials (REMs). Interestingly, a lower ALSFRS-R score (ALS Functioning Rating Scale-Revised) was indicative for a higher mean duration of REMs. Our findings point towards loss of functionality of extraocular motoneurons (EOMs) depending on the stage of the disease.

As found in several studies researching the different calcium metabolism in ALS (Reiner et al., 1995; Nimchinsky et al., 2000; Zang et al., 2004), degeneration of extraocular motor neurons might be decelerated to some measure in the pathogenic process through a higher concentration of calcium binding proteins calbindin-D28k and parvalbumin and would support the loss of functionality of EOMs in our patients.

Pathogenesis in patients with amyotrophic lateral sclerosis is widespread and involves also structures involved in the generation of rapid eye movements. Benefiting from advancements in neuroimaging over the last years, the outcome of several studies substantiate our findings and could show impairment of the brainstem, e.g. pons, in humans with amyotrophic lateral sclerosis (Kato et al., 1997; Ellis et al., 2001; and Turner et al., 2004), as well as in transgenic mouse models of amyotrophic lateral sclerosis (Zang et al., 2004). Post-mortem examinations showed not only degeneration of the entire upper motor neuron system from the cerebral motor cortex through the corticospinal tract of the spinal cord, and the internal capsule, but also in the brainstem in about 47% of patients with amyotrophic lateral sclerosis (Kato et al., 1997).

Recently, Ahmadi and his colleagues (2010) investigated the composition of of extraocular muscles (EOMs) with respect to general morphology, fiber type content, and myosin heavy chain (MyHC) in donors with amyotrophic lateral sclerosis. The group wanted to assess whether EOMs were susceptible to the disease or truly spared. This was the first study to investigate EOMs at the cellular and molecular level in ALS patients. EOMs are unique muscles and fundamentally different to limb and masticatory muscles. They could show that the EOMs were rather spared, although not completely. They still showed signs of convolution with altered fiber type composition, contractile protein content, as well as changes in cellular structure.

These pathologic changes were present in both familiar and sporadic ALS cases, irrespective of whether they had a bulbar or spinal disease onset. However, compared to limb muscles, EOMs showed remarkable preservation.

Another study by Liu et al. (2011) could also show distinct impact of amyotrophic lateral sclerosis on EOMs compared with limb muscles by choosing a different approach. They examined the laminin isoform composition of the basement membranes in extraocular motoneurons in donors with ALS. They found a number of non-neglible pathologic changes in laminin chains Lnα2 and Lnβ2. Both were absent or absent to some extent from the basement membranes in a variable number of muscle fibers in most ALS patients' EOMs. These studies are in support of my finding of impairment of extraocular motoneurons reflected indirectly through decreased rapid eye movements in ALS patients over the progression of the disease.

In several studies ALS patients have been reported to show significantly longer waking periods after sleep onset, increased sleep fragmentation, prolonged stage 1 NREM sleep, and shortened REM sleep (Ferguson et al., 1996; Bourke et al., 2001; Pinto et al., 1999; Sonka et al., 2004; and see study I of this dissertation). REM density in our nine ALS patients significantly decreased with progression of the disease. This result could also be attributed to other factors than motor neuron degeneration.

Sleep fragmentation (i.e. awakenings per hour), a proven feature of sleep complaints in patients with amyotrophic lateral sclerosis, is thought to reduce total rapid eye movement (REM) sleep. Sleep fragmentation or decreased sleep efficiency (Total Sleep Time (TST)/Time in Bed (TIB)) in ALS can be attributed to many factors, such as fasciculations and muscle cramps during the night, nocturia, or pain. These primary and secondary symptoms of ALS cause minor and major sleep deprivation. Several studies on the effect of sleep deprivation on REM density showed that REM density decreased linearly with sleep curtailment (Feinberg et al., 1987). Later, Lucidi et al. (1996), in a gradual sleep restriction paradigm, found that oculomotor activity during rapid eye movement (REM) sleep decreased in recovery nights following total or partial sleep deprivation.

Although decreased sleep efficiency has not been found to be directly correlated with the progression of amyotrophic lateral sclerosis, it very well could be a contributing factor to our results of the almost linear decrease of REM density in accord with progressive impairment in these patients.

Interestingly, we found that mean duration of rapid eye movements was significantly negatively correlated to ALS functioning rating scale (r=-.802), while mean REM amplitude became smaller with progression of the disease in our nine patients with amyotrophic lateral sclerosis.

A shortcoming of this study of rapid eye movements is that no calibration of individual eye movements was conducted prior to polysomnographic recordings. The traditional two-dimensional approach to eye movement analysis normally is conducted by measuring the visual angle of the object under inspection, i.e. between a pair of raw EOG eye movement data points in a time series (Duchowski et al., 2002). The visual angle and the difference in timestamps between the data points in the series would enable calculating eye movement velocity which is expressed in degrees visual angle per second (Duchowski et al., 2002). Our study was based on polysomnographic recordings in the sleep laboratory where adequate equipment for this particular analysis was not available.

As no calibration of rapid eye movements was conducted prior to recording, I can only indirectly hypothesize about the implication of this result in terms of "speed". The decrease in amplitude seems to be a reflection of the decreased firing capability of extraocular motor neurons due to their degeneration over the course of the disease and muscular degeneration. At late stage ALS peak amplitude of rapid eye movements was reached more "slowly" than in the early stage of this disease, indirectly reflected in the prolonged mean REM duration. One might argue that density of oculomotor activity might be due to the generally reduced REM sleep latency and length in ALS patients, but Lucidi et al. (1996) found this not to be the case. Their findings substantiated that the decline of REM density was directly proportional to the amount of sleep loss, but did not have an effect on paradoxical sleep latency and length as such.

Summarizing, my results suggest that despite a higher resilience in extraocular motor neurons against the progression of amyotrophic lateral sclerosis due to a different calcium metabolism or a possible alteration in fiber type composition, protein content, or changes in cellular structure, REM features change over the course of this disease. This is reflected indirectly through significant deterioration in rapid eye movement potentials (REMs) in amplitude, density and duration.

10 P300 – Attention and Information Processing in Patients with Amyotrophic Lateral Sclerosis

10.1 Introduction

The P300 is a positive segment of the event-related brain potential (ERP) that is elicited in psychological tasks when subjects attend to and discriminate stimuli that are distinct from one another in a certain capacity and is thought to indicate an attention-driven cognitive comparison process which can be seen in the electroencephalogram (EEG).

The P300 event-related potential is one of several different electroencephalographic (EEG) brain signals used for brain-computer interfaces (BCI). This technology can provide severely disabled individuals, e.g. patients with amyotrophic lateral sclerosis or other severe neurological or muscular diseases, with non-muscular dependent communication (Wolpaw et al., 2002). Several studies have shown that the P300 is not only dependent on cognitive mechanisms but seems to be susceptible to environmental (exercise, fatigue, drugs) and biological (circadian, ultradian, seasonal, and menstrual) influences (Polich and Kok, 1995).

The aim of this study was to investigate the potential changes of the P300 as an indicator of attention and information processes in patients with amyotrophic lateral sclerosis at four different time points during the day using visual and auditory two-stimulus oddball paradigms.

10.2 Electroencephalography (EEG) and P300

There is the so-called event-related or evoked potential (ERP; EP) which constitutes a stereotyped electrophysiological response to an internal or external stimulus (thought, perception, visual, or auditory), as distinct from spontaneous potentials detected by electroencephalography (EEG). The EEG is a reflection of thousands of simultaneously on-going brain processes, therefore the brain response to a single stimulus of interest is not usually visible in the EEG recording of a single trail.

Evoked potential amplitudes tend to be much lower than that of the spontaneous electroencephalogram (50-100 μV), ranging from less than a microvolt to several micro volts (0.5-15 μV) and therefore go unseen in spontaneous EEG.

Since most ERP components have smaller amplitudes than the background EEG activity, methods for increasing the signal-to-noise ratio must be implemented in order to pick out ERP waves. Such methods are e.g. averaging, filtration, or template matching (Coles et al., 1990).

In most ERP studies, the averaging technique is employed, i.e. many trials (EEG segments time-locked to several identical or similar events) are averaged. This way the background noise is suppressed. This suppression is proportional to the square root of the number of averaged segments.The evoked signal is time-locked to their eliciting event and dependent on the distinct stimulus presented. An outline of various averaged auditory evoked potentials can be seen in figure 10.1.2 below. Evoked potentials are labelled according to their latency as well as their polarity (positive or negative).

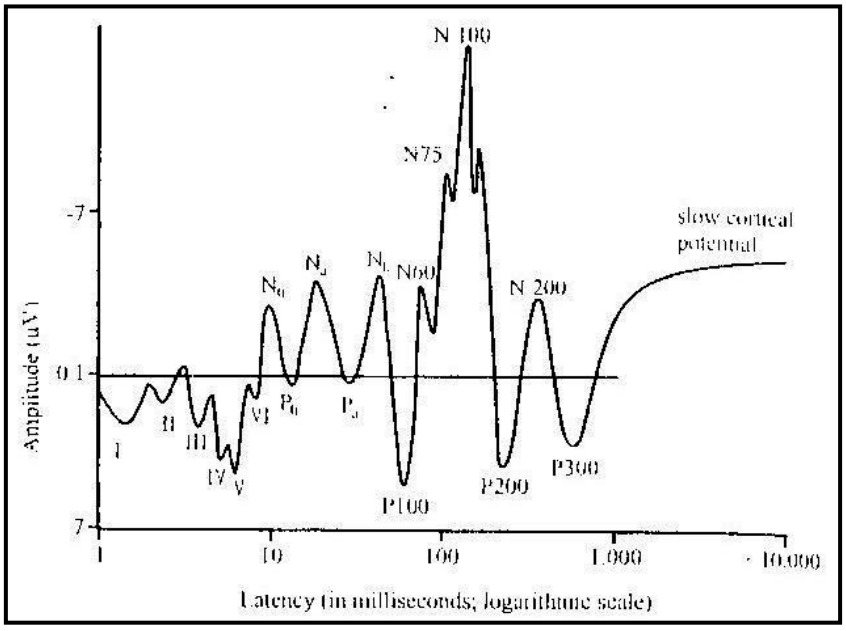


Figure 10.1.2: Averaged event- related potentials in response to auditory stimuli (in Kübler et al., 2001)

10.3 P300

Within this study we particularly concentrated on the P300 component of the ERP (also referred to as P3) which is thought to reflect cognitive processes, for instance attention allocation or activation of immediate memory (Polich & Kok, 1995).

Most often, a simple discrimination task is used to elicit a P300. This positive wave can be elicited through visual, tactile, or auditive stimuli. For example, two tones, distinct from one another, are presented in the auditory task, where the infrequent (or 'target') stimulus occurs less frequently than the frequent (or 'standard') stimulus (e.g. a 0.20 and 0.80 ratio of presentation, respectively). The participant is instructed to discriminate between the tones and e.g. mentally count the 'target' stimulus and not to respond otherwise. The P300 appears in the EEG on those rare stimuli, relevant for the participant.

The P300 is a positive peak of neuroelectric brain activity (10-20 μV) occurring at about 300 ms after presentation of unexpected/rare stimuli at unpredictable times within a sequence of frequently occurring 'standard' stimuli (Colrain & Campbell, 2007). The latency of the P300 can alternate between 200 and 550 ms depending on stimulus modality, age of the participant or the complexity of the task and is generally recorded over central-parietal scalp locations. The P300 component is typically measured by calculating its amplitude (size) and latency (timing) (Cipresso et al., 2012).

Amplitude (μV) is defined as the difference between the mean voltage of pre-stimulus baseline and the most positive peak of the event-related potential (ERP) waveform within a time window (Polich, 2007). The P300's amplitude increases with reduced probability of the infrequent stimulus. Latency (ms) is calculated as the time from onset of stimulus to the point where the positive amplitude reaches its maximum within a time window (Polich, 2007).

Donchin and his colleagues have incorporated this component or 'oddball' response in a brain-computer interface (BCI) (Farwell and Donchin, 1988; Donchin et al., 2000). Patients use a 6x6 matrix of letters and/or numbers, which could also include other symbols, displayed on a computer screen. The P300 is elicited by attention to the desired item in the flashing columns and rows of the described matrix. In this way e.g. paralysed patients are able to learn to select letters with their brain activity and 'write' whole sentences. This component has the big advantage that it will be elicited in almost every person without any practice on the user's part.

Nijboer et al. (2008) presented data that support the initiative that ALS patients are well able using a P300-based brain-computer interface for writing text and were stable in their performance for many months.

10.4 Determinants of P300

The P300 is a measure for neuronal brain activity reflecting cognitive processes such as attention. Generally, P300 latency is interpreted as a measure of stimulus classification speed (Magliero et al., 1984).

The P300 latency in healthy subjects was found to be negatively correlated with mental function, i.e. shorter P300 latency were found in subjects with better cognitive performance (Emmerson et al., 1989; Howard & Polich, 1985; in Hillman et al., 2012). A principal interpretation of P300 amplitude is embedded in the so-called context updating theory. It is said that the P300 component is an index for brain activity occurring when the mental context of a stimulus is updated and is elicited when task require to maintain working memory (Donchin et al., 1986; cited from Polich, 2007)). This theory has been substantiated by studies which demonstrated that higher P300 amplitudes were correlated with outstanding memory performance (Fabiani et al., 1990). Further studies have demonstrated that P300 amplitude is proportional to the amount of attentional reserves necessary to complete a given task (Kramer & Strayer, 1988; Wickens et al., 1983).

It is understood from recent findings that this component's variation is not only dependent on task structure; also the physiological state of the individual constitutes as an important influence. Especially changes in the arousal state of the subject seem to have substantial impact. Polich & Kok (1995) have investigated the influence of different biological and environmental determinants on this component. Most of their findings were derived from experiments which facilitated the classic auditory oddball paradigm. Although they were not able to detect a direct influence of circadian rhythm on the P300 component, close correlations of physiological changes could be obtained very well. Body temperature (BT) as well as heart rate (HR) change over the course of the day and were negatively correlated (BT: $r=-.39$, $p<.001$; HR: $r=-.21$, $p<.02$) with P300 latency (Pz) in 120 young adult subjects who were assessed at different time points of the day (Geisler and Polich, 1990).

Additionally, an indirect influence of circadian rhythms on the P300 component was found for the recency of food intake. The amplitude of the P300 increased if measurements took place shortly after food consumption and reduced when food has not been consumed recently. P300 latency was shown not to be affected by food ingestion. They concluded that circadian rhythms seem to at least have an indirect impact on the P300 component (Geisler and Polich, 1992a).

Besides natural biological influences, other environmentally induced factors such as exercise, sleep deprivation, and 'common' drugs too, seem to modulate the P300. Frequent physical exercise with high exertion seems to have a very positive effect with increase in amplitude and shorter latencies compared to less fit subject groups (Bashore, 1989).

Low arousal state resulting from lack of sleep stands on the other end of the arousal spectrum. Some theorists suggest that sleep deprivation leads to a general decrease in arousal level. This is thought to cause the brain to rely more heavily on the environment to maintain satisfactory levels of functioning (Wilkinson, 1992).

Brain imaging studies have tried to locate the areas affected by total sleep deprivation. The findings of PET and fMRI studies were inconsistent. Some found increased frontal activation (Drummond et al., 2000; Szelenberger and Piotrowski, 2000), while others found increased prefrontal deactivation after total sleep deprivation (Thomas et al., 2000; Drummond et al., 1999).

In a recent study by Habeck et al. (2004) a more prominent deactivation was found over occipital, parietal, and temporal areas in addition to a small deactivation in the dorsal prefrontal region after 48 hrs of total sleep deprivation. The authors are in agreement that not only the nature of the task or but also the extent of sleep deprivation could explain the differences between study outcomes.

ERPs are especially sensitive to arousal levels (Aguirre and Broughton, 1987). The late positive wave, the P300, is particularly sensitive to the effects of sleepiness. Sangal and Sangal (1997) investigated attention and information processing by means of P300 recordings in patients suffering from sleep apnea and daytime sleepiness. They found that sleep efficiency was significantly positively correlated to mean auditory P300 amplitude and negatively to mean visual P300 latencies.

Despite the fact that only a few studies on sleep deprivation have incorporated event related potentials (ERPs), generally, physical fatigue from sleep deprivation was found to decrease P300 amplitude and to result in longer latencies (Wesensten and Badia, 1988; Smulders, 1993).

10.5 P300 in Amyotrophic Lateral Sclerosis

Over the last years various evidences have suggested that patients with amyotrophic lateral sclerosis (ALS) is a multisystemic neuronal degenerative disorder resulting in non-motor abnormalities from cognitive deterioration beyond the primary motor area (Turner et al., 2004; Maekawa et al., 2004; Lloyd et al., 2000; Ellis et al., 2001; Abrahams et al., 1996; Talbot et al., 1995; Kew et al., 1993a,b; Ludolph et al., 1992; Mitsuyama, 1984; Hudson, 1981).

Massmann and his colleagues (1996) reported a cognitive disturbance in 35% cross-sectionally investigated cases of amyotrophic lateral sclerosis. Neuropsychological studies revealed impairments of executive function, visual attention, language, short- and longterm memory deficits, and category formation (Abrahams et al., 2000, 1997; Cobble, 1998; Talbot et al., 1995; Galassi et al., 1989).

Many studies pointed out the difficulty to complete neuropsychological tests due to physical disability, e.g. speech, in some patients. Event-related potential (ERP) recording circumvents this problem and allows the investigation of attention and information processing without interference from motor impairment of ALS. Up until now, only a few studies investigated cognitive dysfunction in amyotrophic lateral sclerosis by means of event-related potentials.

Gil et al. (1995) investigated the auditory event-related potential in patients with sporadic amyotrophic lateral sclerosis and reported a delayed latency of P300 in 12 out of 20 patients. In 1998, Münte and his group assessed recognition memory deficits in ALS patients with event-related potentials. They demonstrated that medium-term memory was affected more than short-term memory reflected in less accurate recognition. They suggested that deviant ERP patterns reflected an encoding deficit.

Paulus et al. (2002) recorded visual and auditory event-related potentials in 16 sporadic ALS patients and conducted a neuropsychological battery of tests to assess cognitive dysfunction. 75% of patients displayed abnormalities in the P300 component essentially related to a delay of latency. They also reported a significant correlation between impaired visual and auditory P300 and neuropsychological scores for attention and executive/frontal functions.

A recent study by Volpato et al. (2010) investigated working memory functions using neuropsychological tests and auditory event-related potentials. They revealed impaired performance on working memory tests in 67% of 24 non-demented patients with ALS and reported a significant delay of N100, P200, and N200 latency. Disease duration was significantly correlated with auditory P300 amplitude.

11 Questions – Study III:

Attention and Information Processing in Patients with Amyotrophic Lateral Sclerosis

Study III was designed to inspect whether patients with amyotrophic lateral sclerosis show differences in attention and information processing over the course of the day compared to healthy controls considering their disrupted sleep architecture (please see study I of this dissertation) and consequently reduced sleep efficiency.

With data reported in this study, the following questions were addressed:

1 Does time of the day affect visually evoked P300 potentials (amplitude, latency, and area) in ALS patients compared with healthy controls?

2 Does time of the day directly affect auditory evoked P300 potentials (amplitude, latency, and area) in ALS patients?

11. 1 Hypotheses

Based on the studies of Bashore et al. (1989), Sangal & Sangal (1997), Smulders et al. (1993), Gil et al. (1995), Paulus et al. (1995), and Volpato et al. (2010), I hypothesise a significant difference in visual and auditory P300 between ALS patients and healthy controls.

1. **H 1(0): ALS patients do (not) differ significantly in visual P300 amplitudes at different time points during the day compared with healthy controls.**

- Statistical test: ANOVA
- Level of significance: $\alpha < .05$
- Direction of hypothesis: 2-way

2. **H 1(0): ALS patients do (not) differ significantly in visual P300 latencies at different time points during the day compared with healthy controls.**

- Statistical test: ANOVA
- Level of significance: $\alpha < .05$
- Direction of hypothesis: 2-way

3. **H 1(0): ALS patients do (not) differ significantly in auditory P300 amplitudes at different time points during the day compared with healthy controls.**

- Statistical test: ANOVA
- Level of significance: $\alpha < .05$
- Direction of hypothesis: 2-way

4. **H 1(0): ALS patients do (not) differ significantly in auditory P300 latencies at different time points during the day compared with healthy controls.**

- Statistical test: ANOVA
- Level of significance: $\alpha < .05$
- Direction of hypothesis: 2-way

12 Methods and Materials

12.1 Participants

Subjects, who participated in the P300 study from July 2006 until February 2007, were 14 ALS patients (8 men and 6 women, between 40 and 77 years old, mean age 61.01; s=10.84) and 14 healthy age and sex matched controls (8 men and 6 women, between 38 and 81 years old, mean age 58.43; s=10.87)(t=.952; F=.052; p=.35) (Please see table 12.1 below where all participating ALS patients are listed including corresponding ALSFRS-R score(mean ALSFRS-R 21.79; s= 10.53).

Table 12.1: ALS patients participating in Study III

ALS Patient	Age	Sex	ALSFRS-R
1	57	Female	25
2	40	Male	2
3	58	Female	13
4	70	Male	25
5	50	Female	9
6	51	Male	36
7	56	Male	10
8	73	Male	32
9	67	Female	24
10	65	Male	30
11	61	Female	34
12	67	Female	24
13	64	Male	28
14	49	Female	13

All subjects who participated in this study gave informed consent for the study, which had been reviewed and approved by the Ethical Review Board of the Medical Faculty, University of Tübingen, Germany. After being informed about the study, patients or their legal representatives signed informed consent (see appendix 16.5 G-J ff). The entry and exclusion criteria are listed below (Table 12.1a).

Table 12.1a – Recruitment Criteria

Inclusion Criteria for ALS-patients

- Diagnosis of ALS with El Escorial Criteria by a neurologist
- Sustained ability for communication, e.g. patients must have residual muscular control for the possibility of „Yes/No"-communication

Exclusion Criteria for ALS-patients and healthy controls

- Psychiatric disorder (depression, anxiety etc.)
- Psychotropic drugs
- Heavy caffeine, alcohol or drug intake

12.2 Data Acquisition

The P300 experiment was recorded with a 16 channel g-tec USB amplifier, bandpass filtered between 0.01 and 30 Hz, and sampled at 256 Hz. To record the evoked potentials, an especially for paralyzed patients developed electrode cap with 16 scalp electrodes based on the international 10-20 System (Jasper, 1958) was applied. These caps were not fixed as normally on the chest but on the chin. For this procedure no intact neck musculature was required.

The electrode sites were FP1, FP2, F3, F4, C3, C4, CP3, CP4, FZ, CZ, PZ, OZ, P3, P4, T7 and T8 (as can be seen in Fig. 12.2 below). Each channel was referenced to the right earlobe and grounded to the left mastoid. Impedances did not exceed 5 kΩ and were checked prior to each recording.

Data processing, storage, and online display of the EEG were implemented using an IBM Thinkpad (Pentium 4 M 1.6 GHz, 512 MB RAM, Windows XP SP2). The matrix was displayed to the participant on a separate 43-cm video screen with a 60-Hz refresh rate.

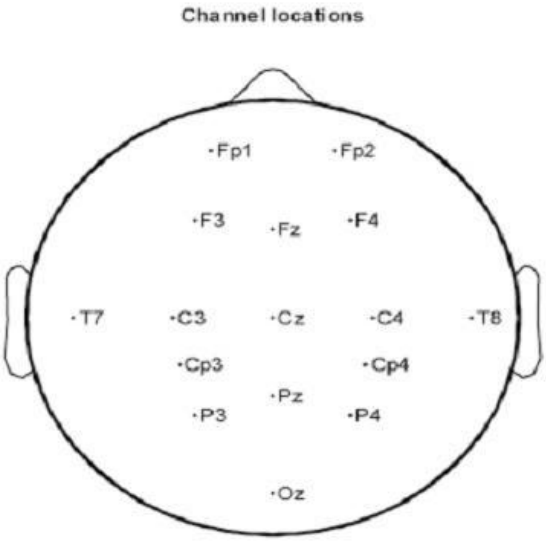


Figure 12.2: Channel locations

12.3 Study Design

The experiment was conducted at the individuals' homes in a suitably quiet room. The participant was sitting comfortably in a chair in front of a computer screen where the test was presented. Subjects were explained the course of the experiment and given an instruction sheet (see appendix 16.5 H). Thereupon participants were asked to sign a consent form (see appendix 16.5 I).

The experiment comprised 12 min and the same set was repeated four times at 2 h intervals at 10:00 am, 12:00 pm, 2:00 pm and 4:00 pm:

1. 4 min continuous EEG recording
2. 4 min P300 visual stimuli presentation
3. 4 min P300 auditory stimuli presentation

Subjects were asked to relax, to not tense any muscles (legs, arms, face), to not talk and to concentrate on the center of the computer screen during the recording. Participants kept the electro cap on during the whole day of the experiment.

12.4 Stimuli

For the first part **resting EEG** of each subject was recorded for four min. For this purpose subjects were asked to relax and to concentrate on a blue circle presented on the computer screen.

For **auditory P300 recordings**, subjects were presented with tones, using loud speakers standing left and right of the computer screen, in an auditory odd-ball paradigm. Of the 200 tones 20% were 2000 Hz and 80% were 1000 Hz, at 99 db peSPL (decibels peak-equivalent sound pressure level). Sound pressure level measurements use 20 micropascals or 0.0002 dyne/cm^2 as a reference level of 0 db< 99 db peSPL corresponds to 60 to 70 db HL or decibels above normal hearing level. It would usually be 60 to 70 db SL or decibels above the individual's hearing threshold). The auditory stimulus was driven by a 50 ms rectangular pulse. The tones were presented in a pseudo-randomized manner (random but with constraints on consecutive presentation of rare stimuli). Subjects were asked to silently count the high tones (rare stimulus) while concentrating on a white cross in the center of the computer screen.

For **visual P300 recordings**, attention was measured with "H" as the frequent stimulus and "S" as the rare stimulus with a 4:1 ratio. The stimuli were white in color on black computer screen background, occurred for 50 ms, and were enlarged 10 times compared to a normal letter presented on monitor (fond size 120 p). The monitor was placed 70 cm from the subject. The 200 stimuli were presented 1.2 +/- 0.15 sec (ISI) apart. Again presentation was pseudo-randomized and subjects were asked to count the appearing letters "S" (rare stimulus) in silence. All experimental conditions were recorded with eyes open, and rest periods were provided between conditions.

12.5 Data analysis

Waveforms were averaged off-line with *Brain Vision Analyzer* (Brain Products GmbH, 1999) such that trials on which the EEG or EOG exceeded +/- 60μV were rejected automatically.

Further, single-trial data were subjected to an EOG correction procedure to remove any remaining artifacts (Semlitsch et al., 1986). Trials contaminated with blinks were rejected from analysis as were trials contaminated with other artifacts such as muscle tension.

The P300 component was defined as the largest positive-going peak occurring within a specific latency window defined by the task conditions, with auditory = 290 – 550 ms and visual = 300 – 600 ms (Picton et al., 2000). Peak amplitude was measured relative to the mean pre-stimulus baseline, and peak latency was defined as the time of maximum voltage for the P300 component only. For each participant the peak was determined with automated peak recognition and validated through visual control by two experienced researchers.

Additionally, P300 area information was calculated. The P300 area was defined as area under the curve. Time period and height of the occurring P300 component with auditory = 270 - 480 ms and visual = 300 – 600 ms, respectively.

12.6 Statistical Analysis

All data were analyzed with the statistics program SPSS. The following electrodes were selected for analysis of auditory and visual P300 amplitude, latency and area information: F3, F4, C3, C4, CP3, CP4, P3, P4, FZ, CZ, and PZ. At this, the central electrodes (midline) are of special importance, as the P300 is most pronounced along the midline recording sites (FZ, CZ, and PZ), and typically increases in magnitude from the frontal to the parietal electrodes and selected for detailed analysis.

