Department of Physics
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SACCADIC EYE MOVEMENTS

ESTIMATE PROLONGED TIME AWAKE

Kati Pettersson

ACADEMIC DISSERTATION

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Cover art: Fit of S (sleep pressure) and C (circadian rhythm) -component of the three-process model of alertness (gray solid line) and S -component (black solid line) with 95% confidence levels (dashed lines). Measured data with (gray circles) and without (black circles) C -component.

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ABSTRACT

Prolonged time awake increases sleep drive and causes sleepiness. Increasing sleep drive induces rapid and uncontrolled sleep initiation leading to unstable cognitive performance which is comparable to alcohol intoxication. Sleepiness causes 10 – 20 % of traffic accidents hence being a major identifiable and preventable cause of accidents. Even though the severeness of sleepiness -related accidents and hazards have been recognized and the state of New Jersey (USA) even has a law that forbids driving after being awake for more than 24 h, there is no reliable on-site test for estimating total time awake of a person.

A reliable, objective, and practical metrics for measuring sleepiness outside the laboratory would be valuable. This thesis presents a novel approach and examines whether an eye movement based metric could serve as an on-site test metric for time awake.

The rationale for the studying the use of eye movements to estimate overall time awake is as follows: Different cognitive functions, especially attentional ones are vulnerable to sleepiness. The attentional and oculomotor processes share neuroanatomical networks in the brain and saccadic eye movements have been used to study attentional functions. Moreover, saccadic eye movements are sensitive to sleepiness.

The thesis consists of two parts: 1) Algorithm development for electro-oculographic (EOG) feature extraction to enable effective and practical analyses of measurements conducted outside the laboratory, and 2) Development of an eye movement based metric to estimate prolonged time awake.

Saccadic eye movements were measured from eleven healthy adults every sixth hour with EOG in a 8-minute saccade task during 60 h of prolonged time awake. The saccade task performance, estimated as the number of saccades, decreased as a function of time awake on an individual level. The saccadic performance differed between the participants but was stable within participants (tested with 5 participants). The circadian rhythm affected the saccade task performance. Thus, the three-process model of alertness (TPMA) was fitted to, and the circadian component (C-component) was removed from, the measured data. After removing the C-component, the linear model revealed a significant trend for six out of eleven participants.

The results imply that saccades measured with EOG could be used as a time awake metric outside the laboratory. The metric needs individual calibration before the time awake of a person can be estimated. More research is needed to study individual differences, optimize the measurement duration, and stimulus parameters.

TIIVISTELMÄ

Pitkittynyt hereilläoloaika lisää unipainetta ja siten väsymystä. Kasvava unen tarve aiheuttaa kontrolloimattomia torkahduksia, jotka heikentävät merkittävästi ihmisen tarkkaavuutta ja siten kognitiivisia toimintoja. Univajeen aiheuttama epävakaa tila on verrattavissa humalatilaan. Liikenneonnettomuuksista 10 – 20 % on väsymyksen aiheuttamia. Väsymys on näin ollen yksi suurimmista tunnetuista, estettävissä olevista onnettomuuksien syistä.

Väsymyksestä johtuvien onnettomuuksien ja katastrofien vakavuus on tunnistettu; mm. New Jerseyssä (Yhdysvallat) on säädetty laki, joka kieltää ajamisen yli 24 tunnin hereilläoloajan jälkeen. Mittalaitetta, jolla kenttäolosuhteissa pystytään mittaamaan luotettavasti, objektiivisesti ja käytännöllisesti kuljettajan hereilläolon kokonaisaikaa ei kuitenkaan ole tällä hetkellä saatavilla.

Tässä väitöskirjassa on kehitetty silmänliikkeisiin perustuva mittausmenetelmä, jonka avulla voidaan mitata hereilläoloaikaa laboratorion kenttäolosuhteissa, laboratorion ulkopuolella. Univajeessa kognitiiviset toiminnot heikkenevät, erityisesti tarkkaavuus sekä visuaalinen, silmänliikkeiden avulla tapahtuva ympäristön havainnointi. Tarkkaavuutta ja okulomotorisia toimintoja säätelevät osittain samat aivojen otsalohkoalueiden hermoverkot. Tästä syystä sakkadisia silmänliikkeitä voidaan käyttää sekä tarkkaavuuden että univajeen ja väsymyksen tutkimiseen.

Väitöskirja koostuu kahdesta osiosta: 1) Algoritmikehitystyöstä silmänliikkeiden tunnistamiseksi luotettavasti kenttäolosuhteissa silmänliikesignaalista, 2) Silmänliikepohjaisen menetelmän kehittäminen hereilläoloajan estimointiin.

Sakkadisia silmänliikkeitä mitattiin yhdeltätoista terveeltä aikuiselta kuuden tunnin välein 60 tunnin yhtäjaksoisen univajeen aikana. Silmänliikkeet rekisteröitiin elektro-okulografia (EOG) -menetelmällä 8 minuuttia kestävän sakkaditestin aikana. Tehtävässä suoriutumista arvioitiin sen aikana suoritettujen sakkadien lukumäärällä. Sakkadien lukumäärä laski hereilläoloajan funktiona kaikilla tutkittavilla. Sakkaditehtävässä suoriutuminen vaihteli henkilöiden välillä. Testin toistettavuutta tutkittiin viidellä henkilöllä ja se todettiin toistettavaksi. Vuorokaudenaika vaikutti tehtävässä suoriutumiseen ja tästä syystä vuorokausivaihteluun liittyvä sirkadiaaninen rytmi poistettiin vireystilaa mallintavan mallin avulla (three-process model of alertness, TPMA). Sirkadiaanisen rytmin poistamisen jälkeen sakkadien lukumäärän lasku hereilläoloajan funktiona oli lineaarinen kuudella tutkimushenkilöllä yhdestätoista.

Väitöskirjassa esitettyjen tulosten perusteella EOG-menetelmällä mitattujen silmänliikeiden avulla voidaan estimoida hereilläoloaikaa kenttäolosuhteissa. Tällä hetkellä mittaus vaatii henkilökohtaisen kalibrointimittauksen ennen varsinaista testimittausta. Lisää tutkimustyötä tarvitaan henkilöiden yksilöllisten erojen tutkimiseen, sekä mittausasetelman optimointiin kenttäolosuhteisiin laajemmin sopivaksi.

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Espoo, 17.8.2018
Kati Pettersson

CONTENTS

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:

I **Hirvonen K**, Puttonen S, Gould KS, Koefoed VF, Korpela J, Müller K. Improving the saccade peak velocity measurement for detecting fatigue. Journal of Neuroscience Methods, 2010; 187: 199-206.

II **Pettersson**[1] **K**, Jagadeesan S, Lukander K, Henelius A, Hæggström E, Müller K. Algorithm for automatic analysis of electro-oculographic data. Biomedical engineering online, 2013; 12(1), 110.

III **Pettersson K**, Müller K, Tietäväinen A, Gould K, Hæggström E. Saccadic eye movements estimate prolonged time awake. Journal of Sleep Research [*in press*].

IV Toivanen M, **Pettersson K**, Lukander K. A probabilistic real-time algorithm for detecting blinks, saccades, and fixations from EOG data. Journal of Eye Movement Research, 2015; 8(2):1, 1-14.

The publications are referred to in the text by their roman numerals.

1 Née Hirvonen

ABBREVIATIONS

AC	Alternating current
BAC	Blood alcohol concentration
C-component	Circadian component
DC	Direct current
EEG	Electroencephalography
EOG	Electro-oculography
EOG_D	Lower eye electrode
EOG_h	Horizontal EOG signal
EOG_{h_diff}	Horizontal eye velocity signal
EOG_L	Left eye electrode
EOG_R	Right eye electrode
EOG_U	Upper eye electrode
EOG_v	Vertical EOG signal
EOG_{v_diff}	Vertical eye velocity signal
FEF	Frontal eye fields
FIT	Fitness Impairment Tester
fMRI	Functional Magnetic Resonance Imaging
IPS	Intraparietal sulcus
IROG	Infrared-oculography
KSS	Karolinska Sleepiness Scale
M2	Left mastoid
MSLT	Multiple Sleep Latency Test
PET	Positron Emission Tomography
PPV	Positive predictive values, precision
PVT	Psychomotor Vigilance Task
REM	Rapid eye movements
RNoN	Royal Norwegian Navy
S-component	Sleep pressure (homeostatic)
SC	Superior colliculus
SCN	Suprachiasmatic nuclei
SEM	Slow eye movements
SPV	Saccadic peak velocity
SPV/D	Index, that describes the shape of saccade velocity curve
TBS	Time between saccades
TPJ	Temporoparietal junction
TPMA	Three-process model of alertness
TPR	True positive rates, sensitivity
VFC	Ventral frontal cortex
VOG	Video-oculography
W-component	Sleep inertia

1 INTRODUCTION

This chapter addresses safety risks and consequences associated with sleepiness. It indicates the need for a reliable metric to quantify sleepiness. Finally, the publications that form the basis for this thesis are summarized.

Sleep is crucial for physical and mental health in humans [1–4]. During the waking hours human alertness and performance is influenced by both homeostatic sleep pressure and endogenous oscillation called the circadian rhythm [3, 5–7]. Prolonged time awake increases sleep pressure (the need to sleep), and a person falls asleep when the sleep pressure exceeds a certain threshold [7, 8]. In this thesis term *time awake* denotes the amount of time that a person has been awake after waking up from sleep. Sleep reduces the sleep pressure; the longer a person has been asleep the higher is the likelihood of waking up. Sleepiness refers to instability in the sleep/wake regulation caused by e.g. prolonged time awake, cumulative sleep deprivation, jet lag or chronic sleep disorder [3, 5]. Sleepiness impairs human performance and increases the probability of human errors and accidents e.g. [9–12].

Cognitive functions, especially attentional ones, are vulnerable to sleepiness [13–21]. The impact of 17 h of sustained wakefulness is comparable to that caused by a blood alcohol concentration level (BAC) of 0.5 ‰, which is the legal driving limit in Finland and many other countries [14, 22]. Reaction times and accuracy in simple reaction time and tracking tasks are significantly lower after 16 – 19 h of wakefulness than in a rested state, which increases the likelihood of missing relevant information [14].

In many safety critical occupations the working hours are long and irregular, and therefore these fields are especially vulnerable to accidents and even catastrophes caused by sleepiness e.g. [23]. Sleepiness-related performance decrement has been recognized in many safety critical sectors e.g. in aviation [24, 25], hospitals [26–29], railway, maritime [30], and road traffic. Traffic kills more than one million people and 20 – 50 million people are injured every year worldwide [31], and 10 – 20 % of the traffic accidents are caused by sleepiness [10, 30, 32–34]. Sleepiness is a major identifiable and preventable cause of transport accidents [34].

At the moment, in most countries, there are no criminal laws against driving while sleep deprived [35]. The first step to criminalize driving while sleep deprived was taken by the state of New Jersey, USA. “Maggie’s law” forbids driving after being awake for more than 24 h [35]. However, the lack of reliable metrics makes it complicated to criminalize driving under sleep deprivation [35–37].

One can estimate BAC quickly on-site with a breathalyzer [38]. Similarly a metric for objectively estimating the level of overall time awake would be

valuable. The development of sleepiness metrics is challenging, since there is inter-individual variability in the response to sleep deprivation, sleep/wake regulation, and sleepiness parameters (see reviews [20, 36]). One way to approach this problem is to find a parameter that reliably estimates how long a person has been awake, or at least estimates whether the person has been awake for longer than a predetermined threshold time (e.g. 24 h in "Maggie's law"). The threshold should be generalizable to everyone, and misuse should be avoided by employing involuntary biomarkers. Moreover, the metrics should be practical and easy to use on-site. The literature concerning such metrics is limited. Currently a posturography based metric is the only one that has shown promising and reliable results in laboratory settings e.g. [39–43]. However, the method requires comprehensive field testing before large scale use.

This thesis examines whether an eye movement based metric could provide an on-site test metrics for time awake. Eye movements and eye closures are sensitive to sleepiness e.g. [44–52]. There are commercial sleepiness monitoring and fit-for-duty solutions that measure eye parameters e.g. [53, 54]. Moreover, the attentional and oculomotor processes share neuroanatomical networks in the brain [55, 56] and saccadic eye movements have been used to study different attentional functions [18, 55, 57].

In this thesis, saccadic eye movements are measured with electro-oculography (EOG), which is a widely used technique that measures eye movements. It has been used in the clinical setting e.g. [58] and in sleep deprivation studies both inside and outside the laboratory to study eye closures, saccadic eye movements, and orienting attention e.g. [44–48, 59–61].

Based on previous findings, eye movements measured with EOG could provide an applicable and reliable metric for an on-site time awake estimator. Consequently, the purpose of this thesis is to examine 1) if the eye movement based metric is sensitive for sleep pressure (time awake) at the individual level, and 2) if the EOG measurements can be reliably performed outside the laboratory.

1.1 PUBLICATIONS AND AUTHOR CONTRIBUTION

Four publications form the basis for this thesis (Fig. 1). The thesis consists of two parts: 1) Algorithm development for EOG feature extraction to permit effective and practical analyses for measurements conducted outside the laboratory (publications II, IV), and 2) Development of an eye movement based metric to estimate time awake (publications I, III).

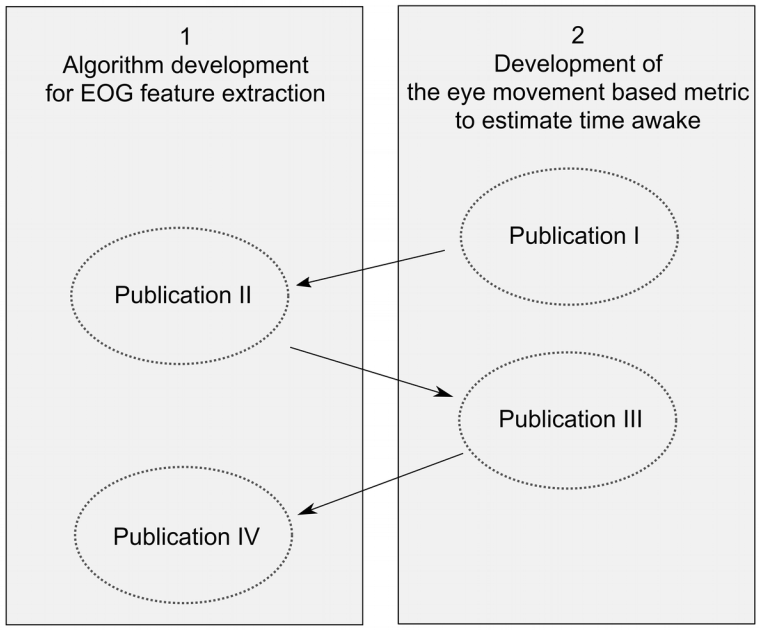

Fig.1. Block diagram of the PhD thesis structure

Publication I

Shows that the group mean of saccadic peak velocity (SPV) measured with EOG outside the laboratory (Naval Academy, Bergen) every sixth hour during 60 h of time awake decreased during sleep deprivation. The eye movements and saccade task performance were analyzed using traditional methods (event by event analyses), which requires synchronizing the EOG signal and saccade task stimulus sequence as well as calibrating the EOG signal relative to eye movement.

