Obstructive sleep apnea (OSA) is one of the most prevalent and detrimental sleep disorders. Conventional severity assessment of OSA, however, relies on the number of airflow limitations, having a weak association with the most prevalent symptoms of OSA: excessive daytime sleepiness and deteriorations in vigilance. In this Ph.D. thesis, novel pulse oximetry-based methods are presented to better associate the severity of OSA with these symptoms.
Samu Kainulainen

PULSE OXIMETRY-DERIVED BIOMARKERS FOR SEVERITY ASSESSMENT OF OBSTRUCTIVE SLEEP APNEA

- ASSOCIATING PARAMETRIC AND FREQUENCY-DOMAIN FEATURES OF SPO$_2$ AND PPG SIGNALS WITH DAYTIME SLEEPINESS AND IMPAIRED VIGILANCE

ACADEMIC DISSERTATION

To be presented by the permission of the Faculty of Science and Forestry for public examination in the Auditorium SN201 in Snellmania Building at the University of Eastern Finland, Kuopio, on October 9$^{th}$, 2020, at 12 o’clock.

University of Eastern Finland
Department of Applied Physics
Kuopio 2020
Author’s address: The University of Eastern Finland
Department of Applied Physics
P.O. Box 1627 (Canthia), 70211
KUOPIO, FINLAND
email: samu.kainulainen@uef.fi

Supervisors:

Adjunct Professor Timo Leppänen
University of Eastern Finland
Department of Applied Physics
KUOPIO, FINLAND
Kuopio University Hospital
Diagnostic Imaging Center
KUOPIO, FINLAND
email: timo.leppanen@uef.fi

Professor Juha Töyräs
The University of Queensland
School of Information Technology
and Electrical Engineering
BRISBANE, AUSTRALIA
University of Eastern Finland
Department of Applied Physics
KUOPIO, FINLAND
Kuopio University Hospital
Diagnostic Imaging Center
KUOPIO, FINLAND
email: juha.toyras@uef.fi/j.toyras@uq.edu.au

Adjunct Professor Antti Kulkas
Seinäjoki Central Hospital
Department of Clinical Neurophysiology
SEINÄJOKI, FINLAND
University of Eastern Finland
Department of Applied Physics
KUOPIO, FINLAND
email: antti.kulkas@epshp.fi

Scientific Director Arie Oksenberg
Loewenstein Hospital - Rehabilitation Center
Sleep Disorders Unit
RAANANA, ISRAEL
email: arieoksenberg@gmail.com
Reviewers:

Professor Zahra Moussavi
University of Manitoba
The Department of Electrical & Computer Engineering
WINNIPEG, CANADA
email: Zahra.Moussavi@umanitoba.ca

Professor Ludger Grote
University of Gothenburg
Department for Internal Medicine and Clinical Nutrition
Institute of Medicine
Centre for Sleep and Wake Disorders
GOTHENBURG, SWEDEN
email: ludger.grote@lungall.gu.se

Opponent:

Associate Professor Raquel Bailón Luesma
University of Zaragoza
The Department of Electronic Engineering and Communications
ZARAGOZA, SPAIN
email: rbailon@unizar.es
ABSTRACT

Obstructive sleep apnea (OSA) is one of the most prevalent and detrimental of the many sleep disorders. In OSA, recurrent collapses of upper airways limit partially (hypopnea) or block completely (apnea) the airflow during sleep. OSA is currently diagnosed based on medical examination, daytime symptoms, and the results of diagnostic sleep study. Diagnostic sleep study is used for severity assessment of OSA, being either polysomnography (PSG) or ambulatory polygraphic recording that both are data-rich physiological measurements. To a significant extent, the severity assessment of OSA is based on the value of the apnea-hypopnea index (AHI). However, the AHI is defined as the average number of apneas and hypopneas per slept hour, thus providing an over-simplistic estimation of the severity of the disease i.e. it has major shortcomings.

The shortcomings of AHI include the poor association with the most common daytime symptoms of OSA: excessive daytime sleepiness (EDS) and reduced vigilance. An EDS assessment is based on subjective questionnaires such as the Epworth sleepiness scale (ESS) or objective measurements e.g. the Multiple sleep latency test (MSLT). In addition, the evaluation of vigilance can be conducted via the Psychomotor vigilance task (PVT). However, the AHI is able to explain only 10% of the variation in daytime sleep latencies and less than 2% of the variation in ESS scores. Moreover, the AHI lacks the capability to explain the prolonged reaction times in PVT, and the severity classification of OSA based on AHI displays little association with impaired vigilance.

Previous literature shows, however, that OSA-related hypoxemia contributes to the development of EDS and vigilance deterioration. Thus, the main hypotheses of this Ph.D. thesis were that a detailed parametric quantification of apneas, hypopneas, and related blood oxygen desaturations and frequency-domain features of pulse oximetry signals could be linked to objective EDS and poor PVT performance. The aim was to test the stated hypotheses by retrospectively investigating sub-populations from two large clinical datasets consisting of suspected OSA patients. The first dataset comprised patients with PSG and MSLT data \(n = 2064\) and the second consisted of patients with PSG and PVT data \(n = 902\).

The severity of intermittent hypoxemia was consistently found to have a significant \(p < 0.05\) association with more severe EDS and impaired vigilance. Relative 10% increases in the Desaturation Severity (DesSev) and in the time spent under 90% oxygen saturation \(t_{90\%}\) were significantly associated with higher odds of having severe \(p < 0.001\) or moderate EDS \(p < 0.05\). Similar increases in DesSev, \(t_{90\%}\), and median desaturation depth were associated with prolonged mean and median reaction times and a higher number of lapses in PVT \(p < 0.05\).
Furthermore, the increase in power within the 15 - 35 mHz frequency band of blood oxygen saturation and heart rate signals indicated a significant \((p < 0.05)\) risk of having severe EDS. In addition, an increase in photoplethysmogram (PPG)-based arterial pulsation frequency (APF) was significantly \((p < 0.001)\) associated with a higher number of lapses and larger within-test variation in PVT in male OSA patients, and a higher number of lapses in female OSA patients \((p < 0.05)\).

In conclusion, a more detailed quantification of desaturations is able to link the severity of OSA more strongly to EDS and impaired psychomotor vigilance than the conventionally used AHI. In addition, large fluctuations in heart rate combined with severe intermittent hypoxemia are a significant predictor of OSA-related EDS. Furthermore, a higher APF in PPG provides a marker for deteriorations in vigilance. These findings emphasize the potential of pulse oximetry-based methods for severity assessment and polysomnographic phenotyping of OSA.

**National Library of Medicine Classifications:** QY 450, WF 143, WL 108

**Medical Subjects Headings:** Dyssomnias/diagnosis; Sleep Apnea, Obstructive/diagnosis; Sleepiness; Oxygen/blood; Hypoxia/diagnosis; Oximetry; Polysomnography; Photoplethysmography; Psychomotor Performance

**Yleinen suomalainen asiasanasto:** unitutkimus; unihäiriöt; uniapnea-oireyhtymä;
You can change what you do.
But you can’t change what you want.

And you have to get what you want your own way.

Thomas Michael Shelby
Peaky Blinder and a proper gentlemen
This is the first book I have ever written, and probably the last. Therefore, I recklessly use my writer’s freedom to shortly reflect this chapter of my life. Loud, tattooed punk rock kid from the East. Few gap years between high-school and uni. Never the brightest star in class. Very few excellent grades. Sometimes bad attitude. Two little kids at home. Part-time and full-time working alongside studies. But even I learned something, not least about myself. I learned how it feels when you overcome struggles and work to understand something. When you don’t give up even though it seems to be the only rational option.

So, I’d like to discuss with you that why should we give a damn about the philosophy of science, the axioms for real numbers, molecules, science in general? Why should we spend time trying to understand the basic concepts of human beings and nature? Why bother to read old books, pick up pen and paper and derive an equation when all answers can be found from the internet within a second? My answer is naive and idealistic, but these thoughts are the most important product of my education.

My answer is that with science and knowledge, we really can make a difference. Over the centuries, we as mankind have made a difference. We have discovered countless wonders of the nature and wonders of the world. Some scientists have gained glory, earned millions. But none has benefited more of science, than mankind and individuals themselves. The intrinsic value of science is not the number of one’s publications. It is not how many companies can be established by new innovations. These are just by-products of something greater. A demonstration of our, also mine, humane need to constantly measure our achievements.

The something greater is being able to understand the world we live in. To me, the value of science is to be able to understand how and why this world works the way it does. To let our curiosity become knowledge. That is also why science and education shouldn’t belong only to those who can afford it. Every human being should have the right to learn; have the right to be curious. Have a right to a teacher, who can sustain the curiosity and help to build it to knowledge. Because scientific education has the power to develop our understanding. Maxwell’s equations, for example. Four lines of plain beauty. After studying what they are, you can take a photo of you driving a Tesla, post it on Instagram with your iPhone and realize, that without those four beautiful equations it wouldn’t be possible. Our prosperity is a by-product of science. We shouldn’t forget that, but awfully often we do.

Don't get me wrong. I don’t mean only natural sciences and technology. I mean all disciplines. And if one wants to understand the real nature of black holes or the globally increasing inequality and its historical roots... Well, that is why we need to give some time for the basics. So that we can enjoy that overwhelming feeling when we learn and understand something. With few-seconds googling we end up knowing something; while studying something from the basics to the top, we end up understanding something. Only after that, we are ready to create something new. Something new that can change the world.

All in all, each finding has a foundation, a preceding result. Each study is based on hypotheses, that are generated based on earlier knowledge. And in my opinion, to be one of the pieces in that constantly growing puzzle of knowledge is an honor beyond measuring. You can call me idealistic and naive as I work in a highly specialized field, in a small university, in a small country. But, all the wonders of this world that improve our understanding are worth exploring.
That is why I advocate open science and public education. This is my small part in the global act of working for a better world for everyone. And as long as we share our knowledge, disseminate knowledge via teaching, and educate our children all over the world, we can and will achieve it. All we need is time and fire inside. I have both and I know that I’m not alone.

"I believe thanks are in order" - Captain James Norrington.

First and foremost, I would like to acknowledge Timo Leppänen and Juha Töyräs for the principal supervision of this thesis. It has been a privilege to work with you and learn from you. I would like to thank you both for your constructive criticism, not so constructive criticism, and endless support. I am sincerely grateful that you have put up with my sometimes spicy character, especially after we moved in the same office with Timo. For my defense, I have had to tolerate Timo’s Spotify-playlists and share a bed with him for a week in Vancouver. I think we are even.

Furthermore, I would like to express my gratitude to my two additional supervisors Antti Kulkas and Arie Oksenberg. Your input to this thesis and support towards my scientific career have been substantial. In addition, I would like to thank Adjunct Professor Sami Myllymäki for super easy and flexible collaboration. Sincere thanks goes also to Scientific Director Brett Duce and medical personnel in Princess Alexandra Hospital for gathering the PVT data and to Natan Gadoth and the whole Sleep Disorders Unit of Loewenstein Hospital for the MSLT data. In addition, I would want to acknowledge all the foundations and organizations that have funded this thesis. I would also like to thank all the reviewers who have peer reviewed my articles, Ewen McDonald for language check, Professor Zahra Moussavi and Professor Ludger Grote for reviewing this thesis and Associate Professor Raquel Bailón for being the opponent of this thesis.

Our research group is entitled to have its own paragraph. I want to thank you all for being such a special colleagues. Special thanks goes to Akseli and Laura for the unforgettable and oxygen-poor office-marriage as well as unprofessional psychotherapy. I also want to thank Henkka for being a co-author and a huge asset in all of my investigations. And not to forget, thank you Saara and Jusa, even though our conversations have mostly been insignificant (p>0.05).

I have been blessed with a line of superior teachers, lecturers and supervisors, who have step by step guided me to this point. Therefore, I would first like to thank Tomi Surakka for lighting the first spark towards mathematics almost twenty years ago. That spark was kept on by Juha Kettunen, Sami Laitela and Antti-Ville Hurskainen later on despite my personal resistance. At the Department of Applied Physics, I was taught by Markku, Lasse, Anna, Ville and Päivi and others, who sparked my curiosity and love towards mathematics and physics again. Thank you for all the lessons, good and bad. None of this would have happened without you. Outside the scope of my scientific career, I would want to acknowledge Jouko Kakkonen from Mustavaara for teaching me true work ethic. I know that you cannot read this anymore, but you would have been proud of the legacy you left. In addition, Pasi, Exxa and others from Guru, Hippo from Ilona, younger Jouko from the pulp mill, Jari from Intro, Tero from Elisa and Jyrki from Kesko: thank you for giving me the opportunity to work. It means a lot to me.