The so-called manipulation check, i.e. differences between rare and frequent stimuli inferring a successful manipulation of P300, was conducted for each electrode separately, using a 3-factor repeated measure ANOVA (within subject factors *stimulus type* (2; frequent and rare) x *time* (4; 10 am, 12 am, 14 pm, and 16 pm) and between subject factor g*roup* (ALS patients vs. healthy controls).

To assess the influence of time point (10 am, 12 am, 14 pm, and 16 pm) and differences between ALS patients and healthy controls, for amplitude, latency and area information of visual and auditory P300, a 3-factor ANOVA for repeated measures was conducted with within-subject factors *time* (4), and *midline* (3; FZ, CZ, and PZ) and between-subject factor *group* (2; ALS patients vs. healthy controls) for target (rare stimuli) only. This analysis was done for both, auditory and visual P300 paradigm separately. For all statistical comparisons a *p*-value of ≤ 0.05 was considered significant.

12.7 Results – Study III: Alertness and Information Processing

12.7.1 Visual P300

12.7.1.1 Manipulation Check for Visual P300

The visual P300 was clearly discernable in all participants upon analysis with Brain Vision analyzer. The differences between frequent and rare stimuli (stimulus) were significant for all electrodes for latency, peak amplitude and area information (see Table 12.7.1.1).

Table 12.7.1.1: Summary of *F*-ratios and probabilities from 3-factor (time x stimulus x group) ANOVA for repeated measures performed on the visual P300 peak amplitude, P300 latency and P300 area

Electrode Position	P300 Amplitude		P300 Latency		P300 Area	
	F	*P*	*F*	*P*	*F*	*P*
Vertex						
Fz	**35.161**	**0.000**	**12.264**	**0.002**	**30.714**	**0.000**
Cz	**39.941**	**0.000**	**10.596**	**0.003**	**38.337**	**0.000**
Pz	**35.558**	**0.000**	**12.153**	**0.002**	**39.028**	**0.000**
Left Hemisphere						
F3	**19.121**	**0.000**	**9.612**	**0.005**	**17.148**	**0.000**
C3	**26.861**	**0.000**	**10.687**	**0.003**	**26.789**	**0.000**
CP3	**21.910**	**0.000**	**9.076**	**0.006**	**25.232**	**0.000**
P3	**15.117**	**0.001**	**12.117**	**0.002**	**17.973**	**0.000**
Right Hemisphere						
F4	**38.998**	**0.000**	**21.014**	**0.000**	**30.767**	**0.000**
C4	**48.291**	**0.000**	**12.357**	**0.002**	**43.478**	**0.000**
CP4	**32.801**	**0.000**	**10.537**	**0.003**	**36.188**	**0.000**
P4	**27.777**	**0.000**	**15.207**	**0.001**	**34.754**	**0.000**

12.7.1.2 Visual P300 – Evaluation of Midline Electrodes

12.7.1.2.1 Visual P300 Amplitude

A 3-factor ANOVA for repeated measures was conducted for the midline electrodes with within-subject factors *time* (4; 10 am, 12 pm, 2 pm, and 4 pm), and *midline* (3; FZ, CZ, and PZ) and between-subject factor *group* (2; ALS patients vs. healthy controls).

No significant difference for between- subject factor *group* between ALS patients and healthy controls could be found (F = 2.505, p = 0.126). Main effect *time* did not yield significance ((F = 1.586, p = 0.199). A main effect for *midline* (F =11.305, p = 0.000) was obtained (see Fig. 12.7.1.2.1a). No significant interactions to report.

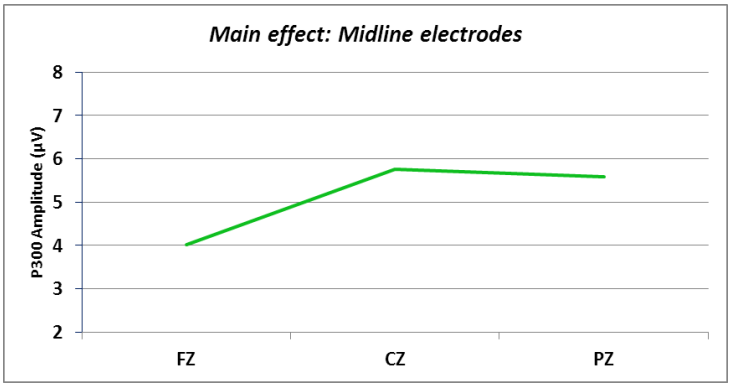


Fig. 12.7.1.2.1a: Main effect Midline for visual P300 amplitude

12.7.1.2.2 Visual P300 Latency

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Similar to the analysis of P300 amplitudes, a 3-factor ANOVA for repeated measures was conducted for the midline electrodes with within-subject factors *time* (4), and *midline* (3) and between-subject factor *group* (2).

As in the analysis above, no significant difference between ALS patients and healthy controls could be found (F = 0.071, p = 0.792). Main effect *time* did not reach significance for midline analysis (F = 1.078, p = 0.363), and neither did main effect for *midline* electrodes (F = 2.883, p = 0.065). No significant interactions to report.

12.7.1.2.3 Visual P300 Area

Similarly, a 3-factor MANOVA for repeated measures was conducted for the midline electrodes with within-subject factors *time* (4), and *midline* (3) and between-subject factor *group* (2). As in the analysis above, no significant difference between ALS patients and healthy controls could be found ($F = 2.655$, $p = 0.115$).

Main effect *time* did not reach significance for the midline analysis ($F = 1.468$, $p = 0.230$). Main effect *midline* ($F = 8.356$, $p = 0.001$) was obtained ($p < 0.05$) (see Fig. 12.7.1.2.3 below). No significant interactions to report.

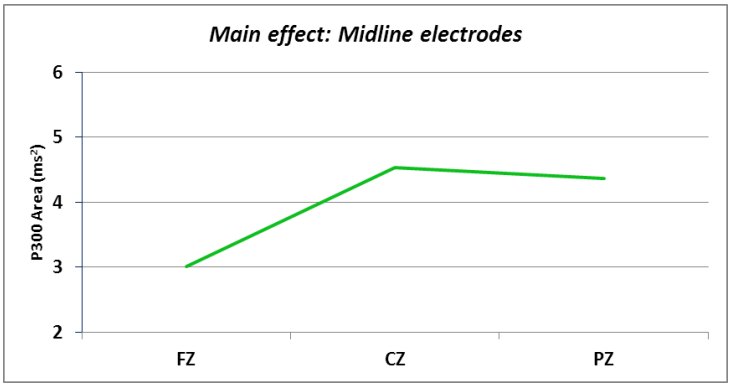


Fig. 12.7.1.2.3: Main effect Midline for visual P300 area

12.7.1.3 Visual P300 – Difference Waveforms

Visual P300 difference waveforms (rare stimuli minus frequent stimuli) of recording sites for Midline electrodes (Fz, Cz, Pz), left hemisphere (F3, C3, CP3, and P3), and right hemisphere (F4, C4, CP4, and P4), and Oz, for ALS patients and controls for all four time points (10 am, 12 pm, 14 pm, and 16 pm) are displayed in the following figures 12.7.1.a-d and an overview of midline electrodes (Fz, Cz, Pz) only at all four time points in figure 12.7.1.e.

Time point 1 at 10 am

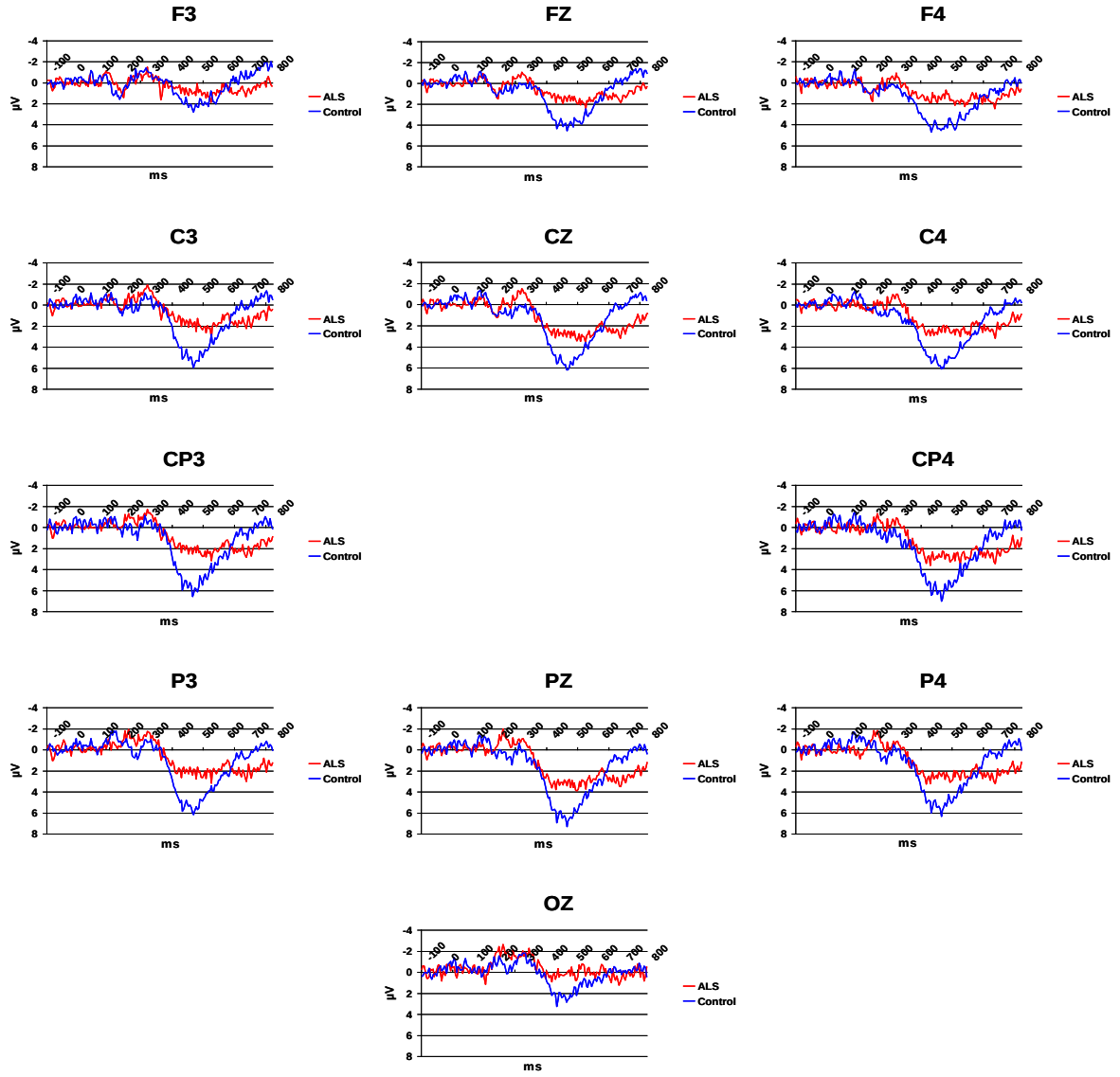


Figure 12.7.1.a: Visual P300 difference waveforms (rare minus frequent stimuli) for electrodes Fz, Cz, Pz, F3, C3, CP3, P3, F4, C4, CP4, and P4 for time point 10 am

Time point 2 at 12 pm

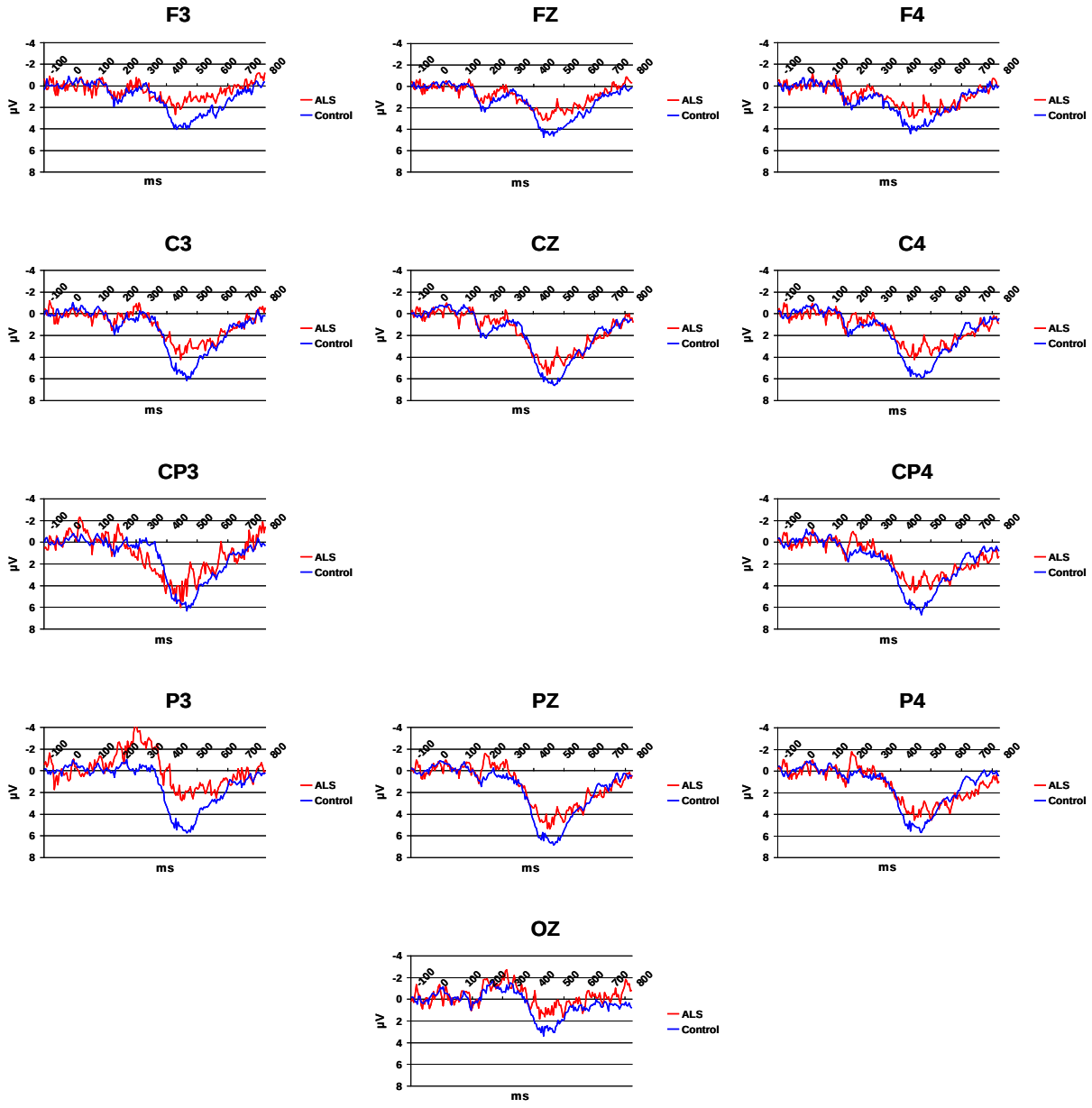


Figure 12.7.1.b: Visual P300 difference waveforms (rare minus frequent stimuli) for electrodes Fz, Cz, Pz, F3, C3, CP3, P3, F4, C4, CP4, and P4 for time point 12 pm

Time point 3 at 14 pm

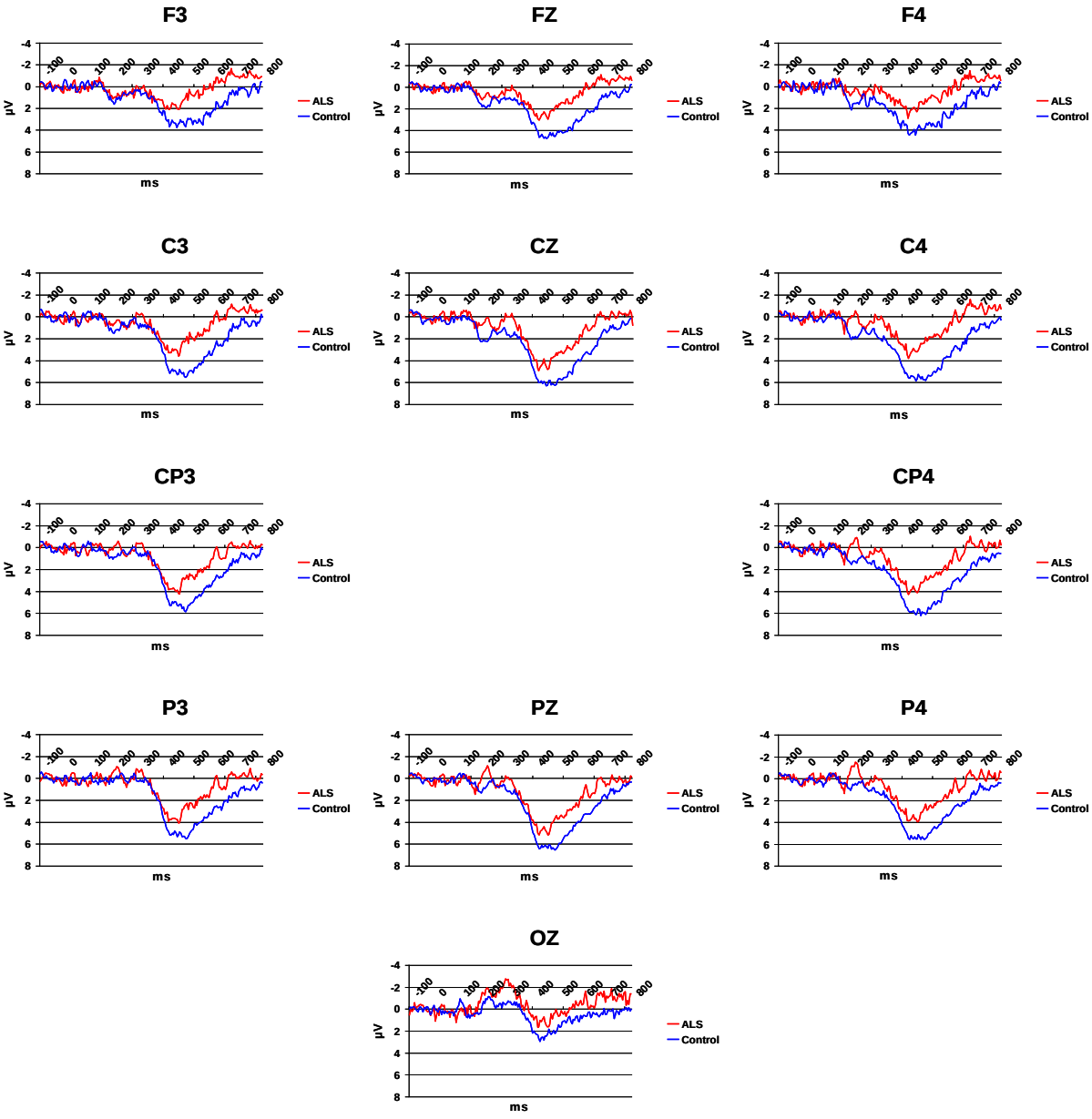


Figure 12.7.1.c: Visual P300 difference waveforms (rare minus frequent stimuli) for electrodes Fz, Cz, Pz, F3, C3, CP3, P3, F4, C4, CP4, and P4 for time point 14 pm

Time point 4 at 16 pm

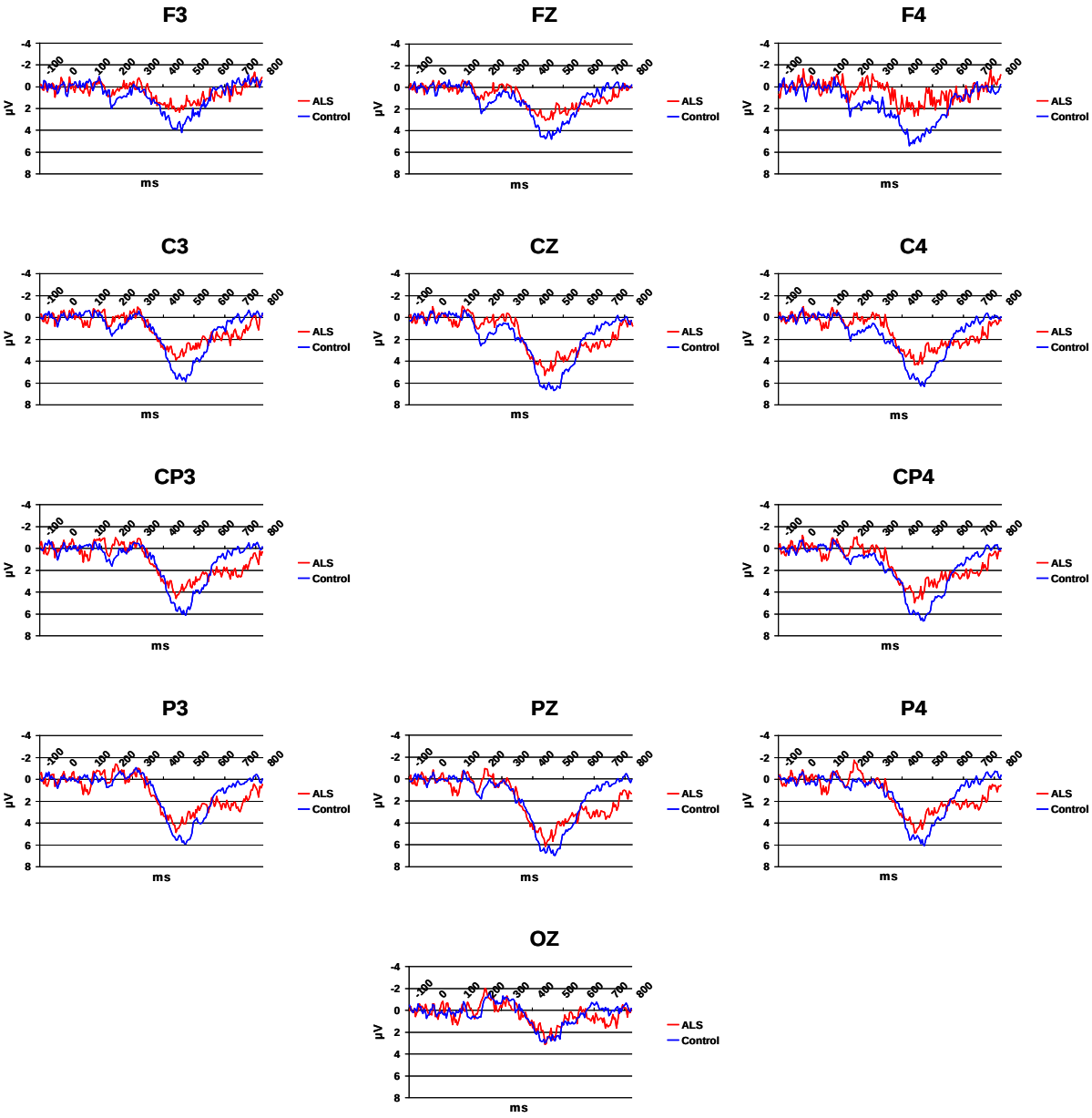
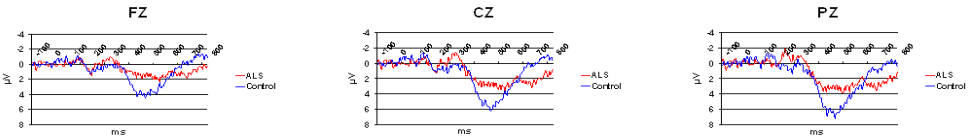


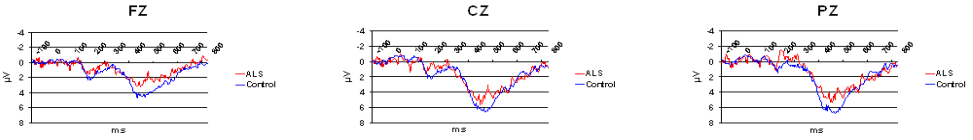
Figure 12.7.1.d: Visual P300 difference waveforms (rare minus frequent stimuli) for electrodes Fz, Cz, Pz, F3, C3, CP3, P3, F4, C4, CP4, and P4 for time point 16 pm

Figure 12.7.1.e: Visual P300 difference waveforms (rare minus frequent stimuli) for midline electrodes FZ, CZ, and PZ for ALS patients and healthy controls at four different time points (10 am, 12 pm, 14 pm, and 16 pm)

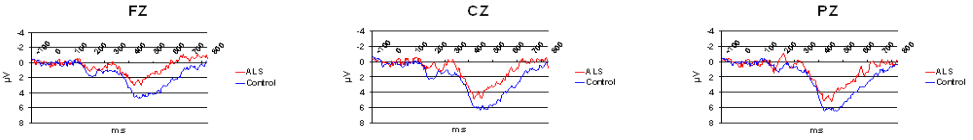
Time point 1: 10 am



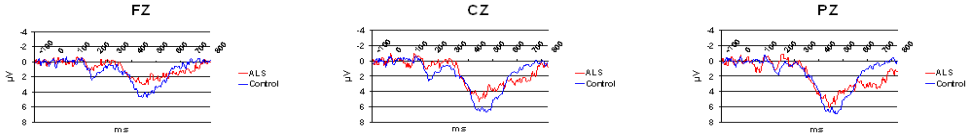
Time point 2: 12 pm



Time point 3: 14 pm



Time point 4: 16 pm



12.7.2 Auditory P300

12.7.2.1 Manipulation Check for Auditory P300

The auditory P300 was clearly discernable in all participants upon analysis with Brain Vision analyser. The differences between frequent and rare stimuli (stimulus) were significant for all electrodes for P300 amplitude, latency, and area (see Table 12.7.2.1).

Table 12.7.2.1: Summary of *F*-ratios and probabilities from 3-factor (time x stimulus x group) ANOVA for repeated measures performed on the auditory P300 peak amplitude, P300 latency, and P300 area

Electrode Position	P300 Amplitude		P300 Latency		P300 Area	
	F	*P*	*F*	*P*	*F*	*P*
Vertex						
Fz	**14.191**	**0.001**	**13.925**	**0.007**	**22.728**	**0.000**
Cz	**26.958**	**0.000**	**20.174**	**0.008**	**34.003**	**0.000**
Pz	**53.564**	**0.000**	**20.015**	**0.049**	**52.386**	**0.000**
Left Hemisphere						
F3	**10.673**	**0.003**	**21.358**	**0.039**	**15.225**	**0.001**
C3	**26.739**	**0.000**	**19.085**	**0.047**	**25.926**	**0.000**
CP3	**35.080**	**0.000**	**21.132**	**0.029**	**32.783**	**0.000**
P3	**35.902**	**0.000**	**20.082**	**0.047**	**36.091**	**0.000**
Right Hemisphere						
F4	**12.844**	**0.001**	**24.269**	**0.049**	**23.928**	**0.000**
C4	**35.023**	**0.000**	**18.002**	**0.051**	**39.739**	**0.000**
CP4	**51.937**	**0.000**	**17.023**	**0.016**	**49.966**	**0.000**
P4	**51.433**	**0.000**	**10.269**	**0.066**	**52.162**	**0.000**

12.7.2.2 Auditory P300 – Evaluation of Midline Electrodes

12.7.2.2.1 Auditory P300 Amplitude

A 3-factor ANOVA for repeated measures was conducted for the midline electrodes for rare stimuli only with within-subject factors *time* (4; 10 am, 12 pm, 14 pm, and 16 pm), and *midline* (3; FZ, CZ, and PZ) and between-subject factor *group* (2; ALS patients vs. healthy controls). Table 12.7.2.3 summarizes the outcome of this analysis.

No significant difference between ALS patients and healthy controls could be found (F = 0.511, p = 0.481). Main effect *time* did not yield significance ((F = 1.338, p = 0.268). But a main effect for *midline* (F = 24.043, p = 0.000) was obtained showing the expected significant smaller auditory P300 amplitude frontal compared with parietal.