> ***KH*** *(K. Hirvonen) planned the eye movement measurement setup and conducted the measurements, made the statistical analyses, and was responsible for writing the manuscript.*

Publication II

Presents an auto-calibration algorithm for automatic analysis of EOG data. The algorithm is based on automatic threshold value estimation. The amplitude threshold values for saccades and blinks were determined based on features in the EOG recorded signal. The presented algorithm extracts EOG signal features without the need of calibration.

> ***KP*** *(K. Pettersson, née Hirvonen) designed and conducted the study, assisted in algorithm designing, made the measurements, data analyses, and was responsible for writing the manuscript.*

Publication III

The auto-calibrating algorithm (publication II) was used to analyze the EOG signal measured during 60 h of prolonged wakefulness (publication I). The number of saccades were analyzed with a new method that calculates the number of horizontal saccades. The number of saccades decreased as a function of time awake. There were inter-individual variability (N = 11), but the results were stable (correlation coefficient between 0.62 and 0.96, mean 0.79) within participants (N = 5). The saccade task performance was affected by the circadian rhythm and was removed from the eye movement data by using the three-process model of alertness (TPMA). After removing the circadian component the monotonous relation between performance in the saccade task and time awake was clearly seen. Results implies that saccades measured with EOG can be used as a time awake metric outside the laboratory.

> ***KP*** *planned the eye movement measurement setup and conducted the measurements, made the analyses, and was responsible for writing the manuscript.*

Publication IV

Presents a computationally light algorithm that automatically detects blinks, saccades, and fixations in EOG data.

> ***KP*** *gave guidance on EOG signal processing and eye movements, assisted on study design, and writing work.*

2 SLEEP DEPRIVATION AND PERFORMANCE

This chapter reviews sleep-wake regulation, basic attentional functions, and effects of acute sleep deprivation on basic attentional functions.

The sleep need per night varies between individuals. Cappuccio and colleagues suggested in their systematic review and meta-analysis that normal sleep need is between 7 and 9 hours per night [62]. Sleep deprivation is an outcome of not getting enough sleep. The condition can be a result of acute and/or chronic partial (cumulative) sleep deprivation. Acute sleep deprivation is either short-term (≤ 45 h of continuous wakefulness without sleep), long-term (> 45 h of continuous wakefulness without sleep) or partial (< 7/24 h of sleep) [11]. Sleep deprivation is chronic when daily sleep is reduced across many days (> 5 d) [4].

Sleep deprivation has serious physiological consequences and significantly impairs human performance e.g. [1–4, 20]. Acute sleep deprivation can affect the speed, accuracy, and variability of human performance. It reduces the ability to do self-evaluation and impairs emotional ability [2, 11, 14, 17, 63]. Long term sleep deprivation has severe health consequences: increasing the risk of diabetes, obesity, depression, heart attack, and stroke e.g. [1, 3, 4, 64].

2.1 SLEEP-WAKE REGULATION

The ascending arousal system of the brain (Fig. 2) maintains wakefulness [3, 6, 65]. During wakefulness the thalamus acts as a gatekeeper by channeling ascending arousal signals from the brainstem (from hypothalamus and somatic sensory impulses) to the cerebral cortex [3, 6, 65]. The master clock of the brain is located at the suprachiasmatic nuclei (SCN) of the hypothalamus. The optic nerve provides information to the SCN on daily light level sensed by light sensitive retinal ganglion cells and the SCN synchronizes the circadian clock to the environmental light-dark cycle [3, 5, 11, 65]. The master clock further synchronizes the cell level clock genes with external light-dark cycle and with each other [3, 5, 66, 67]. It also modulates both sleep and wakefulness, acting as a sleep-wake switch [11, 68].

During the waking hours human performance and alertness is influenced by both the homeostatic sleep drive that builds during wakefulness (sleep pressure) and the endogenous oscillation with a ca 24 h period, called the circadian rhythm [6, 7].

Mathematical models based on alertness have been developed to describe the sleep-wake cycle. The most popular models are the two-process [7, 69] and the three-process model of alertness (TPMA) [8]. Differences between these models are small, since they share a common basis [70]. The TPMA was developed to model neurobehavioral function and it is widely used in the sleep deprivation studies [69].

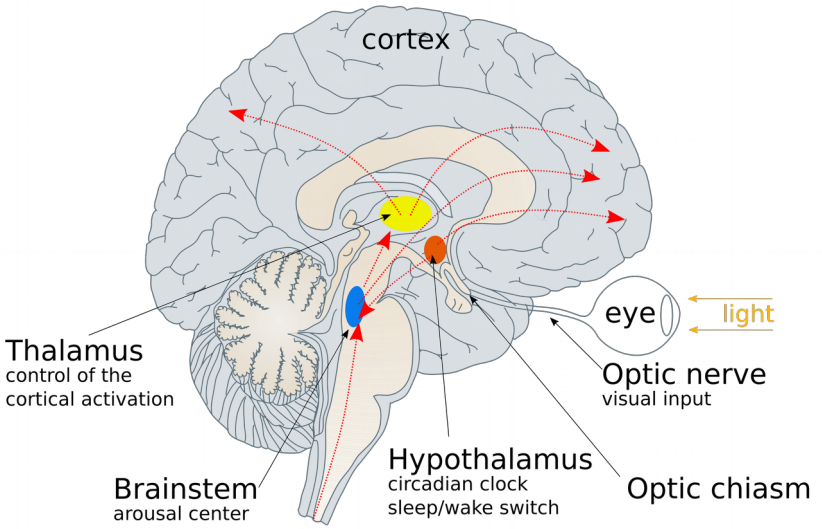

Fig. 2. Schematic figure of the human ascending reticular activation system (modified from [18, 65, 71]).

2.1.1 THREE-PROCESS MODEL OF ALERTNESS (TPMA)

The model has three components; a circadian process (C), a homeostatic process that starts when person wakes up from sleep i.e. at awakening (S), and sleep inertia (W) [8]. The C-process represents alertness due to the circadian influence and has a sinusoidal-like form (Equation 1.1). The S-process is an exponential function that represents time passed since wake up (homeostasis) (Equation 1.2). The S-process is high at wake up and decreases rapidly until it reaches a low asymptote and sleep begins. At sleep onset the S-process is called S' and is reversed, the sleep recovers alertness and performance exponentially until the upper asymptote is reached (Equation 1.3). Sleep inertia, the W-process decreases alertness and performance right after the awakening.

In this thesis acute sleep deprivation is addressed, therefore only the C and S components are used to model alertness and performance during time awake. The estimated alertness/performance (P) is the sum of the C and S processes (Equation 1.4., Fig. 3).

(1.1) $$C = M\cos\left((t_1 - p)\frac{\pi}{12}\right)$$

Here, C = circadian component, M = amplitude of the circadian, p = upper acrophase[2] (decimal hours), t_1 = time of the day (decimal hours).

(1.2) $$S = (S_a - L)e^{-0.0353 t_2} + L$$

where, S = homeostasis component (awake), S_a = value of S at wake up, L=lower asymptote[3] (decimal hours), t_2 = time since awakening (decimal hours)

(1.3) $$S' = U - (U - S_r)e^{-0.381 t_3}$$

where, S' = homeostatic component (sleep), S_r = value of S at retiring, U = upper asymptote[4] (decimal hours), t_3 = time since falling asleep (decimal hours).

The estimated alertness/performance (P) is the sum of the C and S processes:

(1.4) $$P = C + S = M\cos\left((t_1 - p)\frac{\pi}{12}\right) + (S_a - L)e^{-0.0353 t_2} + L$$

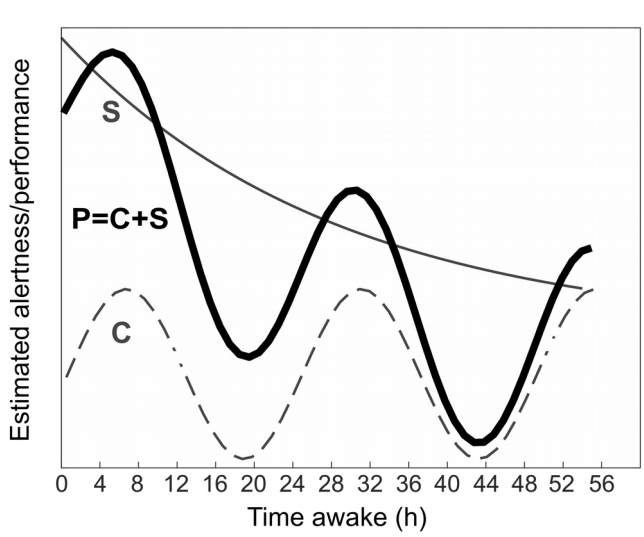

Fig. 3. Schematic figure of two components, C and S, of the three-process model (modified from [8]). The model comprises three components C, S, and W. Here, the C and S processes are presented. The sinusoidal C-process (gray dashed line) represents sleepiness due to circadian influence (wake-up at 07 am). The exponential S-process (gray solid line) represents time lapsed since awakening (homeostasis). The estimated performance/alertness (P) is the sum of the S and C processes (black line).

2 time when the circadian rhythm reaches its peak value

3 lowest value that the exponential function reaches

4 highest value that the exponential function reaches

2.2 ATTENTION

Attention is the focusing state of consciousness and performance resources to meet demands in changing everyday situations. Attention has three main functions 1) to maintain alertness (alerting subsystem), 2) to orient to sensory inputs by selecting modality and/or location (orienting subsystem), and 3) to detect signals for conscious processing, monitoring, and conflict resolution (executive subsystem[5]) [16, 18]. The alerting system, i.e. sustained attention, manages ongoing goal-directed behavior and thus determines the efficiency of the other aspects of attention (orienting and executive) and general performance [18, 72, 73]. The ability to sustain attention and maintain engagement in a specific task over time is crucial for survival. The alerting subsystems catch input from the surrounding environment; you hear a noise and turn to see what causes it. The orienting subsystem places the alert in context; you look around to find the noise source. The executive subsystem makes higher level cognitive decisions after the noise source has been detected and recognized, such as conflict resolution and planning of next actions etc.

The alerting system of attention is vulnerable to sleep deprivation and the orienting system is closely linked to eye movements, therefore these attentional functions are relevant for this thesis and reviewed more closely. Moreover, the orienting subsystem is affected by sleep deprivation through the alerting system, therefore the mechanism behind how sleep deprivation affects the alerting system is reviewed in this chapter. The impact of sleep deprivation on the orienting subsystem and on eye movements is presented in *Chapter 4: "Quantifying sleepiness*".

2.2.1 ALERTING SUBSYSTEM OF ATTENTION

Alertness and sustained attention to the surroundings create a base for other attentional functions and cognitive capacity in general, by maintaining the state of high sensitivity and vigilance to incoming stimuli [18, 72]. These functions rely on multiple underlying brain processes: an important one is the sleep–wake state, which depends on the brainstem-thalamo-cortical pathways, see Fig. 2. [71, 73]. Sustained attention is also vulnerable to sleep deprivation [13, 15, 16, 18, 63]. An increasing sleep drive induces a rapid and uncontrolled sleep initiation (microsleep) e.g. [16, 63]. Microsleep occasions cause lapses in alertness that present as errors of omission and commission, leading to weakened and unstable cognitive performance e.g. [2, 16, 63, 68]. Such varying performance has been hypothesized to present as wake-state instability [16, 63].

In neuroimaging studies using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) methods thalamic activation

5 former detecting subsystem

level has been linked to attentional lapses in sleep deprivated participants. Attentional performance is maintained when the thalamic activity is elevated, but when the activation is considerably decreased, lapses in attention become common [2, 74, 75].

2.2.2 ORIENTING SUBSYSTEM OF ATTENTION

The orienting subsystem aligns attention with sensory input. The aligning can involve eye movements (overt) but can also be executed without eye movements (covert) e.g. [55, 71] Attention shifts can be reflexive (exogenous/bottom-up) or strategic (endogenous/top-down). The posterior brain areas (intraparietal sulcus (IPS) and temporoparietal junction (TPJ)) and the frontal areas (frontal eye fields (FEF) and ventral frontal cortex (VFC)) are employed by the orienting system for visual events (Fig. 4) [55, 56, 71]. The reflexive attentional system is lateralized to the right hemisphere and centered on TPJ and VFC. The endogenous attentional system is centered on the dorsal posterior parietal and frontal cortex [55, 76]. However, according to the premotor theory of attention the mechanism for directing attention to a location is similar to the mechanism for preparing an eye movement [77]. Neuroimaging studies using PET and fMRI have shown a strong overlap between activation of FEF and IPS during covert and overt shifts [55, 76]. Areas in IPS and FEF are functionally connected and they have been suggested to maintain spatial priority maps for covert spatial attention, eye movement planning, and visual working memory [56, 76, 78].

Humans scan the visual scene with rapid, steplike eye movements called saccades. The information thus gathered contributes to how the environment is perceived by the viewer. The saccade command is coordinated by FEF and superior colliculus (SC) (Fig. 4). The saccade command is supposed to originate in the SC where it gets to FEF through the thalamus. The visual information is processed in the visual cortex, IPS, and FEF and these areas compute the spatial location of the upcoming saccade. The FEF forwards the saccade command via SC to oculomotor nuclei that controls each of the six eye muscles [56, 79].

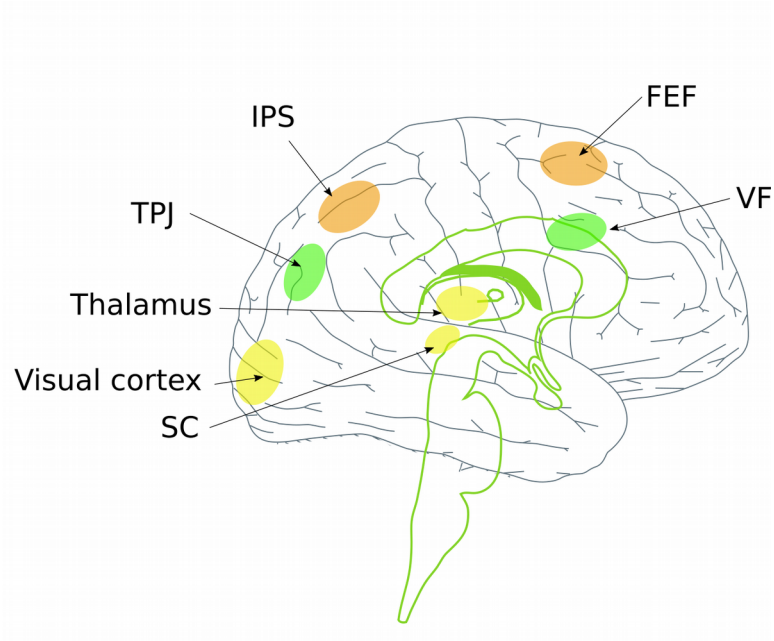

Fig. 4. Schematic figure of the orienting subsystem of attention (modified from [18, 71, 76]). Areas involved in saccade generation are marked with yellow and orange, the endogenous attention system with orange, and the exogenous system with green. IPS = intraparietal sulcus; TPJ = temporoparietal junction; FEF = frontal eye fields; VFC = ventral frontal cortex; SC = superior colliculus.