I’m proud of my roots. I was born and raised in Northern Karelia, by the best parents one could have ever hoped for. There is no words, written or said, that
can ever describe my gratitude towards you. You never told that my dreams are impossible. You showed what is dedication and commitment. You taught, together with the entire family, the value of hard work and the respect towards other human beings. Most importantly, the whole family has always supported me, even though I know some of you disagree with some of the choices I have made. I would also like to thank Mika, for being my biggest competitor and the best older brother one could get. Every child needs heroes and you were and are mine. I love you all and I am honoured to call you my family. Thank you for everything.

This leads to the group of people I call my friends. #talkoot, Yolo, Hamina Tattoo, Joensuu guys, the "bigger boys" in Tampere and Helsinki. I would like to express my sincere gratitude to Asko and Veera for keeping your door always open, to Arttu, Tumi and Bäri for being a friend for over a decade, Jarkko and Aku for all the compulsory fishing man has to do, Tommi for latenight Playstation battles, another Samu for not so scientific conversations, Antti for deadlift coaching and rest of the Yolo+Piia for all the nights out with cucumber water in different locations. I would also like to acknowledge the mother of my children, Hanna. Despite we decided to go separate ways, I will never underrate how much it is because of you that I am here where I am today. List would go on and on forever. I do not know why I have so many of you in my life constantly putting up with me. Nevertheless, I am grateful for each and everyone of you. This being said, I would want to shortly respect the memories of Vili, Andy and Tillu. None of us leaves this world alive; but even though too soon, you left with your boots on. As Carlos Ruis Zafón wrote, "As long as we are being remembered, we remain alive."

Lastly, Erika and Eeka. I truly hope, that the storms you encounter will be milder than ours. However, I hope that you find your own path, your own fire inside. Let that fire burn proudly, regardless of my or other people's opinion. Sometimes it means diving straight into the storm, getting your hands dirty and even leaving hearts broken. I am in no position to give you any other advice for life as I haven’t yet figured out how life should really be lived. So I just say that I loved you then, I love you now and I love you as long as I breathe (pun intended). Hopefully you read this someday, so you see that your dad publicly wrote a "dad joke". "Dad is an embarrassing idiot", you say.

"Do you know what is the name of Bruce Lee’s vegetarian brother?", I answer with a smile that I hope never diminishes.

With appreciation and a heart full of love,

Kuopio, September 2020
Samu Kainulainen

x
LIST OF PUBLICATIONS

This thesis consists of a review of the author’s work in the field of medical physics and sleep medicine, and the following selection of the author’s publications:


Throughout the thesis, these publications will be referred to by Roman numerals I-IV.
AUTHOR’S CONTRIBUTION

The studies included in this thesis were done at the Department of Applied Physics, University of Eastern Finland and at the Diagnostic Imaging Center, Kuopio University Hospital in a collaboration with the School of Information Technology and Electrical Engineering, The University of Queensland (Australia); the Department of Clinical Neurophysiology, Seinäjoki Central Hospital (Finland); the Sleep Disorders unit, Loewenstein Hospital-Rehabilitation Center (Israel); the Department of Respiratory & Sleep Medicine, Sleep Disorders Centre, Princess Alexandra Hospital (Australia); the Department of Engineering, Reykjavik University (Iceland).

The author’s contribution to studies I-IV was as follows:

I The author designed the study with the supervisors and participated in the study conception, was responsible of the manual re-analyses of the sleep recordings together with Sefa S, was responsible of all data analyses, interpreted the results with the co-authors, and was the main writer of the manuscript.

II The author designed the study with the supervisors and participated in the study conception, was responsible of all data analyses, interpreted the results with the co-authors, and was the main writer of the manuscript.

III The author designed the study with the supervisors and participated in the study conception, was responsible of inspection of the automatic analyses, was responsible of all data analyses, interpreted the results with the co-authors, and was the main writer of the manuscript.

IV The author was responsible of the study design, conception, and data analyses. Author interpreted the results with the co-authors and was the main writer of the manuscript.

In all manuscripts the collaboration with the co-authors has been significant.
## LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AASM</td>
<td>American Academy of Sleep Medicine</td>
</tr>
<tr>
<td>AHI</td>
<td>Apnea-hypopnea index (events/hour)</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
</tr>
<tr>
<td>ArI</td>
<td>Arousal index (events/hour)</td>
</tr>
<tr>
<td>APF</td>
<td>Arterial pulsation frequency</td>
</tr>
<tr>
<td>BIC</td>
<td>Bayesian information criterion</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index (kg/m²)</td>
</tr>
<tr>
<td>CDF</td>
<td>Cumulative distribution function</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>COPD</td>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>CVD</td>
<td>Cardiovascular disease</td>
</tr>
<tr>
<td>DC</td>
<td>Direct current</td>
</tr>
<tr>
<td>DesArea</td>
<td>Individual desaturation event area (s%)</td>
</tr>
<tr>
<td>DesDur</td>
<td>Desaturation duration parameter (%)</td>
</tr>
<tr>
<td>DesSev</td>
<td>Desaturation severity parameter (%)</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>EDS</td>
<td>Excessive daytime sleepiness</td>
</tr>
<tr>
<td>EDF</td>
<td>European data format</td>
</tr>
<tr>
<td>EEG</td>
<td>Electroencephalogram</td>
</tr>
<tr>
<td>EMG</td>
<td>Electromyogram</td>
</tr>
<tr>
<td>EOG</td>
<td>Electro-oculogram</td>
</tr>
<tr>
<td>ESS</td>
<td>Epworth sleepiness scale</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>HF-AC</td>
<td>High-frequency alternating current</td>
</tr>
<tr>
<td>HSAT</td>
<td>Home sleep apnea testing</td>
</tr>
<tr>
<td>HR</td>
<td>Heart rate</td>
</tr>
<tr>
<td>HRV</td>
<td>Heart rate variability</td>
</tr>
<tr>
<td>Lapses</td>
<td>Reaction times exceeding 500 ms</td>
</tr>
<tr>
<td>LF</td>
<td>Low-frequency</td>
</tr>
<tr>
<td>LF-AC</td>
<td>Low-frequency alternating current</td>
</tr>
<tr>
<td>mAPF</td>
<td>Median arterial pulsation frequency (1/min)</td>
</tr>
<tr>
<td>mDD</td>
<td>Median desaturation depth</td>
</tr>
<tr>
<td>MSL</td>
<td>Mean daytime sleep latency (min)</td>
</tr>
<tr>
<td>MSLT</td>
<td>Multiple sleep latency test</td>
</tr>
<tr>
<td>mRT</td>
<td>Median reaction time</td>
</tr>
<tr>
<td>NREM</td>
<td>Non-rapid eye movement</td>
</tr>
<tr>
<td>ObsDur</td>
<td>Obstruction duration parameter (s%)</td>
</tr>
<tr>
<td>ObsSev</td>
<td>Obstruction severity parameter (s%)</td>
</tr>
<tr>
<td>ODI</td>
<td>Oxygen desaturation index (events/hour)</td>
</tr>
<tr>
<td>OHb</td>
<td>Oxygenated hemoglobin</td>
</tr>
<tr>
<td>OSA</td>
<td>Obstructive sleep apnea</td>
</tr>
<tr>
<td>$P_{HR}$</td>
<td>Power in 15 - 35 mHz frequency band in heart rate signal</td>
</tr>
<tr>
<td>$P_{SpO_2}$</td>
<td>Power in 15 - 35 mHz frequency band in $SpO_2$ signal</td>
</tr>
<tr>
<td>PPG</td>
<td>Photoplethysmogram</td>
</tr>
<tr>
<td>PSD</td>
<td>Power spectral density</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>PSG</td>
<td>Polysomnography</td>
</tr>
<tr>
<td>PVT</td>
<td>Psychomotor vigilance task</td>
</tr>
<tr>
<td>REM</td>
<td>Rapid eye movement</td>
</tr>
<tr>
<td>RIP</td>
<td>Respiratory inductance plethysmography</td>
</tr>
<tr>
<td>RHb</td>
<td>De-oxygenated hemoglobin</td>
</tr>
<tr>
<td>Q1</td>
<td>Best performing quartile based on PVT outcomes</td>
</tr>
<tr>
<td>Q4</td>
<td>Worst performing quartile based on PVT outcomes</td>
</tr>
<tr>
<td>RRT</td>
<td>Mean reciprocal reaction time</td>
</tr>
<tr>
<td>SpO$_2$</td>
<td>Saturation of peripheral oxygen</td>
</tr>
<tr>
<td>$t_{90%}$</td>
<td>Time spent under 90% blood oxygen saturation</td>
</tr>
<tr>
<td>TST</td>
<td>Total sleep time in PSG</td>
</tr>
<tr>
<td>$\mu_{DD}$</td>
<td>Mean desaturation depth</td>
</tr>
</tbody>
</table>
LIST OF SYMBOLS

$A$  Absorbance
$c$  Speed of light
$C$  Concentration
$d_f$  Downsampling factor
$d/dt$  Time derivative
$E$  Energy of a photon
$f$  Frequency
$f_s$  Sampling frequency
$f_t$  Input for a system at time instance $t$
$g_t$  Output of a system at time instance $t$
$h$  Planck’s constant
$\tilde{h}$  Impulse response of a system
$I$  Intensity
$K$  Total number of arousals
$l$  Optical path length
$L$  Total number of desaturations
$n$  Number of patients or defined objects
$N$  Total number of apneas
$M$  Total number of hypopneas
$p$  Probability to reject the correct null hypothesis
$R$  Ratio-of-Ratios for red and infrared intensity
$maxima$s and minimas
$SO_i$  $SpO_2$ value in $i^{th}$ sampling point of scored desaturation
$SO_0$  $SpO_2$ value in first sampling point of scored desaturation
$t$  Time
$t_A$  Duration of an individual apnea
$t_D$  Duration of an individual hypopnea
$t_H$  Duration of an individual desaturation
$U$  Total number of sampling points within an individual desaturation
$\epsilon$  Molar extinction coefficient
$\lambda$  Wavelength
$\rho$  Spearman’s correlation coefficient
# TABLE OF CONTENTS

1 Introduction ................................................................. 1

2 Obstructive sleep apnea ............................................... 3
   2.1 Diagnostic and symptom assessment methods ................. 3
      2.1.1 Polysomnography .................................................. 4
      2.1.2 Excessive daytime sleepiness .................................. 6
      2.1.3 Cognitive deficits and vigilance ................................ 7

3 Pulse oximetry ............................................................. 9
   3.1 Light-tissue interaction ............................................... 9
      3.1.1 Absorption of red and infrared light ....................... 10
   3.2 Photoplethysmogram ............................................... 11
   3.3 Heart rate .............................................................. 13
   3.4 Blood oxygen saturation ........................................... 14
   3.5 Clinical utility and error sources ................................. 15

4 Aims of the thesis .......................................................... 17

5 Methods ................................................................. 19
   5.1 Patient cohorts and measurement setups ....................... 19
      5.1.1 Polysomnographic parameters ............................... 20
      5.1.2 Multiple sleep latency test and psychomotor vigilance task outcomes .............................................. 22
   5.2 Spectral analysis ..................................................... 23
   5.3 Statistical analyses .................................................. 23

6 Results ........................................................................... 27
   6.1 The connection of polysomnographic parameters with EDS and vigilance deterioration ............................................ 28
   6.2 Pulse oximetry-derived spectral features and their connection to EDS and deterioration of vigilance ......................... 30
   6.3 Demographical risk factors ......................................... 37

7 Discussion ..................................................................... 39
   7.1 Polysomnographic parameters and their association with EDS and impaired vigilance ................................................ 39
   7.2 Association of pulse oximetry-based spectral features with EDS and impaired vigilance ............................................. 41
   7.3 Limitations ............................................................... 42
   7.4 Future studies .......................................................... 43

8 Conclusions .............................................................. 45

BIBLIOGRAPHY ............................................................... 47

xvii
1 Introduction

Various sleep disorders are a growing global health burden causing significant economical, societal, and health impacts [1, 2]. Obstructive sleep apnea (OSA) is recognized to be one of the most prevalent and detrimental of all the many sleep disorders [3–5]. In OSA, recurrent collapses of the upper airways partially limit (hypopnea) or completely block (apnea) the airflow while asleep. Apneas and hypopneas can cause significant physiological stress because of the intermittent hypoxemia, hypercapnia, abnormal heart rate variability, as well as the altered sleep structure [6, 7]. The diagnosis of OSA is based on a clinical interview, medical examination, symptoms, and diagnostic sleep study which is used for severity assessment of OSA. The severity of OSA is usually assessed via type I polysomnography (PSG), which is considered as the gold standard method, or ambulatory polygraphic recordings [8]. Of these, PSG is a comprehensive multi-channel over-night recording, in which multiple physiological signals are measured [8].