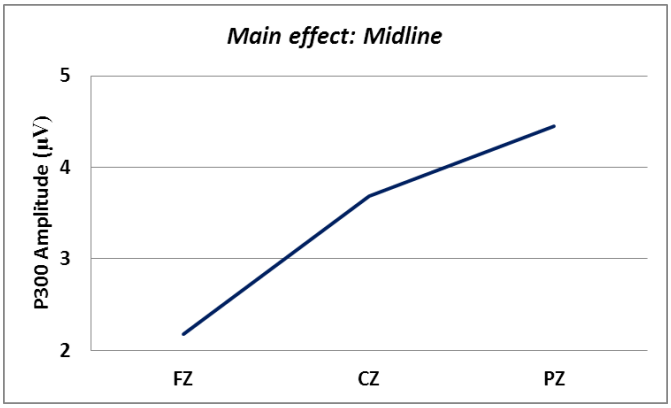


Figure 12.7.2.2.1.a: Main effect Midline for auditory P300 amplitude

A significant interaction for *time x midline x group* was found (F = 2.563, p = 0.021). Healthy controls displayed no changes in auditory P300 amplitude throughout the day while ALS patients yielded maximum auditory amplitude at 12 pm with a decrease at 14:00 pm and reached their smallest amplitude at 16:00 pm. But only PZ showed a significant lower amplitude at 16:00 pm than at 12:00 pm (T=1.879, p=0.0415).

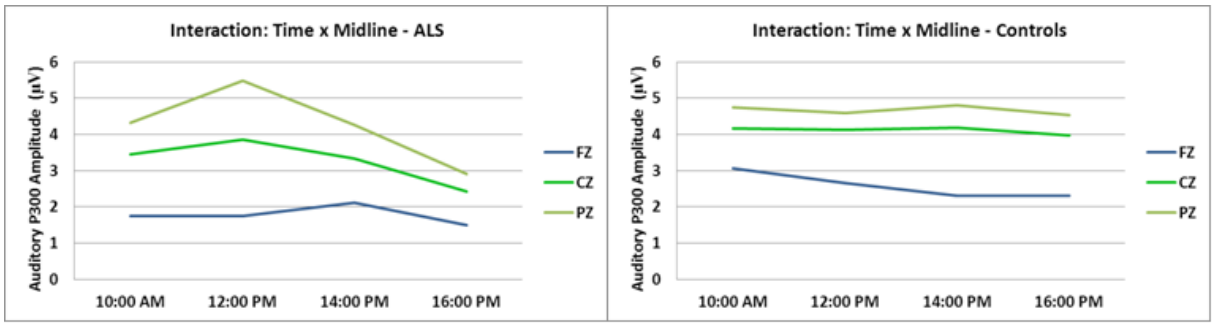


Figure 12.7.2.2.1.b: Time x Midline x Group Interaction for auditory P300 amplitude

12.7.2.2.2 Auditory P300 Latency

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Similar to the analysis of P300 amplitudes, a 3-factor ANOVA for repeated measures was conducted for auditory P300 latencies for midline electrodes (FZ, CZ, PZ) with within-subject factors *time* (4) and *midline* (3) and between-subject factor *group* (2). The results of this analysis can be seen summarized in table 12.7.2.3.

As in the analysis above, no significant difference between ALS patients and healthy controls could be found ($F = 1.773$, $p = 0.195$). Again, main effect *time* did not reach significance ($F = 1.098$, $p = 0.355$). Analysis became significant for main effect *midline* ($F = 5.515$, $p = 0.007$), demonstrating longer P300 latencies the further parietal the electrode site. No significant interactions to report.

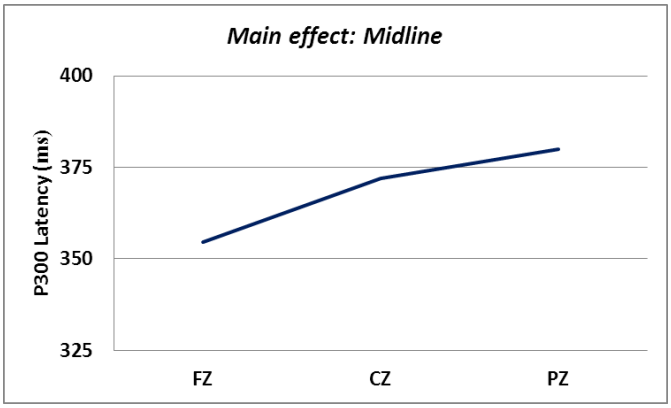


Figure 12.7.2.2.2: Main effect midline for auditory P300 latency

12.7.2.2.3 Auditory P300 Area

Similarly, a 3-factor ANOVA for repeated measures was conducted for the midline electrodes with within-subject factors *time* (4) and *midline* (3) and between-subject factor *group* (2). As in the analysis above, no significant difference between ALS patients and healthy controls could be found (F =0.738, p = 0.398). Main effect *time* did not reach significance (F = 3.058, p = 0.092). Main effects of *midline* (F = 33.297, p = 0.000) was obtained with bigger auditory P300 areas the further parietal the electrode recording site.

A significant interaction for *time* × *midline* × *group* was found (F = 11.082, p = 0.003). Healthy controls displayed no significant changes in auditory P300 amplitude throughout the day while ALS patients yielded maximum auditory P300 area at 12 pm with a steady decrease after reaching their smallest area at 16:00 pm.

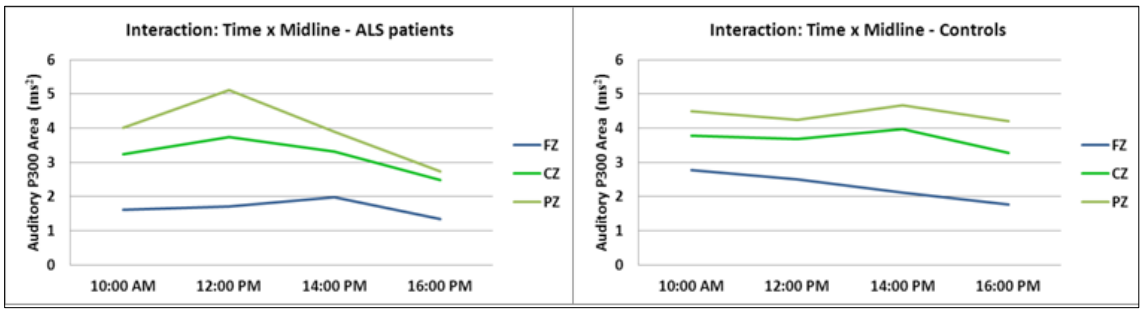


Figure 12.7.2.2.3: Time x Midline x Group Interaction for auditory P300 area

But only PZ showed a significant smaller auditory P300 area at 16:00 pm than at 12:00 pm (T=1.879, p=0.0415).

Please find the summarized outcome of this analysis in table 12.7.2.2.3 below.

Table 12.7.2.2.3: Summary of the 3-factor ANOVA for repeated measures (4 Time points x 3 Midline electrodes) and between-subject factor Group (ALS patients vs. healthy controls) performed on auditory P300 amplitude, latency, and P300 area information data

Source	Amplitude (µV)		Latency (ms)		Area (ms^2)	
	F	***P***	***F***	***P***	***F***	***P***
Group (G)	**-**	**ns.**	**-**	**ns.**	**-**	**ns.**
Time (T)	**-**	**ns.**	**-**	**ns.**	**-**	**ns.**
Midline (M)	**24.043**	**0.000**	**5.515**	**0.007**	**33.297**	**0.000**
T x M x G	**2.563**	**0.021**	**-**	**ns.**	**11.082**	**0.003**

* Further interactions were not listed because of their non-significance. *ns.= no significance

12.7.2.3 Auditory P300 – Difference Waveforms

Auditory P300 difference waveforms (rare stimuli minus frequent stimuli) of recording sites for midline electrodes (Fz, Cz, Pz), left hemisphere (F3, C3, CP3, and P3), and right hemisphere (F4, C4, CP4, and P4), and Oz, for ALS patients and controls for all four time points (10 am, 12 pm, 14 pm, and 16 pm) are reported in the following figures 12.7.2.a-d, and an overview of midline electrodes (Fz, Cz, Pz) only for all four time points in figure 12.7.2.e.

Time point 1 at 10 am

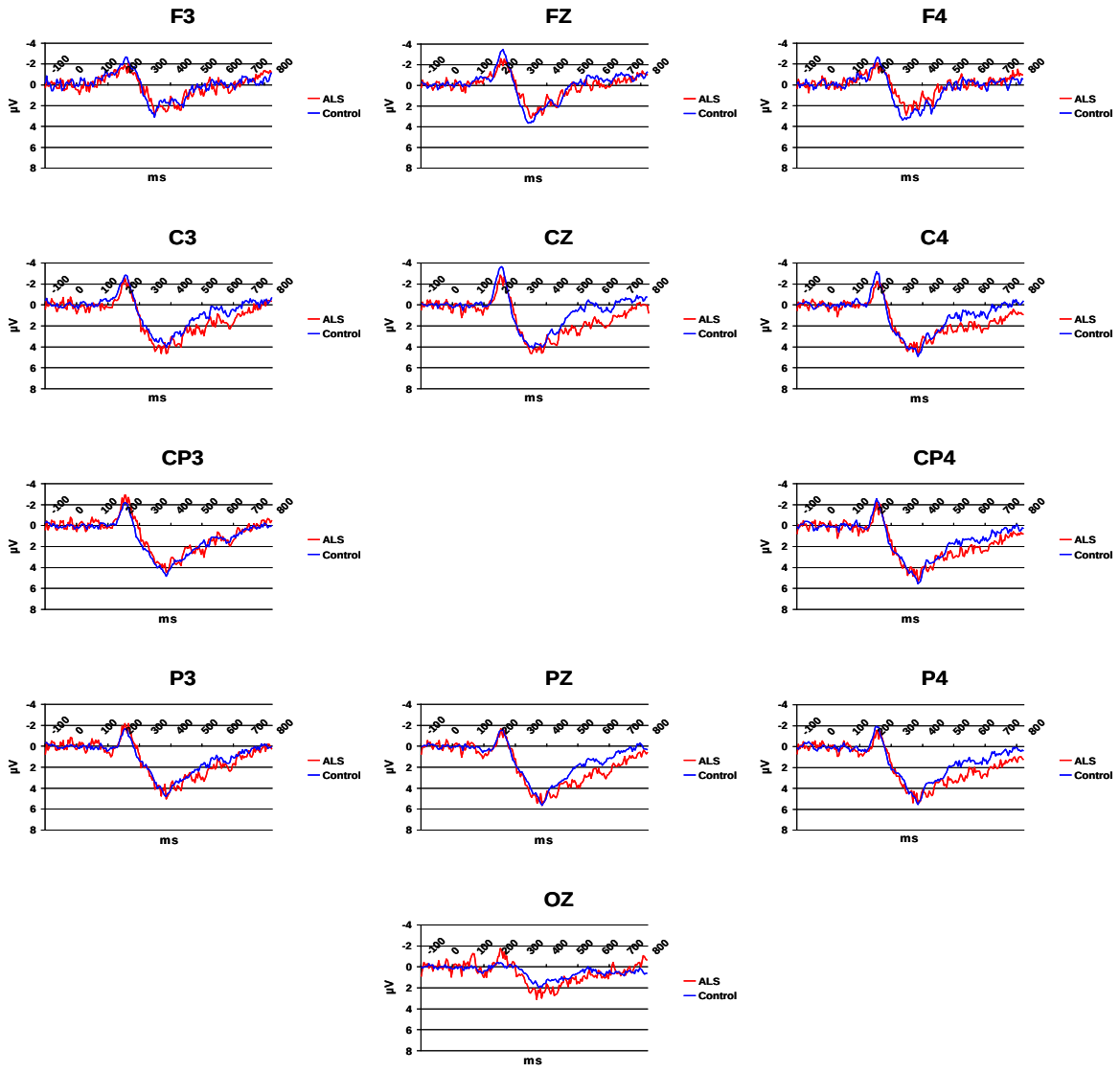


Figure 12.7.2.a: Auditory P300 difference waveforms (rare minus frequent stimuli) for electrodes Fz, Cz, Pz, F3, C3, CP3, P3, F4, C4, CP4, and P4 for time point 10 am

Time point 2 at 12 pm

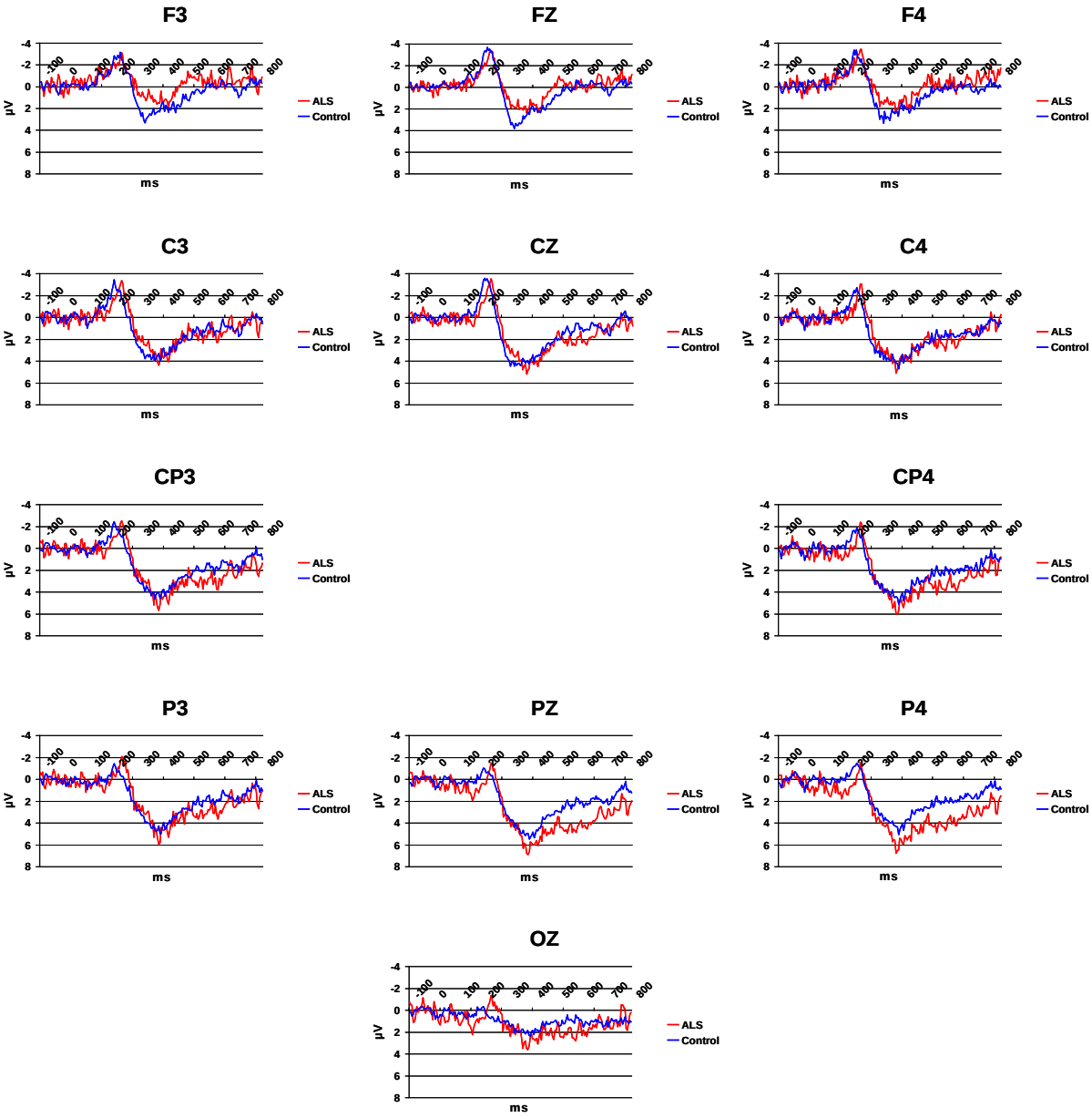


Figure 12.7.2.b: Auditory P300 difference waveforms (rare minus frequent stimuli) for electrodes Fz, Cz, Pz, F3, C3, CP3, P3, F4, C4, CP4, and P4 for time point 12 pm

Time point 3 at 14 pm

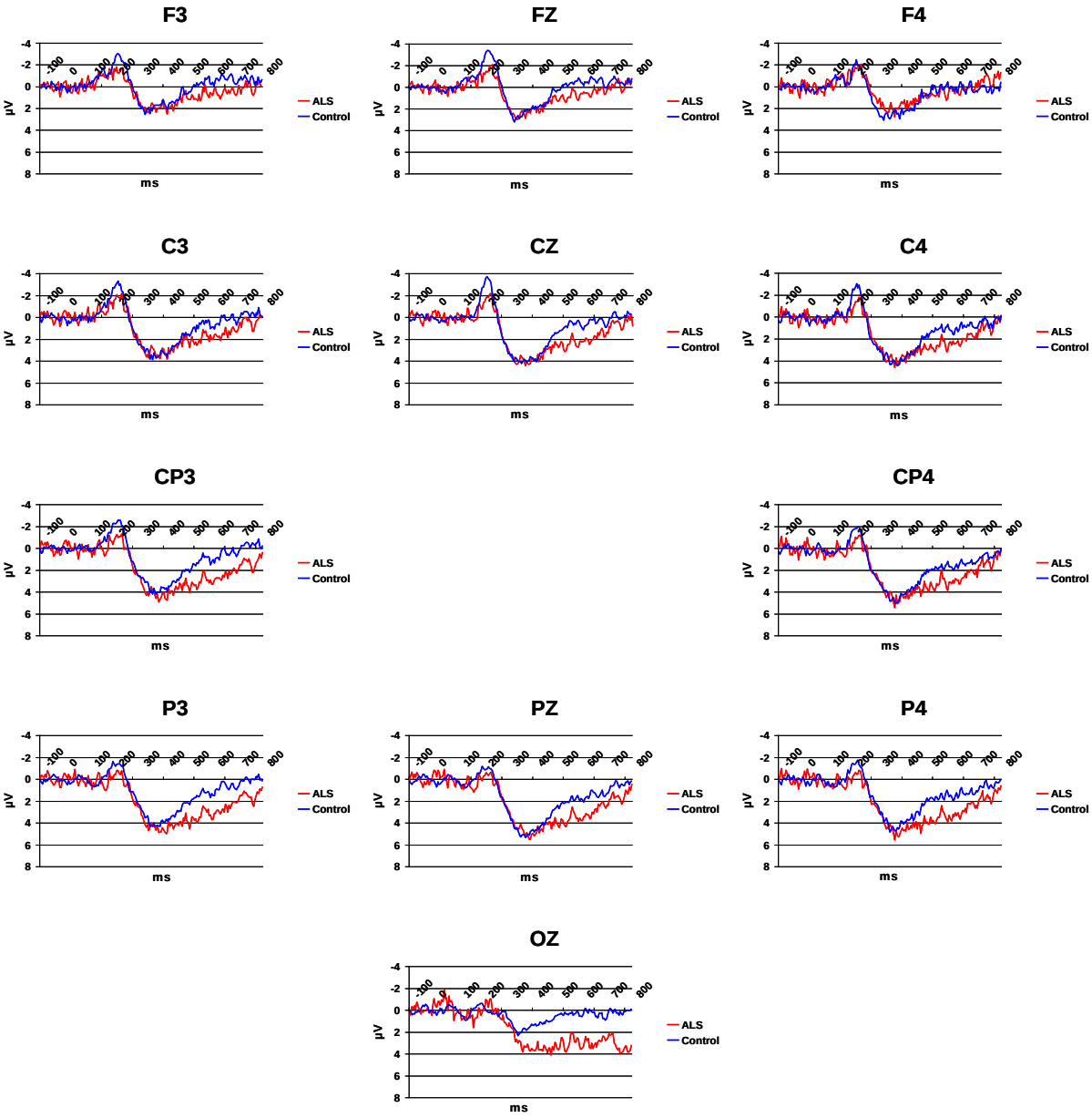


Figure 12.7.2.c: Auditory P300 difference waveforms (rare minus frequent stimuli) for electrodes Fz, Cz, Pz, F3, C3, CP3, P3, F4, C4, CP4, and P4 for time point 14 pm

Time point 4 at 16 pm

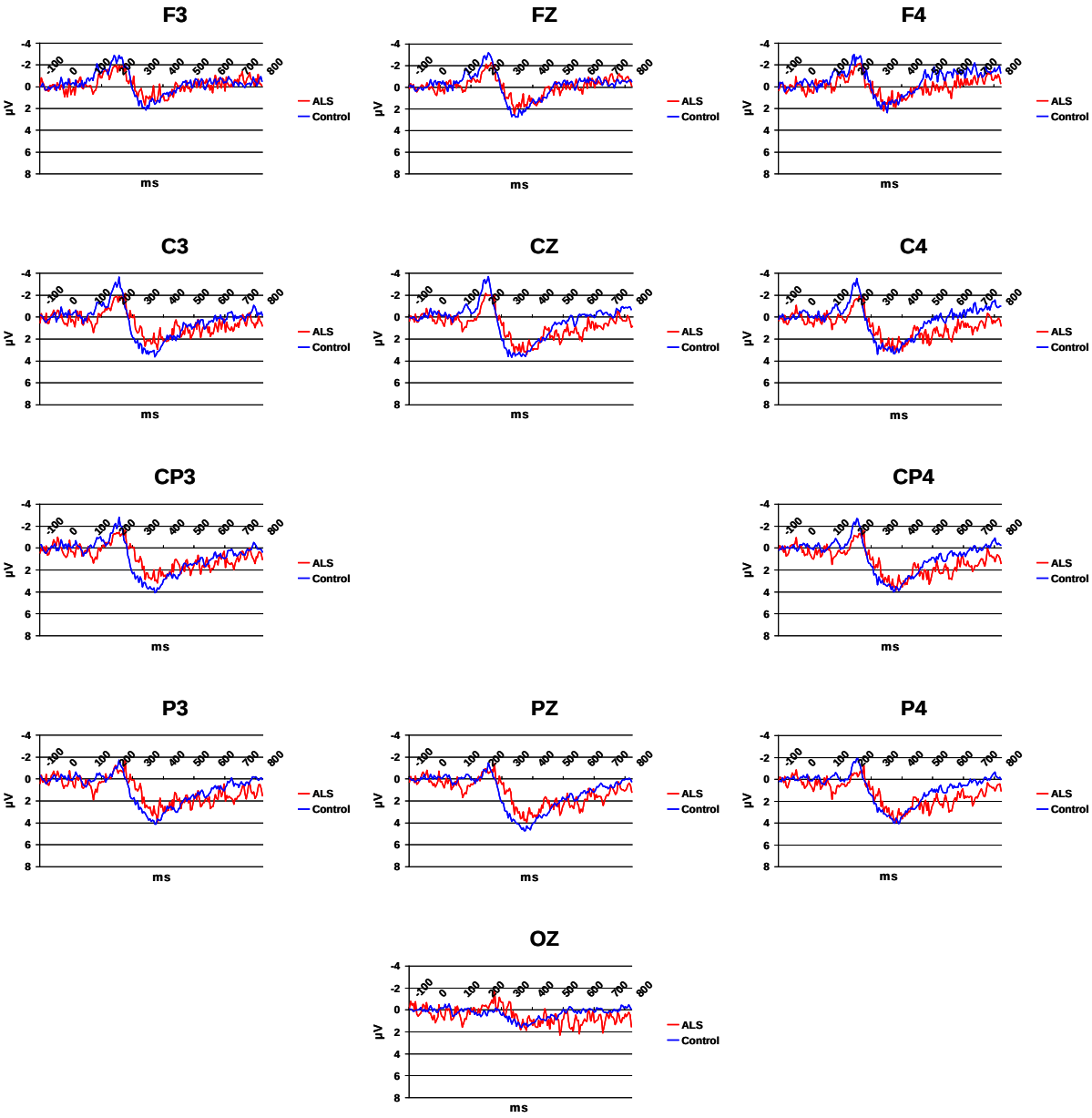
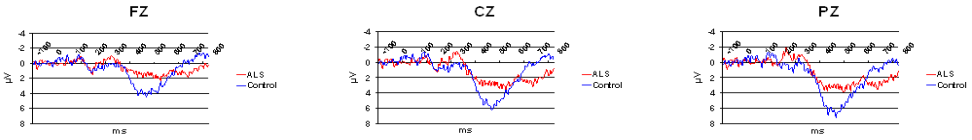


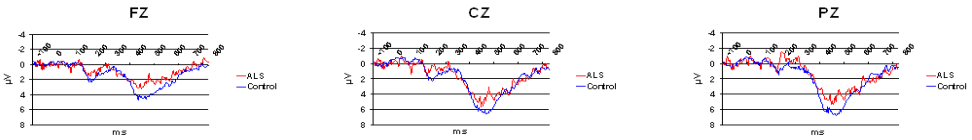
Figure 12.7.2.d: Auditory P300 difference waveforms (rare minus frequent stimuli) for electrodes Fz, Cz, Pz, F3, C3, CP3, P3, F4, C4, CP4, and P4 for time point 16 pm

Figure 12.7.2.e: Auditory P300 difference waveforms (rare minus frequent stimuli) for midline electrodes FZ, CZ, and PZ for ALS patients and healthy controls at four different time points (10 am, 12 pm, 14 pm, and 16 pm)

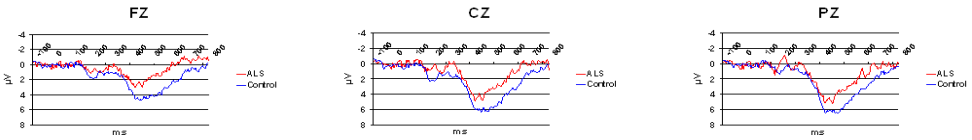
Time point 1: 10 am



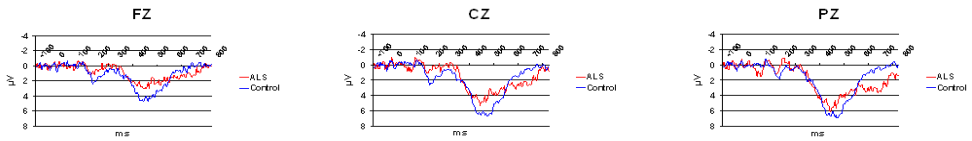
Time point 2: 12 pm



Time point 3: 14 pm



Time point 4: 16 pm



13 Discussion Study III

Several performance studies demonstrated that attention and information processing are affected by changes in the arousal state in the human being. It has been shown that sleep deprivation can severely impede information processing efficiency (Hockey, 1986; Smulders, 1993), the same process assumed to be reflected by P300. Patients with amyotrophic lateral sclerosis could be affected by factors originating from their illness's circumstances such as a low arousal state possibly due to their increased immobility and disrupted sleep architecture as shown in study I, fatigue, and considerable decrease in exercise.

A few studies also assessed processing of attention and information with event-related potentials and their findings point towards cognitive abnormalities in between 60 to 75% of ALS patients who showed impaired or delayed visual and/or auditory P300 and significant delay in N100, P200, and N200 latency (Gil et al., 1995; Paulus et al., 2002; Volpato et al., 2010).

In study III I investigated whether these above mentioned factors were reflected in a change of visual and auditory P300 components at four time points of the day compared with an age and sex matched healthy control group.

VISUAL P300

As expected, statistical analysis showed a change in visually evoked P300 amplitude and area across the scalp increasing in magnitude from the frontal to parietal electrodes. No significant difference was found for visual P300 latencies.

In this study no impaired visual P300 for amplitude, latency or area analysis was found in ALS patients compared with healthy controls. This outcome is in contrast to a study by Paulus et al. (2002). They observed a delayed visual P300 latency in five out of 22 ALS patients. The degree of disability in their study was rated by using the ALS Severity Scale (ALSSS) ("4 worst to 40 best") (Hillel et al., 1989) and a mean ALSSS score of 29.4 (s=8.3). Within this study severity of amyotrophic lateral sclerosis was assessed with the ALS Functional Rating Scale revised ("0 worst to 48 best") (Nakanashi, 1999) with a ALSFRS-R mean score of 21.79 (s=10.53). Interestingly, ALS patients in the current study were comparatively more impaired than the patient group in Paulus et al. (2002) but did not display impaired visual P300 components at the midline electrode sites analysed.

One reason might be that I statistically analysed visual P300 components for FZ, CZ, and PZ only, while his group calculated one single mean P300 amplitude and latency across 30 scalp electrodes. The mean P300 amplitude and latency in the study of Paulus et al. (2002) could possibly reflect impairment in cortical structures at electrode sites which were not detected at midline electrodes in our study.