3 EYE MOVEMENTS

This chapter presents the properties of eye blinks, saccadic eye movements, and the saccade tasks (e.g. for studying orienting attention). Finally, the basics of the EOG method is presented with focus on measuring a person who is awake.

Humans scan the environment with rapid saccadic eye movements. Information is gathered during eye fixations, in foveal vision between saccades. The area of highest acuity at the fovea is small (2 degrees of visual angle[6]) and therefore stabilizing eye movements hold the eye quite steady during the fixation. The vestibulo-ocular reflex stabilizes the eye fixation when the head is moving, while optokinetic, smooth pursuit, and vergence movements stabilize fixations on a moving target [80, 81] These eye movements permit scanning of the environment while e.g. walking, running, and riding in a moving vehicle. Tremor, drift, and microsaccades are miniature eye movements, which reduce neural adaptation during fixation and therefore prevent fading of the visual image e.g. [80, 81].

Even though attention and eye movements are closely linked *(Chapter 2*) they can act independently. Attention is not necessarily located at the point we look at, since information from the surroundings is gathered via the parafoveal vision (ca. 10° area around the fovea) and peripheral vision (ca. 90° area around the fovea) as well. The next fixation point is selected during the ongoing fixation, the selection is either reflexive (overt attention) or voluntary (covert attention). Additionally, the reflexive selection of the new fixation point is quick and made without attention while voluntary fixation selection needs more time e.g. [82].

Eyes are moving even during sleep. The first signs of sleep onset are sinusoidal eye movements called slow eye movements (SEM) [83]. Saccades i.e. rapid eye movements (REM) are present in the sleep stage where dreams are seen [80].

Frequent rapid closures and re-openings of the eyelid take place during wakefulness. Even though blinks are not actually eye movements, they need to be taken into account in eye movement measurements. Importantly, blink parameters have shown sensitivity to sleep deprivation e.g. [53].

Eye movements and eye blinks can be measured with several techniques. The most used ones both in the field and an in laboratory settings are EOG, video-oculography (VOG), and infrared-oculography (IROG). However, EOG is the only eye movement measurement technique that detects eye movements when the eyes are closed. Therefore, it is generally used to determine sleep onset together with electroencephalography (EEG) in standardized clinical measurements [83] and in sleep research e.g. [58, 84].

6 From here on ° refers to degrees of visual angle

3.1 SACCADIC EYE MOVEMENTS

Saccades are fast eye movements between fixations. During a saccade both eyes have the same amplitude and direction i.e. the eyes moves conjunctively. Saccades occur frequently, three to five times per second, more than 100 000 times per day [85], during normal viewing. The eyeball is relatively light and mobile, and therefore the metabolic cost of frequent and fast movements is low [81]. These fast and frequent eye movements permit efficient and thorough scanning of the surrounding world.

The orienting attention captures the next fixation location during the ongoing fixation. The next saccade is programmed in the brain as presented in *Chapter 2.3.2*. The time between the stimulus (i.e. the phenomenon that captures our attention) and the saccade execution is called saccadic latency (Fig. 5). After saccade execution, the eye accelerates to its peak velocity, after which the movement decelerates until the movement stops and the eye fixates again.

The saccade amplitude varies, since it is defined by the next target. The amplitude determines the saccade accuracy. The accuracy is defined by calculating the saccade gain by dividing the saccade amplitude with the target amplitude. Gains below one indicate that the saccades have been too small and undershoot the target (hypometria) whereas the gains larger than one indicate that the saccades have overshooted the target location (hypermetria) [80].

An adult can make saccades large as 40° [81]. However, during normal viewing most saccades are smaller than 15°, otherwise a combined movement of the eye and head occurs [81, 86]. The saccade direction can be horizontal, vertical, and oblique. Vertical saccades are slower than horizontal saccades. An oblique saccade can be faster than either a purely horizontal or a vertical saccade of the same amplitude [87].

3.1.1 PEAK VELOCITY AND VELOCITY PROFILE

Across individuals saccades have a characteristic temporal and velocity profile (Fig. 5) [80, 88, 89]. The duration and velocity of the saccades are not under voluntary control [80]. The burst neurons in the oculomotor nuclei control the eye movement muscles, and thus determine the velocity profile of the saccade. The acceleration phase of the eye lasts as long as the neural signal pulse, the peak velocity of the saccade is reached at the point of the maximum firing rate of the burst neurons [80, 90].

The duration and the peak velocity of the saccades depend on the saccade amplitude. This relation is called “main sequence”[7] [91]. The main sequence relation between saccade duration and amplitude is linear for saccades

7 The term is analogous to the “main sequence” in astronomy; relationship between stellar color versus brightness of dwarf stars

between 6° and 90° amplitude, whereas the relation between amplitude and peak velocity is saturated for larger than 20° saccades [80, 92]. An exponential equation has been used to describe the main sequence between amplitude and peak velocity (see Appendix I).

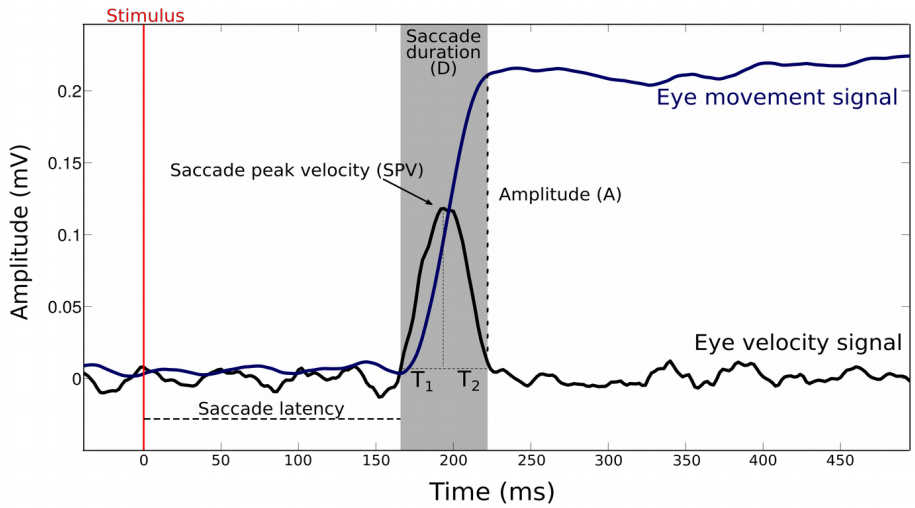

Fig. 5. Schematic figure of a horizontal saccadic eye movement. The eye movement signal (measured with EOG) is marked with blue, the eye velocity signal (black) is a first order time derivative of the eye movement signal. The red line (left) presents the stimulus. Saccade latency is the time between the stimulus onset and the start of the saccadic eye movement. A = saccade amplitude, D = saccade duration (gray area), T_1 = acceleration time of the eye, T_2 = deceleration time of the eye, SPV = saccade peak velocity.

The saturation of the peak velocity of the large saccades leads to skewed velocity profile since the deceleration time (T_2 in Fig 3.1.) is longer than acceleration time (T_1 in Fig 3.1.). The skewness ratio (ratio of acceleration time and saccade duration) is 0.5 for < 10° saccades, and decreases for larger saccades, e.g. for 60° saccades the ratio is 0.2 [80, 88, 92].

3.2 SACCADE TASKS

Saccade tasks have been used to study overt and covert attentional shifts, oculomotor control, brain functions, as well as development and dysfunction in neurological and psychiatric disorders [80, 93]. The basic idea of the prosaccade task is simple; when a visual stimulus jumps from one location to another one, the participant makes a reflexive saccade to the new target location in ca. 200 ms [80]. The fixed timing and target location in the prosaccade task permits comparing oculomotor parameters (e.g. peak velocity, latencies) in different physiological conditions e.g. sleep deprivation.

The voluntary control of the reflexive saccade and covert attention have been studied using antisaccade tasks e.g. [94]. In this task the person is required to suppress a reflexive saccade towards visual stimuli and is asked to generate a voluntary saccade of equal size towards the opposite side (antisaccade). The antisaccade task is challenging; after training, normal

participants fail to suppress the voluntary saccade in 5 – 15 % of antisaccade trials [80, 95, 96]. Furthermore, antisaccades have longer latencies, lower peak velocities, and a skewed velocity profile compared to visually guided prosaccades e.g. [80]. The differences between pro- and antisaccade task performance (errors, latencies) are referred as "antisaccade cost" and are used to measure overt vs. covert attentional shift [82, 97–99].

The saccadic voluntary control and fixational system has been studied by altering the timing between current fixation point and the target stimulus (gap and overlap paradigms) [80]. The gap (ca. 200 ms) between the fixation point and target stimulus decreases the saccadic latencies to ca 100ms [100–102]. When the fixation point disappears, the pre-visual activity increases in the motor neurons (at the SC), and when the target stimulus appears, the saccade is made without any higher order decision about the stimuli or type of the response [103]. Thus, the overlap between the fixation point and target stimulus increases the latency to 220 ms [102]. The gap and overlap paradigms are presented in Fig. 6. The difference between the latencies in these two paradigms is called *gap effect* and is explained by the attentional disengagement process [104]. Moreover, an increased gap effect has been suggested to reflect impairment of attentional disengagement [104].

Normal participants seldom make errors in the overlap task, while a fraction of reactions in the gap task are classified as anticipatory errors (saccades with latencies between 10 – 79 ms). These anticipatory saccades tend to overshoot by more than 20 % from the target location and therefore are corrected with a corrective saccade immediately (with an inter-saccade-interval of 0 – 100 ms) [100, 101].

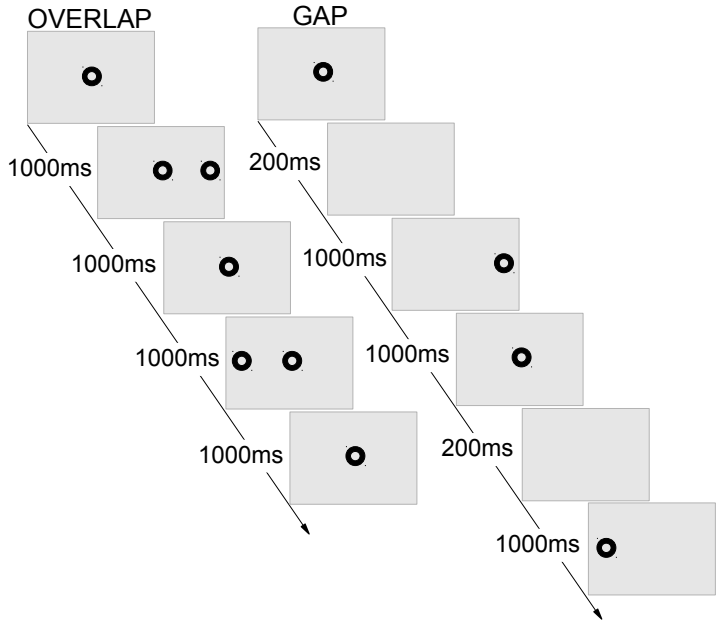

Fig. 6. Example of a saccade task with gap and overlap paradigms. In the overlap paradigm (left) the central fixation point is visible all the time whereas in the gap paradigm (right) the central fixation point disappears 200ms before the stimulus.

3.3 EYE BLINKS

This chapter presents the properties of the spontaneous eye blink, with focus on the waveform of the blink. The origin of the blink and the aspects affecting the blink parameters are outside of the focus of this thesis.

A human blinks 3 – 20 times per minute [80, 105]. The blink rate varies between individuals but the intra-individual variation is small in a specific setting [105]. The visual and cognitive demand of the task affects the blink rate e.g. the blink rate is lower during reading than in rest [106].

The peak velocity of the lid closure and eye opening is a linear function of blink amplitude size from ca. 1 to 60° [107]. The closing peak velocities are more than twice larger than the opening velocities. A spontaneous blink lasts 250 – 1000 ms [108]. The closing phase of the eye lasts < 150 ms (see Fig. 7), while the re-opening phase lasts > 150 ms [108].

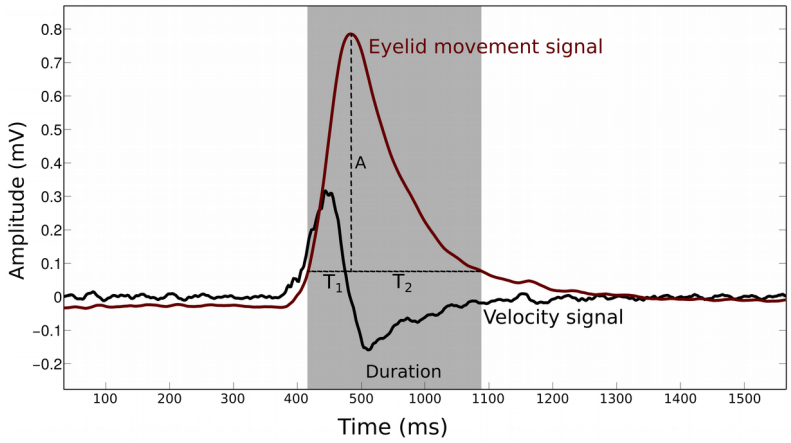

Fig. 7. Schematic figure of an eye blink. The eyelid movement signal (measured with EOG) is marked red, the eyelid velocity signal (black) is a first time derivative of the lid movement signal. A = blink amplitude, blink duration is marked with a gray area, T_1 = the closing time of the eye, T_2 = the opening time of the eye.

3.4 ELECTRO-OCULOGRAHPY (EOG)

EOG is a simple method for measuring eye movements. EOG has been widely used in different settings; clinical oculomotor measurements e.g. [58, 80], in both field and laboratory studies e.g. [109] and in sleep deprivation studies e.g. [44–47, 60, 110–112].