Despite the comprehensive and data-rich diagnostic protocol, the severity assessment of OSA relies almost solely on calculating the apnea-hypopnea index (AHI). The AHI is defined as the average number of apneas and hypopneas per slept hour. Thus, the AHI provides an oversimplistic estimation of the disease severity and suffers from major shortcomings [9, 10]. One of the most evident shortcomings is the weak association with the most common daytime symptoms of OSA: daytime sleepiness [11–13] as well as reduced vigilance and the ability to sustain attention [14, 15]. In addition, the AHI does not display a strong association with the prevalence of cardiovascular comorbidities and incident cardiovascular mortality that are high in OSA patients [16, 17].

Daytime sleepiness is the most prominent symptom of OSA; it is usually quantified utilizing questionnaires such as the Epworth Sleepiness Scale (ESS) [18]. For a more comprehensive evaluation, objective measurements such as Multiple sleep latency test (MSLT) can be conducted in a sleep laboratory to evaluate the patient’s propensity to fall asleep under uninterrupted conditions [19]. However, MSLT is not a general diagnostic procedure for OSA patients due to its time-consuming nature, labor intensiveness, and high cost. In addition to daytime sleepiness, OSA can cause a deterioration of cognitive functioning and vigilance [20]; for example, these symptoms can be assessed with psychomotor vigilance task (PVT). PVT is a simple reaction time task requiring no sleep laboratory facilities. The standard protocol assesses the patient’s reaction times to visual stimuli for 10 minutes [21]. Based on the reaction times, the patient’s ability to sustain attention and vigilance is evaluated using statistical parameters computed from the reaction time series [21].

However, neither the results of MSLT nor PVT correlate well with conventional diagnostic parameters, such as the AHI [11, 15, 22]. Previous literature, however, does imply that nocturnal physiological stress, fragmented sleep, and hypoxemia contribute to the development of daytime symptoms [18]. Thus, the primary hypothesis of this thesis was that detailed parameters incorporating the
characteristic properties of respiratory events would exhibit a significantly stronger association with OSA-related deteriorated vigilance and daytime sleepiness than the AHI. In addition, we hypothesized that manually selected and neural network-based self-learned spectral features of blood oxygen saturation signal, heart rate signal, and photoplethysmogram could be linked to decreased daytime sleep latencies and prolonged reaction times. Therefore, the two main aims for this thesis were set; the first aim was to investigate whether a detailed parametric quantification of apneas, hypopneas, and related blood oxygen desaturations could be linked to short sleep latencies in MSLT and poor PVT performance in large OSA patient cohorts. The second aim was to investigate the usability of the frequency-domain features of nocturnal pulse oximetry signals as biomarkers for daytime sleepiness and deteriorations in vigilance.
Obstructive sleep apnea (OSA) is a sleep-related breathing disorder. It is characterized by repetitive nocturnal upper airway collapses, which partially limit or completely interrupt the airflow. These airflow limitations can cause a significant elevation of sympathetic activity [6], an abnormal heart rate variability [23], rapid but transient decreases in the blood oxygen saturation [24], and brief awakenings i.e. arousals from the sleep as well as negative alterations in the sleep structure [25]. Thus, OSA is a complex and substantially heterogeneous disorder with high variation in the clinical characteristics displayed by those affected.

Even though a few airflow limitations during sleep also occurs in healthy individuals, there is still no solid consensus on the underlying causes of the pathogenesis of OSA. The literature considering the pathophysiology of OSA has shown that the development of the disorder involves a combination of multiple factors [6]; e.g. weakened upper airway muscle control, deteriorated pressure reflex in the genioglossus muscle, fat surrounding the upper airways, low arousal threshold, and disturbed ventilatory regulation via an increased loop gain [6]. However, some explicit risk factors for developing OSA have been found [26]; not only abnormal upper airway structure but also other factors such as obesity and smoking have been associated with OSA [27–30].

OSA is a significant public health problem [1, 5]. It has been estimated that globally, nearly a billion individuals suffer from OSA [5]. In Finland, the latest epidemiological estimates indicate that there are over a million affected individuals [5]. In addition, OSA is often found in patients who are already suffering from either cardiovascular or metabolic diseases or psychiatric disorders [3, 26, 31]. Hence, the connection between OSA and comorbid diseases could be bi-directional, further highlighting the importance of early and accurate OSA diagnosis.

2.1 DIAGNOSTIC AND SYMPTOM ASSESSMENT METHODS

OSA is diagnosed based on the results of a clinical interview, medical examination, and a diagnostic sleep study [8, 32]. The gold standard method, type I polysomnography (PSG) is a comprehensive and data-rich physiological measurement conducted in a sleep laboratory with continuous monitoring of the patient [8]. Type I PSG is the most comprehensive of the four types of diagnostic studies. The other three diagnostic studies are abridged modifications of type I PSG. A type II PSG demands no medical personnel attendance but similar measurements as in type I PSG. A type III PSG comprises a reduced number of measured signals than type II study, being limited to monitoring of cardio-respiratory signals without EEG, although still being suitable for the diagnosis of OSA [8]. A type IV study is the simplest protocol, comprising only a measurement of the blood oxygen saturation and airflow signal. In general, diagnostic studies are type I or type III PSGs.

In addition to the measurements, the diagnosis of OSA depends on the patient’s symptoms. OSA causes both nocturnal and daytime symptoms. In the daytime, the most common symptom is excessive sleepiness [33], which is used as a diagnostic
criterion and also as an indication for the need for treatment in mild OSA. Other
daytime symptoms can include a lack of concentration and a loss of vigilance as well
as mood disorders [34, 35]. The most common nocturnal symptom is snoring [36],
and it is most often recognized by an observer, not by the patient itself. Other
common nocturnal symptoms are excessive sweating [37] and mouth dryness [38].
Since OSA is a highly complex disease, it is evident that its symptoms and their
development are also complex processes with significant variation between patients
[18].

2.1.1 Polysomnography

PSG recording is conducted in a sleep laboratory facility, usually in a hospital. The
indication for PSG can be a suspicion of OSA or other sleep disorders
such as periodic limb movement disorder or narcolepsy [32]. In addition to the
measurements related to sleep-disordered breathing (airflow with nasal pressure
and/or thermistor, blood oxygen saturation (SpO₂), respiratory efforts via inductive
belts), also electrooculogram (EOG), electromyogram (EMG) from facial muscles
and legs, electrocardiogram (ECG), body posture measured with an accelerometer,
EEG and video of the patient are recorded [8]. PSG can also incorporate additional
measurements such as transcutaneous measurement of carbon dioxide partial
pressure and a microphone or piezo-electric vibration sensor-based recording of
snoring [8].

After conducting the diagnostic sleep study, it is manually analyzed in
conformity with the American Academy of Sleep Medicine (AASM) scoring rules
[8]. Sleep stages are scored using the 4-stage classification of sleep: lighter sleep
stages 1-2 of non-rapid eye movement sleep (N1 and N2), stage 3 sleep representing
deep sleep (N3), and fourth being rapid eye movement (REM) sleep. Sleep stage
scoring is conducted utilizing multiple EEG channels, chin EMG, and EOG. In
addition, arousals are scored utilizing these signals, and the arousal index (ArI)
is computed as an average number of arousals per slept hour. Apneas and
hypopneas are scored based on thermistor, nasal pressure, SpO₂, and EEG. A
detailed description of scoring rules for respiratory events is presented in Table 2.1.
Scoring of the apneas and hypopneas and sleep staging yields the apnea-hypopnea
index (AHI) that is defined as the average number of apneas and hypopneas per
slept hour [8]. In addition, the lowest and mean SpO₂ as well as the time spent under
90% oxygenation can be determined, but the computation of these parameters is not
required for the diagnosis of OSA [32]. The final diagnosis is based on the AHI and
self-reported excessive daytime sleepiness (Table 2.1) [32].
Table 2.1: Rules for respiratory event scoring and severity classification of obstructive sleep apnea (OSA).

<table>
<thead>
<tr>
<th>Signal</th>
<th>Apnea</th>
<th>Hypopnea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thermistor</td>
<td>Amplitude reduction of &gt; 90%</td>
<td>Not recommended for scoring</td>
</tr>
<tr>
<td></td>
<td>for ≥ 10 seconds</td>
<td></td>
</tr>
<tr>
<td>Nasal pressure</td>
<td>Not recommended for scoring</td>
<td>Amplitude reduction of &gt; 30%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>for ≥ 10 seconds</td>
</tr>
<tr>
<td>RIP belts</td>
<td>Differentiation between central, mixed and obstructive apneas</td>
<td>Differentiation between central and obstructive hypopneas</td>
</tr>
<tr>
<td>EEG</td>
<td>No required changes</td>
<td>Cortical arousal *</td>
</tr>
<tr>
<td>SpO₂</td>
<td>No required changes</td>
<td>≥ 3% desaturation *</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>OSA severity</th>
<th>AHI</th>
<th>EDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>No diagnosis</td>
<td>&lt; 5</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Mild</td>
<td>5 ≤ AHI &lt; 15</td>
<td>Required</td>
</tr>
<tr>
<td>Moderate</td>
<td>15 ≤ AHI &lt; 30</td>
<td>Not required</td>
</tr>
<tr>
<td>Severe</td>
<td>AHI ≥ 30</td>
<td>Not required</td>
</tr>
</tbody>
</table>

Scoring rules, recommendations, and OSA severity classification are based on guidelines defined by the American Academy of Sleep Medicine scoring manual and ICSD-3 classification of sleep disorders [8,32]. * indicates that either one of marked changes is sufficient for scoring of hypopnea. The apnea-hypopnea index (AHI) is defined as average number of apneas and hypopneas per slept hour. Abbreviations: RIP = respiratory inductance plethysmography, EEG = electroencephalogram, SpO₂ = blood oxygen saturation, EDS = excessive daytime sleepiness.
2.1.2 Excessive daytime sleepiness

Excessive daytime sleepiness (EDS) is one of the most prevalent clinical manifestations of OSA [18]. OSA-related EDS generates a high risk for traffic and occupational accidents; its annual costs are measured in billions of dollars [1, 2]. In OSA patients, EDS is thought to result from an altered sleep structure and repeated arousals, associated with apneas and hypopneas [6, 39, 40]. EDS can be assessed using subjective questionnaires or objective measures of sleepiness. The severity classification of subjectively and objectively measured EDS is presented in Table 2.2.

The most commonly used sleepiness indicator is the **Epworth Sleepiness Scale (ESS)**, which targets an assessment of the chronic nature of the sleepiness [41]. ESS is an eight-part questionnaire that asks the possibility to fall asleep in various situations, for example, while reading or while sitting and talking with another person [41]. Every answer is scored with points ranging from 0 to 3 based on how high is the probability of falling asleep in a particular situation [41]. The total points indicate the status of sleepiness (Table 2.2). ESS is a fast, cost-efficient, and straightforward measure of sleepiness, and it has become the clinical standard for assessing daytime sleepiness especially in OSA patients [32]. However, ESS is highly subjective as the interpretation of the questions and rating system naturally show a high inter-subject variation [42].