The P300 is not a unitary phenomenon but is generally interpreted as a result of many diverse cortical and subcortical structures that contribute to its genesis. Investigations by fMRI have generated evidence of neural generators of the P300 during target detection involving increases in the fMRI signal in the temporal-parietal cortex, middle frontal gyrus, inferior parietal lobe, inferior aspect of the posterior cingulate gyrus, and insular cortex bilaterally (McCarthy et al., 1997Menon et al., 1997; and Linden et al., 1999; in Paulus et al., 2002). The visually evoked P300 was found to be the greatest in the right middle frontal gyrus, bilaterally in the inferior frontal gyrus, premotor area, in the right middle temporal gyrus, and in the anterior cingulate (Paulus et al., 2002). Hence, it might be the case that his result reflects impairment of the visual P300 amplitude and latency that are maybe not found along midline electrodes. Another possibility could be that the impairment of cortical and subcortical structures from amyotrophic lateral sclerosis was different in our patient group.

ALS patients undergo huge continuous state changes in their body over the course of their disease resulting from increasing immobility during progression of the disease, resulting lack of exercise and disrupted sleep. ALS patients did not display different visual P300 components over the course of the day.

AUDITORY P300

Evaluation of auditory P300 components amplitude, latency and area did not show any differences between ALS patients and controls as well as no significant effect for time. As expected, auditory P300 amplitudes and area increased in magnitude towards parietal electrode sites while auditory evoked P300 component latency became longer. We did find a significant interaction for time x midline x group for auditory P300 amplitude and area, but not for latency.

ALS patients displayed a significant decrease in auditory P300 amplitude after 12 pm compared with 16 pm in the late afternoon for electrode site PZ. This trend was found for CZ as well but did not reach significance. Healthy controls showed no differences over the course of the day. The same interaction was found for auditory P300 area. This result could be interpreted as ALS patients being the most alert at noon and the least in the late afternoon.

ALS patients undergo huge continuous body state changes over the course of their disease resulting from increasing immobility over the progression of the disease. Bashore (1989; in Polich and Kok, 1995) evaluated the effects of exercise and fitness on cognition, i.e. on P300 electrophysiological measures. P300 amplitude was smaller and more importantly the P300 component latency was longer for low-fit compared to high-fit subject groups. ERP (event-related potential) studies strongly suggest that exercise is affecting tonic body state and as a result affects P300 values.

Disrupted sleep architecture in amyotrophic lateral sclerosis (ALS) (please see study I; Ferguson et al., 1996; and Sangal et al., 1999) could have been another environmentally induced factor contributing to our results. At the opposite end of the arousal continuum stands the low arousal state induced through sleep deprivation. Only a few studies investigated the effects of sleep deprivation on event-related potentials. Generally, P300 amplitude tends to decrease and latency to increase with sleep onset (Wesensten and Badia, 1988). Sleep disorders resulting in fatigue showed comparable results (Walsleben et al., 1989).

Interestingly, time of the day only showed an influence on the auditory modality of P300 amplitude and area in ALS patients, but not in healthy controls. P300 is said to provide a general index of cognitive processing. While P300 amplitude may be reduced with decreased attention, P300 latency is difficult to alter with attention (Sangal et al., 1997).

In the light of this research, our findings might suggest a general shift of alertness for ALS patients with a peak in alertness at noon and a steady decrease until 16 pm but only for the auditory modality, and not for visually evoked P300 potentials.

Although no main effect of time was found in the visual or auditory modality, results point towards a different pattern of alertness in ALS patients compared with healthy controls in the auditory modality.

One shortcoming of this study that could explain the non-significant differences between ALS patients and control group might be the number of participants. A group of 14 participants in each experimental group might have been not sufficient to turn the trend into a significant difference.

For future investigation of the imfluence of time of the day on auditory P300 an approach including physiological measures such as heart rate or/and body temperature would be advantageous and could lead to support our hypothesis of changes to an altered/lowered arousal state resulting in decreased alertness at certain time points during the day in patients with amyotrophic lateral sclerosis compared with healthy controls within a larger representative experimental group.

14 GENERAL DISCUSSION

14.1 Disrupted sleep architecture in ALS patients

The data presented in this dissertation could confirm previous findings of studies (Sonka et al., 2004; Ferguson et al., 1996; Bourke et al., 2001; Broughton et al., 1984) investigating sleep in patients with amyotrophic lateral sclerosis of prolonged stage I NREM sleep, REM sleep reduction, significantly decreased sleep efficiency and fragmented sleep (expressed in stage changes per hour). Despite this severely disrupted sleeping pattern patients showed high resilience considering the subjective and objective result of poor sleep quality. Every other patient displayed low daytime sleepiness while all patients seem to have no difficulty in staying awake under low-stimulus conditions.

Assessment of emotional well-being showed a similar prevalence of depressive symptoms and disorders as found in other studies in amyotrophic lateral sclerosis (Rabkin et al., 2005). Depressive symptoms only showed in early or mid-stage ALS with the Beck Depression Inventory-Revised (BDI-II) (Beck et al., 1996) and "clinically relevant depression" evaluated with the ALS Depression Inventory (ADI) (Kübler et al., 2005) was found only in one patient who just recently was diagnosed with ALS which is in line with a higher acceptance of illness being correlated to the severity of disease (Hogg et al., 1994).

As other studies on sleep architecture in ALS (e.g., LoCoco et al. (2011)) our study suffers from a small sample size which reduces the generalizability of our results. However, our sample included patients in all stages, i.e., also in later stages of the disease, and thus, renders data collection extremely strenuous for the experimenter and the patients alike. Moreover, our patients were not hospitalised, meaning they came to the hospital only to take part in our study. This may have introduced a selection bias and we very likely present data of a relatively well functioning sample.

For future studies it would be interesting to assess a representative amount of patients for each stage of the disease with nocturnal ventilation. As two out of three patients displayed a reduction of REM sleep despite nocturnal ventilation, this would help to clarify the question whether REM sleep reduction in ALS is connected with impaired ventilation in REM sleep compounded by diaphragm insufficiency or not.

Or actually can be attributed to progressive degeneration of brain areas responsible for REM sleep generation which could be verified if neuroimaging technologies would be implemented beforehand to evaluate the actual stage of brain damage in each patient.

To conclude, despite the above mentioned caveats of our study, our data contribute to the evidence of sleep being disrupted already in early stages of the disease and thus, night-time sleep should not only be monitored with regards to respiratory function. To optimise palliative care in patients with ALS, also daytime sleepiness and wakefulness should be assessed and both physiological recordings should be completed by subjective measures. Subjectively experienced sleep quality is worse at earlier stages of the disease, underlining the need of early intervention, and may improve as the disease progresses, which might indicate that sleep is an increasingly welcome anodyne.

Subjective measures of sleep quality and daytime sleepiness help to specify individual concerns and sleep related problems and may thus, facilitate and improve intervention. As reported previously (Matuz et al., 2010) depressive symptoms seriously hamper coping with and as shown with the present study, are also related to sleep quality and should thus, be routinely assessed and rigorously treated. Taking into account sleep architecture, daytime alertness, and subjective measures thereof may help patients in coping with the disease and as a result improve their quality of life.

14.2 Degeneration of Rapid eye movements in Amyotrophic Lateral Sclerosis

To my knowledge, this was the first study investigating preservation of extraocular eye movement muscles by rapid eye movement analysis in ALS patients. The data presented in this dissertation demonstrate dramatically that degeneration of the motor system also affects extraocular motoneurons. This finding is supported by a study conducted by Haenggeli & Kato (2002) who found selective motoneurons loss depending on the stage of the disease in mice. Depending on the progression of the disease rapid eye movements clearly showed a reduction in density, a decrease in REM amplitude and a prolonged REM duration with high significance.

The fact that no calibration of individual eye movements was conducted prior to polysomnographic EOG recordings, it would be advisable to verify the results of this dissertation in a future study where this particular analysis would be incorporated to enable calculation of eye movement velocity. First, this would strengthen and verify the findings of this study and overcome this shortcoming. Second, despite obtaining such highly significant evidence for the degeneration of extraocular muscles over the progression of the disease, it would be interesting to evaluate these findings with a larger patient group with a representative amount of patients for the different stages of amyotrophic lateral sclerosis.

14.3 Brain Computer Interface Training in amyotrophic lateral sclerosis

The data presented in this dissertation show that no difference between ALS patients and healthy controls could be found for neither the visually nor the auditory evoked P300 potentials. My finding supports that P300 is a valid signal for communication with Brain Computer Interface in patients with amyotrophic lateral sclerosis and the data of demonstrating stable performance in P300-based brain-computer interface training for many months (Nijboer et al., 2008). Investigating alertness at four time points over the day though resulted though in a finding that could be relevant for optimising P300-based brain-computer interface (BCI) training with the auditory P300 for ALS patients.

Interestingly, a different pattern of alertness was found in ALS patients compared with healthy controls. In auditory evoked P300 potentials ALS patients peaked in their performance at 12 pm and showed their lowest at 4pm while healthy participants displayed no differences over the course of the day.

Many factors could be the reason for this result considering the modest group of fourteen participants in either group. But these findings could help choosing not random times for training but taking into consideration, for auditory P300-based training, the best time. Based on the results of this study a training time around noon could prove beneficial to the long-term training effect for auditory P300. Additionally, a thorough assessment of arousal facilitating physiological measures, e.g. heart rate which has been commonly used as an operational definition of arousal level, would be interesting to record over the time of the day to gain insight in this possible factor of influence.

14.4 Conclusion

Taken together, the results of this dissertation indicate that sleep is increasingly disrupted and deep sleep is diminishing over the course of amyotrophic lateral sclerosis. Up to date, studies investigating cognitive performance in ALS patients (Massmann et al., 1996; Abrahams et al., 2000, 1997; Cobble, 1998; Talbot et al., 1995; Galassi et al., 1989; Gil et al., 1995; & Paulus et al., 2002) have not taken into account the significantly impaired sleep efficiency or controlled for this factor. Cognitive deficits could stem from disruptive sleep and should be investigated in that respect.

It was also proven that extraocular eye movements do degenerate over the course of amyotrophic lateral sclerosis. Our findings for P300 could demonstrate that BCI communication in ALS patients is a valid and promising path into the future as this signal stays intact over the progression of the disease (Nijboer et al., 2008). It would be interesting though to investigate the influence of time of the day not just for one day but over the course of many days with a bigger patient group at different stages of the disease.

15 References

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16 APPENDIX

16.1 Abbreviations

AAS	Ascending activating system
ARAS	Ascending reticular activating system
ACC	Anterior cingulate cortex
ALS	Amyotrophic Lateral Sclerosis
ALSFRS-R	Amyotrophic Lateral Sclerosis – Functioning Rating Scale – Revised
CPAP	Continuous positive airway pressure
DLPC	Dorsolateral prefrontal cortex
EEG	Electroencephalogram
EMG	Electromyogram
EOG	Electrooculogram
ERP	Event-related brain potential
MND	Motor neuron disease
MRI	Magnetic resonance imaging
MSLT	Multiple sleep latency test
MWT	Maintenance of wakefulness test
NIV	Non-invasive ventilation
NREM	Non Rapid eye movement
PBBS	Peripheral benzodiazepine binding site
PTS	Period of Total Sleep = sleep onset (first epoch with stage II, III, IV or SP) – last waking up
REM	Rapid eye movement
Sleep Onset	First epoch which is not stage I
SCN	Suprachiasmatic nucleus
SOD1	Superoxide dismutase
TIB	Time in Bed
TST	Total Sleep Time (Duration of stages I, II, III, IV and REM)

16.2 Index of Figures

16.3 Index of Tables

16.4. Index of Pictures

16.5 Individual Polysomnographies for each Patient (A to J) for 1st and 2nd Night

A – 1st night:

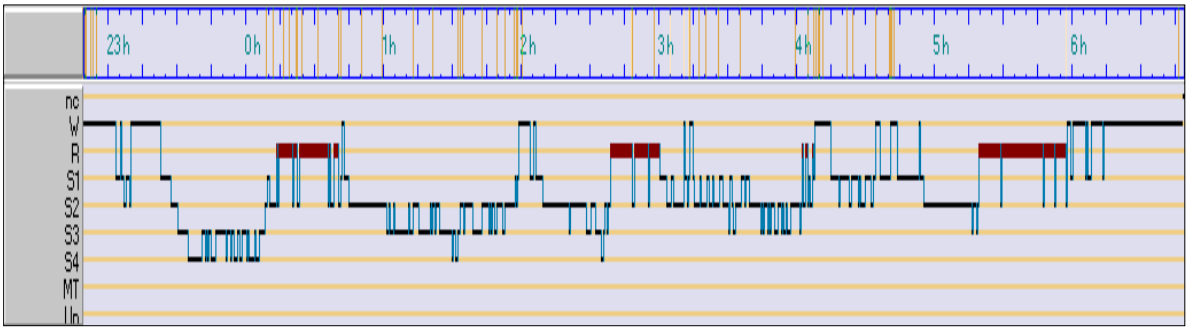

Figure 4.3.3.1.a: Hypnogram for 1st night for patient A

General Sleep parameters

TIB (hh:mm:ss)	08:00:00
TST (hh:mm:ss)	06:23:00
Standard PTS (hh:mm:ss)	07:42:00
Total duration of waking periods	01:37:00
Sleep efficiency index 1 (TST/TIB)	79.79
Amount of stage changes during TIB	201
Amount of stage changes during PTS	200
Fragmentation Index (Amount of Stage Changes / TIB)	25.13
Total REM (hh:mm:ss)	01:21:30
Total NREM (ST I + ST II + ST III + ST IV) (hh:mm:ss)	05:01:30
Duration Slow Wave Sleep Stage III + Stage IV (hh:mm:ss)	01:27:00
Latency between sleep onset and REM (hh:mm:ss)	01:06:30

Polysomnographic Analysis

Awake

The following calculations refer to waking periods after sleep onset (1. epoch stage 2)

Amount of waking periods in sleep (hh:mm:ss)		01:22:00
Sleep stage 1:	**Ratio sleep stage 1 /PTS (after sleep onset)**	**14.29 %**
	Latency stage 1 after lights off (hh:mm:ss)	00:14:30
Sleep stage 2:	**Ratio sleep stage 2 / PTS (after sleep onset)**	**32.14 %**
	Latency stage 2 after lights off (hh:mm:ss)	00:18:00
Sleep stage 3:	**Ratio sleep stage 3 /PTS (after sleep onset)**	**14.61 %**
	Latency stage 3 after lights off (hh:mm:ss)	00:41:30
Sleep stage 4:	**Ratio sleep stage 4 /PTS (after sleep onset)**	**4.22 %**
	Latency stage 4 after lights off (hh:mm:ss)	00:46:00

REM:	**Ratio REM / PTS (after sleep onset)**	**17.64 %**
	Total duration REM (hh:mm:ss)	01:21:30
	Latency REM after lights off (hh:mm:ss)	01:24:30
	Latency REM after 1. stage I (in min)	70

A – 3rd night:

No data available as patient had to abort measurements due to pain in extremities.

B – 1st night:

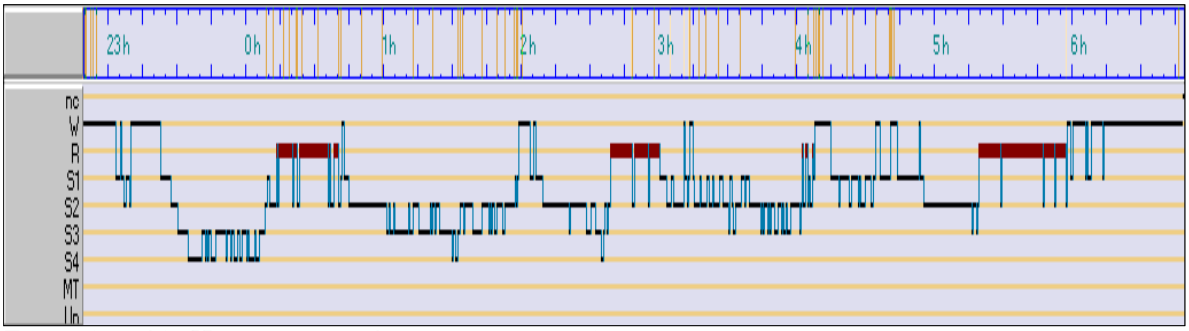

Figure 4.3.3.1.b: Hypnogram for 1st night for patient b

General Sleep parameters

TIB (hh:mm:ss)	08:00:00
TST (hh:mm:ss)	05:01:00
Standard PTS (hh:mm:ss)	07:09:00
Total duration of waking periods	02:59:00
Sleep efficiency index 1 (TST/TIB)	62.71
Amount of stage changes during TIB	100
Amount of stage changes during PTS	99
Fragmentation Index (Amount of Stage Changes / TIB)	12.50
Total REM (hh:mm:ss)	00:21:30
Total NREM (ST I + ST II + ST III + ST IV) (hh:mm:ss)	04:39:30
Duration Slow Wave Sleep Stage III + Stage IV (hh:mm:ss)	01:43:30
Latency between sleep onset and REM (hh:mm:ss)	01:08:30

Polysomnographic Analysis

Awake

The following calculations refer to waking periods after sleep onset (1. epoch stage 2)

Amount of waking periods in sleep (hh:mm:ss)		02:20:00
Sleep stage 1:	**Ratio sleep stage 1 /PTS (after sleep onset)**	**11.31 %**
	Latency stage 1 after lights off (hh:mm:ss)	00:39:00
Sleep stage 2:	**Ratio sleep stage 2 / PTS (after sleep onset)**	**29.72 %**
	Latency stage 2 after lights off (hh:mm:ss)	00:43:30
Sleep stage 3:	**Ratio sleep stage 3 /PTS (after sleep onset)**	**18.18 %**
	Latency stage 3 after lights off (hh:mm:ss)	00:50:30
Sleep stage 4:	**Ratio sleep stage 4 /PTS (after sleep onset)**	**5.94 %**
	Latency stage 4 after lights off (hh:mm:ss)	01:00:30
REM:	**Ratio REM / PTS (after sleep onset)**	**5.01 %**
	Total duration REM (hh:mm:ss)	00:21:30
	Latency REM after lights off (hh:mm:ss)	01:52:00
	Latency REM after 1. stage I (in min)	73

B – 2nd night:

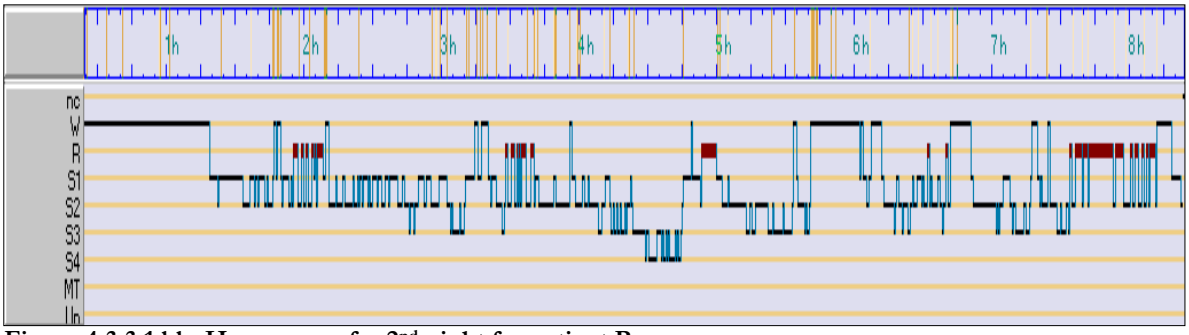

Figure 4.3.3.1.bb: Hypnogram for 2nd night for patient B

General Sleep parameters

TIB (hh:mm:ss)	08:00:00
TST (hh:mm:ss)	06:07:30
Standard PTS (hh:mm:ss)	07:01:30
Total duration of waking periods	01:52:30
Sleep efficiency index 1 (TST/TIB)	76.56
Amount of stage changes during TIB	254
Amount of stage changes during PTS	253
Fragmentation Index (Amount of Stage Changes / TIB)	31.75
Total REM (hh:mm:ss)	00:50:30
Total NREM (ST I + ST II + ST III + ST IV) (hh:mm:ss)	05:17:00
Duration Slow Wave Sleep Stage III + Stage IV (hh:mm:ss)	01:02:00
Latency between sleep onset and REM (hh:mm:ss)	00:33:00

Polysomnographic Analysis

Awake

The following calculations refer to waking periods after sleep onset (1. epoch stage 2)

Amount of waking periods in sleep (hh:mm:ss)		00:57:30
Sleep stage 1:	**Ratio sleep stage 1 /PTS (after sleep onset)**	**22.78 %**
	Latency stage 1 after lights off (hh:mm:ss)	00:55:00
Sleep stage 2:	**Ratio sleep stage 2 / PTS (after sleep onset)**	**37.72 %**
	Latency stage 2 after lights off (hh:mm:ss)	00:58:30
Sleep stage 3:	**Ratio sleep stage 3 /PTS (after sleep onset)**	**12.34 %**
	Latency stage 3 after lights off (hh:mm:ss)	02:22:00
Sleep stage 4:	**Ratio sleep stage 4 /PTS (after sleep onset)**	**2.37 %**
	Latency stage 4 after lights off (hh:mm:ss)	04:05:00
REM:	**Ratio REM / PTS (after sleep onset)**	**11.98 %**
	Total duration REM (hh:mm:ss)	00:50:30
	Latency REM after lights off (hh:mm:ss)	01:31:30
	Latency REM after 1. stage I (in min)	36

C – 1st night:

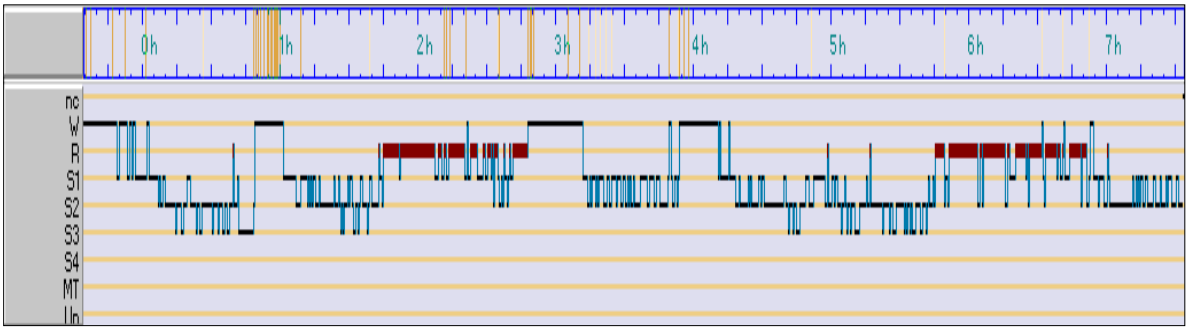

Figure 4.3.3.1.c: Hypnogram for 1st night for patient C

General Sleep parameters

TIB (hh:mm:ss)	08:00:00
TST (hh:mm:ss)	06:40:00
Standard PTS (hh:mm:ss)	07:27:00
Total duration of waking periods	01:20:00
Sleep efficiency index 1 (TST/TIB)	83.33
Amount of stage changes during TIB	278
Amount of stage changes during PTS	277
Fragmentation Index (Amount of Stage Changes / TIB)	34.75
Total REM (hh:mm:ss)	01:41:00
Total NREM (ST I + ST II + ST III + ST IV) (hh:mm:ss)	04:59:00
Duration Slow Wave Sleep Stage III + Stage IV (hh:mm:ss)	00:28:30
Latency between sleep onset and REM (hh:mm:ss)	00:32:30

Polysomnographic Analysis

Awake

The following calculations refer to waking periods after sleep onset (1. epoch stage 2)

Amount of waking periods in sleep (hh:mm:ss)		00:58:30
Sleep stage 1:	**Ratio sleep stage 1 /PTS (after sleep onset)**	**24.72 %**
	Latency stage 1 after lights off (hh:mm:ss)	00:15:00
Sleep stage 2:	**Ratio sleep stage 2 / PTS (after sleep onset)**	**35.79 %**
	Latency stage 2 after lights off (hh:mm:ss)	00:33:00
Sleep stage 3:	**Ratio sleep stage 3 /PTS (after sleep onset)**	**6.38 %**
	Latency stage 3 after lights off (hh:mm:ss)	00:40:30
Sleep stage 4:	**Ratio sleep stage 4 /PTS (after sleep onset)**	**0.00 %**
	Latency stage 4 after lights off (hh:mm:ss)	----------
REM:	**Ratio REM / PTS (after sleep onset)**	**22.60 %**
	Total duration REM (hh:mm:ss)	01:41:00
	Latency REM after lights off (hh:mm:ss)	01:05:30
	Latency REM after 1. stage I (in min)	50

C – 2nd night:

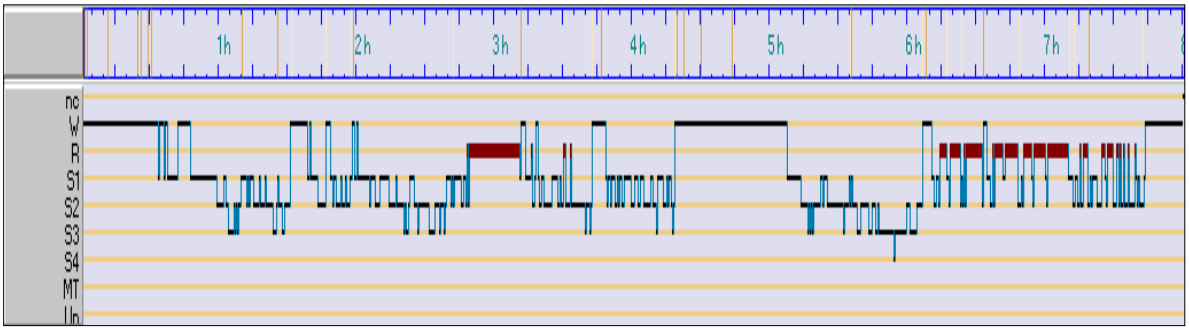

Figure 4.3.3.1.cc: Hypnogram for 2nd night for patient C

General Sleep parameters

TIB (hh:mm:ss)	08:00:00
TST (hh:mm:ss)	05:46:30
Standard PTS (hh:mm:ss)	07:01:30
Total duration of waking periods	02:13:30
Sleep efficiency index 1 (TST/TIB)	72.19
Amount of stage changes during TIB	232
Amount of stage changes during PTS	231
Fragmentation Index (Amount of Stage Changes / TIB)	29.00
Total REM (hh:mm:ss)	01:16:00
Total NREM (ST I + ST II + ST III + ST IV) (hh:mm:ss)	04:30:30
Duration Slow Wave Sleep Stage III + Stage IV (hh:mm:ss)	00:34:30
Latency between sleep onset and REM (hh:mm:ss)	01:49:00

Polysomnographic Analysis

Awake

The following calculations refer to waking periods after sleep onset (1. epoch stage 2)

Amount of waking periods in sleep (hh:mm:ss)		01:32:00
Sleep stage 1:	**Ratio sleep stage 1 /PTS (after sleep onset)**	**23.96 %**
	Latency stage 1 after lights off (hh:mm:ss)	00:33:00
Sleep stage 2:	**Ratio sleep stage 2 / PTS (after sleep onset)**	**32.03 %**
	Latency stage 2 after lights off (hh:mm:ss)	00:58:30
Sleep stage 3:	**Ratio sleep stage 3 /PTS (after sleep onset)**	**8.07 %**
	Latency stage 3 after lights off (hh:mm:ss)	01:03:30
Sleep stage 4:	**Ratio sleep stage 4 /PTS (after sleep onset)**	**0.12 %**
	Latency stage 4 after lights off (hh:mm:ss)	05:53:30
REM:	**Ratio REM / PTS (after sleep onset)**	**18.03 %**
	Total duration REM (hh:mm:ss)	01:16:00
	Latency REM after lights off (hh:mm:ss)	02:47:30
	Latency REM after 1. stage I (in min)	134

D – 1st night:

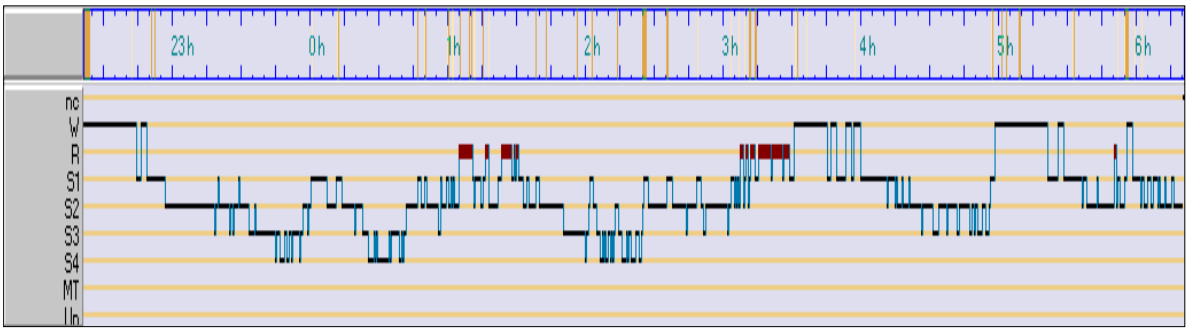

Figure 4.3.3.1.d: Hypnogram for 1st night for patient D

General Sleep parameters

TIB (hh:mm:ss)	08:00:00
TST (hh:mm:ss)	06:43:30
Standard PTS (hh:mm:ss)	07:24:00
Total duration of waking periods	01:16:30
Sleep efficiency index 1 (TST/TIB)	84.06
Amount of stage changes during TIB	207
Amount of stage changes during PTS	206
Fragmentation Index (Amount of Stage Changes / TIB)	25.88
Total REM (hh:mm:ss)	00:31:30
Total NREM (ST I + ST II + ST III + ST IV) (hh:mm:ss)	06:12:00
Duration Slow Wave Sleep Stage III + Stage IV (hh:mm:ss)	01:27:00
Latency between sleep onset and REM (hh:mm:ss)	02:08:00

Polysomnographic Analysis

Awake

The following calculations refer to waking periods after sleep onset (1. epoch stage 2)

Amount of waking periods in sleep (hh:mm:ss)		00:50:30
Sleep stage 1:	**Ratio sleep stage 1 /PTS (after sleep onset)**	**23.42 %**
	Latency stage 1 after lights off (hh:mm:ss)	00:23:30
Sleep stage 2:	**Ratio sleep stage 2 / PTS (after sleep onset)**	**40.77 %**
	Latency stage 2 after lights off (hh:mm:ss)	00:36:00
Sleep stage 3:	**Ratio sleep stage 3 /PTS (after sleep onset)**	**14.08 %**
	Latency stage 3 after lights off (hh:mm:ss)	00:57:30
Sleep stage 4:	**Ratio sleep stage 4 /PTS (after sleep onset)**	**5.52 %**
	Latency stage 4 after lights off (hh:mm:ss)	01:24:00
REM:	**Ratio REM / PTS (after sleep onset)**	**7.09 %**
	Total duration REM (hh:mm:ss)	00:31:30
	Latency REM after lights off (hh:mm:ss)	02:44:00
	Latency REM after 1. stage I (in min)	140

D – 2nd night:

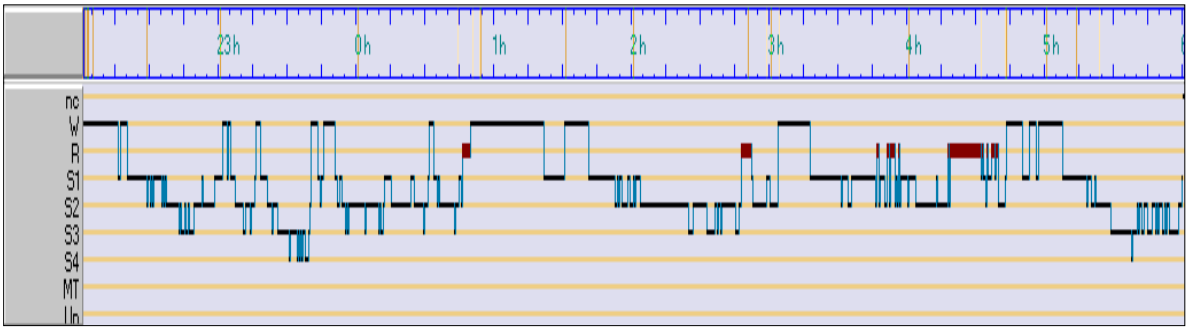

Figure 4.3.3.1.dd: Hypnogram for 2nd night for patient D

General Sleep parameters

TIB (hh:mm:ss)	08:00:00
TST (hh:mm:ss)	06:09:30
Standard PTS (hh:mm:ss)	07:32:00
Total duration of waking periods	01:50:30
Sleep efficiency index 1 (TST/TIB)	76.98
Amount of stage changes during TIB	190
Amount of stage changes during PTS	189
Fragmentation Index (Amount of Stage Changes / TIB)	23.75
Total REM (hh:mm:ss)	00:30:00
Total NREM (ST I + ST II + ST III + ST IV) (hh:mm:ss)	05:39:30
Duration Slow Wave Sleep Stage III + Stage IV (hh:mm:ss)	00:54:30
Latency between sleep onset and REM (hh:mm:ss)	02:17:30

Polysomnographic Analysis

Awake

The following calculations refer to waking periods after sleep onset (1. epoch stage 2)

Amount of waking periods in sleep (hh:mm:ss)		01:32:00
Sleep stage 1:	**Ratio sleep stage 1 /PTS (after sleep onset)**	**26.99 %**
	Latency stage 1 after lights off (hh:mm:ss)	00:15:30
Sleep stage 2:	**Ratio sleep stage 2 / PTS (after sleep onset)**	**36.06 %**
	Latency stage 2 after lights off (hh:mm:ss)	00:28:00
Sleep stage 3:	**Ratio sleep stage 3 /PTS (after sleep onset)**	**11.17 %**
	Latency stage 3 after lights off (hh:mm:ss)	00:42:00
Sleep stage 4:	**Ratio sleep stage 4 /PTS (after sleep onset)**	**0.88 %**
	Latency stage 4 after lights off (hh:mm:ss)	01:30:00
REM:	**Ratio REM / PTS (after sleep onset)**	**6.64 %**
	Total duration REM (hh:mm:ss)	00:30:00
	Latency REM after lights off (hh:mm:ss)	02:45:30
	Latency REM after 1. stage I (in min)	150

E – 1st night:

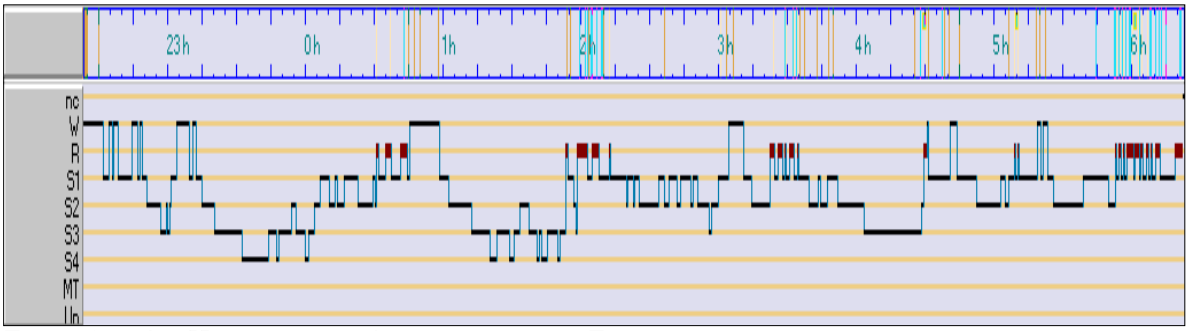

Figure 4.3.3.1.e: Hypnogram for 1st night for patient E

General Sleep parameters

TIB (hh:mm:ss)	08:00:00
TST (hh:mm:ss)	07:10:00
Standard PTS (hh:mm:ss)	07:32:00
Total duration of waking periods	00:49:30
Sleep efficiency index 1 (TST/TIB)	89.58
Amount of stage changes during TIB	146
Amount of stage changes during PTS	145
Fragmentation Index (Amount of Stage Changes / TIB)	18.25
Total REM (hh:mm:ss)	00:40:00
Total NREM (ST I + ST II + ST III + ST IV) (hh:mm:ss)	06:30:00
Duration Slow Wave Sleep Stage III + Stage IV (hh:mm:ss)	01:48:30
Latency between sleep onset and REM (hh:mm:ss)	01:40:00

Polysomnographic Analysis

Awake

The following calculations refer to waking periods after sleep onset (1. epoch stage 2)

Amount of waking periods in sleep (hh:mm:ss)		00:33:30
Sleep stage 1:	**Ratio sleep stage 1 /PTS (after sleep onset)**	**35.29 %**
	Latency stage 1 after lights off (hh:mm:ss)	00:09:00
Sleep stage 2:	**Ratio sleep stage 2 / PTS (after sleep onset)**	**26.99 %**
	Latency stage 2 after lights off (hh:mm:ss)	00:28:00
Sleep stage 3:	**Ratio sleep stage 3 /PTS (after sleep onset)**	**18.81 %**
	Latency stage 3 after lights off (hh:mm:ss)	00:34:00
Sleep stage 4:	**Ratio sleep stage 4 /PTS (after sleep onset)**	**5.20 %**
	Latency stage 4 after lights off (hh:mm:ss)	01:09:30
REM:	**Ratio REM / PTS (after sleep onset)**	**8.85 %**
	Total duration REM (hh:mm:ss)	00:40:00
	Latency REM after lights off (hh:mm:ss)	02:08:00
	Latency REM after 1. stage I (in min)	119

E – 2nd night:

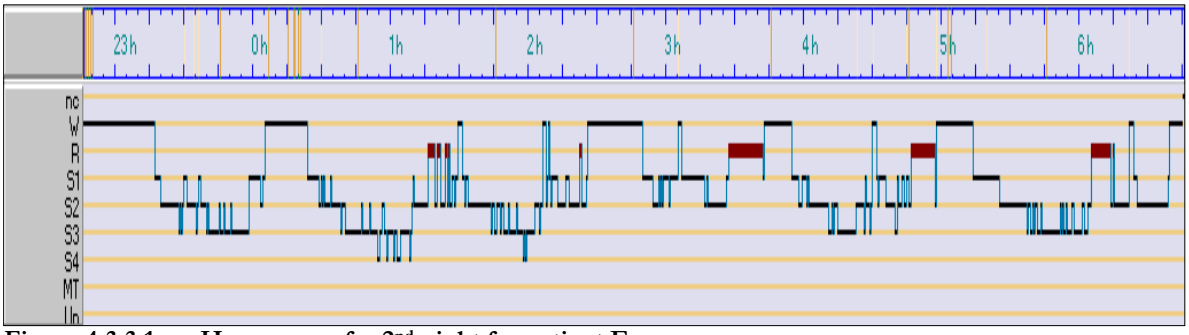

Figure 4.3.3.1.ee: Hypnogram for 2nd night for patient E

General Sleep parameters

TIB (hh:mm:ss)	08:00:00
TST (hh:mm:ss)	06:02:00
Standard PTS (hh:mm:ss)	07:19:30
Total duration of waking periods	01:58:00
Sleep efficiency index 1 (TST/TIB)	75.42
Amount of stage changes during TIB	185
Amount of stage changes during PTS	184
Fragmentation Index (Amount of Stage Changes / TIB)	23.13
Total REM (hh:mm:ss)	00:41:30
Total NREM (ST I + ST II + ST III + ST IV) (hh:mm:ss)	05:20:30
Duration Slow Wave Sleep Stage III + Stage IV (hh:mm:ss)	01:32:30
Latency between sleep onset and REM (hh:mm:ss)	01:56:30

Polysomnographic Analysis

Awake

The following calculations refer to waking periods after sleep onset (1. epoch stage 2)

Amount of waking periods in sleep (hh:mm:ss)		01:26:30
Sleep stage 1:	**Ratio sleep stage 1 /PTS (after sleep onset)**	**17.41 %**
	Latency stage 1 after lights off (hh:mm:ss)	00:31:30
Sleep stage 2:	**Ratio sleep stage 2 / PTS (after sleep onset)**	**34.47 %**
	Latency stage 2 after lights off (hh:mm:ss)	00:34:00
Sleep stage 3:	**Ratio sleep stage 3 /PTS (after sleep onset)**	**19.91 %**
	Latency stage 3 after lights off (hh:mm:ss)	00:42:00
Sleep stage 4:	**Ratio sleep stage 4 /PTS (after sleep onset)**	**1.14 %**
	Latency stage 4 after lights off (hh:mm:ss)	02:08:30
REM:	**Ratio REM / PTS (after sleep onset)**	**9.44 %**
	Total duration REM (hh:mm:ss)	00:41:30
	Latency REM after lights off (hh:mm:ss)	02:30:30
	Latency REM after 1. stage I (in min)	119

F – 1st night:

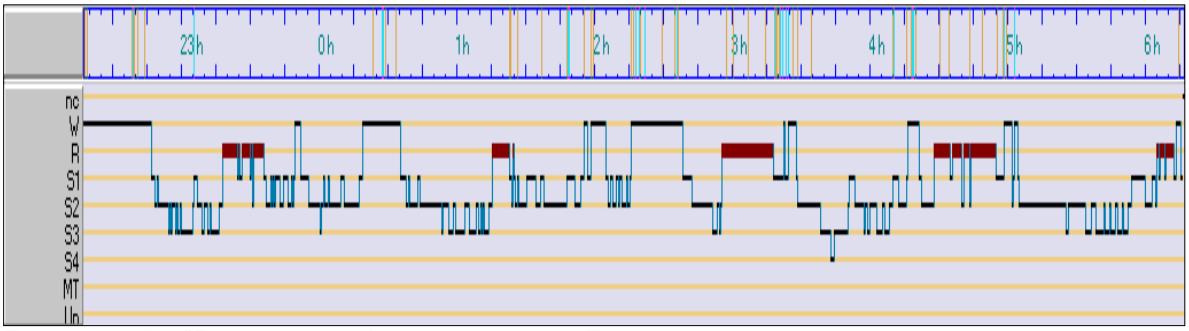

Figure 4.3.3.1.f: Hypnogram for 1st night for patient F

General Sleep parameters

TIB (hh:mm:ss)	08:00:00
TST (hh:mm:ss)	06:24:30
Standard PTS (hh:mm:ss)	07:28:30
Total duration of waking periods	01:35:30
Sleep efficiency index 1 (TST/TIB)	80.10
Amount of stage changes during TIB	181
Amount of stage changes during PTS	180
Fragmentation Index (Amount of Stage Changes / TIB)	22.63
Total REM (hh:mm:ss)	01:17:00
Total NREM (ST I + ST II + ST III + ST IV) (hh:mm:ss)	05:07:30
Duration Slow Wave Sleep Stage III + Stage IV (hh:mm:ss)	01:02:00
Latency between sleep onset and REM (hh:mm:ss)	00:29:30

Polysomnographic Analysis

Awake

The following calculations refer to waking periods after sleep onset (1. epoch stage 2)

Amount of waking periods in sleep (hh:mm:ss)		01:05:30
Sleep stage 1:	**Ratio sleep stage 1 /PTS (after sleep onset)**	**17.06 %**
	Latency stage 1 after lights off (hh:mm:ss)	00:30:00
Sleep stage 2:	**Ratio sleep stage 2 / PTS (after sleep onset)**	**37.68 %**
	Latency stage 2 after lights off (hh:mm:ss)	00:31:30
Sleep stage 3:	**Ratio sleep stage 3 /PTS (after sleep onset)**	**13.49 %**
	Latency stage 3 after lights off (hh:mm:ss)	00:37:30
Sleep stage 4:	**Ratio sleep stage 4 /PTS (after sleep onset)**	**0.33 %**
	Latency stage 4 after lights off (hh:mm:ss)	05:26:00
REM:	**Ratio REM / PTS (after sleep onset)**	**17.17 %**
	Total duration REM (hh:mm:ss)	01:17:00
	Latency REM after lights off (hh:mm:ss)	01:01:00
	Latency REM after 1. stage I (in min)	31

F – 2nd night:

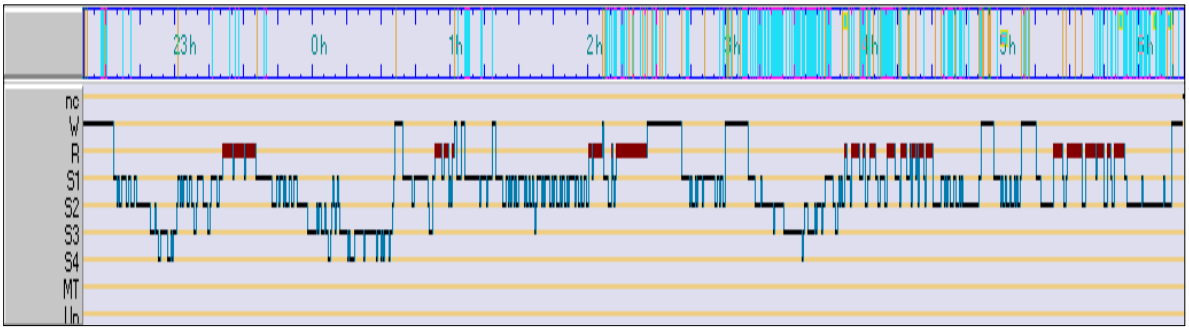

Figure 4.3.3.1.ff: Hypnogram for 2nd night for patient F

General Sleep parameters

TIB (hh:mm:ss)	08:00:00
TST (hh:mm:ss)	06:56:00
Standard PTS (hh:mm:ss)	07:39:30
Total duration of waking periods	01:04:00
Sleep efficiency index 1 (TST/TIB)	86.67
Amount of stage changes during TIB	286
Amount of stage changes during PTS	285
Fragmentation Index (Amount of Stage Changes / TIB)	35.75
Total REM (hh:mm:ss)	01:24:30
Total NREM (ST I + ST II + ST III + ST IV) (hh:mm:ss)	05:31:30
Duration Slow Wave Sleep Stage III + Stage IV (hh:mm:ss)	01:01:30
Latency between sleep onset and REM (hh:mm:ss)	00:46:00

Polysomnographic Analysis

Awake

The following calculations refer to waking periods after sleep onset (1. epoch stage 2)

Amount of waking periods in sleep (hh:mm:ss)		00:50:30
Sleep stage 1:	**Ratio sleep stage 1 /PTS (after sleep onset)**	**29.27 %**
	Latency stage 1 after lights off (hh:mm:ss)	00:13:30
Sleep stage 2:	**Ratio sleep stage 2 / PTS (after sleep onset)**	**29.49 %**
	Latency stage 2 after lights off (hh:mm:ss)	00:15:00
Sleep stage 3:	**Ratio sleep stage 3 /PTS (after sleep onset)**	**11.32 %**
	Latency stage 3 after lights off (hh:mm:ss)	00:29:30
Sleep stage 4:	**Ratio sleep stage 4 /PTS (after sleep onset)**	**2.07 %**
	Latency stage 4 after lights off (hh:mm:ss)	00:33:00
REM:	**Ratio REM / PTS (after sleep onset)**	**18.39 %**
	Total duration REM (hh:mm:ss)	01:24:30
	Latency REM after lights off (hh:mm:ss)	01:01:00
	Latency REM after 1. stage I (in min)	47

G – 1st night:

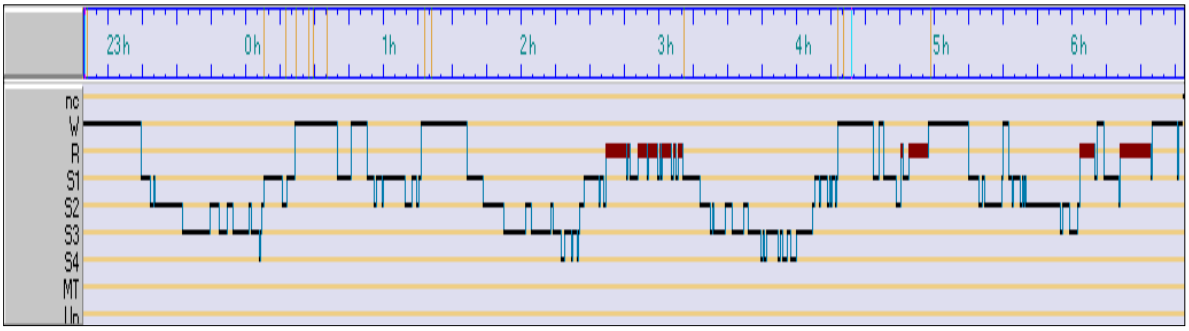

Figure 4.3.3.1.g: Hypnogram for 1st night for patient G

General Sleep parameters

TIB (hh:mm:ss)	08:00:00
TST (hh:mm:ss)	05:55:30
Standard PTS (hh:mm:ss)	07:30:30
Total duration of waking periods	02:04:30
Sleep efficiency index 1 (TST/TIB)	74.06
Amount of stage changes during TIB	131
Amount of stage changes during PTS	130
Fragmentation Index (Amount of Stage Changes / TIB)	16.38
Total REM (hh:mm:ss)	00:55:00
Total NREM (ST I + ST II + ST III + ST IV) (hh:mm:ss)	05:00:30
Duration Slow Wave Sleep Stage III + Stage IV (hh:mm:ss)	01:40:00
Latency between sleep onset and REM (hh:mm:ss)	03:18:30

Polysomnographic Analysis

Awake

The following calculations refer to waking periods after sleep onset (1. epoch stage 2)

Amount of waking periods in sleep (hh:mm:ss)		01:39:00
Sleep stage 1:	**Ratio sleep stage 1 /PTS (after sleep onset)**	**24.20 %**
	Latency stage 1 after lights off (hh:mm:ss)	00:25:30
Sleep stage 2:	**Ratio sleep stage 2 / PTS (after sleep onset)**	**20.31 %**
	Latency stage 2 after lights off (hh:mm:ss)	00:29:30
Sleep stage 3:	**Ratio sleep stage 3 /PTS (after sleep onset)**	**19.87 %**
	Latency stage 3 after lights off (hh:mm:ss)	00:43:30
Sleep stage 4:	**Ratio sleep stage 4 /PTS (after sleep onset)**	**2.33 %**
	Latency stage 4 after lights off (hh:mm:ss)	01:17:00
REM:	**Ratio REM / PTS (after sleep onset)**	**12.21 %**
	Total duration REM (hh:mm:ss)	00:55:00
	Latency REM after lights off (hh:mm:ss)	03:48:00
	Latency REM after 1. stage I (in min)	202

G – 2nd night:

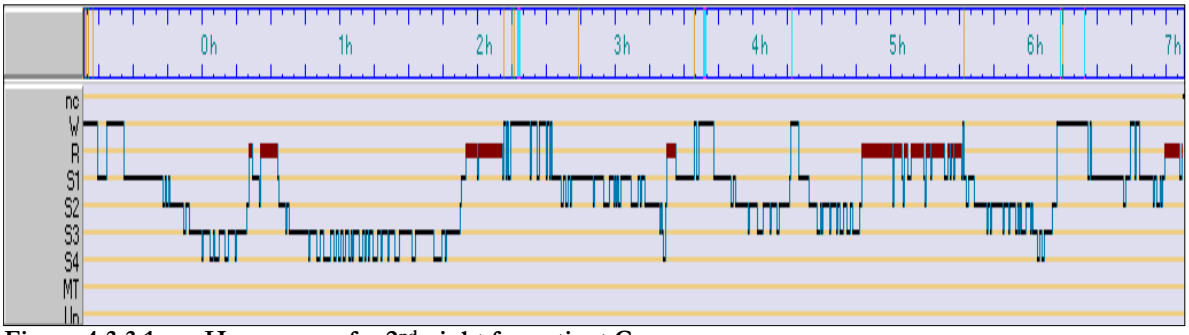

Figure 4.3.3.1.gg: Hypnogram for 2nd night for patient G

General Sleep parameters

TIB (hh:mm:ss)	08:00:00
TST (hh:mm:ss)	07:00:00
Standard PTS (hh:mm:ss)	07:25:00
Total duration of waking periods	01:00:00
Sleep efficiency index 1 (TST/TIB)	87.50
Amount of stage changes during TIB	215
Amount of stage changes during PTS	214
Fragmentation Index (Amount of Stage Changes / TIB)	26.88
Total REM (hh:mm:ss)	01:12:30
Total NREM (ST I + ST II + ST III + ST IV) (hh:mm:ss)	05:47:30
Duration Slow Wave Sleep Stage III + Stage IV (hh:mm:ss)	02:11:00
Latency between sleep onset and REM (hh:mm:ss)	00:37:30

Polysomnographic Analysis

Awake

The following calculations refer to waking periods after sleep onset (1. epoch stage 2)

Amount of waking periods in sleep (hh:mm:ss)		00:46:00
Sleep stage 1:	**Ratio sleep stage 1 /PTS (after sleep onset)**	**27.19 %**
	Latency stage 1 after lights off (hh:mm:ss)	00:06:30
Sleep stage 2:	**Ratio sleep stage 2 / PTS (after sleep onset)**	**21.46 %**
	Latency stage 2 after lights off (hh:mm:ss)	00:35:00
Sleep stage 3:	**Ratio sleep stage 3 /PTS (after sleep onset)**	**22.36 %**
	Latency stage 3 after lights off (hh:mm:ss)	00:44:00
Sleep stage 4:	**Ratio sleep stage 4 /PTS (after sleep onset)**	**7.08 %**
	Latency stage 4 after lights off (hh:mm:ss)	00:52:00
REM:	**Ratio REM / PTS (after sleep onset)**	**16.29 %**
	Total duration REM (hh :mm :ss)	01 :12 :30
	Latency REM after lights off (hh:mm:ss)	01:12:30
	Latency REM after 1. stage I (in min)	66

H – 1st night:

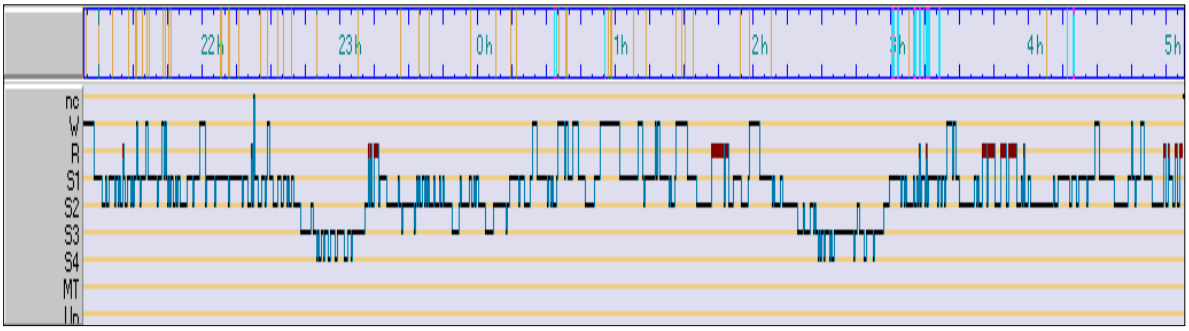

Figure 4.3.3.1.h: Hypnogram for 1st night for patient H

General Sleep parameters

TIB (hh:mm:ss)	08:00:00
TST (hh:mm:ss)	07:10:30
Standard PTS (hh:mm:ss)	07:51:30
Total duration of waking periods	00:49:00
Sleep efficiency index 1 (TST/TIB)	89.69
Amount of stage changes during TIB	286
Amount of stage changes during PTS	285
Fragmentation Index (Amount of Stage Changes / TIB)	35.75
Total REM (hh:mm:ss)	00:27:30
Total NREM (ST I + ST II + ST III + ST IV) (hh:mm:ss)	06:43:00
Duration Slow Wave Sleep Stage III + Stage IV (hh:mm:ss)	01:09:00
Latency between sleep onset and REM (hh:mm:ss)	00:09:00

Polysomnographic Analysis

Awake

The following calculations refer to waking periods after sleep onset (1. epoch stage 2)