The EOG measurement relies on electrical features of the human eye. The corneo-retinal potential, 0.4 – 1.0 mV, is present between the front (cornea) and back (retina) of the eye e.g. [58]. The negative charge at the retina is due to its higher metabolic rate compared to that of the cornea e.g. [58, 113]. When the eye moves, the dipole rotates which causes a small difference between the electrical potential at the electrodes attached to the skin around the eyes (see Fig. 8) [114]. If the eyes move to the right the surface potential increases at the right eye canthi (Fig. 8. electrode EOG_R) and decreases the

surface potential at the left eye canthi (Fig. 8. electrode EOG_L). The potential differences can be measured using a differential amplifier. The vertical eye movement signal, EOG_v is the difference between the voltage recorded by the upper and lower eye electrode, whereas the horizontal eye movement signal, EOG_h is the difference between the voltage recorded by the right and left eye electrodes[8]. The saccades are visible in both the vertical and horizontal signals whereas blinks are large peaks in the vertical EOG signal only (see Figs. 7, 8, and 9).

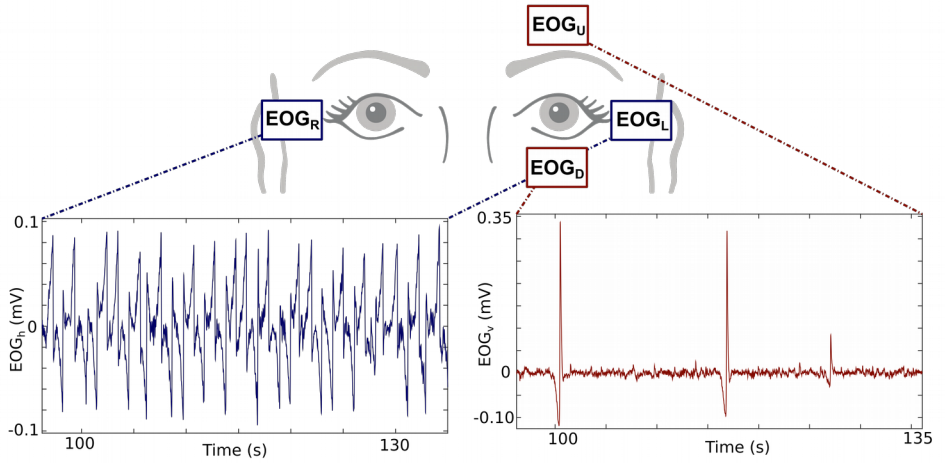

Fig. 8. The EOG is measured with four electrodes from the outer canthi of both eyes, and from above and below of the right eye[9]. The vertical eye movement signal (red), EOG_v is the difference between the voltage recorded by the upper and lower eye electrode ($EOG_v = EOG_U - EOG_D$) whereas the horizontal eye movement signal (blue), EOG_h is the difference between the voltage recorded by the right and left eye electrodes ($EOG_h = EOG_R - EOG_L$).

The magnitude of the corneo-retinal amplitude, a function of the amount of ambient light, affects the EOG signal amplitude[10]. The amplitude changes can reach 50 % e.g. [58]. Therefore ca. 10 min of light adaptation before any measurement is necessary, if the illumination level has changed before the measurements e.g. [58, 113]. A headrest is usually used to prevent interfering eye movements that compensate for head movements. Calibration between EOG and eye movements (mV to visual angle degree) is needed before each measurement.

The temporal resolution of EOG depends on the sampling frequency of the signal amplifier. A sampling rate exceeding 200 Hz enables reliable

8 This "cyclopean eye" electrode configuration is commonly used for measuring an awake person [58]. For sleep electrode configuration see "*The American Academy of Sleep Medicine Manual for the scoring of sleep and associated events*" [83], and for clinical oculomor measurements [58].

9 In this thesis the vertical EOG (EOG_v) was measured from the left eye. However, the electrodes can be attached above and below the right eye as well.

10 Phenomena arise from ion permeability changes across the retina. In the dark the metabolic activity at the retina is slow which reduces the negative charge of the retina. This reduces the corneal-retinal potential and the EOG signal amplitude e.g. [115].

latency, duration, and velocity analyses of the saccades. However, the spatial resolution of the EOG is poor, since eyelid movements and muscle activity induce major artifacts into the vertical EOG signal [58, 116].

Both slow baseline drift and high frequency artifacts influence the EOG signal (Fig. 9). The baseline drift is caused by changes in contact impedance due to e.g. sweating [58]. High frequency noise is picked up from e.g. powerlines, muscle activity, and participant movement [58]. Denoising the EOG signal is challenging since eye movements are usually non-repetitive which makes the EOG signal unpredictable. Consequently, methods that need structural and temporal knowledge about the expected signal cannot be used. Additionally, reliable eye movement classification and further analyses require undistorted edges (e.g. step-like saccades), amplitude, and durations of the eye movements signal. Baseline drift has been removed from EOG signals by high-pass filters e.g. [58, 117] and wavelet filters [109] whereas low-pass [118] and median filters [109, 118, 119] have been used to remove high frequency noise. Unfortunately, digital filtering distorts the saccade parameters by distorting the edges and by increasing saccade duration and lowering velocity estimates [118–120].

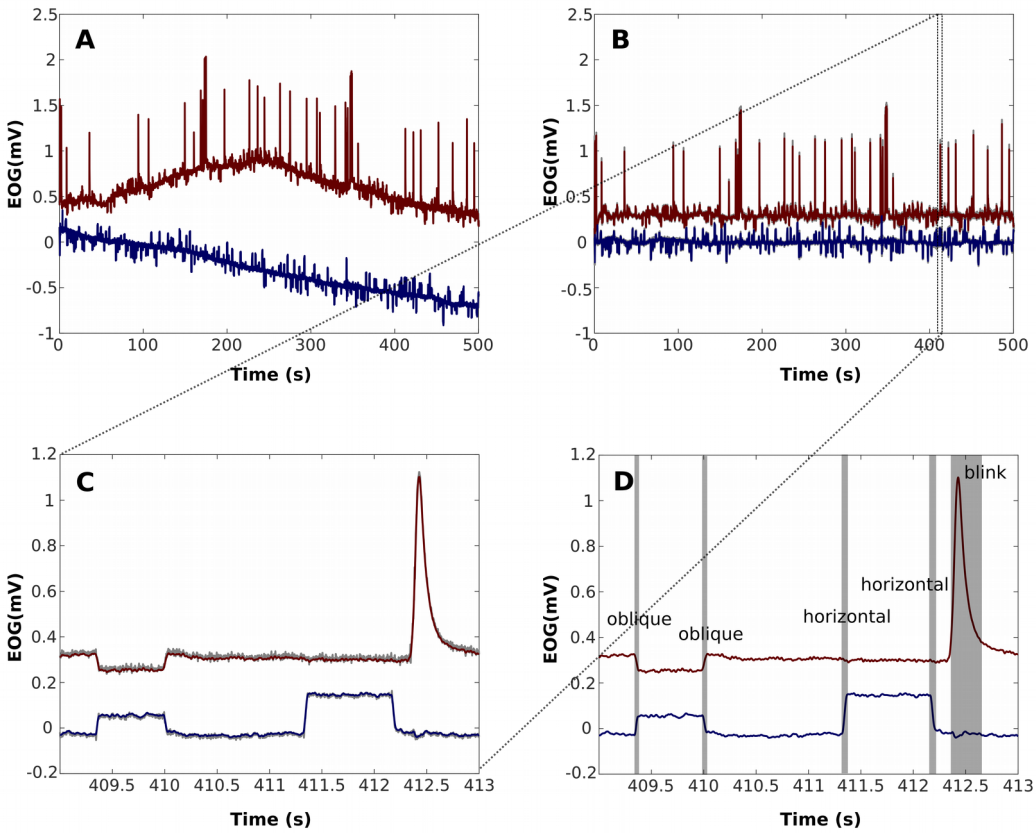

Fig. 9. Example of the EOG signal denoising. A) Raw EOG signals (EOG_v is red and EOG_h is blue) and B) EOG signals without baseline drift. C) Denoised EOG signals, the gray signal represents the EOG signal before the high-frequency denoising. D) Saccades and blinks are marked gray. Oblique saccades on the left causes a step like jump to both EOG_v and EOG_h signals while horizontal saccades are visible on only in the EOG_h signal. The blink is a large signal jump (right) in the EOG_v signal.

4 QUANTIFYING SLEEPINESS

This chapter reviews sleepiness metrics, with a focus on ocular parameters and attentional functions as well as on potential time awake metrics.

Sleepiness biomarkers are extracted by objective and subjective methods. Subjective methods include both simple questions about current sleepiness state and large questionnaires that estimate possible pathologies behind the sleepiness.

A popular and simple questionnaire is Karolinska Sleepiness Scale (KSS) [121]; a nine-point scale from 1, “very alert,” to 9, “very sleepy, great effort to stay awake or fighting sleep.” The KSS estimates the psycho-physical state experienced in the last 10 minutes [121]. KSS scores increase with prolonged wakefulness [121] and correlate with sleep deprivation [122]. KSS has been used in studies of shift-work, driving ability, on-duty alertness, attention, and cognitive performance e.g. [24, 123–125]. Even though simply asking about the person’s alertness level would be easy do on-site, this would rely on self-reporting which is vulnerable to environmental and motivational issues: The ability to estimate internal states, tendency to minimize or magnify the feelings, and any underlying agenda [126, 127] Moreover, sleep deprivation itself influences an individual's ability to estimate his/her own performance [128, 129].

Objective measures are divided into behavioral performance and physiology-based methods. Behavioral methods aim to measure sleepiness indirectly via performance decrement in a specific task that requires e.g. attention, memory, and/or motor function [126, 127, 130]. Behavioral methods are vulnerable to external and motivational factors [126]. Physiological methods include monitoring spontaneous fluctuations in physiological parameters, biological markers, and clinical methods for measuring sleep propensity or sleep pressure [126, 127].

The gold standard for quantifying sleepiness, the Multiple Sleep Latency Test (MSLT), measures sleep latency. How fast a person falls asleep estimates the intensity of the current sleep pressure. The test is widely used in clinical and laboratory settings [126, 130]. In MSLT a person is asked to rest (lie on the bed) (20 – 30 min) in a darkened room and is encouraged to fall asleep. The test is repeated several times per day. Sleep onset is assessed with EEG and EOG recordings [126, 127]. Sleep latency may be the optimal parameter for measuring sleepiness in isolation from real-world demands and laboratory settings, but not in the field.

Arousal decrement measures can be used to measure sleepiness of an awake, actively operating person [126]. They are based on monitoring spontaneous variation in physiology: Brain activity parameters (e.g. EEG

patterns, spectral parameters), ocular parameters (e.g. derived from EOG, VOG, or IROG), and autonomic indicators (e.g. pupillography) [126].

Most sleepiness detection and prediction systems are based on objective measurements [53, 131–133]. These systems can be divided into monitoring methods and fitness-for-duty methods. Real time sleepiness monitoring aims e.g. to alarm a driver when sleepiness reaches a severe level. Fitness for duty is a complex concept that aims to estimate whether a person is able to perform his/her duty (e.g. work-shift) (see reviews [134, 135]. Many factors may degrade performance, e.g. medical factors, drugs, alcohol, and sleepiness. Additionally, these methods aim to estimate (e.g. using mathematical models) whether a person's sleepiness may reach a severe level during a work-shift e.g. [131, 132].

4.1 AROUSAL DECREMENT MEASURES: OCULAR PARAMETERS

Ocular parameters are widely used as a sleepiness measure in sleep deprivation studies and sleepiness monitoring assessment e.g. [44, 45, 136, 137]. Spontaneous blink parameters are suitable for monitoring an actively operating person, while some saccade parameters such as peak velocity, amplitude, and duration are challenging to measure reliably in naturalistic settings.

Oculomotor activity decreases when sleep deprived; blinks and saccades cease, fixations get longer, and an increasing number of SEMs occur before sleep onset [138–140]. The relationship between blink frequency and sleepiness is inversely U-shaped. Increasing sleepiness first increases the blink frequency e.g. [59, 141, 142] until the person is lapsing/having microsleeps (wake-state instability) [44]. Blink duration [44, 49, 137, 141], especially the duration of the opening phase increases when sleep deprived [44]. Additionally the blink amplitude and peak velocity of the eye closure decreases [59, 137, 143] and the ratio between blink amplitude and the peak velocity of the eye closure have been used in real time monitoring, e.g. with commercial drivers [53, 137].

Saccade main sequence parameters: Saccade amplitude, duration, and SPV decrease with increasing time on task (e.g. in driving simulator) [44, 142, 144–147]. However, SPV values are challenging to measure in an actively operating person because the velocity depends on the saccade amplitude. In tasks that simulate real-life situations (e.g. a driving simulation) where the participant can view their environment freely, the changes in saccade parameters (SPV, amplitude, and duration) can be the result of many factors: e.g. changes in viewing strategy (smaller saccades leads to shorter durations and slower velocities), sleepiness related deceleration, etc. Di Stasi *et al.* (2012, 2013) measured eye movements during a 2 h driving simulation. They compared the peak velocity values by dividing the saccades into four 30

minute windows and estimated the main sequence curve for each window [146, 147]. They found that the slope of the saccade decreased with increasing time on task. Ueno and colleagues suggested that the bluntness of the saccade velocity curve depicted by the SPV/duration (SPV/D) index is sensitive to sleepiness and suitable for on-line monitoring for e.g. drivers sleepiness [148, 149].

4.2 ATTENTION-BASED BEHAVIORAL METHODS

Sleep deprivation impairs human performance, which increases reaction times, the number of response omissions, memory deficits etc. e.g. [11, 12, 126]. The behavioral methods can be divided into two main categories 1) cognitive and 2) psychomotor tests. Cognitive tests include memory, logical reasoning, and attentional tasks whereas psychomotor tasks include tracking and tapping tasks.

The Psychomotor Vigilance Task (PVT) is much used to study sustained attention in sleep deprivation studies e.g. [16, 63]. The test is a simple reaction time task where the person responds to a visual stimulus by pressing a button. The task lasts 10 minutes with 2 – 10 s inter-stimulus-interval. The number of lapses (reaction times > 500 ms), errors (omissions and commissions), and reaction times in PVT increases during acute and cumulative sleep deprivation e.g. [16, 36, 63, 150–152]. Long reaction times and omissions in the PVT task have been suggested to be a result of attentional lapses and microsleeps caused by wake state instability [11, 63]. Balkin *et al.* made a profound comparison study of instruments that assess sleepiness in an operational environment. They found PVT to be one of the most sensitive tests to identify sleepiness related performance decrement [153]. A shorter, 3-minute version of PVT has shown promising results as a fitness for duty measure for luggage screeners and possibly other professional screeners in operational environments [154].