Sleepiness can be assessed objectively via a **Multiple sleep latency test (MSLT)**. In MSLT, measurements are conducted during the day in a sleep laboratory to minimize all external distractions [19]. When MSLT is started, the patient is instructed to lie still with permission to fall asleep. The target outcome in MSLT is sleep latency which is the time from the start of the measurement to the time of sleep onset. The MSLT protocol comprises four or five sleep latency measurements with two hour-intervals and the preceding night’s PSG to ensure that patient has slept at least six hours before the MSLT. In MSLT, at least EEG, EOG, EMG, and ECG are recorded to detect the sleep onset and the possible short onset REM sleep. The first sleep latency measurement starts within two hours after waking up. If at least one 30 second epoch can be scored as sleep instead of wake in any time point during a 20-minute trial, the measurement is continued for another 15 minutes to detect possibly occurring deeper sleep stages. If no NREM or REM sleep is detected, the measurement is terminated after 20 minutes. Based on all sleep latency measurements, the mean sleep latency (MSL) is computed for the determination of EDS severity (Table 2.2).

Recent studies have indicated that OSA patients have more N1 sleep as well as less N3 and REM sleep in PSG together with a higher number of arousals than healthy individuals [43, 44]. Despite these differences, parameters describing fragmented sleep are not fully capable of explaining the severity of daytime sleepiness [39, 45]. The AHI has suffered from the same shortcoming [12, 40, 46]. On average, patients with higher ESS scores and shorter MSL have higher AHI [12, 45]. However, the AHI has been able to explain only 10% of the variation in MSL in different patients cohorts [12, 13, 40] and less than 2% of the variation in ESS scores [47]. In addition, the ESS scores and MSLT results of OSA patients do not correlate well [48]; this implies that the cause of sleepiness is multifactorial and several factors contribute to the development of EDS.

As well as sleep fragmentation, more severe nocturnal hypoxemia as well as higher heart rate variability (HRV) in the low-frequency range have been associated with EDS [18, 23]. Both hypoxemia and high LF-HRV are associated...
Table 2.2: Normal values and severity classification thresholds for the Epworth Sleepiness Scale (ESS) and Multiple Sleep Latency Test (MSLT).

<table>
<thead>
<tr>
<th>Test</th>
<th>Normal values</th>
<th>Interpretation and clinical guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESS</td>
<td>5.9 ± 2.2*</td>
<td>Threshold for sleepiness: &gt; 10 points</td>
</tr>
<tr>
<td></td>
<td>2 - 10 points*</td>
<td>Threshold for severe sleepiness: ≥ 16 points</td>
</tr>
<tr>
<td>MSLT</td>
<td>10.4 ± 4.3 min**</td>
<td>Abnormal sleepiness: MSL ≤ 5 min</td>
</tr>
<tr>
<td></td>
<td>11.6 ± 5.2 min***</td>
<td>Mild or moderate sleepiness: 5 &lt; MSL ≤ 8 min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diagnostic grey area: 8 &lt; MSL &lt; 10 min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Normal: MSL ≥ 10 min</td>
</tr>
</tbody>
</table>

Abbreviations: MSL = mean sleep latency. The ESS normal values marked with * are based on [41]. MSLT normal values, marked with ** and ***, are presented for four and five nap protocols, respectively, and are based on [19]. Interpretation and guidelines are based on recommendations by Dr. Murray Johns, the developer of the ESS, and recommendations in the European Sleep Research Society’s Sleep Medicine textbook [32].

with high sympathetic activity. In normal sleep, sympathetic activity decreases from N1 towards N3 while simultaneously parasympathetic activity increases [49]. In contrast, OSA patients exhibit sympathetic overdrive due to the intermittent hypoxemia and hypercapnia caused by repetitive collapses of the upper airways [6,49]. Therefore, EEG of an OSA patient could comprise features related to a deeper stage of sleep, despite simultaneous high sympathetic activity. A combination of severe hypoxemia, high sympathetic activity and increased physiological stress during sleep are therefore logical predictors of daytime sleepiness, although seldom used in the severity assessment of OSA.

2.1.3 Cognitive deficits and vigilance

OSA detrimentally affects vigilance and the ability to sustain attention [20, 50]. Regardless of the presence of EDS, OSA has been shown to independently impair performance in various cognitive tests [50]. Furthermore, OSA negatively affects a multitude of cognitive domains, including executive functioning, memory and learning, vigilance as well as sustained, selective, and divided attention [20, 50]. Evaluation of sustained attention and psychomotor vigilance can be conducted via the Psychomotor vigilance task (PVT) [21]. The PVT is a short and simple visual stimulus-response task. Standard PVT protocol’s duration is 10 minutes and comprises stimuli appearing at 2 - 9 second intervals [21]. The reaction time to each stimulus is recorded and statistical characteristics of the trial series are computed, including the number of reaction times exceeding 500 ms (i.e. lapses) and the median reaction time [21]. In addition to lapses and median reaction time, standard PVT outcome measures include mean reciprocal reaction time (RRT) as well as the mean of the slowest 10% and the fastest 10% of reaction times. Two examples of PVT time series are presented in Figure 2.1.

PVT is considered to be a reliable and sensitive test with an extremely low learning effect [51, 52]. Generally, poor vigilance is associated with an inadequate
Figure 2.1: Two examples of reaction time series measured in a psychomotor vigilance task (PVT). Example series 1 demonstrates good PVT performance with only a single lapse (reaction time over 500 ms) and minor time-on-task effect after 80 stimuli. Example series 2, in contrast, illustrates poor PVT performance: consistently prolonged reaction times and 39 lapses.

duration of sleep. Previous studies have demonstrated decreasing PVT performance in both acute sleep deprivation and chronic sleep restriction [15,53–55]. On the other hand, the conventional diagnostic parameters for OSA and sleep fragmentation, such as AHI or ArI, have not been able to explain the prolonged reaction times and lapses in PVT [14,15,56–58]. Moreover, the severity classification of OSA via AHI shows little connection towards poor vigilance even at the group level [15].

Nonetheless, the impairment of cognitive functioning and vigilance have been associated with the presence of OSA [20,55,56]. It has been shown that peripheral hypoxemia can translate to a deoxygenation of brain tissue [59], causing similar changes in various regions of the brain as encountered in an ischemic injury [20]. These changes increase the amount of free radicals and inflammation leading to endothelial dysfunction and therefore, elevated blood pressure [20]. In addition, new discoveries related to the glymphatic system of the brain and its role in protein clearance [60–62] have produced additional hypotheses on how especially cardiovascular regulation and slow-wave sleep (SWS) affect vigilance and cognitive performance. These findings have revealed that SWS together with the pulsatility in the cerebral arteries are mechanisms through which the brain can perform clearance of metabolic waste such as amyloid-β [60,63]. These metabolic mechanisms of the brain can be disrupted with the combined influence of a decreased amount of N3 sleep, sleep fragmentation, and atherosclerosis as well as increased blood pressure dampening the pulsatility of arteries. Thus, cardiorespiratory regulation and sleep are more closely connected than previously thought, providing novel possibilities to associate OSA with vigilance deterioration and cognitive deficits.
Pulse oximetry

Pulse oximetry is an optical measurement technique, predominantly developed for the non-invasive evaluation of blood oxygen saturation (SpO₂). The pulse oximeter can apply either a reflective or transmissive measurement technique and can utilize a multitude of different wavelengths, i.e. characteristic colors. In this chapter, the principles of the light-tissue interaction and signal derivations related to the transmissive technique when using the conventional red and infrared wavelengths will be presented. Furthermore, in the last section, the clinical utility and error sources of pulse oximeter are discussed.

3.1 LIGHT-TISSUE INTERACTION

Electromagnetic radiation, including visible light, is carried by photons. Photons interact with matter via different processes including absorption, scattering, and pair production. The interaction mechanism is dependent on the energy of the photon and the properties of the material it is propagating. It can be expressed as

\[ E = hf, \]  

where \( h \) is Planck’s constant and \( f \) the frequency of the photon. Furthermore, the frequency of the photon can be written in the form

\[ f = \frac{c}{\lambda}, \]

where \( c \) is the speed of light and \( \lambda \) the wavelength of the photon. Thus, the energy of the photon as a function of wavelength takes the form

\[ E = \frac{hc}{\lambda}. \]

Therefore, the photons having wavelengths in the visible light range have relatively small energies for example, when compared to x-ray photons. In the photon-tissue interaction this confers certain benefits: visible light is low-energy radiation, therefore unionizing and unharmful for biological tissue per se. However, as the energy of the photon is low, it is easily absorbed in the medium into which it enters. The absorption process for one absorbent species can be mathematically expressed by the Beer-Lambert law so that

\[ I = I_0 e^{-\epsilon Cl}, \]

where \( I_0 \) is the intensity of the incident light, \( \epsilon \) is the molar extinction coefficient, \( C \) is the concentration of the absorbent, and \( l \) is optical path length [64]. When multiple absorbents are present in the optical path, the Beer-Lambert law is of the form

\[ I = I_0 e^{-\sum_{i=1}^{n} \epsilon_i C_i l_i}, \]
where \( n \) is the number of absorbents in the medium. By linearizing the Beer-Lambert law, the mathematical presentation of the amount of transmitted light (transmission, \( T \)) is yielded. The logarithmic complement of \( T \) is absorbance \( A \), which is of the form

\[
A = -\log \frac{T}{I_0} = \sum_{i=1}^{n} \epsilon_i C_i l_i,
\]

(3.6)
describing how much the medium absorbs the incident light. From these parameters, \( \epsilon \) depends on the wavelength of the photon (Figure 3.1). However, this dependence is affected more by the molecular structure of the absorbent than by the energy of the photons in the visible light range [64, 65]. Moreover, the Beer-Lambert law does not take into account the reflection and scattering of incident light at the interfaces of the mediums decreasing the number of transmitted photons.

### 3.1.1 Absorption of red and infrared light

Conventional two-source pulse oximetry readings are based on the absorption of the incident light in the peripheral arterial blood (Figure 3.1). More specifically, it is based on the absorption induced by the two most common types of hemoglobin [66, 67]. These types are the oxygen-carrying hemoglobin (oxyhemoglobin, OHb) and deoxygenated hemoglobin (deoxygenated hemoglobin, RHb). When oxygen is bound to the Fe\(^{2+} \) ion in one of the four heme sub-units in Hb, the three-dimensional

![Figure 3.1: Schematic representation of the logarithmic molar extinction coefficients (\( \epsilon \)) as a function of wavelength for oxygenated hemoglobin (OHb), deoxygenated hemoglobin (RHb), and water (H\(_2\)O) between 400nm and 1000nm. 660nm and 940nm correspond to the red and infrared light wavelengths commonly applied in pulse oximetry, respectively. Illustration is drawn based on [64].](image)
structure of the heme-group in the binding site is altered from a non-planar to a planar orientation [65]. Thus, changes in the molecular structure are responsible for differences in the absorption of light by OHb and RHb (Figure 3.1).

The molar extinction coefficients of OHb, RHb, and water as a function of wavelength are presented in Figure 3.1. At 660nm, the absorption is predominantly attributable to RHb in blood, and red light readily passes through peripheral anatomical locations such as the ear lobe or finger due to the relatively low $\epsilon_{H_2O}$ and the absence of bony structures (Figure 3.1). Conversely, at 940nm, the molar extinction coefficient of OHb is higher than that of RHb; thus, absorption predominantly occurs due to OHb. In addition, $\epsilon_{H_2O}$ is increased but still remains below $\epsilon_{OHb}$ and $\epsilon_{RHb}$. As soft tissue consists predominantly of water, both red and infrared light are able to penetrate through soft tissue in the periphery with a measurable amount of transmitted light despite the scattering of the light within the medium and reflections from the surfaces [64].

### 3.2 PHOTOPLETHYSMOGRAM

When the incident light travels through a medium, the transmitted light measured via photodetector forms an absorption signal. This signal contains information on the absorption process in multiple absorptive mediums, such as soft tissue, bone, and blood (Figure 3.2). If the measurement site consisted only of static blood and tissue structures, the signal would be flat without any temporally changing components.