Amount of waking periods in sleep (hh:mm:ss)		00:44:00
Sleep stage 1:	**Ratio sleep stage 1 /PTS (after sleep onset)**	**36.37 %**
	Latency stage 1 after lights off (hh:mm:ss)	00:05:00
Sleep stage 2:	**Ratio sleep stage 2 / PTS (after sleep onset)**	**34.46 %**
	Latency stage 2 after lights off (hh:mm:ss)	00:08:30
Sleep stage 3:	**Ratio sleep stage 3 /PTS (after sleep onset)**	**12.30 %**
	Latency stage 3 after lights off (hh:mm:ss)	01:35:00
Sleep stage 4:	**Ratio sleep stage 4 /PTS (after sleep onset)**	**2.33 %**
	Latency stage 4 after lights off (hh:mm:ss)	01:42:00
REM:	**Ratio REM / PTS (after sleep onset)**	**5.83 %**
	Total duration REM (hh:mm:ss)	00:27:30
	Latency REM after lights off (hh:mm:ss)	00:17:30
	Latency REM after 1. stage I (in min)	12

H – 2nd night:

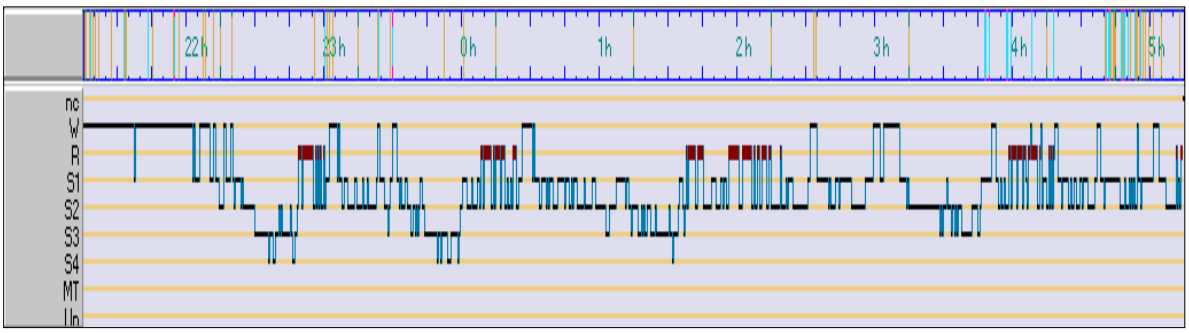

Figure 4.3.3.1.hh: Hypnogram for 2nd night for patient H

General Sleep parameters

TIB (hh:mm:ss)	08:00:00
TST (hh:mm:ss)	06:30:30
Standard PTS (hh:mm:ss)	07:00:30
Total duration of waking periods	01:29:30
Sleep efficiency index 1 (TST/TIB)	81.35
Amount of stage changes during TIB	298
Amount of stage changes during PTS	297
Fragmentation Index (Amount of Stage Changes / TIB)	37.25
Total REM (hh:mm:ss)	00:50:30
Total NREM (ST I + ST II + ST III + ST IV) (hh:mm:ss)	05:40:00
Duration Slow Wave Sleep Stage III + Stage IV (hh:mm:ss)	00:59:30
Latency between sleep onset and REM (hh:mm:ss)	00:34:30

Polysomnographic Analysis

Awake

The following calculations refer to waking periods after sleep onset (1. epoch stage 2)

Amount of waking periods in sleep (hh:mm:ss)		00:36:00
Sleep stage 1:	**Ratio sleep stage 1 /PTS (after sleep onset)**	**28.18 %**
	Latency stage 1 after lights off (hh:mm:ss)	00:22:30
Sleep stage 2:	**Ratio sleep stage 2 / PTS (after sleep onset)**	**38.53 %**
	Latency stage 2 after lights off (hh:mm:ss)	00:59:30
Sleep stage 3:	**Ratio sleep stage 3 /PTS (after sleep onset)**	**12.72 %**
	Latency stage 3 after lights off (hh:mm:ss)	01:15:00
Sleep stage 4:	**Ratio sleep stage 4 /PTS (after sleep onset)**	**1.43 %**
	Latency stage 4 after lights off (hh:mm:ss)	01:21:00
REM:	**Ratio REM / PTS (after sleep onset)**	**12.01 %**
	Total duration REM (hh:mm:ss)	00:50:30
	Latency REM after lights off (hh:mm:ss)	01:34:00
	Latency REM after 1. stage I (in min)	71

I – 1st night:

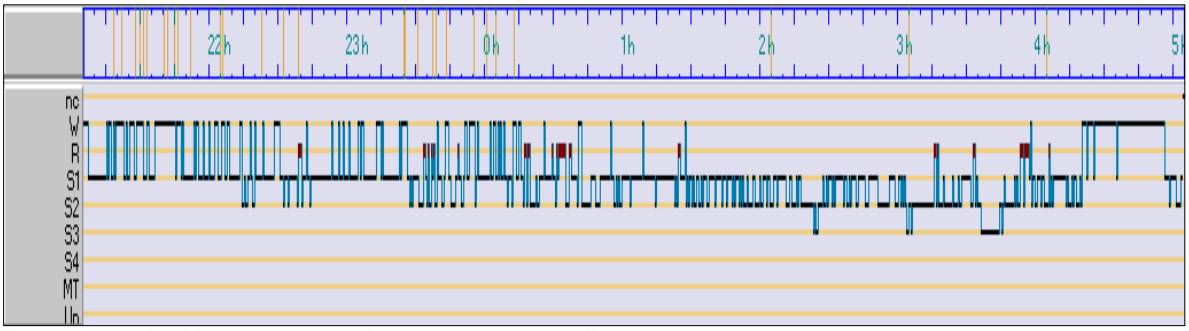

Figure 4.3.3.1.i: Hypnogram for 1st night for patient I

General Sleep parameters

TIB (hh:mm:ss)	08:00:00
TST (hh:mm:ss)	06:22:00
Standard PTS (hh:mm:ss)	06:50:00
Total duration of waking periods	01:38:00
Sleep efficiency index 1 (TST/TIB)	79.58
Amount of stage changes during TIB	329
Amount of stage changes during PTS	328
Fragmentation Index (Amount of Stage Changes / TIB)	41.13
Total REM (hh:mm:ss)	00:19:00
Total NREM (ST I + ST II + ST III + ST IV) (hh:mm:ss)	06:03:00
Duration Slow Wave Sleep Stage III + Stage IV (hh:mm:ss)	00:11:30
Latency between sleep onset and REM (hh:mm:ss)	00:24:30

Polysomnographic Analysis

Awake

The following calculations refer to waking periods after sleep onset (1. epoch stage 2)

Amount of waking periods in sleep (hh:mm:ss)		01:04:30
Sleep stage 1:	**Ratio sleep stage 1 /PTS (after sleep onset)**	**56.34 %**
	Latency stage 1 after lights off (hh:mm:ss)	00:02:30
Sleep stage 2:	**Ratio sleep stage 2 / PTS (after sleep onset)**	**29.39 %**
	Latency stage 2 after lights off (hh:mm:ss)	01:09:30
Sleep stage 3:	**Ratio sleep stage 3 /PTS (after sleep onset)**	**2.80 %**
	Latency stage 3 after lights off (hh:mm:ss)	05:18:30
Sleep stage 4:	**Ratio sleep stage 4 /PTS (after sleep onset)**	**0.00 %**
	Latency stage 4 after lights off (hh:mm:ss)	----------
REM:	**Ratio REM / PTS (after sleep onset)**	**4.63 %**
	Total duration REM (hh:mm:ss)	00:19:00
	Latency REM after lights off (hh:mm:ss)	01:34:00
	Latency REM after 1. stage I (in min)	91

I – 2nd night:

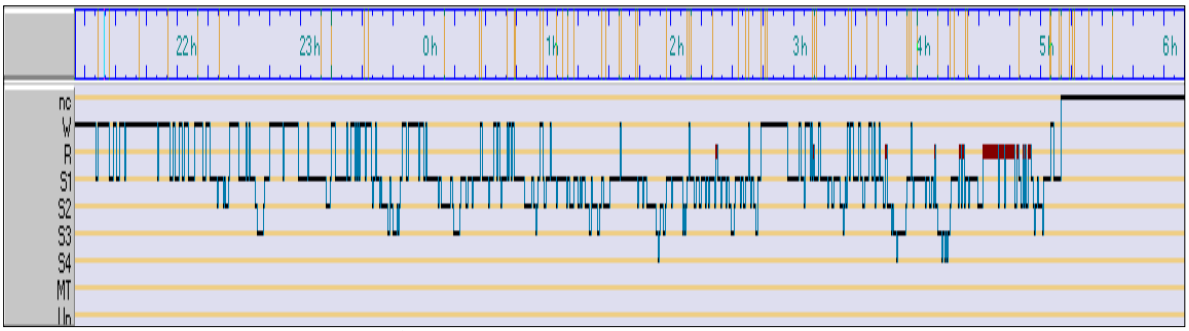

Figure 4.3.3.1.ii: Hypnogram for 2nd night for patient I

General Sleep parameters

TIB (hh:mm:ss)	08:00:00
TST (hh:mm:ss)	05:53:00
Standard PTS (hh:mm:ss)	06:50:30
Total duration of waking periods	01:07:00
Sleep efficiency index 1 (TST/TIB)	65.37
Amount of stage changes during TIB	295
Amount of stage changes during PTS	294
Fragmentation Index (Amount of Stage Changes / TIB)	32.78
Total REM (hh:mm:ss)	00:23:00
Total NREM (ST I + ST II + ST III + ST IV) (hh:mm:ss)	05:30:00
Duration Slow Wave Sleep Stage III + Stage IV (hh:mm:ss)	00:32:30
Latency between sleep onset and REM (hh:mm:ss)	04:02:30

Polysomnographic Analysis

Awake

The following calculations refer to waking periods after sleep onset (1. epoch stage 2)

Amount of waking periods in sleep (hh:mm:ss)		01:15:30
Sleep stage 1:	**Ratio sleep stage 1 /PTS (after sleep onset)**	**45.38 %**
	Latency stage 1 after lights off (hh:mm:ss)	00:10:30
Sleep stage 2:	**Ratio sleep stage 2 / PTS (after sleep onset)**	**17.85 %**
	Latency stage 2 after lights off (hh:mm:ss)	01:09:30
Sleep stage 3:	**Ratio sleep stage 3 /PTS (after sleep onset)**	**6.38 %**
	Latency stage 3 after lights off (hh:mm:ss)	01:29:00
Sleep stage 4:	**Ratio sleep stage 4 /PTS (after sleep onset)**	**0.53 %**
	Latency stage 4 after lights off (hh:mm:ss)	04:44:00
REM:	**Ratio REM / PTS (after sleep onset)**	**4.89 %**
	Total duration REM (hh:mm:ss)	00:23:00
	Latency REM after lights off (hh:mm:ss)	00:12:00
	Latency REM after 1. stage I (in min)	301

J – 1st night:

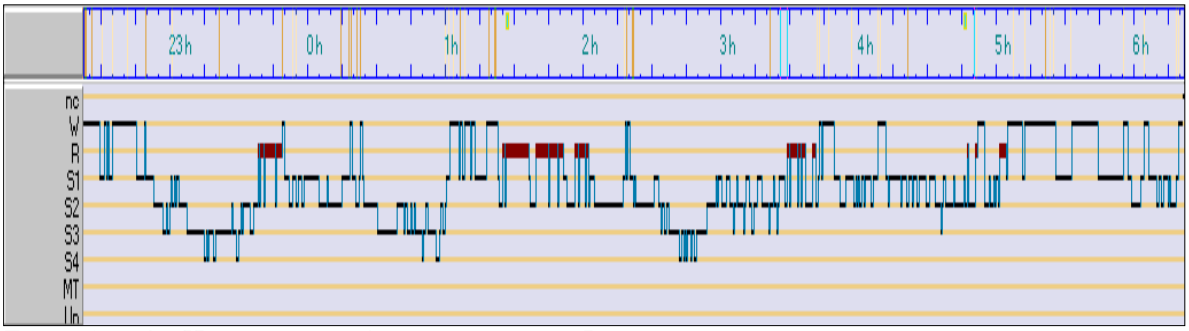

Figure 4.3.3.1.j: Hypnogram for 1st night for patient J

General Sleep parameters

TIB (hh:mm:ss)	08:00:00
TST (hh:mm:ss)	06:31:00
Standard PTS (hh:mm:ss)	07:26:30
Total duration of waking periods	01:29:00
Sleep efficiency index 1 (TST/TIB)	81.46
Amount of stage changes during TIB	249
Amount of stage changes during PTS	248
Fragmentation Index (Amount of Stage Changes / TIB)	31.13
Total REM (hh:mm:ss)	00:48:30
Total NREM (ST I + ST II + ST III + ST IV) (hh:mm:ss)	05:42:30
Duration Slow Wave Sleep Stage III + Stage IV (hh:mm:ss)	01:11:30
Latency between sleep onset and REM (hh:mm:ss)	00:45:30

Polysomnographic Analysis

Awake

The following calculations refer to waking periods after sleep onset (1. epoch stage 2)

Amount of waking periods in sleep (hh:mm:ss)		01:09:00
Sleep stage 1:	**Ratio sleep stage 1 /PTS (after sleep onset)**	**27.88 %**
	Latency stage 1 after lights off (hh:mm:ss)	00:07:30
Sleep stage 2:	**Ratio sleep stage 2 / PTS (after sleep onset)**	**32.81 %**
	Latency stage 2 after lights off (hh:mm:ss)	00:31:00
Sleep stage 3:	**Ratio sleep stage 3 /PTS (after sleep onset)**	**14.00 %**
	Latency stage 3 after lights off (hh:mm:ss)	00:35:00
Sleep stage 4:	**Ratio sleep stage 4 /PTS (after sleep onset)**	**2.02 %**
	Latency stage 4 after lights off (hh:mm:ss)	00:53:00
REM:	**Ratio REM / PTS (after sleep onset)**	**10.86 %**
	Total duration REM (hh:mm:ss)	00:48:30
	Latency REM after lights off (hh:mm:ss)	01:16:30
	Latency REM after 1. stage I (in min)	69

J – 2nd night:

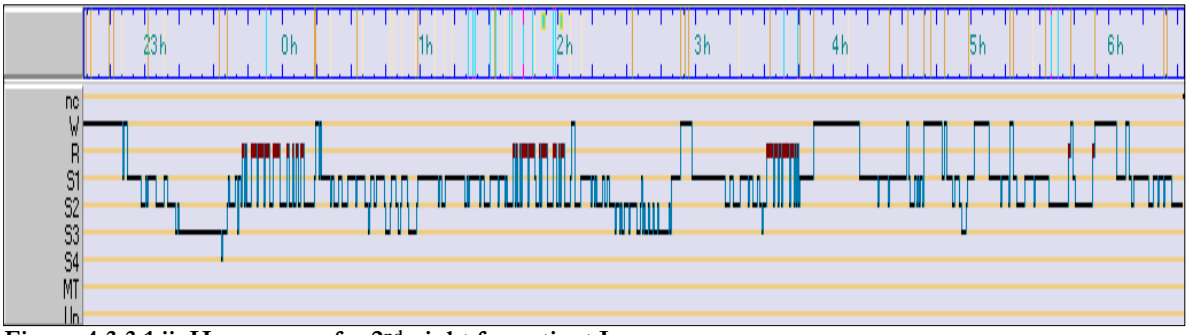

Figure 4.3.3.1.jj: Hypnogram for 2nd night for patient J

General Sleep parameters

TIB (hh:mm:ss)	08:00:00
TST (hh:mm:ss)	06:42:30
Standard PTS (hh:mm:ss)	07:34:30
Total duration of waking periods	01:17:30
Sleep efficiency index 1 (TST/TIB)	83.85
Amount of stage changes during TIB	232
Amount of stage changes during PTS	231
Fragmentation Index (Amount of Stage Changes / TIB)	29.00
Total REM (hh:mm:ss)	00:42:30
Total NREM (ST I + ST II + ST III + ST IV) (hh:mm:ss)	06:00:00
Duration Slow Wave Sleep Stage III + Stage IV (hh:mm:ss)	00:46:00
Latency between sleep onset and REM (hh:mm:ss)	00:44:00

Polysomnographic Analysis

Awake

The following calculations refer to waking periods after sleep onset (1. epoch stage 2)

Amount of waking periods in sleep (hh:mm:ss)		00:58:30
Sleep stage 1:	**Ratio sleep stage 1 /PTS (after sleep onset)**	**39.93 %**
	Latency stage 1 after lights off (hh:mm:ss)	00:17:30
Sleep stage 2:	**Ratio sleep stage 2 / PTS (after sleep onset)**	**29.15 %**
	Latency stage 2 after lights off (hh:mm:ss)	00:25:30
Sleep stage 3:	**Ratio sleep stage 3 /PTS (after sleep onset)**	**10.01 %**
	Latency stage 3 after lights off (hh:mm:ss)	00:40:30
Sleep stage 4:	**Ratio sleep stage 4 /PTS (after sleep onset)**	**0.11 %**
	Latency stage 4 after lights off (hh:mm:ss)	01:00:30
REM:	**Ratio REM / PTS (after sleep onset)**	**9.35 %**
	Total duration REM (hh:mm:ss)	00:42:30
	Latency REM after lights off (hh:mm:ss)	01:09:30
	Latency REM after 1. stage I (in min)	52

16.6 Consent Form (German)

SCHLAFSTUDIE

Veränderung des Schlafprofils und derAugenbewegungen

Während des REM[1] Schlafes bei Patienten mit amyotropher Lateralsklerose (ALS)

Sehr geehrte Dame, sehr geehrter Herr,

Wir möchten Sie gerne über unsere Schlafstudie informiern. Im folgenden warden die Methoden sowie der erwartete Nutzen und mögliche Risiken dieser Studie dargestellt.

Schlaf spielt eine wichtige Rolle bei der Regeneration unseres Gehirns und Körpers. Ein nicht intakter Schlaf kann diese wichtigen Mechanismen beeinträchtigen. Eine gute Schlafqualität ist unabdingbar für körperliche und geistige Leistungen und eine gute Lebensqualität.

Ziele und Nutzen der Untersuchung?

Das Ziel dieser Studie ist die Untersuchung des Schlafmusters bei 10 Patienten mit amyotroper Lateralsklerose (ALS). Mit dieser Studie soll untersucht warden, ob sich das Schlafprofil (Anteile des Tief-, Leicht- und REM-Schlafes innerhalb einer Nacht), v.a. der REM-Schlaf bei ALS Patienten verändert. Es gibt zwei ARten von Schlaf – rapid eye movement (REM) und non-REM. Diese Arten von Schlaf werden über ihre elektrophysiologischen Signale im EEG (Elektroenzephalografie, Aufzeichnung der elektrischen Aktivität im Gehirn) und dem EOG (Elektrookulogramm, Aufzeichnung der Augenbewegungen) unterschieden. REM Schlaf (auch aktiver oder paradoxer Schlaf genannt) ist durch eine dem Wachzustand ähnliche Aktivität im EEG gekennzeichnet. Im REM Stadium des Schlafes gibt es aber im Unterschied zum Wachzustand nur eine sehr geringfügige Muskelanspannung. Ein weiteres Unterscheidungsmerkmal sind starke Augenbewegungen (REM, rapid eye movements, schnelle Augenbewegungen) in diesem Stadium des Schlafes. Non-REM Schlaf (alle Schlafstadien, die nicht REM-Schlaf sind) wird in 4 Stufen eingeteilt, die sich in der Tiefe des Schlafes unterscheiden (Leichtschlaf als Stadium 1 und 2, Tiefschlaf als Stadium 3 und 4).

Viele ALS Patienten klagen über Schlafstörungen, Müdigkeit, Schläfrigkeit während des Tages oder Verschiebungen des Schlaf-Wach-Rhythmus. Zur Zeit weiβ man noch wenig über das Schlafprofil bei ALS Patienten, da dazu kaum Studien vorliegen. Störungen der willentlichen motorischen Kontrolle (Arm-, Beinbewegungen etc.) beeinträchtigen das Schlafprofil nicht. Eine genaue Kenntnis der Auswirkungen von ALS auf das Schlafprofil würde eine Behandlung zur Verbesserung der Schlafqualität ermöglichen und könnte damit auch zur Verbesserung der Lebensqualität beitragen.

Was ist eine "Polysomnografie"?

Die Registrierung verschiedener körperlicher Funktionen während des Schlafes ist ein ausgezeichnetes Hilfsmittel, um die Schlafqualität zu erheben und eventuelle Schlafstörungen oder Schlafbeeinträchtigungen zu diagnostizieren. Solche Störungen können die Ursache von starker Schläfrigkeit während des Tages sein. Während einer Schlafmessung werden nachts über die Dauer von 8 Stunden, entsprechend dem internationalen Standard für Schlafaufzeichnungen, verschiedene körperliche Funktionen wie die elektrische Aktivität des Gehirns (EEG), Herzrate, Augenbewegungen, Muskelaktivität, Atmung, und die Sauerstoffsättigung des Blutes erhoben, die wertvolle Informationen liefern.

Durchführung

Vor der eigentlichen Schlafaufzeichnung werden wir Sie bitten, verschiedene Fragebögen auszufüllen, damit wir uns von Ihnen und Ihren Schlafgewohnheiten bzw. –problemen ein möglichst umfassendes Bild machen können. Die nächtliche Schlafregistrierung (Polysomnografie) im Schlaflabor umfasst auch eine videografische Aufnahme, die Bewegung und die genaue Körperlage erfasst, um die erhobenen Daten eindeutig den Schlafstadien zuordnen zu können. Wir werden 4 Elektroden für das EEG (Elektroenzephalografie, Aufzeichnung der elektrischen Hirnaktivität), 2 Elektroden für das EOG (Elektrookulogramm, Aufzeichnung der Augenbewegungen), 3 Elektroden für das EMG (Elektromyogramm, Muskelaktivität, 3 Elektroden für das EKG (Elektrokardiogramm, Herzaktivität, 3flexible Brustgurte für die Atmung und Lage, je 1 Fingerclip für die Sauerstoffsättigung und den Puls anbringen.

Die Vorbereitung wird ca. 1 h dauern. Nach der 8-stündigen Aufzeichnung Ihres Schlafes werden während des Tages viermal in 2-stündigen Abständen zwei Tests durchgeführt. Damit untersuchen wir Ihre Tagesmüdigkeit und Aufmerksamkeit während des Tages. Wir werden Sie für 20 Minuten bitten, einzuschlafen oder wach zu bleiben. Die Messungen finden in der Klinik für die Dauer von 8 h statt und wrd in 3 aufeinanderfolgenden Nächten/Tagen durchgeführt.

Die Schlafregistrierung (Polysomnografie) als auch das EEG (Elektroenzephalografie; Ableitung der elektrischen Hirnaktivität) sind mit **keinerlei** Risiken oder Nebenwirkungen verbunden.

Nach erfolgter Messung erhalten Sie Informationen über Ihren Schlaf. Die Messergebnissen können auf Ihren Wunsch an das Schlaflabor der Neurologie der Universitätsklinik Tübingen weitergeleitet werden und somit unter ärztlicher Betreuung Ausgangspunkt für mögliche schlaftherapeutische Maβnahmen sein, bei denen wir Sie gerne unterstützen.

Die Daten Ihrer Polysomnografie (Schlafregistrierung) inkl. Videoaufzeichnung werden unter einem für Sie spezifischen Code für die Dauer der Studie archiviert (Ordner und CDs) und für die Auswertung am Institut für Medizinische Psychologie und Verhaltensneurobiologie aufbewahrt. Der Zugriff auf Ihre Daten ist auf die Durchführenden der Studie, Dipl. Psych. Mochty Ursula und Dr. Andrea Kübler, beschränkt.

Sie können die Teilnahme an der Studie jederzeit, auch während der Schlafmessung, ohne Angabe von Gründen abbrechen, ohne dass Ihnen dadurch Nachteile entstehen.

EINWILLIGUNGSERKLÄRUNG

Veränderung des Schlafprofils und der Augenbewegungen während des REM Schlafes bei Patienten mit amyotropher Lateralsklerose (ALS)

Mit dieser Unterschrift bestätige ich, über die Bedeutung der o. g. Studie aufgeklärt worden zu sein und dass die Teilnahme an dieser Studie mit *keinerlei* Risiken oder Nebenwirkungen verbunden ist. Ich nehme freiwillig an der Stude teil und bin darüber informiert worden, dass ich meine Teilnahme an der Untersuchung jederzeit und ohne weitere Angabe von Gründen abbrechen kann und mir daraus keine Nachteile entstehen werden. Meine Daten werden vertraulich behandelt und alle Mitarbeiter des Projektes stehen unter ärztlicher Schweigpflicht.

(Name des Teilnehmers / der Teilnehmerin), Geburtsdatum

Datum, Ort

Unterschrift des/r Teilnehmers/Teilnehmerin oder Bevollmächtigten (falls erforderlich)

EINWILLIGUNGSERKLÄRUNG

Veränderung des Schlafprofils und der Augenbewegunge während des REM Schlafes bei Patienten mit amyotropher Lateralsklerose (ALS) – Videoaufnahmen

Die nächtliche Schlafregistrierung (Polysomnografie) im Schlaflabor oder zu Hause umfasst auch eine videografische Aufnahme, die Bewegung und die genaue Körperlage erfasst. Diese Infrarot-Videgrafie arbeitet ohne Licht im Dunkeln und ist deshalb nicht störend.

Ich bin darüber informiert worden, dass die Aufnahmen ausschlieβlich innerhalb der Arbeitsgruppe zu Forschungszwecken verwendet werden. Ich weiβ, dass ich diese Einwilligung jederzeit zurückziehen kann. Sollte die Videoaufzeichnung im wissenschaftlichen Rahmen publiziert werden (ohne Publikation, Kongress), wird eine gesonderte Einwilligung von mir eingeholt.

(Name des Teilnehmers / der Teilnehmerin), Geburtsdatum

Datum, Ort

Unterschrift des/r Teilnehmer / Teilnehmerin oder Bevollmächtigten (falls erforderlich)

16.7 Questionnaires

A Das ALS-Depressionsinventar (ADI)

B Beck's Depression Inventory (BDI)

C Epworth Sleepiness Scale (ESS)

D The Parkinson's Disease Sleep Scale (PDSS)

E The Pittsburgh Sleep Quality Index (PSQI)

F Tübingen Sleep Questionnaire (Institute of Neurology)

A

Subject Code:_____

Date:_____

Session:_____

ALS-Depressionsinventar (ADI)

	Stimme voll zu	Stimme zu	Stimme nicht zu	Stimme überhaupt nicht zu
Ich fühle mich meistens leer.	1	2	3	4
Meistens bin ich traurig.	1	2	3	4
Ich kann das Leben den Umständen Entsprechend Genießen.	1	2	3	4
Es gibt nichts, worüber ich mich freuen oder was ich genießen kann.	1	2	3	4
Ich habe jedes Interesse für Familie und Freunde verloren.	1	2	3	4
Ich kann abschalten und bin oft entspannt.	1	2	3	4
Ich fühle mich lebendig und vital.	1	2	3	4
Ich fühle mich, als ob ich meine ganze Energie Verloren hätte.	1	2	3	4
Ich freue mich auf jeden neuen Tag.	1	2	3	4
Ich wünsche oft, tot zu sein.	1	2	3	4
Ich fühle mich oft verloren und aufgegeben und Weiß nicht, wie es weitergehen soll.	1	2	3	4
Ich bin glücklich und lache häufig.	1	2	3	4

B *Beck Depression Inventory*

Datum ☐☐ ☐☐ ☐☐ A ☐☐☐

Dieser Fragebogen enthält 21 Aussagen. Bitte lesen Sie jede Gruppe sorgfältig durch. Suchen Sie dann die eine Aussage in jeder Gruppe heraus, die am besten beschreibt, wie Sie sich in dieser Woche einschließlich heute gefühlt haben und kreuzen Sie die dazugehörige Ziffer (0, 1, 2, oder 3) an. Falls mehrere Aussagen einer Gruppe gleichermaßen zutreffen, können Sie auch mehrere Ziffern markieren. Lesen Sie auf jeden Fall alle Aussagen in jeder Gruppe, bevor Sie Ihre Wahl treffen.