4.2.1 ORIENTING ATTENTION AND EYE MOVEMENTS

Saccade tasks permit simultaneous attention and sleepiness assessment; the performance parameters in the saccade tasks (e.g. saccade latency, error rate) measure visuospatial attention whereas oculomotor parameters (e.g. SPV, saccade accuracy) measure decrement in arousal [111].

The SPV of visually guided saccades decreases during partial sleep deprivation, total sleep deprivation, and it is affected by the circadian rhythm [46–48, 50, 51, 133]. The decrease in SPV during sleep deprivation has been suggested to be a result of a reduced burst rate in the brainstem [48].

The latency of visually guided prosaccades increases with increasing sleep deprivation and varies with circadian rhythm e.g. [46, 47, 50]. Fimm and Blankenheim found that the saccade latencies increase in overlap paradigm

but not in gap paradigm between low and high arousal stages during 24 h of time awake [61]. Also antisaccade latencies increase during 30 h of time awake [155].

Bocca and Denise found that after one night's sleep deprivation the gap effect (difference between overlap and gap latencies) increased, which suggests that disengagement of attention was impaired. The gap effect increased in every participant (N = 10) [111]. However, the saccadic peak velocity did not decrease which suggests that the disengagement of attention was not a result of decreased alertness [111].

Error rates in saccade tasks have been reported only in a few sleep deprivation studies [19, 110]. Porcu *et al.* found a significant linear trend between the prosaccade error rate (fraction of rejected saccades) and time awake after one night of sleep deprivation [110]. Five participants executed the saccade task every 2 h from 12 h until 24 h of time awake. Saccade task performance correlated with the shortening of sleep latency at MSLT. Similar results have been achieved in a cumulative sleep deprivation study with 24 participants using a modified spatial cueing task [19]. Wachowicz *et al.* found that false starts, failures in response selection, and direction errors were linked to circadian variations [19]. They also found that an increasing sleep drive increased the number of omissions and commissions. They suggested that the former could be related to the impairment of the orienting attentional system while the latter could be explained with failures of sustained attention [19].

The fitness impairment tester (FIT, Pulse Medical Instruments, Inc., Rockville, MD) is a commercially available fit-for-duty device. FIT measures pupillographic (initial pupil diameter, pupil-constriction latency, and pupil-constriction amplitude) and saccade velocity in a short (30 s) horizontal saccade task. The SPV measured with FIT has shown significant decrement in sleep deprivation studies e.g. [54, 133]. Balkin *et al.* on the other hand found no significant decrease in SPV values measured with FIT in their comparison study on partial sleep deprivation [153].

4.3 TIME AWAKE METRICS

This thesis focus on acute sleep deprivation caused by prolonged time awake. The approach was chosen to limit the broad concept of sleepiness. Sleepiness and time awake are related: Sustained wakefulness causes acute sleep deprivation and increases the homeostatic sleep drive. Moreover, acute sleep deprivation is easier to generate and administer in research setups than e.g. cumulative sleep deprivation.

Even though it is known that many cognitive functions are vulnerable to prolonged time awake, the literature concerning time awake metrics is limited. There is only one convincing attempt to develop a time awake tester;

a 30-second postural balance test was accurate and precise in estimating time awake [39–43]. However, a portable, on-site usable balance tester requires comprehensive field testing before large scale initialization [42].

Additionally, a recent conference abstract reports on a study where several oculomotor behavior parameters measured in a visual tracking task changed as a function of circadian rhythm and time awake [52].

5 AIM

This thesis examines whether an eye movement based metric, measured with EOG, can estimate time awake outside the laboratory. The metric should work on individual level and be practical to use.

Research question: **Can an EOG based method estimate time awake outside the laboratory?**

The thesis consists of two parts: 1) Algorithm development for EOG feature extraction (publications II, IV), 2) Sleep deprivation (60 h total sleep deprivation) study conducted outside the laboratory (publications I, III). The specific publication aims are presented below.

Publication I
EOG measurement conducted outside the laboratory: The aim was to study whether saccade peak velocity (SPV) values are sensitive to sleep deprivation using a conventional study setup and analyses.

Publication II
The aim was to develop a reliable calibration-free algorithm for EOG feature extraction (blinks and saccades).

Publication III
The aim was to examine if an eye based metric, measured with EOG can estimate time awake outside the laboratory.

Publication IV
The aim was to develop a computationally light algorithm for EOG feature extraction (blinks and saccades).

6 FEATURE EXTRACTION

Two algorithms for EOG signal feature extraction were developed. The automated auto-calibrating algorithm (publication II) was developed to automatically estimate threshold values for saccades and blinks, this to allow testing the SPV analyses without calibration in a sleep deprivation study. The semi-supervised probabilistic algorithm (publication IV) is computationally light to allow fast analysis of the EOG data.

6.1 ALGORITHM II (AUTO-CALIBRATING)

The algorithm consists of four blocks (for details see publication II): A) artifact removal, B) estimation of amplitude threshold values, C) feature extraction, and D) feature classification. The input for the algorithm are the EOG_h and EOG_v signals (see electrode configuration and signals in Fig. 8). The EOG signal drift is removed using polynomial detrending and the high frequency artifact by using wavelets. The automatic thresholds are estimated separately for blinks and saccades by using peaks present in the eye movement signal and in the eye velocity signal (EOG_{h_diff} and EOG_{v_diff}). Estimated threshold values are used to detect peaks related to eye movement features (saccades and blinks) in the EOG signal and the found features are classified into correct eye movement classes.

6.2 ALGORITHM IV (PROBABILISTIC)

The algorithm employs filtering, feature extraction, training, and event detection stages (details in publication IV). The detection method is probabilistic, meaning that each sample (in the EOG signal) is assumed to be a part of a saccade, blink or fixation. The sum of probabilities is always one.

The algorithm uses Bayes theorem to estimate the probability of a certain event. Prior to event detection, the algorithm is trained to determine the likelihood and the prior probability of each feature class. The training is unsupervised which means that the class identities of the training samples are unknown. During training, the features (saccades, blinks, and fixations) are detected from eye movement signals (EOG_h and EOG_v) (electrode configuration shown in Fig. 8.) and from velocity signals (EOG_{h_diff} and EOG_{v_diff}).

Signal denoising is performed using two-stage filtering with two separate FIR low-pass filters with cutoff frequencies at 1 Hz and 40 Hz. In the feature extraction stage the EOG signal is filtered with the preceding low-pass filter that removes high frequency noise to make feature (blink, saccade, and

fixation) detection easier. The temporal parameters of the detected features are then estimated from the raw signal filtered with the latter low-pass filter to avoid distorting the temporal parameters.

6.3 TESTING

The EOG was measured with four AgAg-Cl electrodes (Technomed Europe, Maastricht, The Netherlands) (see electrode placement in Fig. 8) and the electrodes were grounded to the left mastoid (M2). The EOG signal was recorded with a NeurOne amplifier (Mega Electronics Ltd., Kuopio, Finland); 500Hz sampling rate, lowpass filter (-3 dB cutoff 125 Hz). In ALGORITHM II testing the direct current (DC) measurement was used and in ALGORITHM IV testing an alternating current (AC) measurement was done (highpass filter -3 db cutoff 0.16 Hz).

Prior to the experiments ALGORITHM IV was trained with a short training procedure. The training set included five black dots, whose size was one degree of viewing angle. The subjects were instructed to fixate on the dots for random durations in random order, and to blink freely when needed. The training lasted one minute. Since the method was unsupervised, the times of the occurrence of the events was not recorded.

The performance of the algorithms was determined using two different kinds of experiments to estimate the robustness (sensitivity, specificity) and consistency of the algorithm. In testing ALGORITHM II, a controlled saccade task (experiment 1) and a free viewing task (experiment 2) were used. In testing ALGORITHM IV, a fixed saccade-saccade-saccade-blink sequence task was used in both experiments. In experiment 1 the saccade amplitude was fixed (7.1°, 5.7°, 4.3°, 2.9°, 1.4°) and in experiment 2 the amplitude was randomized (between 2.2° and 35.7°).

In ALGORITHM II tests the eye movements were recorded simultaneously with a VOG device (EyeLink, SensoMotor Instruments GmbH., Teltow, German) with 250 Hz sampling rate. The EyeLink was calibrated with a 9-point calibration before the experiments for each subject. The EOG signal was used as a test signal for the algorithm whereas the the VOG data provided an estimate of the participants eye movements. Using the two eye movement measurement techniques made it possible to study the robustness of the algorithm. The number of blinks were visually scored from the vertical EOG signal according to the *American Academy of Sleep Medicine* Manual for Scoring of Sleep and Associated Events [83] in both testing protocols. More details of the test protocols are reported in publications II and IV.

Analyzing the performance of the feature extraction algorithms for eye movements is challenging, since no ‘ground truth’ is available. The presented estimates of the algorithm performance depend on the measurement result

of the VOG device (EyeLink), the visual scoring (blinks), and that participants performed the given saccade tasks as instructed.

6.4 RESULTS

The performance of the algorithms was evaluated using true positive rates (TPR = sensitivity) and positive predictive values (PPV = precision)[11] [156]. Equations are presented in Appendix II. The results of the performance tests are presented in Table 1.

In ALGORITHM II testing 1920 saccades and 213 blinks were analyzed in experiment 1. The TPR of the saccade detection was 95 % for all saccades. The blink detection TPR was 93 % whereas PPV was 96. In experiment 2 the EyeLink found 2895 saccades. The TPR for the EOG measurement was 74 and PPV 73. However, when only saccades with 30–80 ms duration were used, the EyeLink detected 1351 saccades and ALGORITHM II TPR for saccade detection was 97 and PPV 94. Altogether 96 blinks were visually scored during experiment 2. Detection TPR for blinks was 74 with PPV of 90. The blink durations, the durations of the horizontal saccades, and peak velocities of the horizontal saccades were similar to those reported in the literature.

In ALGORITHM VI testing 777 saccades and 259 blinks were analyzed in experiment 1. The detection TPR for blinks was 100 and PPV 99 whereas for saccade detection TPR was 77 and PPV 86. In experiment 2 the blink detection TPR was 99 with 99 PPV whereas the saccade detection TPR was 93 and PPV 88, respectively. The saccade and blink durations are similar to those reported in the literature.

Small saccades, especially vertical ones, are difficult to detect because the vertical components of the EOG signal are weaker than the horizontal components and because eyelid movement induces a major artifact into the vertical EOG signal [116]. This phenomenon is seen in the performance of both algorithms. If the smallest saccades are removed from the dataset, the performance of the ALGORITHM II improves. In addition, the performance of the ALGORITHM IV is better in experiment 2 where the participants made larger saccades than in experiment 1.

11 PPV were used when the false positive (FP) values were available

Table 1. Results of the performance tests

Algorithm	Experiment	Eye movement	Number of events	TPR (Sensitivity)	PPV (Precision)
II	**1**	blink	213	93	96
	N=3	saccade	1920	95	-
	2	blink	96	75	90
	N=3	saccade	2895	74	73
		saccade (30–80ms)	1351	97	94
IV	**1**	blink	259	100	99
	N=7	saccade	777	77	86
	2	blink	148	99	99
	N=4	saccade	444	93	88

7 MATERIALS AND METHODS

This chapter presents eye movement data collected during 60 h prolonged time awake. The eye movement measures were conducted as part of a research project in which the effect of sleep deprivation on performance in two high-speed navigation systems was studied [157]. The study was carried out in ship simulators at the Naval Academy, Bergen. The EOG data were used in publications I and III to develop the eye movement based time awake metrics.

7.1 PARTICIPANTS

Eleven male navigators from the Royal Norwegian Navy (RNoN) volunteered for the study (I, III) (mean age = 26.6, SD 2.2, range 23 – 30 years). The participants had no somatic or psychiatric health issues (including sleep disorders and abnormal sleep habits), and they reported no current use of medication [157]. The participants reported normal sleep length (before working days: mean 6.9, SD 0.7, range 6 – 8 h), and were all classified as "intermediate" types using the Composite Morningness Questionnaire [158].

7.2 STUDY DESIGN

Measurements were performed during two separate study weeks, each comprising 60 h of sleep deprivation. A 10-week washout period between the study weeks eliminated carryover effects. The eye movements were measured in eight participants during the first measurement week. Five participated in both measurement weeks.

On the first study day, the participants arrived at 8:00 am and the first navigation session started at 9:00 am A single navigation session lasted 2.5 h, including preparation and rest breaks. After navigation, the participants filled out questionnaires. Next an 80-min period followed where the participants underwent eight vision tests in a darkened test room (< 5 cd), including the saccade tasks measured with EOG. The test cycle (preparation - simulator navigation session - questionnaires - vision tests) was repeated 10 times. The same test cycle was followed throughout the study. Participants who showed signs of falling asleep were prompted to stay awake by a research assistant. The eye movement data from the first nine test cycles is presented in this thesis, since the saccade task measured with EOG was not measured during the 10th test cycle as the participants were too tired to carry out the saccade task.

To emulate realistic conditions the participants were allowed to use caffeine and tobacco. The use was limited to the number of units that each participant reported that he consumed during an ordinary workday (this information was obtained at the time of recruitment). None of the participants smoked, but one used smoke-free tobacco during the measurements.

7.3 SACCADE TASK MEASURED WITH EOG

EOG was measured using bipolar coupling and the electrodes were grounded to M2. Horizontal and vertical EOG was measured with four AgAg-Cl electrodes (Technomed Europe, Maastricht, The Netherlands) placed at the outer canthi of both eyes, as well as above and below the left eye, see Fig. 8. The EOG signal was recorded with an Embla A10 device (Medcare, Reykjavik, Iceland) at 200 Hz sampling rate and 0.5 – 90 Hz bandwidth (AC measurement).

The saccade task was implemented using the Presentation software (Neurobehavioural systems, Albany, CA, version 9.70). The participants sat in a chair at 70 cm distance from the computer screen. The distance was confirmed before every measurement. Participants were instructed to sit still, avoid blinks, and to look at the location of the central fixation point until the target stimulus appeared, after which they were supposed to move their gaze as quickly as possible to the target stimulus. When the stimulus disappeared, they were instructed to move their gaze back to the central fixation point. The saccade was 10° (degrees of visual angle) whereas the size of the fixation point and the target stimulus was 1°. The saccade task consisted of alternating A (overlap stimulus) and B (gap stimulus) blocks (see *Chapter* 3, Fig.6, and publication I and III for further details).

7.4 ANALYSES

7.4.1 SACCADE PEAK VELOCITY (SPV)

In publication I the calibration between EOG and eye movement was used and the saccades and blinks were estimated using a velocity threshold method. The SPV values were estimated from the correctly executed saccades. The difference between the number of correctly executed saccades between the overlap and gap paradigms were tested with the Kruskal-Wallis test.