However, cardiac and respiratory functions cause both the blood volume and composition to change in the arterial blood. Thus, neither the concentrations of OHb and RHb nor the optical path length for the incident light remain constant [66, 67]. By utilizing the Beer-Lambert law, the absorption of incident light as a function of time, *i.e.*, photoplethysmogram (PPG), can be mathematically expressed as

$$PPG(t) = -\log \frac{I(t)}{I_0} = \sum_{i=1}^{n} \epsilon_i(\lambda)C_i(t)l_i(t), \quad (3.7)$$

where $t$ is time and $\lambda$ is the wavelength of the incident light. The PPG can be formed either from red-light absorbance or infrared-light absorbance. Due to higher $\epsilon$ for RHb as well as its lower water absorption, red light is more sensitive to changes in oxygenation than infrared light (figure 3.1). Moreover, infrared light has a lower total absorption and relatively similar absorption in water, OHb, and RHb, being more stable and therefore more commonly used for PPG signal generation [69].

$l_i(t)$ is modulated by a multitude of physiological factors and thus, the PPG can be described via at least three physiological components (figure 3.2); the first is the DC component, which includes the absorption to soft tissue and other static media [68]. The second component is the low-frequency AC (LF-AC) component, which includes slow oscillatory changes in the blood volume due to respiration, venous blood flow, and temperature changes as well as temporal changes in the hemoglobin concentration (figure 3.2) [68, 70]. The third is the high-frequency AC (HF-AC) component which is attributable to the rapid changes in blood volume due to the arterial pulsations, coupled with oscillating blood pressure and heart rate (figure 3.2). When oxygenated blood enters the systemic circulation, the elasticity of the arteries allows short-term expansion of the blood vessels [70]. This phenomenon causes the typical PPG waveform as the $l_i$ increases along with an increase in the
Figure 3.2: Graphical illustration describing the formation and waveforms of PPG signal based on the Beer-Lambert law. The total absorbance comprises three signal components: the DC component, the low-frequency AC component (LF-AC), and the high-frequency AC component (HF-AC). The DC component does not vary temporally, and describes the absorption in static mediums through which light passes. The LF-AC component consists of changes in blood volume due to breathing, thermal regulation, changes in autonomic nervous system activity, and alterations in the hemoglobin concentration. In general, the pure DC-component and LF-AC components are described as one component. The HF-AC component illustrates the typical PPG signal, which is modulated by the pulsatility of arteries. The waveform consists of decreasing transmitted intensity ($I_{\text{trans}}$) in the systolic phase as the optical path length is longest, and increasing $I_{\text{trans}}$ in the diastolic phase as the optical path length is shortest. The primary path length maximum, indicating the absorbance maximum, is caused by the first pressure wave originating from the opening of the aortic valve. The secondary maximum before the diastolic minimum, Dicrotic Notch, is caused by the pressure wave originating from the closure of the aortic valve. In contrast to the illustration, in vivo, the strength of both AC-components is only a few percentages of the total absorption. The illustration is drawn based on [68].
cross-sectional area of the arteries via increased blood volume. Therefore, during systole, an absorption maximum is achieved and vice versa, during diastole, the absorption is at its minimum.

### 3.3 HEART RATE

An exact measure of heart rate is obtained from the electrocardiogram (ECG) i.e. detecting R-peaks and the corresponding time-intervals between consecutive R-peaks. However, the pulsatility of arteries causing the typical PPG waveform is directly coupled with heart rate. The rapid closure of the atrioventricular valves and opening and closing of the aortic valve generates longitudinal pressure waves, also known as heart beats or heart sounds [70,71]. In a healthy heart, the first heart sound has a duration of approximately 50 ms, starting almost instantaneously when the R-peak occurs in the ECG [70,71]. It is generated by the closure of the atrioventricular valves and the opening of the aortic valve [70,71]. After 200 ms the next heart sound occurs when the aortic valve closes after the contraction of the left ventricle [70,71].

To evaluate heart rate based on PPG, the time difference between dominant pulse wave peaks has to be determined. Thus the heart rate can be expressed as

\[
HR = \frac{60}{(t_{i+1} - t_i)},
\]

where \( t_i \) denotes the time of \( i^{th} \) PPG amplitude maxima. However, the PPG waveform is affected by various factors: for example, by the elasticity of the peripheral arteries and functioning of the heart valves. Hence, the pulse wave peak seen in PPG is not an instantaneous high energy maximum like the R-peak in ECG, but rather it is a sine-wave like slow-onset and slow-offset curve [67,72]. Therefore, the accuracy of determining the HR can be enhanced by computing the 1\textsuperscript{st} or 2\textsuperscript{nd} time derivatives of the original PPG. The operations are defined for the first and second derivative so that

\[
g_t = f_t - f_{t-1},
\]

and

\[
g_t = f_t - 2f_{t-1} + f_{t-2},
\]

respectively. In both 1\textsuperscript{st} and 2\textsuperscript{nd} derivatives \( g_t \) denotes the output and \( f_t \) the input of the system. Both of the derivatives can be computationally found by convolving the original PPG with the impulse response of the derivative filters so that

\[
PPG' = PPG \ast \bar{h}_{1st},
\]

where \( \bar{h}_{1st} = [1 \ -1] \) and further

\[
PPG'' = PPG \ast \bar{h}_{2nd},
\]

where \( \bar{h}_{2nd} = [1 \ -2 \ 1] \). Both derivative filters are high-pass filters that strengthen the rapidly changing components of the signal. Therefore, sharper peaks are seen in the differentiated PPG enabling more accurate peak-to-peak detection [72].

13
3.4 BLOOD OXYGEN SATURATION

The blood oxygen saturation (SpO$_2$) is defined as

$$SpO_2 = \frac{C(OHb)}{C(OHb) + C(RHb)} \times 100\%, \quad (3.13)$$

where $C$ is the concentration of absorption species. The concentrations cannot be defined non-invasively; however, a non-invasive evaluation of SpO$_2$ can be conducted based on the absorption of red and infrared light. Both wavelengths produce a PPG signal; its amplitude changes as the blood volume oscillates along with the arterial pulsation. Red-based PPG and infrared-based PPG oscillate in the same phase, with infrared-based PPG having a smaller amplitude due to smaller $\epsilon_{RHb}$ and $\epsilon_{OHb}$ and higher $\epsilon_{H2O}$. Assuming that the changes in the total hemoglobin concentration and body temperature are negligible during one complete heart cycle, only time-dependent variable in the Beer-Lambert law is the optical path length. Further assuming that only the arterial blood volume changes the optical path length, the AC component of both signals can be theoretically expressed via differential absorption ($dA$) so that

$$dA = \frac{d}{dt} \left( - \log \frac{I(t)}{I_0} \right) = \sum_{i=1}^{n} \epsilon_i(\lambda)C_i \frac{d(l_i(t))}{dt}. \quad (3.14)$$

However, $dA$ and SpO$_2$ both comprise unknown concentrations and optical path length within each absorbent. Therefore, we form the $dA$ equation based on the measured transmitted light. Determining the time derivative of absorbance yields

$$dA = \frac{d}{dt} \left( - \log \frac{I(t)}{I_0} \right) = - \frac{I'(t)}{I}. \quad (3.15)$$

Now the DC component of the PPG signal represents over 95% of the measured absorption (Figure 3.2). Thus, by further approximating the derivative of the intensity to equal the AC component of PPG and the measured intensity to equal the DC component during one heart cycle, $dA$ can be written in a form

$$dA = - \frac{I'(t)}{I} \approx \frac{I_{AC}}{I_{DC}} = \frac{I_{max} - I_{min}}{I_{max}}, \quad (3.16)$$

where $I_{min}$ and $I_{max}$ are the measured intensity minima and maxima during one pulse wave [66, 67]. Let us now define the ratio-of-ratios, $R$. Based on the difference of the absorption in red and infrared wavelengths (660nm and 940nm) and the assumption that the only absorbents are OHB and RHb, $R$ can be defined via differential absorptions so that

$$R = \frac{dA(\lambda_1)}{dA(\lambda_2)} = \frac{(\epsilon_{OHB}(\lambda_1)C_{OHB} + \epsilon_{RHb}(\lambda_1)C_{RHb})\frac{d{l(l(t,\lambda_1))}}{dt}}{(\epsilon_{OHB}(\lambda_2)C_{OHB} + \epsilon_{RHb}(\lambda_2)C_{RHb})\frac{d{l(l(t,\lambda_2))}}{dt}}, \quad (3.17)$$

where $dA(R)$ and $dA(IR)$ denotes the differential absorptions for red ($\lambda_1$) and infrared ($\lambda_2$) lights, respectively. By assuming that

$$l(t, \lambda_1) \approx l(t, \lambda_2), \quad \forall t, \quad (3.18)$$
equation (3.17) is simplified to

\[ R = \frac{dA(\lambda_1)}{dA(\lambda_2)} = \frac{(\epsilon_{OHb}(\lambda_1)C_{OHb} + \epsilon_{RHb}(\lambda_1)C_{RHb})}{(\epsilon_{OHb}(\lambda_2)C_{OHb} + \epsilon_{RHb}(\lambda_2)C_{RHb})}. \]  

(3.19)

Further, assuming

\[ C_{OHb} \approx C_{tot} \cdot SpO_2, \]  

(3.20)

and taking into account that the initial model for SpO_2 assumes that \( C_{tot} = C_{OHb} + C_{RHb}, \) substituting these two relations into the equation (3.19), \( R \) can be written in the form

\[ R = \frac{dA(\lambda_1)}{dA(\lambda_2)} = \frac{\epsilon_{OHb}(\lambda_1)SpO_2 + \epsilon_{RHb}(\lambda_1)(1 - SpO_2)}{\epsilon_{OHb}(\lambda_2)SpO_2 + \epsilon_{RHb}(\lambda_2)(1 - SpO_2)}. \]  

(3.21)

Further solving equation (3.21) for SpO_2 yields

\[ SpO_2 = \frac{\epsilon_{RHb}(\lambda_1) - Re RHb(\lambda_2)}{R(\epsilon_{OHb}(\lambda_2) - \epsilon_{RHb}(\lambda_2)) - \epsilon_{OHb}(\lambda_1) + \epsilon_{RHb}(\lambda_1)}, \]  

(3.22)

that can be solved utilizing the known absorption spectra (Figure 3.1) as well as utilizing both red and infrared based PPG [66, 67].

### 3.5 CLINICAL UTILITY AND ERROR SOURCES

Pulse oximeter is a highly common measurement device, for example being exploited in intensive care units and during surgical operations [73]. In the scope of sleep medicine, a pulse oximeter measurement is required in all types of diagnostic sleep studies [8]. It is most often utilized in detecting the apnea or hypopnea-related intermittent hypoxemia and determining the mean and minimum nocturnal SpO_2 within a diagnostic study. Pulse oximetry is therefore a fundamental part of diagnosing protocol for OSA as well as in the assessment of its severity.