A

0 Ich bin nicht traurig.
1 Ich bin traurig.
2 Ich bin die ganze Zeit traurig und komme nicht davon los.
3 Ich bin so traurig oder unglücklich, dass ich es kaum noch ertrage.

B

0 Ich sehe nicht besonders mutlos in die Zukunft.
1 Ich sehe mutlos in die Zukunft.
2 Ich habe nichts, worauf ich mich freuen kann.
3 Ich habe das Gefühl, dass die Zukunft hoffnungslos ist, und dass die Situation nicht besser werden kann.

C

0 Ich fühle mich nicht als Versager.
1 Ich habe das Gefühl, öfter versagt zu haben als der Durchschnitt.
2 Wenn ich auf mein Leben zurückblicke, sehe ich bloß eine Menge Fehlschläge.
3 Ich habe das Gefühl, als Mensch ein völliger Versager zu sein.

D

0 Ich kann die Dinge genauso genießen wie früher.
1 Ich kann die Dinge nicht mehr so genießen wie früher.
2 Ich kann aus nichts mehr eine echte Befriedigung ziehen.
3 Ich bin mit allem unzufrieden oder gelangweilt.

E

0 Ich habe keine Schuldgefühle.
1 Ich habe häufig Schuldgefühle.
2 Ich habe fast immer Schuldgefühle.
3 Ich habe immer Schuldgefühle.

F

0 Ich habe nicht das Gefühlt, gestraft zu sein.
1 Ich habe das Gefühl, vielleicht bestraft zu werden.
2 Ich erwarte, bestraft zu werden.
3 Ich habe das Gefühl, bestraft zu sein.

G

0 Ich bin nicht von mir enttäuscht.
1 Ich bin von mir enttäuscht.
2 Ich finde mich fürchterlich.
3 Ich hasse mich.

H

0 Ich habe nicht das Gefühl, schlechter zu sein als alle anderen.
1 Ich kritisiere mich wegen meiner Fehler und Schwächen.
2 Ich mache mir die ganze Zeit Vorwürfe wegen meiner Mängel.
3 Ich gebe mir für alles die Schuld, was schief geht.

I

0 Ich denke nicht daran, mir etwas anzutun.
1 Ich denke manchmal an Selbstmord, aber ich würde es nicht tun.
2 Ich möchte mich am liebsten umbringen.
3 Ich würde mich umbringen, wenn ich die Gelegenheit hätte.

J

0 Ich weine nicht öfter als früher.
1 Ich weine jetzt mehr als früher.
2 Ich weine jetzt die ganze Zeit.
3 Früher konnte ich weinen, aber jetzt kann ich es nicht mehr, obwohl ich es möchte.

Subtotal Seite 1_____

Fortsetzung auf der Rückseite

K

0 Ich bin nicht reizbarer als sonst.
1 Ich bin jetzt leichter verärgert oder gereizt als früher.
2 Ich fühle mich dauernd gereizt.
3 Die Dinge, die mich früher geärgert haben, berühren mich nicht mehr.

L

0 Ich habe nicht das Interesse an Menschen verloren.
1 Ich interessiere mich jetzt weniger für Menschen als früher.
2 Ich habe mein Interesse an anderen Menschen zum größten Teil verloren.
3 Ich habe mein ganzes Interesse an anderen Menschen verloren.

M

0 Ich bin so entschlußfreudig wie immer.
1 Ich schiebe Entscheidungen jetzt öfter als früher auf.
2 Es fällt mir jetzt schwerer als früher, Entscheidungen zu treffen.
3 Ich kann überhaupt keine Entscheidungen mehr treffen.

N

0 Ich habe nicht das Gefühl, schlechter auszusehen als früher.
1 Ich mache mir Sorgen, dass ich alt oder unattraktiv aussehe.
2 Ich habe das Gefühl, dass Veränderungen in meinem Aussehen eintreten, die mich hässlich machen.
3 Ich finde mich hässlich.

O

0 Ich kann so gut arbeiten wie früher.
1 Ich muß mir einen Ruck geben, bevor ich eine Tätigkeit in Angriff nehme.
2 Ich muß mich zu jeder Tätigkeit zwingen.
3 Ich bin unfähig zu arbeiten.

P

0 Ich schlafe so gut wie sonst.
1 Ich schlafe nicht mehr so gut wie früher.
2 Ich wache 1 bis 2 Stunden früher auf als sonst, und es fällt mir schwer, wieder einzuschlafen.
3 Ich wache mehrere Stunden früher auf als sonst und kann nicht mehr einschlafen.

Q

0 Ich ermüde nicht stärker als sonst.
1 Ich ermüde schneller als früher.
2 Fast alles ermüdet mich.
3 Ich bin zu müde, um etwas zu tun.

R

0 Mein Appetit ist nicht schlechter als sonst.
1 Mein Appetit ist nicht mehr so gut wie früher.
2 Mein Appetit hat sehr stark nachgelassen.
3 Ich habe überhaupt keinen Appetit mehr

S

0 Ich habe in letzter Zeit kaum abgenommen.
1 Ich habe mehr als 2 Kilo abgenommen.
2 Ich habe mehr als 5 Kilo abgenommen.
3 Ich habe mehr als 8 Kilo abgenommen.

Ich esse absichtlich weniger, um abzunehmen:
Ja Nein

T

0 Ich mache mir keine größeren Sorgen um meine Gesundheit als sonst.
1 Ich mache mir Sorgen über körperliche Probleme, wie Schmerzen, Magenbeschwerden oder Verstopfung.
2 Ich mache mir so große Sorgen über gesundheitliche Probleme, dass es mir schwer fällt, an etwas anderes zu denken.
3 Ich mache mir so große Sorgen über gesundheitliche Probleme, dass ich an nichts anderes mehr denken kann.

U

0 Ich habe in letzter Zeit keine Veränderungen meines Interesses an Sex bemerkt.
1 Ich interessiere mich weniger für Sex als früher.
2 Ich interessiere mich jetzt viel weniger für Sex als früher.
3 Ich habe das Interesse an Sex völlig verloren.

Subtotal Seite 2 _____

Subtotal Seite 1 _____

Summenwert _____

C Epworth Sleepiness Scale (included in F Tübingen Sleep Questionnaire, p.8 ff)

D The Parkinson's Disease Sleeping Scale (PDSS)

Subject Code:_____

Date:_____

Session:_____

Fragebogen zur Erfassung Schlafqualität (PDSS)

Wir möchten gerne wissen, wie Sie Ihren Schlaf der letzten Woche einschätzen. Dazu sehen Sie im folgenden einige Fragen. Wir würden Sie bitten, den entsprechenden Wert auf einer Skala von 1-10 anzugeben.

1. Wie schlafen Sie nachts im Allgemeinen?

Sehr schlecht ***Hervorragend***

1	2	3	4	5	6	7	8	9	10

	Immer								Nie
2. Haben Sie Probleme beim Einschlafen?	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
3. Spüren Sie in Ihren Beinen oder Armen nachts oder abends einen Bewegungsdrang, der Sie am Schlafen hindert?	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
4. Haben Sie Durchschlafstörungen?	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
5. Sind Sie im Bett unruhig?	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
6. Haben Sie nachts Träume, die Ihnen zu schaffen machen (Albträume)?	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**

	Immer									Nie
7. Haben Sie nachts Halluzinationen, die Sie beeinträchtigen? (Sehen oder hören Sie Dinge, die es nicht gibt?)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
8. Stehen Sie nachts auf, um Wasser zu lassen?	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
9. Kommen Sie nachts nicht rechtzeitig zur Toilette wegen Unbeweglichkeit?	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
10. Spüren Sie in Ihren Armen oder Beinen ein Taubheitsgefühl oder Kribbeln, wenn Sie nachts aufwachen?	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
11. Haben Sie schmerzhafte Muskelkrämpfe in Armen und Beinen, wenn Sie nachts aufwachen?	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
12. Wachen Sie sehr früh am Morgen auf mit Schmerzen in Armen und/oder Beinen?	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
13. Zittern Sie, wenn Sie aufwachen?	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
14. Fühlen Sie sich morgens nach dem Aufwachen müde und schläfrig?	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
15. Schlafen Sie tagsüber plötzlich ein?	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**

E

Schlafqualitäts-Fragebogen (PSQI)
(Pittsburg Sleep Quality Index)

Die folgenden Fragen beziehen sich auf Ihre üblichen Schlafgewohnheiten und zwar NUR *während der letzten vier Wochen.* Ihre Antworten sollten möglichst genau sein und sich auf die Mehrzahl der Tage und Nächte während der letzten vier Wochen beziehen. Beantworten Sie bitte alle Fragen.

1. Wann sind Sie während der letzten vier Wochen gewöhnlich abends zu Bett gegangen?

   Übliche Uhrzeit: .....

2. Wie lange hat es während der letzen vier Wochen gewöhnlich gedauert, bis Sie nachts eingeschlafen sind?

   In Minuten: .....

3. Wann sind Sie während der letzten vier Wochen gewöhnlich morgens aufgestanden?

   Übliche Uhrzeit: .....

4. Wieviele Stunden haben Sie während der letzten vier Wochen pro Nacht tatsächlich geschlafen? (Das muss nicht mit der Anzahl der Stunden, die Sie im Bett verbracht haben, übereinstimmen.)

   Effektive Schlafzeit (Stunden) pro Nacht: .....

Kreuzen Sie bitte für jede der folgenden Fragen die für Sie zutreffende Antwort an.
Beantworten Sie bitte ALLE Fragen.

5. Wie oft haben Sie während der letzten vier Wochen schlecht geschlafen, ...

a) weil Sie nicht innerhalb von 30 Minuten einschlafen konnten?

- □ Während der letzten vier Wochen gar nicht
- □ Weniger als einmal pro Woche
- □ Einmal oder zweimal pro Woche
- □ Dreimal oder häufiger pro Woche

b) weil Sie mitten in der Nacht oder früh morgens aufgewacht sind?

- □ Während der letzten vier Wochen gar nicht
- □ Weniger als einmal pro Woche
- □ Einmal oder zweimal pro Woche
- □ Dreimal oder häufiger pro Woche

c) weil Sie aufstehen mussten, um zur Toilette zu gehen?

- □ Während der letzten vier Wochen gar nicht
- □ Weniger als einmal pro Woche
- □ Einmal oder zweimal pro Woche
- □ Dreimal oder häufiger pro Woche

d) weil Sie Beschwerden beim Atmen hatten?

- □ Während der letzten vier Wochen gar nicht
- □ Weniger als einmal pro Woche
- □ Einmal oder zweimal pro Woche
- □ Dreimal oder häufiger pro Woche

e) weil Sie husten mussten oder laut geschnarcht haben?

- □ Während der letzten vier Wochen gar nicht
- □ Weniger als einmal pro Woche
- □ Einmal oder zweimal pro Woche
- □ Dreimal oder häufiger pro Woche

f) weil Ihnen zu kalt war?

- □ Während der letzten vier Wochen gar nicht
- □ Weniger als einmal pro Woche

- ☐ Einmal oder zweimal pro Woche
- ☐ Dreimal oder häufiger pro Woche

g) weil Ihnen zu warm war?

- ☐ Während der letzten vier Wochen gar nicht
- ☐ Weniger als einmal pro Woche
- ☐ Einmal oder zweimal pro Woche
- ☐ Dreimal oder häufiger pro Woche

h) weil Sie schlecht geträumt hatten?

- ☐ Während der letzten vier Wochen gar nicht
- ☐ Weniger als einmal pro Woche
- ☐ Einmal oder zweimal pro Woche
- ☐ Dreimal oder häufiger pro Woche

i) weil Sie Schmerzen hatten?

- ☐ Während der letzten vier Wochen gar nicht
- ☐ Weniger als einmal pro Woche
- ☐ Einmal oder zweimal pro Woche
- ☐ Dreimal oder häufiger pro Woche

j) aus anderen Gründen? Bitte beschreiben:

Und wie oft während des letzten Monats konnten Sie aus diesem Grund schlecht schlafen?

- ☐ Während der letzten vier Wochen gar nicht
- ☐ Weniger als einmal pro Woche
- ☐ Einmal oder zweimal pro Woche
- ☐ Dreimal oder häufiger pro Woche

6. Wie würden Sie insgesamt die Qualität Ihres Schlafes Ihres Schlafes während der letzten vier Wochen beurteilen?

- Sehr gut
- Ziemlich gut
- Ziemlich schlecht
- Sehr schlecht

7. Wie oft haben Sie während der letzten vier Wochen Schlafmittel eingenommen (vom Arzt verschriebene oder frei verkäufliche)?

- Während der letzten vier Wochen gar nicht
- Weniger als einmal pro Woche
- Einmal oder zweimal pro Woche
- Dreimal oder häufiger pro Woche

8. Wie oft hatten Sie während der letzten vier Wochen Schwierigkeiten wachzubleiben, etwa beim Autofahren, beim Essen oder bei gesellschaftlichen Anlässen?

- Während der letzten vier Wochen gar nicht
- Weniger als einmal pro Woche
- Einmal oder zweimal pro Woche
- Dreimal oder häufiger pro Woche

9. Hatten Sie während der letzten vier Wochen Probleme, mit genügend Schwung die üblichen Alltagsaufgaben zu erledigen?

- Keine Probleme
- Kaum Probleme
- Etwas Probleme
- Große Probleme

10. Schlafen Sie allein in Ihrem Zimmer?

- Ja
- Ja, aber ein Partner/Mitbewohner schläft in einem anderen Zimmer
- Nein, der Partner schläft im selben Zimmer, aber nicht im selben Bett
- Nein, der Partner schläft im selben Bett

11. Falls Sie einen Mitbewohner/Partner haben, fragen Sie sie/ihn bitte, ob und wie oft er/sie bei Ihnen folgendes bemerkt hat.

a) Lautes Schnarchen:

- ☐ Während der letzten vier Wochen gar nicht
- ☐ Weniger als einmal pro Woche
- ☐ Einmal oder zweimal pro Woche
- ☐ Dreimal oder häufiger pro Woche

b) Lange Atempausen während des Schlafes:

- ☐ Während der letzten vier Wochen gar nicht
- ☐ Weniger als einmal pro Woche
- ☐ Einmal oder zweimal pro Woche
- ☐ Dreimal oder häufiger pro Woche

c) Zucken oder ruckartige Bewegungen der Beine während des Schlafes:

- ☐ Während der letzten vier Wochen gar nicht
- ☐ Weniger als einmal pro Woche
- ☐ Einmal oder zweimal pro Woche
- ☐ Dreimal oder häufiger pro Woche

d) Nächtliche Phasen von Verwirrung oder Desorientierung während des Schlafes:

- ☐ Während der letzten vier Wochen gar nicht
- ☐ Weniger als einmal pro Woche
- ☐ Einmal oder zweimal pro Woche
- ☐ Dreimal oder häufiger pro Woche

e) Oder andere Formen von Unruhe während des Schlafes. Bitte beschreiben:

_____

_____

- ☐ Während der letzten vier Wochen gar nicht
- ☐ Weniger als einmal pro Woche
- ☐ Einmal oder zweimal pro Woche
- ☐ Dreimal oder häufiger pro Woche

Machen Sie bitte noch folgende Angaben zu Ihrer Person:

Vornahme/Code: *Alter:* ___ *Jahre*

Geschlecht: □ *weiblich* □ *männlich*

F Tübingen Sleep Questionnaire

Universitätsklinikum Tübingen

Neurologische Klinik

Zentrum für Neurologie

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Tübinger Schlaf-Fragebogen*

Damit wir uns von Ihnen und Ihren Schlafproblemen ein möglichst umfassendes Bild machen können, bitten wir Sie, den beiliegenden Schlaffragebogen genau und vollständig auszufüllen. Beachten Sie, dass Sie für die Beantwortung einiger Fragen die Hilfe Ihres Lebenspartners oder einer anderen Ihnen nahestehenden Person benötigen. Dieser Fragebogen wird streng vertraulich behandelt.

Grundsätzlich beziehen sich die Fragen auf die letzten 6 Monate.

Viele Fragen beginnen mit „Wie oft...?“, bei diesen Fragen sind 5 Antworten möglich. Wählen Sie die zutreffende:

Nie	selten (<1x/Monat)	manchmal (1-3x/Monat)	oft (1-2x/Woche)	fast immer

Name _____

Geburtsdatum_____

Heutiges Datum_____

---

*mit freundlicher Genehmigung von Prof. Dr. C. Bassetti, Schlaflabor Zürich

Allgemeines zum Schlaf

1. Um welche Zeit gehen Sie durchschnittlich zu Bett?

- während der Woche _____
- am Wochenende _____

2. Um welche Zeit erwachen Sie?

- während der Woche _____
- am Wochenende _____

3. Wieviele Stunden schlafen Sie ca. pro Nacht? _____

4. Wie oft schlafen Sie allein?

□ nie □ selten □ manchmal □ oft □ fast immer

5. Sind Sie ein □ Morgentyp □ Nachttyp □ weder noch

6. Schlafen Sie meist □ tief □ oberflächlich □ verschieden

7. Sind Ihre Schlafzeiten unregelmässig? □ Ja □ Nein

(Schwankungen der Bettzeit von 3-4 Stunden)

8. Haben Sie Schlafprobleme? □ Ja □ Nein

Welche?_____

9. Seit wie vielen Jahren haben Sie diese Schlafprobleme? _____

10. Bestand ein bestimmter Auslöser für diese Schlafprobleme? □ Ja □ Nein

11. Haben Sie versucht, Ihre Schlafprobleme zu behandeln? □ Ja □ Nein

Wie?_____

Einschlafen – Durchschlafen

12. Wie oft können Sie nicht einschlafen?

□ nie □ selten □ manchmal □ oft □ fast immer

13. Wie lange brauchen Sie im Durchschnitt zum Einschlafen (in Minuten)?

□ >40 □ 31-40 □ 21-30 □ 10-20 □ <10

14. Wie oft können Sie nicht durchschlafen?

□ nie □ selten □ manchmal □ oft □ fast immer

15. Wie viele Male wachen Sie im Durchschnitt pro Nacht auf? _____

16. Wie oft wachen Sie am Morgen früh auf?

□ nie □ selten □ manchmal □ oft □ fast immer

Atmung/Kreislauf

17. Wie oft schnarchen Sie?

□ nie □ selten □ manchmal □ oft □ fast immer

18. Wie oft schnarchen Sie laut und störend?

□ nie □ selten □ manchmal □ oft □ fast immer

19. Wie oft setzen Sie in der Nacht mit der Atmung aus?

□ nie □ selten □ manchmal □ oft □ fast immer

20. Wie oft sind Sie mit dem Gefühl der Atemnot oder der Beklemmung auf der Brust aufgewacht oder aufgeschreckt?

□ nie □ selten □ manchmal □ oft □ fast immer

21. Wie oft schwitzen Sie stark in der Nacht?

□ nie □ selten □ manchmal □ oft □ fast immer

22. Wie oft ist im Schlaf Ihre Nasenatmung blockiert?

□ nie □ selten □ manchmal □ oft □ fast immer

23. Haben Sie einen hohen Blutdruck?

□ Nein □ eher Nein □ weiß nicht □ eher Ja □ Ja

24. Ist Ihr Schnarchen lauter, wenn Sie auf dem Rücken schlafen?

□ Nein □ eher Nein □ weiß nicht □ eher Ja □ Ja

25. Ist Ihr Schnarchen lauter, wenn Sie Alkohol trinken?

□ Nein □ eher Nein □ weiß nicht □ eher Ja □ Ja

26. Ihr Gewicht ist jetzt (in kg): _____kg

□ <61 □ 61-72 □ 72-82 □ 82-94 □ > 94

27. Wie viele Jahre haben Sie geraucht? □ nie □ 1 □ 2-12 □ 13-25 □ >25

28. Ihr Alter: _____Jahre

29. Ihre Größe: _____cm

Parasomnien

30. Wie oft haben Sie ein Fuß-/Beinzittern beim Einschlafen?

□ nie □ selten □ manchmal □ oft □ fast immer

31. Wie oft merken Sie ein plötzliches, kurzes Zusammenzucken Ihres Körpers beim Einschlafen?

□ nie □ selten □ manchmal □ oft □ fast immer

32. Wie oft haben Sie Bewegungen oder Zuckungen von Armen und/oder Beinen während des Schlafes?

□ nie □ selten □ manchmal □ oft □ fast immer

33. Wie oft haben Sie während der Nacht Wadenkrämpfe oder andere Muskelkrämpfe? □ nie □ selten □ manchmal □ oft □ fast immer

34. Wie oft schlafwandeln Sie?

□ nie □ selten □ manchmal □ oft □ fast immer

35. Wie oft können Sie sich daran erinnern, was Sie beim Schlafwandeln gemacht haben?

□ nie □ selten □ manchmal □ oft □ fast immer

36. Wie oft haben Sie sich beim Schlafwandeln verletzt?

□ nie □ selten □ manchmal □ oft □ fast immer

37. Wie oft haben Sie als Kind schlafgewandelt?

□ nie □ selten □ manchmal □ oft □ fast immer

38. Wie oft stehen Sie im Schlaf auf, um etwas zu essen oder zu trinken?

□ nie □ selten □ manchmal □ oft □ fast immer

39. Wie oft sprechen Sie im Schlaf?

□ nie □ selten □ manchmal □ oft □ fast immer

40. Wie oft knirschen Sie nachts mit den Zähnen?

□ nie □ selten □ manchmal □ oft □ fast immer

41. Wie oft schreien Sie im Schlaf?

□ nie □ selten □ manchmal □ oft □ fast immer

42. Wie oft kommt es zu Beschimpfungen oder gar Gewalttätigkeiten im Schlaf (wie wen Träume ausagiert würden)?

□ nie □ selten □ manchmal □ oft □ fast immer

zum Beispiel: _____

43. Wie oft haben Sie ein unangenehmes brennendes, beissendes oder kribbelndes Gefühl in den Beinen, welches Sie zwingt, die Beine zu bewegen oder zu reiben?

□ nie □ selten □ manchmal □ oft □ fast immer

44. Mit wie vielen Jahren haben Sie Störungen erstmals bemerkt? _____

45. Wie oft fühlen haben Sie sich gelähmt (können Sie nichts bewegen)?

- beim Einschlafen □ nie □ selten □ manchmal □ oft □ fast immer

- im Schlaf □ nie □ selten □ manchmal □ oft □ fast immer

- beim Aufwachen □ nie □ selten □ manchmal □ oft □ fast immer

46. Hat das sonst jemand in der Familie? □ Ja □ weiß nicht □ Nein

47. Wie oft haben Sie traumähnliche Erlebnisse/Halluzinationen?

- beim Einschlafen □ nie □ selten □ manchmal □ oft □ fast immer

- beim Aufwachen □ nie □ selten □ manchmal □ oft □ fast immer

- am Tag(„Tagträume“) □ nie □ selten □ manchmal □ oft □ fast immer

Was?_____

48. Wie oft haben Sie den Eindruck/die Täuschung vor oder während des Einschlafens, dass sich jemand in Ihrem Zimmer befindet oder eindringen könnte?

- Jetzt □ nie □ selten □ manchmal □ oft □ fast immer

- Als Kind □ nie □ selten □ manchmal □ oft □ fast immer

49. Haben Sie dabei Angst?

□ nie □ selten □ manchmal □ oft □ fast immer

50. Wie oft träumen Sie?

□ nie □ selten □ manchmal □ oft □ fast immer

51. Wie oft träumen Sie von:

- Menschen □ nie □ selten □ manchmal □ oft □ fast immer

- Tieren □ nie □ selten □ manchmal □ oft □ fast immer

welche am häufigsten: _____

- ireelle Gestalten (z. B. Monster)

□ nie □ selten □ manchmal □ oft □ fast immer

52. Wie oft haben Sie Albträume, d.h. Angst- oder Horrorträume?

□ nie □ selten □ manchmal □ oft □ fast immer

53. Wie viele Male müssen Sie Wasserlassen pro Nacht? _____

54. Wie oft passiert es, dass Sie das Bett im Schlaf nässen?

□ nie □ selten □ manchmal □ oft □ fast immer

55. Mit wie vielen Jahren waren Sie nachts „trocken“? _____Jahre

Aufwachen

56. Wie wachen Sie am Morgen auf? □ Selbst □ Wecker □ Zweitperson

57. Wie oft schlafen Sie mehr als 10 Stunden pro Nacht?

□ nie □ selten □ manchmal □ oft □ fast immer

58. Wie oft fühlen Sie sich am Morgen schlecht/unausgeschlafen?

□ nie □ selten □ manchmal □ oft □ fast immer

59. wie oft haben Sie das Gefühl, dass Sie am Morgen nur langsam und unvollständig wach werden?

□ nie □ selten □ manchmal □ oft □ fast immer

60. Wie oft passiert es, dass Sie am Morgen verwirrt (wie betrunken) sind?

□ nie □ selten □ manchmal □ oft □ fast immer

Machen Sie ein Beispiel: _____

61. Wie viele Minuten brauchen Sie morgens, um in Gang zu kommen?

_____min

Müdigkeit/Schläfrigkeit

62. Wie oft fühlen Sie sich während des Tages müde (ohne Energie, erschöpft)?

□ nie □ selten □ manchmal □ oft □ fast immer

63. Wie oft schlafen Sie dabei ein?

□ nie □ selten □ manchmal □ oft □ fast immer

64. Wie oft fühlen Sie sich schläfrig (müssen gegen das Einnicken/Einschlafen kämpfen)?

□ nie □ selten □ manchmal □ oft □ fast immer

65. Wie oft machen Sie einen Mittagsschlaf/Nickerchen?

□ nie □ würde gerne, kann aber nicht □ 1-2x/Woche □ 3-5x/Wo □ fast tägl.

66. Glauben Sie eine abnorme Tagesschläfrigkeit zu haben?

□ sicher nicht □ eher nicht □ so-so □ eher Ja □ sicher Ja

67. Wie alt waren Sie, als Sie oder sonst jemand

die abnorme Tagesschläfrigkeit erstmals merkten? _____

68. Ist die Tagesschläfrigkeit jetzt stärker als damals?

□ sicher nicht □ eher nicht □ so-so □ eher Ja □ sicher Ja

69. Wie oft haben Sie Probleme in der Schule/bei der Arbeit wegen Müdigkeit/ Schläfrigkeit (gehabt)?

□ nie □ selten □ manchmal □ oft □ fast immer

70. Wie oft schlafen Sie ungewollt in diesen Situationen ein?

- Lesen □ nie □ selten □ manchmal □ oft □ fast immer

- Fahren (im Zug, als Beifahrer)

□ nie □ selten □ manchmal □ oft □ fast immer

- Stehen □ nie □ selten □ manchmal □ oft □ fast immer

- Essen □ nie □ selten □ manchmal □ oft □ fast immer

- Andere ungewöhnliche Situationen

□ nie □ selten □ manchmal □ oft □ fast immer

Beispiele: _____

71. Wie viele Male haben Sie schon Unfälle erlitten oder verursacht, weil Sie ungewollt eingeschlafen sind?

□ nie □ selten □ manchmal □ oft □ fast immer

Beispiele: _____

72. Wie oft passiert es, dass Sie Dinge tun, die keinen Sinn haben ? (Bsp: Salz in den Kaffee, unverständliches Schreiben, Fahren zum falschen Ort)?