The first measurement after 6 h of time awake was used as a baseline measurement, and was set to 100 %. The relative change from the baseline was calculated from the individual baseline value in all time-awake measures. The Mann-Whitney U test was used to compare the difference between baseline and each consequential time-awake data point. The comparisons

was made for the all SPV measurements measured with EOG. Bonferroni correction was applied to all baseline vs. time-awake classes, with the level of significance, p, set 0.006 (0.05/8).

7.4.2 NUMBER OF SACCADES

The analysis chain for the number of saccades is presented in Fig. 10. The number of saccades was calculated from the saccades collected during the saccade task. All horizontal saccades with a duration between 40 ms and 100ms were analyzed and deemed to represent the participant's performance in the saccade task[12]. Based on Porcu et al. [110] results a simple linear regression model was fitted to estimate the linearity of the decrease in number of saccades as a function of time awake.

The time between saccades (TBS) was calculated from the saccade time series by subtracting the starting time of a saccade from the previous saccade's starting time. TBS values were also used to examine how the novel analysis is related to the traditional event by event method (described in detail in publication I).

The C and S components of the TPMA were fitted to the eye movement data (see *Chapter 2*). After fitting, the C-process was subtracted from the predictor (P) and from the original number of saccades to estimate the time awake/ sleep pressure (S).

12 The durations of the 10° horizontal saccades are between 43—59 ms [159], therefore the saccades which lasts 40—100 ms are possibly related to reactions to saccade task stimuli.

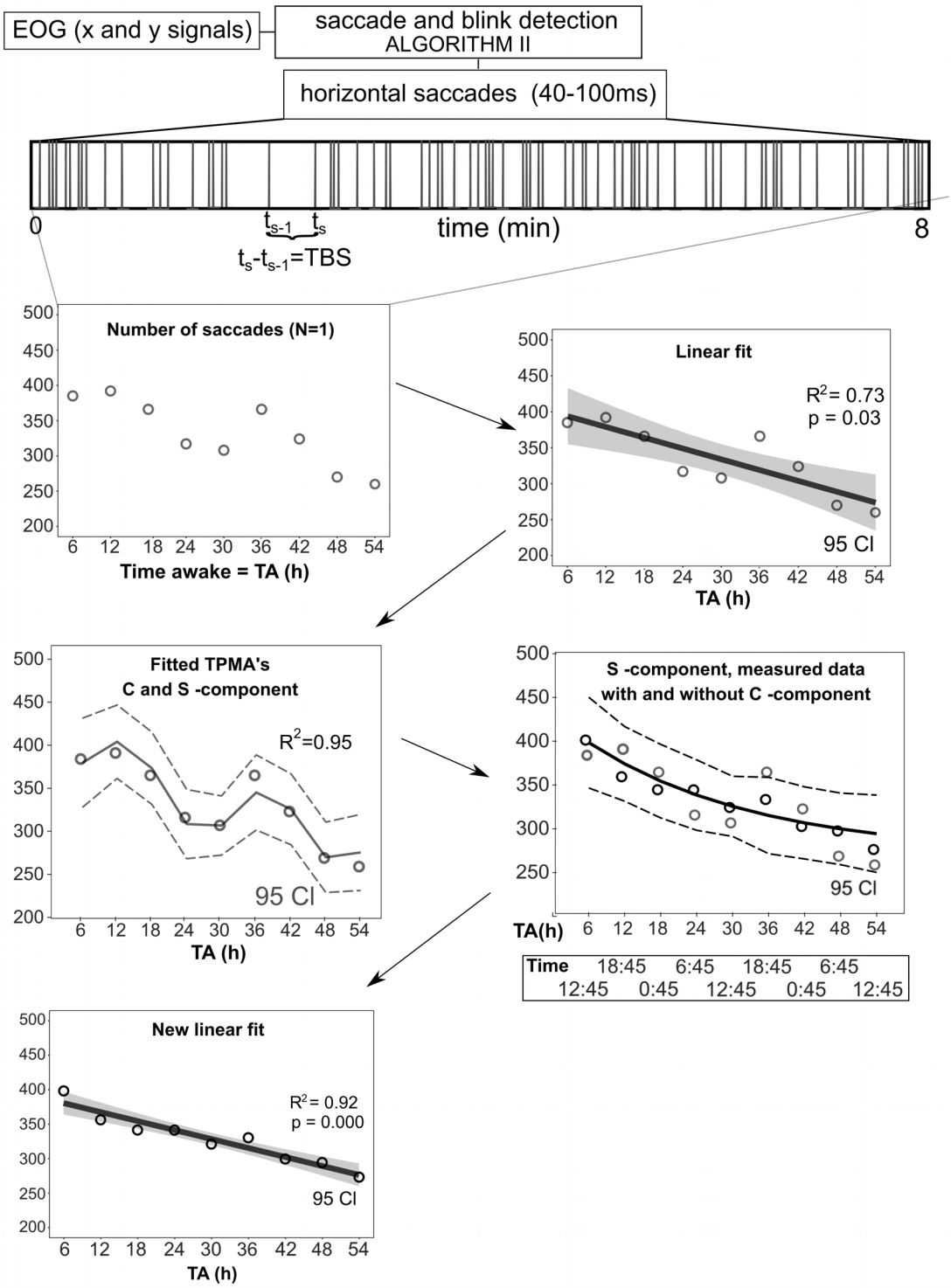

Fig. 10. The analysis chain for the number of saccades. The number of saccades for each participant was measured in the saccade task using EOG. The linear model was fitted to examine the linearity of the decrease in the number of saccades. To improve the linear fit the three-process model of alertness was fitted to the data. After fitting, the C component was removed from the measured data to allow us to examine the exponential function without interference from the sinusoidal component.

8 MAIN RESULTS

8.1 SACCADE PEAK VELOCITY (SPV)

The SPV values were estimated for saccades collected during the overlap paradigm (A-block) since the number of correctly executed saccades in the gap paradigm (B-block) was significantly lower (Fig. 11) in every measurement block.

The high error rate in the gap paradigm was due to the high number of anticipatory responses (saccade latencies with < 100 ms), direction errors, and blinks compared to the overlap paradigm.

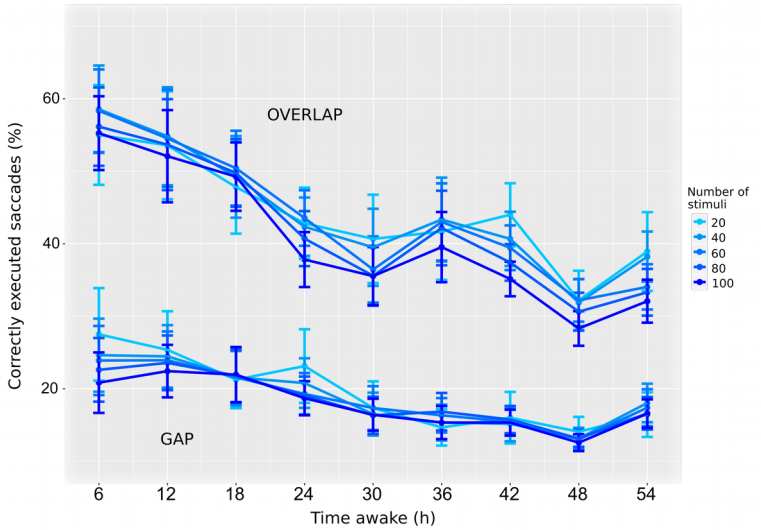

Fig. 11. Mean fraction of correctly executed saccades to presented stimuli. In the overlap condition the number of correctly made saccades were significantly higher than in the gap condition. The cumulative measurement blocks (20 saccades = light blue, … ,100 saccades = dark blue) are presented and the error bars are standard error of mean.

The SPV values measured with EOG decreased with increasing time awake compared to a baseline (6 h) (Fig. 12). The mean SPV values were calculated for each 20 saccade block (A1, A2, A3, A4, and A5) separately and for cumulative blocks (A1=A_{20}, A_{40}, A_{60}, A_{80}, and A_{100}) to study how an increasing time on task effects the SPV values.

The SPV values differed significantly from the baseline after 12 h of time awake for A1, A2, A3, A_{40}, and A_{60} blocks. The blocks A4, A5, A_{80} and A100 differed significantly after 18 h of time awake. Fig. 12. shows that in short measurements (A1, A2, A3, A_{40}, and A_{60}) the SPV values are more affected by the circadian rhythm than in long measurements (A4, A5, A_{80} and A_{100}).

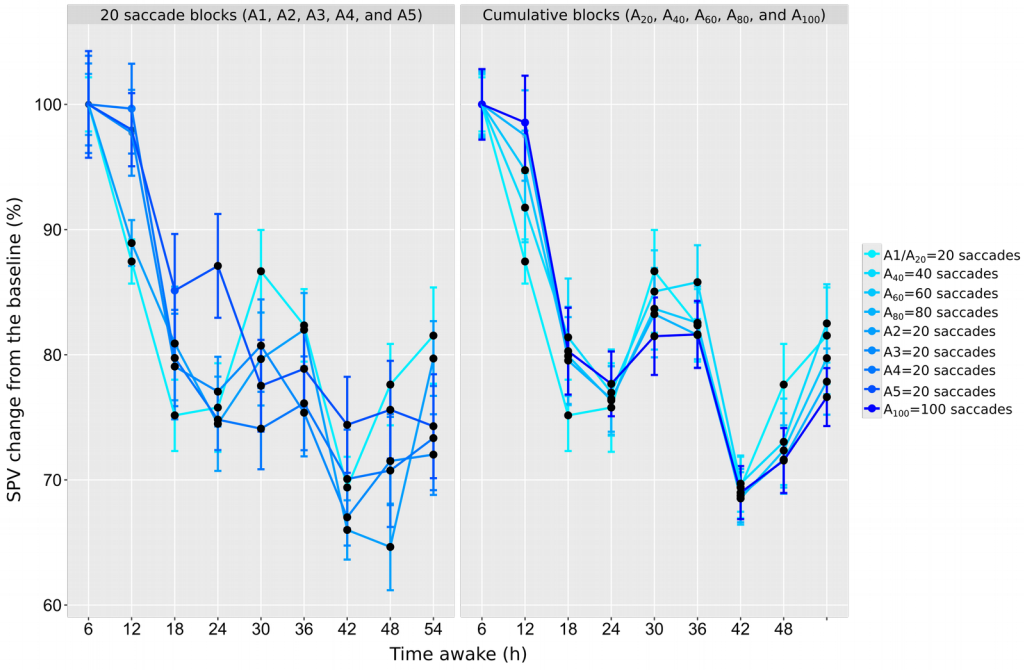

Fig. 12. Relative change in peak velocity compared to the baseline (set as 100 %) for each 20 saccade block: A1, A2, A3, A4, and A5, and cumulative blocks: A_{20}, A_{40}, A_{60}, A_{80}, and A_{100} Measurement points that differ significantly ($p < 0.006$) from the baseline are marked with black.

8.2 NUMBER OF SACCADES

Fig. 13 shows the number of saccades as a function of time awake for each participant (N = 11). The linear fit were calculated for each participant to estimate the linearity of the decrease in the number of saccades as a function of time awake and to examine individual differences. The saccade task included 200 stimuli and 200 return saccades, which means that when the participant has performed the task correctly the number of saccades should be close to 400.

Fig. 14. shows the proportion of correctly executed saccades (dark blue bars) as well as different kind of errors in the individual level analyzed using a traditional event by event analyses. The saccades have been analyzed by comparing the participants reaction to each saccade stimulus (altogether 200 stimulus per measurement). Correctly executed saccades were responses that have been to the same direction than the stimulus in 80 – 700 ms window after the stimulus have appeared and the accuracy of the executed saccade was between 0.5 – 1.5 [160, 161]. Trials including blinks, oblique saccades, omissions, direction errors, undershoot (gain < 0,5), overshoot (gain > 1.5), and anticipatory reaction (< 80 ms) have been classified as erroneous reactions.

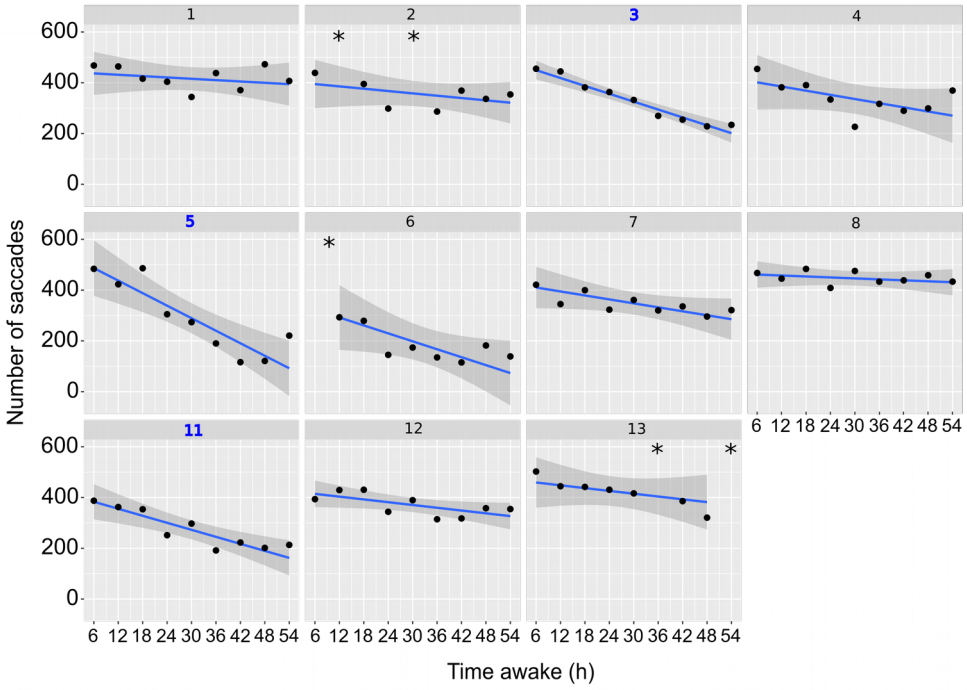

Fig. 13. Number of saccades as a function of time awake. The number of saccades as a function of time awake and estimated linear fits (blue line, gray areas denote 95 % CI) for each participant. The caption above each plot represents the participant number, blue participant number denotes for $p < 0.05$ for the linear fit. Due to technical problems (e.g. loose electrodes) some measurements are missing, they are marked with a star in the figure.