However, the derivation of SpO_2 suffers from the assumptions in the Beer-Lambert law [67]. Assuming absorption only in OHb and RHb and an equal path length of red and infrared light within each heart cycle distorts the accuracy of the evaluated SpO_2. Furthermore, the assumption of negligible reflection, scattering, and refraction of the photons introduces an error into the evaluated absorbance. Due to these assumptions, SpO_2 values determined with a pulse oximeter and equation (3.22) are not directly applicable. Therefore, each pulse oximeter needs to be calibrated with the measured \( R \)-values being compared to oxygen saturation determined from arterial blood samples. The Food and Drug Administration (FDA) recommends that at least 200 data points should be measured for calibration and the difference between pulse oximeter-based SpO_2 and the true blood oxygenation measured from arterial blood samples should not exceed 3.5% [74]. In the calibration, the test subject’s oxygenation is controlled via a gas mixture, and then gradually the amount of oxygen is reduced. The calibration starts at 100% arterial blood saturation, and measurements are conducted usually to 70% arterial blood saturation. After data collection, the calibration curve between arterial blood saturation and \( R \)-values is determined. Due to the calibration protocol, SpO_2 values under 70% are not reliable. It is also noteworthy, that the relationship between SpO_2 and partial pressure of oxygen is non-linear and sigmoidal. For example, SpO_2 values of 80% indicate detrimentally low partial pressure of oxygen [73].
In addition to calibration errors, the pulse oximeter is sensitive to motion and perfusion artifacts [73]. Motion can cause sensor displacement from the measurement site leading to the loss of absorption information. Furthermore, motion of the measurement site can cause rapid motion of the measured blood volume. These rapid changes cause high-frequency noise in both red and infrared PPG, distorting the measured SpO$_2$ and heart rate. This is a critical aspect considering the possibility that motion artifacts are observed in OSA patients due to their frequent arousals, and for example tremor-related artifacts in patients with Parkinson’s disease. In addition, if there is decreased perfusion in the measurement site, this compromises the signal quality. Low perfusion leads to a lowered signal-to-noise ratio as a significantly higher proportion of the absorption takes place in the soft tissue rather than in blood. Various clinical conditions can affect the signal quality of PPG and thus, lead to errors in heart rate and SpO$_2$ [73]. Examples of these conditions are intense peripheral vasoconstriction caused by severely long apneas and hypovolemic shock, peripheral ischemia, diabetes-related decreased perfusion and hypothermia [73,75,76].
4 Aims of the thesis

The current diagnosis of obstructive sleep apnea relies on clinical interview, medical examination, questionnaires, and polysomnography. Even though the process is comprehensive, the vast amount of data gathered during polysomnography is not used optimally. Furthermore, the most important diagnostic parameter, the apnea-hypopnea index, does not correlate well neither with the objective nor subjective evaluation of the most detrimental and common daytime symptoms. Thus the first main aim was to investigate whether a detailed parametric quantification of apneas hypopneas, and related blood oxygen desaturations could be linked to short sleep latencies in MSLT and poor PVT performance in large OSA patient cohorts. The second main aim was to investigate the usability of the frequency-domain features of nocturnal pulse oximetry signals as biomarkers for daytime sleepiness and deteriorations in vigilance.

The study-specific aims of the original publications I-IV with respect to the two main aims were:

I To investigate whether the severity of individual respiratory events and desaturations affect objectively measured daytime sleepiness (1st main aim).

II To study how the severity of individual respiratory events and desaturations would be related to deteriorations in psychomotor vigilance and ability to sustain attention (1st main aim).

III To examine whether frequency-domain features of pulse oximetry data are associated with objectively measured daytime sleepiness (2nd main aim).

IV To determine whether frequency-domain features of pulse oximetry data are associated with impaired vigilance and ability to sustain attention (2nd main aim).
5 Methods

This chapter consists of a description of patient datasets, summarized in Table 5.1, and the main methods used in studies I-IV. Computational and statistical analyses were conducted either in MatLab (ver. 2017b and 2018b, MathWorks Inc., USA) utilizing Statistics and Machine Learning and Signal processing toolboxes or in Python 3.6, using Keras API with Tensorflow 1.10 backend. For detailed information on the methods and patient datasets, please see the original publications attached.

5.1 PATIENT COHORTS AND MEASUREMENT SETUPS

Studies I and III were based on a patient cohort collected in the Sleep Disorders Unit of the Loewenstein Hospital - Rehabilitation Center (Raanana, Israel). This cohort consists of patients who had undergone PSG and attended to MSLT on the following day. Both PSG and MSLT recordings were conducted using Embla REMbrandt Manager System and scored using Embla REMbrandt Manager 9.1 software (Medcare, Amsterdam, Netherlands). For MSLT, a four-nap protocol was used with a 20-minute termination time. 533 successful PSG recordings was manually re-analyzed for study I in conformity with the AASM 2007 respiratory event scoring criteria [77]. The final cohort in study I, 362 patients, further consisted only of patients who had slept over 4 hours in PSG and had AHI ≥ 5. In contrast to study I, oxygen desaturation index (ODI) was used as an inclusion parameter in

<table>
<thead>
<tr>
<th>Study</th>
<th>Type 1 PSG and MSLT</th>
<th>Type 1 PSG and PVT</th>
<th>Type 1 PSG and MSLT</th>
<th>Type 1 PSG and PVT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Material</td>
<td>Study I</td>
<td>Study II</td>
<td>Study III</td>
<td>Study IV</td>
</tr>
<tr>
<td>n (male%)</td>
<td>362 (82%)</td>
<td>743 (59%)</td>
<td>915 (77%)</td>
<td>567 (58%)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>68 (61-74)</td>
<td>57 (46-67)</td>
<td>52 (42-58)</td>
<td>55 (45-65)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>30.8 (28.2-35.0)</td>
<td>35.1 (30.3-41.3)</td>
<td>30.4 (27.1-34.3)</td>
<td>35.1 (30.4-40.7)</td>
</tr>
<tr>
<td>AHI (1/h)</td>
<td>25.5 (12.2-56.8)</td>
<td>23.7 (12.5-45.0)</td>
<td>-</td>
<td>22.0 (12.0-39.4)</td>
</tr>
<tr>
<td>ODI (1/h)</td>
<td>22.7 (10.4-52.6)</td>
<td>15.8 (6.1-31.9)</td>
<td>27.9 (14.4-53.7)</td>
<td>14.6 (5.9-29.5)</td>
</tr>
</tbody>
</table>

Values are presented as a number (% of the population) or as median (interquartile range). Abbreviations and symbols: n = number of patients, PSG = polysomnography, MSLT = multiple sleep latency test, PVT = psychomotor vigilance task, BMI = body mass index, AHI = apnea-hypopnea index, ODI = oxygen desaturation index.
The usage of ODI enabled automated re-analyzing of the whole patient cohort \((n>2000)\) in conformity with the AASM 2012 updated scoring criteria [8]. The \(\text{SpO}_2\) signals of the patients were scored using Noxturnal 5.1.1 (Nox Medical, Reykjavik, Iceland) software. In study III, the inclusion criteria were ODI \(\geq 5\) and total sleep time of six hours was selected for the total sleep time, yielding a total of 915 included patients.

Studies II and IV were based on a cohort of over 1000 patients obtained from the Sleep Disorders Center, Princess Alexandra Hospital (Brisbane, Australia). This cohort comprises patients with PSG and PVT measurement pairs, where PVTs were conducted between 7-9 p.m. prior to the PSG. All PVT measurements were made using the PEBL PVT program on an ASUS Transformer Pad with external keyboard. All PSGs were conducted using Compumedics Grael acquisition system. PSG recordings were scored by experienced technicians in Princess Alexandra Hospital in conformity with AASM 2012 updated scoring manual [8], using Compumedics ProFusion PSG 4 software (Compumedics, Abbotsford, Australia). In study II, the final cohort consisted of 743 patients who met the inclusion criteria of having AHI \(\geq 5\), full comorbidity information based on medical records and an interview conducted in sleep clinic, and successfully performed PVT. In study IV, the final cohort consisted of 567 patients via similar inclusion criteria than in study II. However, an additional 176 patients were excluded as having total sleep time less than 4 hours in PSG.

5.1.1 Polysomnographic parameters

All investigated PSG parameters were computed based on manual annotations of apneas, hypopneas, desaturations, arousals, and sleep stages. Parameters and their mathematical definitions are presented in Table 5.2 and illustrated in Figure 5.1. Definitions are based on previous literature [16, 24, 78, 79]. Total sleep times and percentages of sleep stages were computed based on manual sleep staging. Computation of the desaturation areas, times spent below 90% saturation \((t_{90\%})\) as well as median and mean desaturation depths were based either on complete nocturnal \(\text{SpO}_2\) signals or manually scored desaturations. The start and end times of scored desaturation events were used to extract the corresponding parts from the \(\text{SpO}_2\) signal. Furthermore, the desaturation areas were numerically integrated via the trapezoidal method from the extracted part of \(\text{SpO}_2\). The depth of the desaturation was determined as the difference between the minimum \(\text{SpO}_2\) value within the desaturation with respect to the \(\text{SpO}_2\) value at the beginning of the desaturation. In studies I and III, the endpoint of desaturation was set to the point where the recovery of oxygenation started. In studies II and IV, the endpoint was set to the point where oxygenation reached the baseline. If the baseline was not reached, the endpoint was set to the point where the plateau started.
<table>
<thead>
<tr>
<th>Parameter (unit)</th>
<th>Source</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total sleep time (s); TST&lt;sub&gt;s&lt;/sub&gt;</td>
<td>EEG, EOG</td>
<td>TR − t&lt;sub&gt;wake&lt;/sub&gt;</td>
</tr>
<tr>
<td>Total sleep time (h); TST</td>
<td>EEG, EOG</td>
<td>TST&lt;sub&gt;s&lt;/sub&gt; / 3600</td>
</tr>
<tr>
<td>Apnea-hypopnea index (1/h); AHI</td>
<td>Thermistor, Nasal pressure</td>
<td>(N + M) / TST</td>
</tr>
<tr>
<td>Oxygen desaturation index (1/h); ODI</td>
<td>SpO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>L / TST</td>
</tr>
<tr>
<td>Arousal index (1/h); ArI</td>
<td>EEG</td>
<td>K / TST</td>
</tr>
<tr>
<td>Time under 90% saturation (s); t&lt;sub&gt;90%&lt;/sub&gt;</td>
<td>SpO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>n&lt;sub&gt;S&lt;/sub&gt; / f&lt;sub&gt;s&lt;/sub&gt;</td>
</tr>
<tr>
<td>Obstruction duration (%); ObsDur</td>
<td>Thermistor, Nasal pressure</td>
<td>( \frac{\sum_{i=1}^{N} t_{A_i} + \sum_{j=1}^{M} t_{H_j}}{TST} ) × 100%</td>
</tr>
<tr>
<td>Desaturation duration (%); DesDur</td>
<td>SpO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>( \frac{\sum_{i=1}^{L} t_{D_i}}{TST} ) × 100%</td>
</tr>
<tr>
<td>Desaturation area (s%); DesArea</td>
<td>SpO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>( \frac{\sum_{i=1}^{U} (2SO_{i0} - SO_{i} - SO_{i-1})}{2} \times \frac{1}{f_s} )</td>
</tr>
<tr>
<td>Desaturation severity (%); DesSev</td>
<td>SpO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>( \frac{\sum_{i=1}^{L} DesArea_i}{TST} )</td>
</tr>
<tr>
<td>Obstruction Severity (s%); ObsSev</td>
<td>Thermistor, Nasal pressure</td>
<td>( \frac{\sum_{i=1}^{N} (t_{A_i} \times DesArea_i) + \sum_{j=1}^{M} (t_{H_j} \times DesArea_j)}{TST} )</td>
</tr>
</tbody>
</table>

Abbreviations and symbols: EEG = electroencephalogram, EOG = electro-oculogram, TR = total recording time, t<sub>wake</sub> = total time scored in wake, N = total number of apneas, M = total number of hypopneas, SpO<sub>2</sub> = blood oxygen saturation, L = total number of desaturations, K = total number of arousals, n<sub>S</sub> = number of sampling points where SpO<sub>2</sub> < 90%, f<sub>s</sub> = sampling frequency, t<sub>A</sub> = duration of individual apnea, t<sub>H</sub> = duration of individual hypopnea, t<sub>D</sub> = duration of individual desaturation, SO<sub>i0</sub> = SpO<sub>2</sub> value in i’th sampling point, SO<sub>i</sub> = SpO<sub>2</sub> value in first sampling point, U = total number of sampling points within individual desaturation.
Figure 5.1: Illustrative description of the features used for the computation of the polysomnographic parameters corresponding with equations in Table 5.2 and scoring manner used in study II. In studies I and III, the endpoint of desaturation was set to the point where the recovery of oxygenation started. Abbreviations and symbols: \( \text{SpO}_2 \) = blood oxygen saturation, \( t_A \) = duration of individual apnea, \( t_H \) = duration of individual hypopnea, \( t_D \) = duration of individual desaturation, DesArea = area of individual desaturation. Figure is modified from original publication II and reprinted with kind permission of the © ERS 2020: European Respiratory Journal.

5.1.2 Multiple sleep latency test and psychomotor vigilance task outcomes

In studies I and III, clinical guidelines were utilized in the interpretation of the MSLT results [32]. The outcome measure was the mean sleep latency (MSL) of four naps, all four having an upper limit of 20-minutes according to the MSLT protocol [19]. In study I, patients were grouped into severe EDS (MSL ≤ 5 min), moderate EDS (5 < MSL ≤ 10 min) and normal (MSL > 10 min) groups to maintain similar sample size within the groups. In addition, patients were grouped to OSA severity categories (Table 2.1), and within these categories, patients were further grouped into those with (MSL ≤ 8 minutes) and without EDS (MSL > 8 minutes). In study III, patients were divided to EDS severity categories similarly as in study I, with the exception that the MSL threshold for the normal group was set to 8 minutes.