□ nie □ selten □ manchmal □ oft □ fast immer

Beispiele: _____

Epworth Sleepiness Score

73. Wie oft passiert es, dass Sie in den folgenden Situationen einnicken oder einschlafen?

Wenn Sie gewisse Situationen nicht erlebt haben, versuchen Sie sich bitte vorzustellen wie es Ihnen dabei ergangen wäre. (0=nie 1=selten 2=gelegentlich 3=oft)

- Beim Lesen (sitzend) □ 0 □ 1 □ 2 □ 3
- Beim Fernsehen □ 0 □ 1 □ 2 □ 3
- An öffentlichem Ort inaktiv sitzend (z. B. Theater, Konferenz) □ 0 □ 1 □ 2 □ 3
- Als Beifahrer im Auto (>1 h ohne Unterbrechung) □ 0 □ 1 □ 2 □ 3
- Beim Hinlegen am Nachmittag □ 0 □ 1 □ 2 □ 3
- Sitzen und sich mit jemandem unterhalten □ 0 □ 1 □ 2 □ 3
- nach dem Mittagessen ruhig sitzend (ohne Alkohol) □ 0 □ 1 □ 2 □ 3
- in einem Auto, welches für einige Minuten im Verkehr stehengeblieben ist. □ 0 □ 1 □ 2 □ 3

Wird vom Arzt ausgefüllt

Epworth Sleepiness Score = _____ (0-24)

74. Einige Fragen zu Ihrer Tagesschläfrigkeit:

- Die Tagesschläfrigkeit ist unüberwindbar

□ nie □ selten □ manchmal □ oft □ fast immer

- Die Tagesschläfchen dauern kürzer als 1 Stunde

□ nie □ selten □ manchmal □ oft □ fast immer

- Die Tagesschläfchen werden durch Reize leicht beendet

□ nie □ selten □ manchmal □ oft □ fast immer

- Die Tagesschläfchen sind erfrischend/erholsam

□ nie □ selten □ manchmal □ oft □ fast immer

- Stimulantien (Ritalin, Teronac, ...) sind/waren hilfreich ?

□ sicher nicht □ nicht □ so-so □ Ja □ Ja, sehr

welches und in welcher Dosis: _____

wird vom Arzt ausgefüllt:

Classic Narcolepsy-Type EDS Score (Frage 74): _____ (0-1)

Kataplexie

75. Wie oft haben Sie eine der folgenden Beschwerden bei Emotionen wie Lachen, Freude oder Wut empfunden?

Weiche Knie/Knieschlottern □ nie □ selten □ manchmal □ oft □ fast immer

Absinken des Unterkiefers □ nie □ selten □ manchmal □ oft □ fast immer

Vorfallen des Kopfes □ nie □ selten □ manchmal □ oft □ fast immer

Sturz □ nie □ selten □ manchmal □ oft □ fast immer

Ullannllinna Narcolepsy Score (Summe Fragen 13, 65, 70 & 75) –11= __(0-44)

Wird vom Arzt ausgefüllt.

Wenn Sie nie solche Beschwerden haben, gehen Sie direkt zur Frage 79.

Wie häufig lösen folgende Gefühle bei Ihnen eine plötzliche Muskelschwäche aus?

Freude, Glück, Zufriedenheit □ nie □ selten □ manchmal □ oft □ fast immer

Zorn, Ärger, Aggression □ nie □ selten □ manchmal □ oft □ fast immer

Furcht, Angst, Verzweiflung □ nie □ selten □ manchmal □ oft □ fast immer

Ekel, Abneigung, Verachtung □ nie □ selten □ manchmal □ oft □ fast immer

Kummer, Trauer, Sorge □ nie □ selten □ manchmal □ oft □ fast immer

Überraschung, Verwunderung □ nie □ selten □ manchmal □ oft □ fast immer

Interesse, Spannung □ nie □ selten □ manchmal □ oft □ fast immer

Scham □ nie □ selten □ manchmal □ oft □ fast immer

Schuld □ nie □ selten □ manchmal □ oft □ fast immer

Geringschätzung □ nie □ selten □ manchmal □ oft □ fast immer

Stress □ nie □ selten □ manchmal □ oft □ fast immer

Verwirrung □ nie □ selten □ manchmal □ oft □ fast immer

76. Wie oft haben Sie bei Episoden plötzlicher Muskelschwäche (Frage 75):

Urin verloren □ nie □ selten □ manchmal □ oft □ fast immer

Das Bewusstsein verloren □ nie □ selten □ manchmal □ oft □ fast immer

Geträumt □ nie □ selten □ manchmal □ oft □ fast immer

Unwillkürliche Bewegungen (Zittern/Krampf) vom Gesicht

□ nie □ selten □ manchmal □ oft □ fast immer

unwillkürliche Bewegungen (Zittern/Krampf) von Arm oder Bein

□ nie □ selten □ manchmal □ oft □ fast immer

unangenehme Gefühle (Würgen im Hals, Atemnot, aufsteigende Wärme, Druck auf der Brust)

□ nie □ selten □ manchmal □ oft □ fast immer

anschliessend geschlafen □ nie □ selten □ manchmal □ oft □ fast immer

77. Wie oft haben Sie eine plötzliche Muskelschwäche (Frage 75) gehabt:

beim Weinen □ nie □ selten □ manchmal □ oft □ fast immer

bei Schmerzen □ nie □ selten □ manchmal □ oft □ fast immer

bei plötzlichem Lärm □ nie □ selten □ manchmal □ oft □ fast immer

bei Ungeduld □ nie □ selten □ manchmal □ oft □ fast immer

bei körperlicher Tätigkeit (Sport)

□ nie □ selten □ manchmal □ oft □ fast immer

wenn Sie gekitzelt werden □ nie □ selten □ manchmal □ oft □ fast immer

nur in einem Arm oder einem Bein

□ nie □ selten □ manchmal □ oft □ fast immer

beim Alkoholtrinken □ nie □ selten □ manchmal □ oft □ fast immer

wenn Sie allein sind □ nie □ selten □ manchmal □ oft □ fast immer

wenn Sie zusammen mit bekannten Personen sind

□ nie □ selten □ manchmal □ oft □ fast immer

wenn Sie zusammen mit fremden Personen sind

□ nie □ selten □ manchmal □ oft □ fast immer

wenn Sie zusammen mit einer bestimmten Person sind

□ nie □ selten □ manchmal □ oft □ fast immer

welcher? _____

ohne auslösende Emotion (spontan)

□ nie □ selten □ manchmal □ oft □ fast immer

über mehr als 10 Minuten □ nie □ selten □ manchmal □ oft □ fast immer

ohne sichtbaren Effekt □ nie □ selten □ manchmal □ oft □ fast immer

an Tagen, an denen Sie körperlich besonders hart gearbeitet haben

□ nie □ selten □ manchmal □ oft □ fast immer

an Tagen, an denen Sie besonders müde sind

□ nie □ selten □ manchmal □ oft □ fast immer

an Tagen, an welchen Sie lange auf ein bestimmtes Ereignis warten (Vorfreude, Spannung, etc.).

□ nie □ selten □ manchmal □ oft □ fast immer

an Tagen, an denen sowieso alles schief geht (negative Voreinstellung).

□ nie □ selten □ manchmal □ oft □ fast immer

78. Mit wie vielen Jahren haben Sie die erste Episode einer plötzlichen Muskelschwäche (Frage 75) gehabt? _____

Varia

79. Wie oft haben Sie Probleme, sich zu konzentrieren?

□ nie □ selten □ manchmal □ oft □ fast immer

80. Wie oft haben Sie Probleme mit Ihrem Gedächtnis?

□ nie □ selten □ manchmal □ oft □ fast immer

81. Wie oft fühlen Sie sich nervös, reizbar oder „gestresst"?

□ nie □ selten □ manchmal □ oft □ fast immer

82. Wie oft fühlen Sie sich deprimiert?

□ nie □ selten □ manchmal □ oft □ fast immer

83. Wie oft haben Sie Kopfschmerzen?

□ nie □ selten □ manchmal □ oft □ fast immer

84. Wie oft haben Sie kalte Hände oder ein „Sturmgefühl" beim schnellen Aufstehen?

□ nie □ selten □ manchmal □ oft □ fast immer

85. Gibt es Personen in Ihrer Familie, die eine der folgenden Schlafbeschwerden haben oder hatten?

Tagesschläfrigkeit □ Ja □ weiß nicht □ Nein

Plötzliche Muskelschwäche (Frage 75) □ Ja □ weiß nicht □ Nein

Schlaflosigkeit □ Ja □ weiß nicht □ Nein

Unruhige, beissende oder kribbelnde Beine (Frage 43)

□ Ja □ weiß nicht □ Nein

Schlafwandeln □ Ja □ weiß nicht □ Nein

Völlige Lähmung beim Einschlafen/Aufwachen (Frage 45)

□ Ja □ weiß nicht □ Nein

andere: _____

86. Nehmen Sie regelmässig Medikamente? □ Ja □ Nein

welche: _____

87. Wie oft nehmen Sie Schlafmittel)

□ nie □ selten □ manchmal □ oft □ fast immer

88. Trinken Sie Alkohol? □ Ja □ Nein

Was?_____

Wieviel (Gläser/Tag)? _____

89. Wieviel Tassen Kaffee oder Tee trinken Sie pro Tag? _____

90. Was arbeiten bzw. arbeiteten Sie? _____

91. Arbeiten Sie in Schicht? □ Ja □ Nein

92. Fahren Sie Auto? □ Ja □ Nein

Wieviele Km pro Jahr im Durchschnitt? _____

Wieviele Autounfälle (als Lenker hatten Sie im letzten Jahr? _____

In wie vielen Situationen kam es wegen Schläfrigkeit am Steuer fast zum Unfall? _____

Bemerkungen:

Träume

93. Wie häufig träumen Sie und erinnern sich an den Trauminhalt?

- fast jede Nacht mehrere Träume
- jede Nacht
- häufig, aber nicht jede Nacht
- hin und wieder
- selten
- nie

94. Wie häufig träumen Sie und erinnern sich nicht mehr an den Trauminhalt?

- fast jede Nacht mehrere Träume
- jede Nacht
- häufig, aber nicht jede Nacht
- hin und wieder
- selten
- nie

95. Wie häufig sind Träume, welche Sie nach dem Erwachen noch nachhaltig beschäftigen?

- fast jede Nacht mehrere Träume
- jede Nacht
- häufig, aber nicht jede Nacht
- hin und wieder
- selten
- nie

96. Wie häufig träumen Sie wiederholt den gleichen Traum?

□ fast jede Nacht mehrere Träume

□ jede Nacht

□ häufig, aber nicht jede Nacht

□ hin und wieder

□ selten

□ nie

97. Wie häufig haben Sie Träume, welche Sie bewusst steuern können?

□ nie □ selten □ manchmal □ oft □ fast immer

98. Wie häufig leiden Sie unter Gedankenjagen (Sorgen, Gedanken bei der Familie, Arbeit etc.) beim Einschlafen?

□ nie □ selten □ manchmal □ oft □ fast immer

99. Wie häufig kommt im Traum folgender Inhalt vor?

Monster (nicht existierende Lebewesen)

□ nie □ selten □ manchmal □ oft □ fast immer

bekannte/verwandte Personen

□ nie □ selten □ manchmal □ oft □ fast immer

unbekannte Personen □ nie □ selten □ manchmal □ oft □ fast immer

unbestimmte Personen □ nie □ selten □ manchmal □ oft □ fast immer

Sie fühlen sich wie gelähmt

□ nie □ selten □ manchmal □ oft □ fast immer

Sie haben Atemnot, können sich nicht bewegen, was große Angst verursacht.

□ nie □ selten □ manchmal □ oft □ fast immer

Ein Einbrecher oder sonst eine fremde Person ist in der Wohnung, im Zimmer.

□ nie □ selten □ manchmal □ oft □ fast immer

Sie fallen in einen tiefen Schacht.

□ nie □ selten □ manchmal □ oft □ fast immer

Sie können fliegen/schweben.

□ nie □ selten □ manchmal □ oft □ fast immer

Sie kriechen durch eine Röhre.

□ nie □ selten □ manchmal □ oft □ fast immer

Sie werden verfolgt. □ nie □ selten □ manchmal □ oft □ fast immer

100. Wie oft empfinden Sie in den Träumen auch Gefühle?

□ nie □ selten □ manchmal □ oft □ fast immer

Falls Sie die Frage 100 mit „nie" beantwortet haben, bitte weiter mit Frage 102.

101. Wie oft empfinden Sie in den Träumen folgende Gefühle?

Freude, Glück, Zufriedenheit □ nie □ selten □ manchmal □ oft □ fast immer

Zorn, Ärger, Aggression □ nie □ selten □ manchmal □ oft □ fast immer

Furcht, Angst, Verzweiflung □ nie □ selten □ manchmal □ oft □ fast immer

Ekel, Abneigung, Verachtung □ nie □ selten □ manchmal □ oft □ fast immer

Kummer, Trauer, Sorge □ nie □ selten □ manchmal □ oft □ fast immer

Überraschung, Verwunderung □ nie □ selten □ manchmal □ oft □ fast immer

Interesse, Spannung □ nie □ selten □ manchmal □ oft □ fast immer

Scham □ nie □ selten □ manchmal □ oft □ fast immer

Schuld □ nie □ selten □ manchmal □ oft □ fast immer

Geringschätzung □ nie □ selten □ manchmal □ oft □ fast immer

Stress □ nie □ selten □ manchmal □ oft □ fast immer

Verwirrung □ nie □ selten □ manchmal □ oft □ fast immer

102. Der Inhalt Ihrer Träume ist meistens:

□ realistisch □ teilweise realistisch □ ganz unrealistisch

103. Welche Aussagen treffen für Sie zu?

- An Tagen an denen ich viele plötzliche Muskelschwächen (Kataplexien, Frage 75) habe, träume ich nachts häufiger. □ Ja □ Nein

- An Tagen an denen ich viele plötzliche Muskelschwächen (Kataplexien, Frage 75) habe, weisen meine Träume einen anderen Inhalt auf.

□ Ja □ Nein

wenn Ja, inwiefern: _____

104. Verändern sich Ihre Träume, wenn Sie Medikamente nehmen?

□ Ja □ Nein

Wenn Ja, bei welchen Medikamenten: _____

Und in wiefern: _____

Für Frauen:

105. Während den vergangenen Schwangerschaften waren die Muskelschwäche-Attacken (Frage 75):

- viel weniger häufig/stark
- etwas weniger häufig/stark
- unverändert
- etwas häufiger/stärker
- viel häufiger/stärker

106. Während den vergangenen Schwangerschaften war die Tagesschläfrigkeit:

- viel weniger häufig/stark
- etwas weniger häufig/stark
- unverändert
- etwas häufiger/stärker
- viel häufiger/stärker

107. Jeweils während der Periode waren die Muskelschwäche-Attacken (Frage 75):

- viel weniger häufig/stark
- etwas weniger häufig/stark
- unverändert
- etwas häufiger/stärker
- viel häufiger/stärker

108. Jeweils während der Periode war die Tagesschläfrigkeit:

- ☐ viel weniger häufig/stark
- ☐ etwas weniger häufig/stark
- ☐ unverändert
- ☐ etwas häufiger/stärker
- ☐ viel häufiger/stärker

Bemerkungen:

Danke für Ihre Mitarbeit ☺

G

Fragebogen zum Chronotyp (D-MEQ)

Name(Code): .....

Wohnort: .....

Datum: .....

1. Bitte lesen Sie jede Frage sorgfältig durch, bevor Sie antworten.
2. Beantworten Sie bitte alle Fragen, auch dann, wenn Sie sich bei einer Frage unsicher sind.
3. Beantworten Sie die Fragen bitte in der vorgegebenen Reihenfolge.
4. Beantworten Sie die Fragen so schnell wie möglich. Es sind die ersten Reaktionen auf die Fragen, die uns mehr interessieren als eine lang überlegte Antwort.
5. Beantworten Sie jede Frage ehrlich. Es gibt keine richtige oder falsche Antwort.

Beantwortungsbeispiele

a) Um wie viel Uhr werden Sie abends müde und haben das Bedürfnis, schlafen zu gehen?
*Hier sind die **Zeitpunkte** gefragt. Kreuzen Sie bitte die für Sie zutreffende Zeit an. Z. B.,*

--/----------/----------/----X----/----------/----------/----------/----------/---
20 21 22 23 24 1 2 3

b) Wenn Sie um 23 Uhr zu Bett gehen sollten, wie müde wären Sie dann?
Kreuzen Sie bitte jeweils nur eine Antwortmöglichkeit an.

- ☐ Überhaupt nicht müde
- ☐ Ziemlich müde
- X ☐ Sehr müde

1. Wenn es nur nach Ihrem eigenen Wohlbefinden ginge und Sie Ihren Tag völlig frei einteilen könnten, wann würden Sie dann aufstehen?

--/----------/----------/----------/----------/----------/----------/----------/----------/----------/-
5 6 7 8 9 10 11 12 13 14

2. Wenn es nur nach Ihrem eigenen Wohlbefinden ginge und Sie Ihren Abend völlig frei gestalten könnten, wann würden Sie dann zu Bett gehen?

--/----------/----------/----------/----------/----------/----------/----------/----------/-
20 21 22 23 24 1 2 3 4

3. Wie sehr sind Sie von Ihrem Wecker abhängig, wenn Sie morgens zu einer bestimmten Zeit aufstehen müssen?

- Überhaupt nicht abhängig
- Etwas abhängig
- Ziemlich abhängig
- Sehr abhängig

4. Wie leicht fällt es Ihnen üblicherweise morgens aufzustehen?

- Überhaupt nicht leicht
- Nicht sehr leicht
- Ziemlich leicht
- Sehr leicht

5. Wie wach fühlen Sie sich morgens in der ersten halben Stunde nach dem Aufwachen?

- Überhaupt nicht wach
- Nicht sehr wach
- Ziemlich wach
- Sehr wach

6. Wie ist Ihr Appetit in der ersten halben Stunde nach dem Aufwachen?

- Sehr gering
- Ziemlich gering
- Ziemlich gut
- Sehr gut

7. Wie müde fühlen Sie sich morgens in der ersten halben Stunde nach dem Aufwachen?

□ Sehr müde
□ Ziemlich müde
□ Ziemlich frisch
□ Sehr frisch

8. Wenn Sie am folgenden Tag keinerlei Verpflichtungen haben, wann gehen Sie dann – verglichen mit Ihrer üblichen Schlafenszeit - zu Bett?

□ Selten oder nie später
□ Weniger als eine Stunde später
□ 1-2 Stunden später
□ Mehr als 2 Stunden später

9. Sie haben beschlossen, sich körperlich zu betätigen. Ein Freund rät Ihnen, zweimal wöchentlich eine Stunde zu trainieren; für ihn sei die beste Zeit zwischen 7 und 8 Uhr. Ausgehend von Ihrem eigenen Wohlbefinden, wie schätzen Sie Ihre Leistungsfähigkeit zu dieser Zeit ein?

□ Ich wäre gut in Form
□ Ich wäre ziemlich in Form
□ Es wäre ziemlich schwierig für mich
□ Es wäre sehr schwierig für mich

10. Um wie viel Uhr werden Sie abends müde und haben das Bedürfnis, schlafen zu gehen?

---/----------/----------/----------/----------/----------/----------/----------/----------/-
20 21 22 23 24 1 2 3 4

11. Sie möchten für einen 2-stündigen Test, von dem Sie wissen, dass er mental sehr beansprucht, in Bestform sein. Wenn es nur nach Ihrem eigenen Wohlbefinden ginge und wenn Sie Ihren Tag völlig frei einteilen könnten, welchen der vier Test-Zeiträume würden Sie wählen?

□ 8 -10 Uhr
□ 11-13 Uhr
□ 15-17 Uhr
□ 19-21 Uhr

12. Wenn Sie um 23 Uhr zu Bett gehen sollten, wie müde wären Sie dann?

- Überhaupt nicht müde
- Etwas müde
- Ziemlich müde
- Sehr müde

13. Aus irgendeinem Grund sind Sie einige Stunden später als gewöhnlich zu Bett gegangen. Es besteht jedoch keine Notwendigkeit, am nächsten Morgen zu einer bestimmten Zeit aufzustehen. Welcher der folgenden Fälle wird bei Ihnen am ehesten eintreten?

- Ich werde zur üblichen Zeit wach und schlafe nicht wieder ein
- Ich werde zur üblichen Zeit wach und döse danach noch ein wenig
- Ich werde zur üblichen Zeit wach, schlafe dann aber wieder ein
- Ich wache erst später als üblich auf

14. In einer Nacht müssen Sie für eine Nachtwache zwischen 4 und 6 Uhr wach sein. Am darauffolgenden Tag haben Sie keine weiteren Verpflichtungen. Welche der nachfolgenden Alternativen sagt Ihnen am ehesten zu?

- Ich werde erst nach der Nachtwache zu Bett zu gehen
- Ich werde vorher ein Nickerchen machen und nach der Nachtwache schlafen
- Ich werde vorher richtig schlafen und hinterher noch ein Nickerchen machen
- Ich werde nur vorher schlafen

15. Sie müssen zwei Stunden körperlich schwer arbeiten und können sich Ihren Tag völlig frei einteilen. Wenn es nur nach Ihrem eigenen Wohlbefinden ginge, welche der folgenden Zeiten würden Sie wählen?

- 8 -10 Uhr
- 11-13 Uhr
- 15-17 Uhr
- 19-21 Uhr

16. Sie haben sich zu einem anstrengenden körperlichen Training entschlossen. Ein Freund rät Ihnen, zweimal wöchentlich eine Stunde zu trainieren; für ihn sei die beste Zeit zwischen 22 und 23 Uhr. Ausgehend von Ihrem eigenen Wohlbefinden, wie schätzen Sie Ihre Leistungsfähigkeit zu dieser Zeit ein?

- Ich wäre gut in Form
- Ich wäre ziemlich in Form
- Es wäre ziemlich schwierig für mich
- Es wäre sehr schwierig für mich

17. Angenommen, Sie könnten Ihre Arbeitszeit frei wählen und Ihre Arbeitszeit beträgt 5 Stunden pro Tag (einschließlich der Pausen), die Tätigkeit ist interessant und wird nach Erfolg bezahlt. Welche 5 aufeinanderfolgenden Stunden würden Sie wählen?

24 1 2 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23

18. Zu welcher Tageszeit fühlen Sie sich Ihrer Meinung nach am besten? (**Bitte nur 1 Feld ankreuzen!)**

24 1 2 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23

19. Man spricht bei Menschen von „Morgen“- und „Abendtypen“. Zu welchem der folgenden Typen zählen Sie sich?

- □ Eindeutig „Morgentyp“
- □ Eher „Morgen“- als „Abendtyp“
- □ Eher „Abend“- als „Morgentyp“
- □ Eindeutig „Abendtyp“

Geschlecht: □ weiblich □ männlich

Alter: Jahre

16.8 Instruction P300

Aufmerksamkeit- und Informationsverarbeitungsprozesse während des Tages

Wir freuen uns über Ihre Teilnahme an diesem Experiment. Zu vier verschiedenen Test-Zeitpunkten werden wir den gleichen Versuch mit Ihnen machen, das heißt um 10 Uhr, 12 Uhr, 14 Uhr und 16 Uhr. Der Versuch dauert jedes Mal 20 min.

EEG-Ableitung

Zunächst werden wir werden Ihnen eine EEG-Kappe aufsetzen. Diese werden Sie den ganzen Tag aufbehalten. Dazu wird eine 16-Elektrodenkappe benutzt, die an Ihrem Kopf befestigt wird. Mit Hilfe dieser EEG-Kappe wird Ihr EEG, das heißt Ihre elektrische Gehirnaktivität, abgeleitet. Um die Leitfähigkeit zu verbessern, werden wir an den 16 Elektroden Gel verwenden und in die EEG-Kappe füllen. Daher werden Sie im Anschluss an den Versuch das Gel aus Ihren Haaren waschen müssen. Die EEG-Kappe selbst wird an einen Verstärker angeschlossen, um die EEG-Wellen sichtbar zu machen. Das Aufsetzen der Kappe und die Ableitung des EEGs sind für Sie völlig ungefährlich. Der Aufbau des Systems und das Anschließen werden ca. 45 Minuten betragen.

Versuchs-Ablauf:

Bitte setzen Sie sich ruhig und entspannt vor den Bildschirm. Überkreuzen Sie bitte weder Beine noch Arme, versuchen Sie auch Ihre Gesichtsmuskulatur zu entspannen und sich auf die Mitte des
Bildschirms zu konzentrieren. Bitte auch während des Versuchs nicht sprechen.

Der Versuch besteht aus 3 Teilen und dauert in Summe 12 Minuten je Messzeitpunkt. Zwischen den 3 Aufgaben haben Sie die Möglichkeit zu einer kurzen Pause von etwa 2 Minuten, in der Sie sich kurz stricken oder bewegen können.

Im 1. Teil werden wir für 4 Minuten Ihr Ruhe-EEG erheben, d.h. wir werden Sie bitten, für 4 Minuten entspannt auf einen blauen Kreis am Bildschirm zu schauen.

Im 2. Teil des Experiments beginnen wir mit der auditorischen Aufmerksamkeitstestung. Wir werden Sie bitten, sich auf ein Kreuz in der Mitte des Bildschirms zu konzentrieren. Während der 4 Minuten des Versuchs werden Sie Töne aus den Lautsprechern links und rechts von Ihnen hören. Es wird sich um tiefe und leicht höhere Töne handeln. Bitte zählen Sie nur die Anzahl der höheren Töne und teilen Sie uns das Ergebnis am Ende mit.

Im 3. Teil werden wir Ihre Aufmerksamkeit visuell testen. In diesem Teil des Versuchs werden Ihnen schnell nacheinander auf dem Bildschirm die Buchstaben „H" und „S" in zufälliger Reihenfolge dargeboten. Ihre Aufgabe ist es nun, zu zählen, wie oft der Buchstabe „S" auftaucht. Bitte teilen Sie uns auch hier wieder das Ergebnis am Ende des Versuchs mit. Dieser Ablauf des Versuchs bleibt gleich für alle weiteren Messzeitpunkte um 12 Uhr, 14 Uhr und zuletzt 16 Uhr.

Haben Sie noch Fragen?

16.9 CONSENT FORM P300 (GERMAN)

Einwilligungserklärung

Aufmerksamkeit- und Informationsverarbeitungsprozesse während des Tages. Mit dieser Unterschrift bestätige ich, über die Bedeutung der o. g. Studie aufgeklärt worden zu sein und dass die Teilnahme an dieser Studie mit *keinerlei* Risiken oder Nebenwirkungen verbunden ist. Ich nehme freiwillig an der Studie teil und bin darüber informiert worden, dass ich meine Teilnahme an der Untersuchung jederzeit und ohne weitere Angabe von Gründen abbrechen kann und mir daraus keine Nachteile entstehen werden. Meine Daten werden vertraulich behandelt und alle Mitarbeiter des Projektes stehen unter der ärztlichen Schweigepflicht.

(Name des Teilnehmers / der Teilnehmerin), Geburtsdatum

Datum, Ort

Unterschrift des/r Teilnehmers/Teilnehmerin

Bei weiteren Fragen wenden Sie sich bitte an:
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16.10 PROTOCOL P300

Time	Versuchsperson:	P300	Nr.	ok
10:00	Run 1	Baseline	001	
	Run 2	Auditiv	001	
	Run 3	Visuell	001	
12:00	Run 4	Baseline	002	
	Run 5	Auditiv	002	
	Run 6	Visuell	002	
14:00	Run 7	Baseline	003	
	Run 8	Auditiv	003	
	Run 9	Visuell	003	
16:00	Run 10	Baseline	004	
	Run 11	Auditiv	004	
	Run 12	Visuell	004	

Acknowledgements

My PhD - my personal odyssey or me, as Sindbad of the Seven Seas. I am at the end of a very long journey through five countries, counted 32 (!) relocations within and between these coasts, different lives and relationships, life choices and "seven bridges" ("Über sieben Brücken musst du gehen", Peter Maffay) I had to cross. Now that I find words to capture my experiences, I know I have reached the finish line and the point to let go of those years of emotional growth. I am a different person now, yet oddly the same. I have returned to where I left to find the treasures I was seeking ("The Alchemist", Paolo Coehlo).

I would like to thank Jonathan Wolpaw, and in particular Theresa Vaughan, who enabled me to start this PhD not only by financing but through lovingly pushing me towards pursuing this route when I was still at Master's level. Prof. Andrea Kübler I would like to thank for her patience and support, opening up all the important venues and having made this research possible at all. I would like to thank Allan Hobson, MD, for his mischievousness and tremendous knowledge which made sleep research fun. Thank you to Prof. Niels Birbaumer who supported this research with his expertise and institute. A special thank you I would like to say to my participating patients. They taught me mindfulness, the importance of family and love, and showed me by example how courage can conquer all.

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Ursula Mochty

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