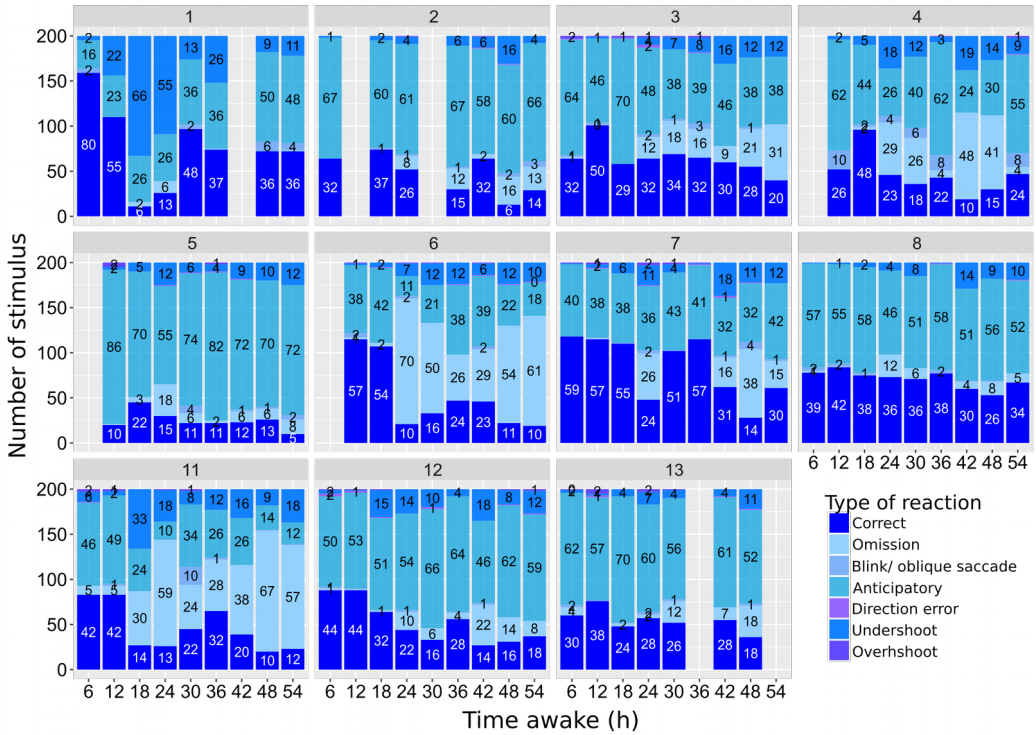

Fig. 14. Proportion of correctly executed saccades and different kind of errors in the saccade task. The numbers on the colored bar denotes for proportion of each response type to the saccade stimulus. The caption above each plot represents the participant number. The proportion of correctly executed saccades are marked with dark blue bars.

TBS values were calculated to examine individual differences in saccade task performance as well as to link the proposed novel saccade task analysis method to traditional event by event analysis. Some participants exhibited bimodal TBS distributions, with peaks on both sides of one second (Fig. 15). If the participant performs the task correctly the TBS value should be approximately one second. However, if the TBS value is much less than 1 sec the participant probably made an corrective right after the erroneous reaction (anticipatory saccade, direction error, undershoot, or overshoot) (*Chapter 3)*. TBS values much larger than 1 s imply that the participant blinked or did not respond to the stimulus (omission). Based on these observations the TBS were divided into three groups: fast response (< 0.5 s), normal response (0.5 – 1.5 s), and late response (> 1.5 s). Fig. 16 shows a cumulative sum of TBS values in each TBS class relative to the duration of the saccade task.

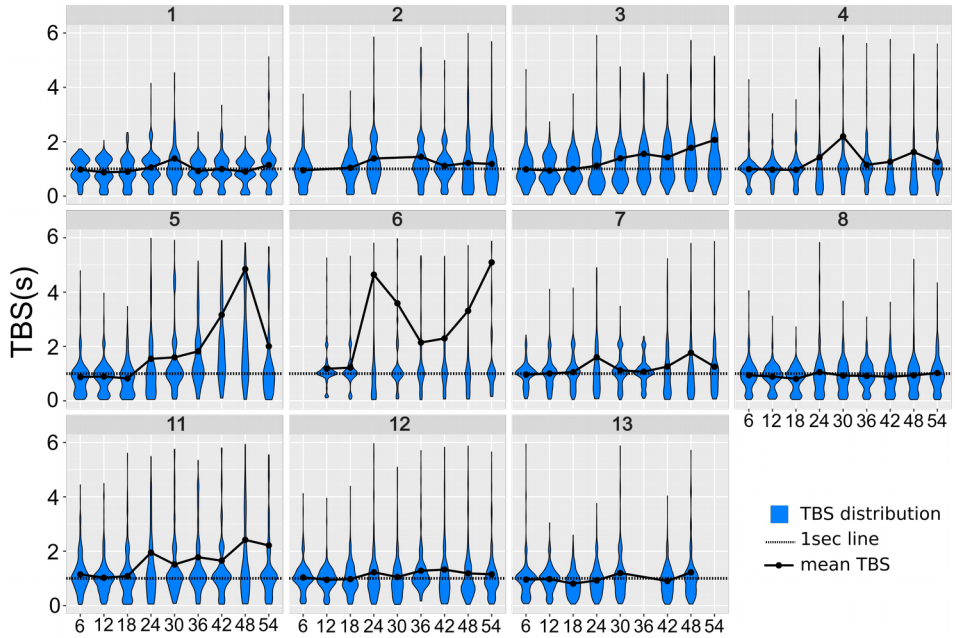

Fig. 15. TBS violin distributions and mean TBS values. TBS distributions (blue) and mean TBS value (black line) for each time awake measurement. The y-axis range is set from 0 to 6 to visualize the individual differences. The participant ID is marked above each plot.

Fig. 17 shows the number of saccades of the first and second measurement in five participants (2, 3, 5, 6, and 7) who performed the study twice. The correlations between the time series are calculated using cross-correlation (lag = 0). The correlation coefficient values were 0.62 – 0.96 (mean 0.79).

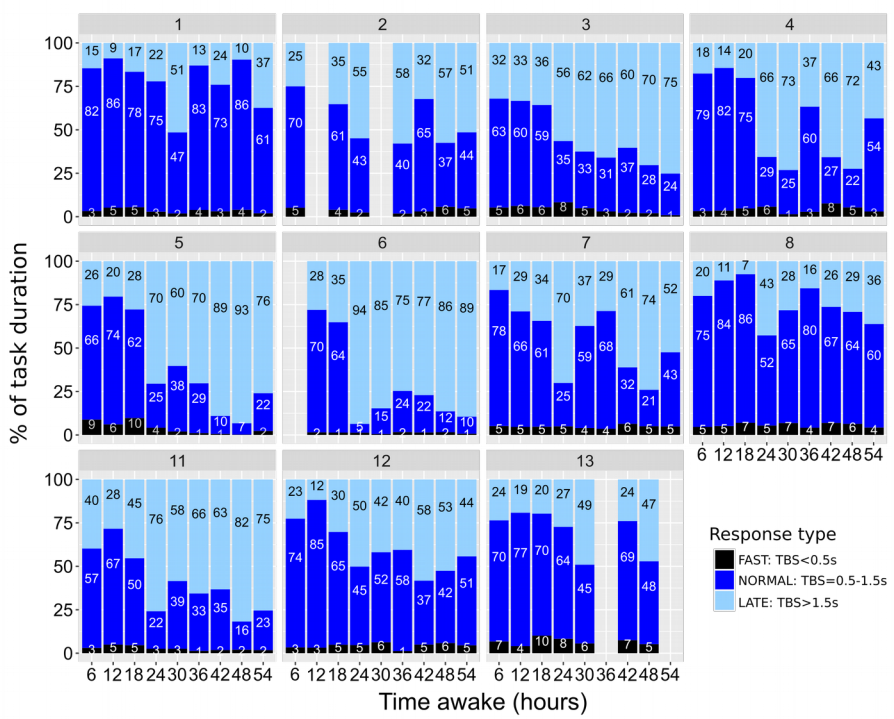

Fig. 16. Time between saccades. The proportion of time (cumulative sum of TBS) of fast < 0.5 sec (black), normal 0.5 – 1.5 sec (dark blue), and late > 1.5 sec (light blue) TBS values for each participant. The caption above each plot represents the participant number.

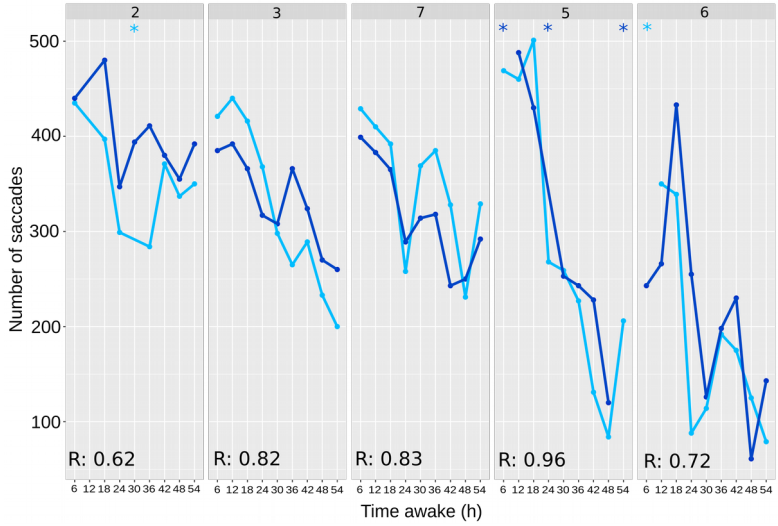

Fig. 17. Repeatability (N = 5). Number of saccades, the first measurement is light blue whereas the second one is dark blue. The correlation coefficient (R) is presented at the lower left. Missing values are marked with a star.

The three-process model of alertness (*Chapter 2.1*) was used to model the saccade task performance. We fitted the model's C and S components to the number of saccades and removed the C component from the fit model. In Fig. 18 the results of fits and the remaining S component are presented. The goodness of fit differs between the participants. The results of the linear fits after removing the C component are presented in Fig. 19.

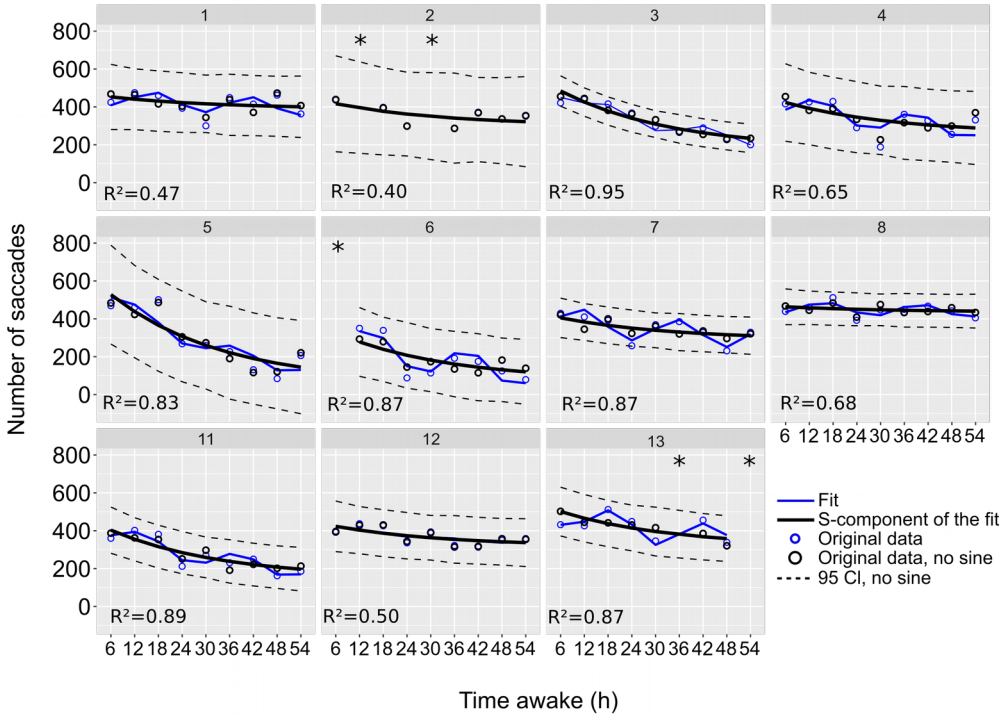

Fig. 18. Fit of TPMA model's S and C -components. A monotonous relation between TBS and time awake for each participant (caption above each plot indicates participant number). Blue circles represent original data, the blue line is the result of fitting, the black line is the S component of the model whereas the black dashed line is a 95 % CL for the S component. The black circles are the original data without the C component. The missing measurements are marked with a star, and R² values are shown for each fit.

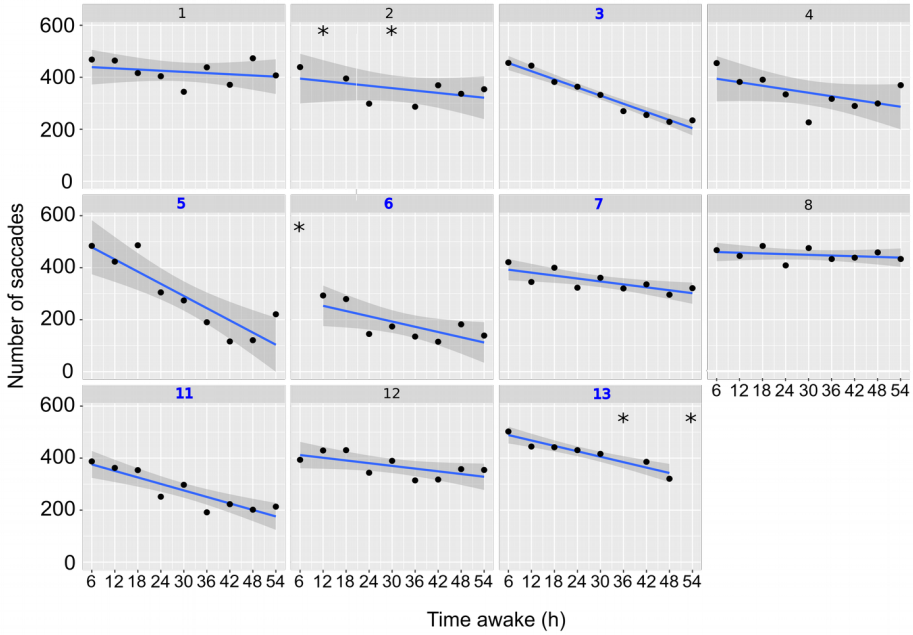

Fig. 19. Number of saccades as a function of time awake after removing the C-component. The number of saccades after removing the C-component as a function of time awake and estimated linear fits (blue line, gray areas denote 95 % CI) for each participant. The caption above each plot represents the participant number, the blue participant number denotes for $p < 0.05$ for the linear fit. The missing values are marked with a star in the figure.