In study II considering the PVT results, standard statistical outcomes were utilized, i.e. lapses (RTs ≥ 500 ms), median RT, mean reciprocal reaction time (RRT), mean of slowest 10% RT and mean of fastest 10% RT. As PVT does not have clinical thresholds, the patients were divided into quartiles based on all of the PVT outcomes. In study IV, patients were grouped to quartiles based on lapses...
and Sample Entropy estimates. Sample Entropy estimates were computed from repeated reaction times, to quantify in-test variation and time-on-task effect within PVT [80]. Computation of Sample Entropy estimates were conducted utilizing a template vector of 5 consequent reaction times and a threshold of 0.4 for Chebyshev distance-tolerance. Before analyses, each PVT trial series was normalized to have zero mean and a standard deviation of 1.

5.2 SPECTRAL ANALYSIS

In study III, spectral analyses of pulse oximeter-derived SpO$_2$, heart rate, and PPG signals were conducted. Before the spectral estimation, signals were decimated to reduce the amount of data from the frequency regions out of interest. Decimation was conducted utilizing an 8th order Chebyshev type I anti-aliasing filter with a cutoff frequency of \((f_s/2) \times 0.8/d_f\) where \(f_s\) is the original sampling frequency and \(d_f\) is the downsampling factor. Heart rate and SpO$_2$ signals were exported at a sampling frequency of 256 Hz to EDF-format using RemBrandt EDF Export. Both signals were afterwards decimated to 16 Hz. PPG was decimated from the original 256 Hz sampling frequency to 64 Hz. Lomb-Scargle power spectral density (PSD) estimates were computed for SpO$_2$, heart rate, and PPG. Lomb-Scargle estimates were chosen due to the artifacts in signals, which were treated as missing data. For all three signals, an equally spaced 991-point frequency grid was used, ranging from 0.001 to 0.1 Hz. In addition, a similar frequency grid in the range of 0.1-10 Hz was used for the PPG. From the PSDs of heart rate and SpO$_2$, mean power in frequency range between 15-35 mHz was computed by means of numerical integration.

In study IV, spectral analyses were conducted utilizing only PPG signals. Before spectral estimation, PPG signals were decimated as in study III. An 8th order Chebyshev type II filter with 60 dB ripple threshold and 6 Hz cut-off frequency were used for further filtering of non-physiological noise at higher frequencies. Complete signals were divided into 512 segments, and for each segment, Welch’s power spectrum, with 8-part division and 50% overlap, was computed to obtain a non-stationary estimate of frequency content throughout the night (Figure 5.2). From the spectrograms, a median power spectrum was extracted. The dominant arterial pulsation frequency (APF) curve was determined from the spectrograms as a peak-power frequency curve between 0.5 - 4 Hz.

5.3 STATISTICAL ANALYSES

In study I, Wilcoxon rank-sum test and nominal \(\chi^2\) test were utilized for group-level comparisons of the demographic data. Correlations between PSG parameters and MSL were computed using Spearman’s \(\rho\) and the statistical difference between correlation coefficients was assessed using Meng’s Z-test. The effect of the 10% relative increase in PSG parameters on the odds for belonging to the different sleepiness groups was assessed by utilizing multinomial and binomial logistic regression where appropriate. The statistical significance of the association of the severity of nocturnal hypoxemia with decreased MSL was examined also utilizing a generalized stepwise regression model with Bayesian information criterion (BIC) and assuming MSL to be \(\Gamma\)-distributed. In addition, to study extremities in the data, linear quantile regressions with 10%, 50%, and 90% quantiles for AHI, DesSev, and
ObsSev were computed.

In study II, binomial logistic regression was utilized for statistical testing. The effect of a relative 10% increase in PSG parameters was examined to evaluate the likelihood of belonging to the worst-performing PVT quartile instead of belonging to the best-performing quartile. Two regression models were used; the first model included sex, age, BMI, ESS score, smoking, and co-existence of hypertension, chronic obstructive pulmonary disease, and depression as adjusting factors. The second model was additionally adjusted for AHI and ObsDur to better quantify the independent effect of intermittent hypoxemia.

In study III, the statistical difference in mean power of the SpO$_2$, heart rate, and PPG PSD estimates between severe EDS, moderate EDS, and patients without EDS were assessed using one-way analysis of variance (ANOVA) test. In addition, the effect of increase in power within 15-35 mHz band in SpO$_2$ and heart rate PSDs to the probability of belonging to the severe or the moderate EDS group was investigated utilizing binomial logistic regression. The group of patients without EDS was used as a reference. In addition, similar analyses for ODI, mean desaturation depth and duration as well as for DesSev were conducted to verify the analyses made in study I in a larger patient cohort. In addition to the conventional statistical testing, a convolutional neural network (CNN) was developed to examine the possibility of differentiating the OSA patients with severe EDS. The 5-minute threshold was used instead of the 8-minute threshold for classification due to the...
largest differences in average PSDs. The detection of the patients was based on self-learned spectral features. The classification ability of CNN was validated using repeated random sub-sampling i.e. Monte-Carlo cross-validation. Furthermore, the sensitivity, specificity, positive predictive value, and negative predictive value for each validation subsample were computed.

In study IV, the patient population was first divided into men and women and further to quartiles based on lapses and Sample Entropy. Statistical significance of the differences in demographics and PSG parameters were assessed utilizing Wilcoxon’s rank-test and $\chi^2$ between the best and the worst performing quartiles. The cumulative distributions of nocturnal APFs were compared between the best and the worst performing PVT quartiles with a two-tailed Kolmogorov-Smirnov test. Cumulative distributions and corresponding 95% confidence intervals were computed utilizing Kaplan-Meier estimates. In addition, generalized logistic stepwise regression analyses were conducted to quantify the significance of a 6 pulsations/minute increase in the nocturnal median APF to the probability of belonging to the worst-performing PVT quartile. In the stepwise regression, BIC was used as an entering criterion for the model. The model’s capability of classifying the patients into the worst or best-performing PVT quartiles was assessed by computing $\chi^2$ statistics with respect to the constant model without any predictor variable.
6 Results

This chapter summarizes the results of studies I-IV. The specific aims and main findings of each study are listed in Table 6.1.

Table 6.1: The primary aims and main findings of studies I-IV.

<table>
<thead>
<tr>
<th>Study</th>
<th>Aim</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Study the connection between respiratory event severity and EDS.</td>
<td>The durations of apneas and hypopneas, and especially the severity of related desaturations, had a significantly stronger connection to decreased MSL than conventional AHI and ODI.</td>
</tr>
<tr>
<td>II</td>
<td>Evaluate the connection between respiratory event severity and impaired daytime vigilance.</td>
<td>Parameters incorporating the severity of intermittent hypoxemia were associated with poor PVT performance but this was not the case for conventional diagnostic parameters and sleep fragmentation metrics.</td>
</tr>
<tr>
<td>III</td>
<td>Examine, whether spectral features of pulse oximetry signals differ between OSA patients with and without EDS.</td>
<td>OSA patients with moderate and severe EDS had a distinguishable increase in power within 15-35 mHz frequency band in SpO2 and heart rate signals.</td>
</tr>
<tr>
<td>IV</td>
<td>Investigate, whether the spectral features of PPG signal are associated with poor PVT performance.</td>
<td>Increased arterial pulsation frequency was associated with a higher number of lapses and increased within-test variation in male OSA patients.</td>
</tr>
</tbody>
</table>

Abbreviations and symbols: EDS = excessive daytime sleepiness, MSL = mean daytime sleep latency, AHI = apnea-hypopnea index, ODI = oxygen desaturation index, PVT = psychomotor vigilance task, OSA = obstructive sleep apnea, SpO2 = blood oxygen saturation signal, PPG = photoplethysmogram.
6.1 THE CONNECTION OF POLYSOMNOGRAPHIC PARAMETERS WITH EDS AND VIGILANCE DETERIORATION

The parameters incorporating the severity of intermittent hypoxemia (Table 5.2) were consistently found to display a significant ($p < 0.05$) association with decreased MSL in MSLT and with prolonged reaction times during PVT (Table 6.2). The relative 10% increases in DesSev and $t_{90\%}$ were significantly ($p < 0.05$) associated with higher odds of belonging to severe EDS or moderate EDS group (Table 6.2). Furthermore, a similar increase in either DesSev, $t_{90\%}$, or median desaturation depth was associated with prolonged mean and median reaction times and a higher number of lapses in PVT (Table 6.2). For comparison, an increase either in AHI and ODI did not show association with deteriorated PVT performance ($p > 0.4$). In addition, increases in AHI and ODI elevated the odds of having severe EDS, but not the odds of belonging to moderate EDS group (Table 6.2). An increase in the values of parameters describing the duration of apneas, hypopneas and desaturations, i.e. ObsDur and DesDur, increased the odds of having severe EDS, but did not increase the odds of having moderate EDS or poor PVT performance (Table 6.2).

The results of Spearman-correlation analyses between MSL and PSG parameters are presented in Table 6.3. In the entire studied patient population, all correlations were statistically significant and the absolute values of the correlation coefficients varied between 0.27 - 0.38. In the severe OSA group, DesSev exhibited the strongest correlation ($\rho = -0.49, p < 0.01$) with MSL, being significantly ($p < 0.05$) higher than the correlations of AHI or ODI with MSL. In mild and moderate OSA groups, all correlations diminished and were not statistically significant. In addition, correlation analyses performed separately for men and women revealed differences between the sexes in severe OSA. DesSev showed the strongest correlation ($\rho = -0.49, p < 0.01$) with MSL in men. Conversely, ObsDur ($\rho = -0.57, p < 0.05$) and DesDur ($\rho = -0.58, p < 0.05$) had the strongest correlations with MSL in women.

The stepwise regression analysis between investigated PSG parameters, demographical parameters, and MSL showed that DesSev had the highest power to explain decreased MSL. AHI, ObsSev, and $t_{90\%}$ had statistically significant ($p < 0.05$) association with MSL in regression analysis, but the order of magnitude of the $\beta$-coefficients was less than 0.001 and they were discarded from the model based on the Bayesian Information Criterion (BIC). Thus, only two variables were accepted into the model: male sex ($\beta = 0.192, p < 0.001$, standard error = 0.069) and DesSev ($\beta = 0.155, p < 0.001$, standard error = 0.015).
Table 6.2: The effect of relative 10% increase in parameter values to the odds ratio of belonging to either one of the EDS groups and odds for belonging to the worst-performing PVT quartile (Q4) in studies I-II.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Severe EDS</th>
<th>Moderate EDS</th>
<th>RRT</th>
<th>mRT</th>
<th>Lapses</th>
<th>RRT*</th>
<th>mRT*</th>
<th>Lapses*</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST (h)</td>
<td>-</td>
<td>-</td>
<td>1.05</td>
<td>1.07</td>
<td>1.02</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>AHI (1/h)</td>
<td>1.63</td>
<td>1.12</td>
<td>1.05</td>
<td>1.07</td>
<td>1.02</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ODI (1/h)</td>
<td>1.61</td>
<td>1.13</td>
<td>1.07</td>
<td>1.09</td>
<td>1.00</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ArI (1/h)</td>
<td>-</td>
<td>-</td>
<td>0.99</td>
<td>0.98</td>
<td>0.95</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ObsDur (%)</td>
<td>1.41</td>
<td>1.08</td>
<td>1.04</td>
<td>1.09</td>
<td>1.02</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>DesDur (%)</td>
<td>1.44</td>
<td>1.10</td>
<td>1.07</td>
<td>1.09</td>
<td>1.02</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>DesSev (%)</td>
<td>2.01</td>
<td>1.30</td>
<td>1.24</td>
<td>1.26</td>
<td>1.17</td>
<td>1.43</td>
<td>1.52</td>
<td>1.48</td>
</tr>
<tr>
<td>ObsSev (%)</td>
<td>2.18</td>
<td>1.31</td>
<td>1.18</td>
<td>1.17</td>
<td>1.14</td>
<td>1.33</td>
<td>1.38</td>
<td>1.36</td>
</tr>
<tr>
<td>Avg. SpO2 (%)</td>
<td>0.24</td>
<td>0.66</td>
<td>0.51</td>
<td>0.63</td>
<td>0.54</td>
<td>0.55</td>
<td>0.60</td>
<td>0.47</td>
</tr>
<tr>
<td>Min. SpO2 (%)</td>
<td>0.55</td>
<td>0.73</td>
<td>0.88</td>
<td>0.94</td>
<td>0.94</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$t_{90%}$ (s)</td>
<td>2.05</td>
<td>1.41</td>
<td>1.14</td>
<td>1.17</td>
<td>1.18</td>
<td>1.11</td>
<td>1.16</td>
<td>1.23</td>
</tr>
<tr>
<td>$\mu_{DD}$ (%)</td>
<td>-</td>
<td>-</td>
<td>1.21</td>
<td>1.21</td>
<td>1.16</td>
<td>1.27</td>
<td>1.26</td>
<td>1.27</td>
</tr>
<tr>
<td>$m_{DD}$ (%)</td>
<td>-</td>
<td>-</td>
<td>1.26</td>
<td>1.25</td>
<td>1.20</td>
<td>1.36</td>
<td>1.34</td>
<td>1.37</td>
</tr>
</tbody>
</table>