9 DISCUSSION

This thesis examines whether saccadic eye movements derived from an EOG signal could be used as an one-site estimator for time awake. This approach was chosen since eye movements are sensitive to sleep deprivation e.g. [44–48, 50–52, 132] and since EOG is a widely used technique to measure saccadic eye movement during sleep deprivation studies carried out both inside and outside the laboratory e.g. [44–48, 59, 60, 132] Moreover, cognitive functions, especially the attentional ones, are susceptible to sleep deprivation e.g. [13, 14, 20]. The oculomotor and attentional functions share neuroanatomical networks in the brain [55, 56]. Therefore, saccadic eye movement have been used to study attentional functions e.g. [18, 55, 57]. The oculomotor parameters are usually measured in a saccade task. This neurobehavioral task permits simultaneous attention and sleepiness assessment; the performance parameters measure visuospatial attention whereas the oculomotor parameters measure the decrement of arousal (compared to a baseline) [111].

The approach was tested in this thesis work on eleven male navigators from the RNoN. They performed a 8-minute saccade task every 6th hour until 60 h of time awake. Five navigators repeated the protocol after a 10-week washout period. The study was designed to emulate real life conditions: Participants were allowed to use caffeine and tobacco, stimulants which are usually prohibited in sleep deprivation studies e.g. reviews [20, 162].

9.1 SACCADE PEAK VELOCITY (SPV) ESTIMATION OUTSIDE THE LABORATORY

The relative changes in SPV compared to the baseline showed a decreasing trend in group level analyses. The SPV decreased significantly after 12h of time awake compared to the baseline (Fig. 12) (publication I). This result is line with the literature e.g. [46–48, 51, 61, 133, 163, 164]. The SPV values were estimated from correctly executed saccades in the saccade task. This requires event by event analyses and thus triggering between the stimulus and the EOG signal. Additionally, calibration between the eye movement signal and the actual eye movement was needed in order to reliably estimate the SPVs.

An auto-calibrating algorithm (ALGORITHM II) was developed to extract features from the EOG signal without calibration (publication II). In ALGORITHM II the signal denoising was executed in a way that does not distort the temporal parameters of horizontal saccades, especially the SPVs. ALGORITHM II is slow, since it estimates the threshold values for feature detection from the entire data batch.

ALGORITHM II extracted features from the EOG signal collected during a saccade task done every sixth hour until 60 h of time awake. The SPV/D index of every executed saccade during the saccade task was analyzed. The index estimates the bluntness of saccade velocity curve [148, 149]. This approach could have made the SPV estimation easier to execute on-site by circumventing the need to calibrate the eye movement signal and to use event by event saccade task analysis.

The results showed that the changes in the SPV/index were mainly due to amplitude changes in the EOG signal. The correlation between the amplitude and SPV/index was 0.9 (SD = 0.2, N = 16). The amplitude, duration, and the peak velocity of the saccade are closely related to each other according to the main sequence theory [91, 92]. However, the reason for the saccade amplitude changes and thus changes in the SPV/D index was unknown. The participants went through adaptation before the EOG measurements but the magnitude of the EOG amplitude is also related to e.g. electrode placements. In long measurements (several days) the EOG electrodes may partly detach for many reasons (e.g the glue/paste of the electrode dries, the participant scratches the electrode). In 60 h sleep deprivation study the EOG electrodes were changed when needed and these interventions were not recorded. Consequently our data does not permit studying the SPV/D index during prolonged time awake. The lack of confidence in the amplitude measurements made us choose the number of saccades as biomarker instead of the SPV.

9.2 NUMBER OF SACCADES ESTIMATION OUTSIDE THE LABORATORY

The number of correctly executed saccades in the saccade task decreased during prolonged time awake in publication I (Fig. 10). The results were similar to those reported by Porcu and colleagues after one night of sleep deprivation [110].

To closely study the executed saccades and timing between them in the saccade task, all detected horizontal saccades (40 – 100 ms duration) were analysed (publication III). ALGORITHM II was used to detect saccades. This analysis technique does not require event by event analysis of the saccade task. Fig. 13. shows that the number of saccades decreased as a function of time awake and that the linear trend was significant in three participants. Since, the circadian rhythm affected the number of executed saccades (Figs. 13, 15, and 16), the TPMA was fit to the data and the circadian component (C-component) was removed from the measured data (Fig. 18). After removing the circadian component a mathematically monotonous relation between performance in the saccade task and time awake was evident and the linear model showed a significant trend for six out of eleven participants (Fig. 19).

The decreasing number of saccades was a result of increasing TBS in the saccade task (Figs. 15 and 16). TBS values were divided in to fast, normal, and late responses to permit linking the studied analysis method result to results obtained with traditional saccade task analyses. Figs. 14 and 16 shows that TBS values > 1.5 s were mostly due to omissions (lapses) and anticipatory reactions (false starts). Both omission and commissions (e.g. reactions without stimulus or false starts), have been associated with sustained attention deficits caused by wake-state instability e.g. [2, 16, 63, 68]. The number of lapses e.g. [36] and false starts [165] have been reported to increase when being measured with PVT during prolonged wakefulness.

Sleep deprivation has been reported to increase the number of anticipatory saccades and omissions in a saccade task [110]. In a cumulative sleep deprivation study failures in response selection (anticipatory or premature responses) and direction errors during a cued saccade task (orienting attention task) were suggested to be linked to circadian rhythm whereas increased errors in response execution were proposed to be linked to sleep drive [19]. These authors concluded that the former could be related to impairment in the function of the orienting attentional system whereas the latter could be explained by failure to sustain attention.

Even though the results in publication III suggest that there are large differences between individuals in saccade task execution under sleep deprivation (Figs. 14 – 18), the proposed saccade task analysis method identifies sustained visual attention deficit on individual level.

Five participants went through the study protocol twice, which allowed us to study the repeatability of the saccade task performance. Fig. 16 shows that the performance was rather stable within individuals: The correlation was between 0.62 and 0.96 (mean 0.79). Similar results have been obtained with PVT and other cognitive and reaction time tasks [166–169]. Further, genetic factors may explain sleepiness related inter-individual variations in neurobehavioral decrements [20, 170, 171]. There is evidence that phenotypic neurobehavioral responses to sleepiness are stable over long-time intervals, even years [168, 172]. This suggests that even though the current system needs personal calibration before the actual time awake measurements, probably no frequent calibration is needed.

9.3 FEATURE EXTRACTION FROM THE EOG SIGNAL

SPV estimation from the EOG signal is more challenging, from a signal processing perspective, than estimating the number of saccades. The SPV estimation requires calibration between the eye movement and EOG signal as well as denoising methods that do not distort the temporal parameters of the eye movements e.g. [119, 120, 173]. The auto-calibrating algorithm for feature extraction (ALGORITHM II) was developed to extract features from the EOG signal without calibration. ALGORITHM II was developed for horizontal

saccade analyses and the signal denoising was executed in a way that does not distort the temporal parameters, especially those in the SPV. However, ALGORITHM II is slow, since it estimates the threshold values for feature detection from the entire data batch. A computationally light, probabilistic ALGORITHM IV was developed to rapidly extract features from the EOG signal publication IV). The algorithm processes data sample-by-sample and can therefore extract features from the EOG data faster than ALGORITHM II. The performance of ALGORITHM IV was better than that of the auto-calibrating algorithm (publication II) with respect to the sensitivity and precision of saccade and blink detection (Table 1). Even though ALGORITHM IV is a semi-supervised method (requires a short training period before feature extraction), it offers a reliable, robust, and fast tool for EOG signal feature extraction suitable for field studies.

Lately Korda *et al.* (2018) published an automated algorithm that employs the mean value of the logarithm of divergence and the largest lyapunov exponent to identify saccades and blinks [174]. The algorithm was developed for IROG data but achieved high precision when used to detect the saccades and blinks from the EOG signal; saccades with 91.1 % precision and blinks with 100 % precision (N = 300, altogether 25000 saccades and 2366 blinks). Therefore, Korda's calibration free and automatic feature extraction method should be tested using EOG data recorded in different kinds of setups (e.g. outside the laboratory) in future studies.

9.4 STRENGTHS AND LIMITATIONS

The time awake metric should estimate for how long a person has been awake with a certain confidence, and potentially be generalizable to everyone with or without personal calibration. Cheating should be avoided/identified by using physiological parameters which are under involuntary control. The metrics should be practical, easy to use on site, be as unobtrusive as possible, low-cost, and permit large scale use. The strengths and limitations of this thesis work are discussed relative to these requirements.

RELIABILITY, REPEATABILITY, AND GENERALIZABILITY

The results showed a monotonic relation between saccade task performance and time awake for all eleven participants. The repeatability test with five subject showed high correlation between the first and second week measurements. These results suggest that the metric could be used as time awake metrics as long as personal calibration has been done beforehand. In this thesis prolonged time awake was used as a metric for sleepiness: Sustained wakefulness causes sleepiness and increases homeostatic sleep drive. Therefore, the achieved result was not validated against other sleepiness metrics e.g. EEG, MSLT, and PVT.

The results are based on data measured from eleven naval officers but the repeatability was estimated only from five participants who were. Moreover, the participants were trained professionals, who were highly motivated to do their best in every situation and who were used to staying awake for long periods of time. Therefore, a limitation of this thesis is the small and homogeneous participant group. Individual variability in a normal population need to be studied.

A strength of the thesis is the prolonged wakefulness setup, which was designed to preserve real life conditions. A decreasing trend of saccadic eye movement was evident, even though the participants were allowed to use caffeine and tobacco, stimulants which are usually prohibited in sleep deprivation studies e.g. reviews [20, 162]. However, the setup allowed us to examine eye movements for almost three 24 h-cycles of the circadian rhythm, but the saccade task was measured only every six hours. Therefore, the effect of sampling rate (time between the eye movement measurements) on the confidence limits as well as the effect of individual differences in the circadian rhythm should be studied carefully.

VOLUNTARY CONTROL OF THE SACCADIC EYE MOVEMENTS

The saccade task requires cooperation from the person who takes the test. If he/she refuses to execute the task or performs the task incorrectly (willfully or not) the test result cannot be used to estimate prolonged time wake. In this case, it matters little whether the measured and observed parameter is under involuntary control. The saccade execution is under voluntary control, however trying to achieve better performance by cheating in the saccade task is difficult or even impossible under sleep deprivation: The person needs to move her/his eyes every second when the stimulus appears for eight minutes. Such performance requires the ability to maintain sustained attention, something which is affected by sleep deprivation.

USABILITY OF THE METRICS

In this thesis the EOG signals were measured using a robust, medical device certificated to record physiological signals (e.g. EEG, electrocardiogram, respiratory). However, the EOG signal could of course be measured using a light ambulatory system, e.g Bittium Faros (Bittium, Oulu, Finland). These portable systems make measurements outside the laboratory easy to carry out e.g. [84]. New unobtrusive techniques for measuring EOG have emerged, e.g. dry electrodes integrated into eyewear frames e.g. [175, 176] and in-ear EOG [177]. Before large scale use, the reliability and usability of these new EOG measurement techniques should be evaluated.

A strength of this thesis is that the feature extraction from the EOG signal and the saccade task analysis method were executed with no need to calibrate between the EOG signal and eye movements. In addition, no triggering between the saccade task and the EOG signal was necessary. These features make the metric practical and easy to use on site.

9.5 FUTURE RESEARCH

When developing new testers and biomarkers hindsight has a 20/20 vision. While many of the presented results are encouraging there are still issues left for future work. First more work is needed to study individual differences in saccade task performance during acute sleep deprivation. The saccade task performance varies between individuals (e.g. express saccade makers, [178]) as well as the ability to cope with sleep deprivation (reviews [2, 20, 179]). Therefore, optimizing or even individualizing the saccade task parameters could potentially improve the sensitivity of the time awake estimator.

In real life sleep deprivation is seldom induced by prolonged wakefulness but it is rather a cumulative partial sleep deprivation resulting from e.g. poor night's sleep, irregular working hours, jet lag etc. The performance deficit in the saccade task should be studied systematically in the same individuals during sustained wakefulness and partial sleep deprivation (e.g. Van Dongen *et al.* (2003) executed such a systematic comparison for PVT [180]). Moreover, in conditions where the sleep deprivation is partial or cumulative, the performance deficit in the saccade task should be validated against a widely used sleepiness measurement technique (e.g. MSLT, EEG, or PVT) in the laboratory.

New unobtrusive eye movement measurement approaches could offer solutions to make our metric easier to use and cost-effective for large scale use. Our approach to analyze the saccade task and eye movement data is simple, robust, and requires a modest sampling rate for eye movement recordings. The eye movements could possibly be measured with a slow VOG device (e.g. a tablet or a smartphone) or with a disposable in-the-ear EOG [177]. Additionally, the saccade task could be presented by a tablet or a smartphone since no event by event analyses are required to estimate the saccade task performance. Moreover, the eye movement signal processing could be lighter and faster (depending on the measurement method) since only the occurrence of the saccades and blinks needs to be detected.

9.6 CONCLUSION

Prolonged time awake increases sleepiness. Increasing sleep drive induces rapid and uncontrolled sleep initiation leading to unstable cognitive performance, which is comparable to alcohol intoxication. Even though sleepiness is a major identifiable and preventable cause of accidents, there is no reliable on-site time awake tester comparable to a breathalyzer for blood alcohol concentration.

This thesis presents an attempt to develop a time awake tester based on eye movements derived from the electro-oculographic signal. The proposed novel metric worked on individual level and the measurements were repeatable. Based on these results the proposed approach could be used as a

time awake metric outside the laboratory. The metric needs individual calibration before the time awake of a person can be estimated. More research is needed to study individual differences, optimize the measurement duration, and stimulus parameters.

In the future a time awake tester could provide a tool to penalize sleepy driving and also prevent sleep related accidents. In addition, a time awake tester could increase people's awareness of how prolonged time awake affects one’s attentional functions and that way can help people to find a balance between activity and rest. Applications for such a product range from safety critical work, shift work, global work across time zones to everyday activities, and health related problems.

10 REFERENCES

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APPENDIX I

A exponential equation has been used to describe the main sequence between amplitude and peak velocity (Equation A.1).

(A1.1) $$V_m = V_a\left(1 - e^{[-A/C]}\right)$$

Here, V_m = vectorial peak velocity, V_a = asymptotic V_m, value for large saccade, A = saccade amplitude, and C = angular constant that determines how fast V_m increases with saccade size [92].

APPENDIX II

The performance of the algorithm was evaluated using the conventional true positive rates (TPR, sensitivity), and positive predictive values (PPV, precision) (when the false positive (FP) values were available), defined as e.g. [156]

(A2.1) $$TPR = 100\frac{TP}{N_{true}}$$ and

(A2.2) $$PPV = 100\frac{TP}{N_{method}}$$

where TP indicates the number of true positives (correctly identified events) N_{true} is the total number of true events (TP + false negative (FN)), and N_{method} is the total number of events detected by the method (TP + FP).