Statistically significant ($p < 0.05$) odds are highlighted with bold typeface. Severe EDS and moderate EDS indicates patients with mean daytime sleep latency (MSL) $\leq$ 5 min and patients with 5 min $<$ MSL $\leq$ 10, respectively. Q1/Q4 thresholds for mean reciprocal reaction time (RRT), median reaction time (mRT), and lapses were 2.9/2.2, 340 ms/445 ms, and 5/36, respectively. All odds are adjusted for sex, age, and body mass index. In addition, odds for PVT were adjusted for subjective sleepiness, hypertension, depression, chronic obstructive pulmonary disease, and smoking status. * indicates that the model was additionally adjusted for total sleep time (TST), apnea-hypopnea index (AHI), arousal index (ArI), and Obstruction Duration (ObsDur). If parameter was not used in particular analysis, it is marked with hyphen. Abbreviations: EDS = excessive daytime sleepiness, RRT = mean reciprocal reaction time, mRT = median reaction time, ODI = oxygen desaturation index, DesDur = Desaturation Duration, DesSev = Desaturation Severity, ObsSev = Obstruction Severity, Avg. SpO2 = average blood oxygen saturation, Min. SpO2 = minimum oxygen saturation, $t_{90\%}$ = time under 90% saturation, $\mu_{DD}$ = mean desaturation depth, $m_{DD}$ = median desaturation depth.
Table 6.3: Spearman’s $\rho$-coefficients between mean daytime sleep latency and diagnostic parameters separately in obstructive sleep apnea (OSA) severity categories and in the whole population of study I.

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Mild OSA</th>
<th>Moderate OSA</th>
<th>Severe OSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHI (1/h)</td>
<td>-0.35</td>
<td>-0.01</td>
<td>0.14</td>
<td>-0.40</td>
</tr>
<tr>
<td>ODI (1/h)</td>
<td>-0.34</td>
<td>-0.03</td>
<td>0.07</td>
<td>-0.40</td>
</tr>
<tr>
<td>Avg. SpO$_2$ (%)</td>
<td>0.27</td>
<td>0.02</td>
<td>0.07</td>
<td>0.40</td>
</tr>
<tr>
<td>Min. SpO$_2$(%)</td>
<td>0.31</td>
<td>-0.01</td>
<td>0.18</td>
<td>0.32</td>
</tr>
<tr>
<td>$t_{90%}$ (s)</td>
<td>-0.38</td>
<td>0.07</td>
<td>-0.17</td>
<td>-0.44</td>
</tr>
<tr>
<td>ObsDur (%)</td>
<td>-0.36</td>
<td>-0.09</td>
<td>0.16</td>
<td>-0.46</td>
</tr>
<tr>
<td>DesDur (%)</td>
<td>-0.34</td>
<td>0.02</td>
<td>0.15</td>
<td>-0.44</td>
</tr>
<tr>
<td>DesSev (%)</td>
<td>-0.36</td>
<td>-0.01</td>
<td>0.01</td>
<td>-0.49*</td>
</tr>
<tr>
<td>ObsSev (%)</td>
<td>-0.35</td>
<td>-0.01</td>
<td>0.05</td>
<td>-0.43</td>
</tr>
</tbody>
</table>

Correlation coefficient is bolded if the correlation is statistically significant ($p < 0.05$), and marked with * if the coefficient is significantly higher than those of AHI and ODI. Abbreviations: AHI = apnea-hypopnea index, ODI = oxygen desaturation index, Avg. SpO$_2$ = average blood oxygen saturation, Min. SpO$_2$ = minimum oxygen saturation, $t_{90\%}$ = time under 90% saturation, ObsDur = Obstruction Duration, DesDur = Desaturation Duration, DesSev = Desaturation Severity, ObsSev = Obstruction Severity. Table modified from original study I.

6.2 PULSE OXIMETRY-DERIVED SPECTRAL FEATURES AND THEIR CONNECTION TO EDS AND DETERIORATION OF VIGILANCE

In the regression analyses, the increase in power within the 15 - 35 mHz frequency band of SpO$_2$ ($P_{SpO_2}$) and heart rate ($P_{HR}$) demonstrated a significant ($p < 0.05$) risk of having severe EDS (Table 6.4). However, neither the increase in $P_{SpO_2}$ nor $P_{HR}$ affected the probability of belonging to the moderate EDS group compared to the normal group. Furthermore, an increase of 6 pulsations/minute in median nocturnal arterial pulsation frequency (mAPF) significantly ($p < 0.02$) elevated the odds of belonging to the Q4 based on the number of lapses in PVT (Table 6.4). However, a similar increase in mAPF did not elevate the odds of belonging to the Q4 based on Sample Entropy computed from PVT trial series.

In the spectral morphology analysis concerning EDS, significantly ($p < 0.01$) higher powers in the mean PSD estimates of nocturnal SpO$_2$ and heart rate were observed in patients with severe EDS compared to patients without EDS (Figure 6.1). A significantly ($p < 0.01$) higher power in mean PSDs of SpO$_2$ was also seen in the moderate EDS group compared to normal group. No significant differences were observed between the mean PSDs of heart rate between moderate EDS group and normal group. Both high and low-frequency range PSDs of PPG were very similar between the groups, except significantly ($p < 0.05$) lower mean power in low
Table 6.4: The effect of increase in quantified spectral features in studies III-IV to the odds of belonging to a certain EDS group or to the worst-performing (Q4) quartiles in PVT instead of best-performing quartile (Q1).

<table>
<thead>
<tr>
<th>Spectral feature</th>
<th>Severe EDS vs Moderate EDS</th>
<th>Severe EDS vs normal group</th>
<th>Moderate EDS vs normal group</th>
</tr>
</thead>
<tbody>
<tr>
<td>$P_{HR}$</td>
<td>1.81</td>
<td>1.83</td>
<td>1.09</td>
</tr>
<tr>
<td>$P_{SpO_2}$</td>
<td>1.19</td>
<td>1.29</td>
<td>1.01</td>
</tr>
<tr>
<td></td>
<td>Q4 vs Q1</td>
<td>Lapses</td>
<td>Q4 vs Q1</td>
</tr>
<tr>
<td>mAPF</td>
<td>1.27</td>
<td>NS</td>
<td>Sample Entropy</td>
</tr>
</tbody>
</table>

Severe EDS, moderate EDS and normal group indicates patients with mean daytime sleep latency (MSL) ≤ 5 min, patients with 5 min < MSL ≤ 10 and patients with MSL > 10min, respectively. Q1/Q4 thresholds for lapses and Sample Entropy were 4/35 and 0.12/0.71, respectively. Both models were adjusted for sex, age, and body mass index. The odds for belonging to certain EDS group were computed utilizing binomial logistic regression-based $\beta$-coefficients. The odds for belonging to Q4 instead of Q1 were determined via stepwise logistic regression. NS indicates that when Sample Entropy was used as a response variable, corresponding predictor variable was discarded from the regression model as a non-significant. Abbreviations: EDS = excessive daytime sleepiness, $P_{HR}$ = power in 15 - 35 mHz frequency band in heart rate power spectral density estimate, $P_{SpO_2}$ = power in 15 - 35 mHz band in blood oxygen saturation power spectral density estimate, mAPF = median nocturnal arterial pulsation frequency.

---

frequency PPG-PSD of severe OSA group. In addition, the detection of OSA patients (AHI ≥ 5) with severe EDS via convolutional neural network and PSD inputs achieved accuracy of 72.8 ± 4.5%, sensitivity of 49.5 ± 13.9%, positive predictive value (PPV) of 46.2 ± 15.5%, specificity of 80.4 ± 7.1%, and negative predictive value (NPV) of 83.0 ± 5.9%. Same performance statistics for moderate-to-severe OSA patients (AHI ≥ 15) were 75.3 ± 5.9%, 55.6 ± 15.2%, 52.0 ± 12.2%, 81.9 ± 6.5% and 84.2 ± 5.9%, respectively.

Significant ($p < 0.05$) differences in the nocturnal PPG frequency content between good and poor performers in PVT were observed. In both men and women, the higher and more varying APF associated with a higher number of lapses (Figures 6.2 and 6.3). However, similar findings were observed only in men when PVT performance was quantified using Sample Entropy (Figures 6.4 and 6.5). In addition, cumulative distribution function (CDF) comprised significantly ($p < 0.05$) higher APF values in lapses Q4 than in Q1 both in men and women. In men, higher APF values in CDF were observed in Sample Entropy Q4 than in Q1, but not in women.
Figure 6.1: Mean (± SD) power spectral density (PSD) estimates in obstructive sleep apnea patients with different severity of excessive daytime sleepiness (EDS). A): PSD of the blood oxygen saturation (SpO$_2$); B): PSD of pulse oximetry-based heart rate; C) and D): spectra of low-frequency and high-frequency ranges of photoplethysmogram (PPG) signal, respectively. Figure is reprinted with kind permission of Elsevier as originally published in study III.
Figure 6.2: Frequency domain features of the nocturnal photoplethysmogram (PPG) signal in the best (Q1) and the worst (Q4) performing quartiles of men based on the number of lapses in PVT. A) and B): temporal frequency content of the PPG in Q1 and Q4, respectively. C): The median power spectrum of the PPG. D): The cumulative distribution function (CDF) of the nocturnal arterial pulsation frequencies (APF). Figure is modified from original study IV.
Figure 6.3: Frequency domain features of the nocturnal photoplethysmogram (PPG) signal in the best (Q1) and the worst (Q4) performing quartiles of women based on the number of lapses in PVT. A) and B): temporal frequency content of the PPG in Q1 and Q4, respectively. C): The median power spectrum of the PPG. D): The cumulative distribution function (CDF) of the nocturnal arterial pulsation frequencies (APF). Figure is modified from original study IV.
Figure 6.4: Frequency domain features of the nocturnal photoplethysmogram (PPG) signal in the best (Q1) and the worst (Q4) performing quartiles of men based on the Sample Entropy (SE) computed from PVT trial series. A) and B): temporal frequency content of the PPG in Q1 and Q4, respectively. C): The median power spectrum of the PPG. D): The cumulative distribution function (CDF) of the nocturnal arterial pulsation frequencies (APF). Figure is modified from original study IV.
Figure 6.5: Frequency domain features of the nocturnal photoplethysmogram (PPG) signal in the best (Q1) and the worst (Q4) performing quartiles of women based on the Sample Entropy (SE) computed from PVT trial series. A) and B): temporal frequency content of the PPG in Q1 and Q4, respectively. C): The median power spectrum of the PPG. D): The cumulative distribution function (CDF) of the nocturnal arterial pulsation frequencies (APF). Figure is modified from original study IV.
6.3 DEMOGRAPHICAL RISK FACTORS

Demographical risk factors were found to differ when analysing EDS and vigilance (Table 6.5). Male OSA patients had a significantly higher risk of suffering from EDS. Conversely, female OSA patients had a substantially higher risk of a poor PVT performance. In addition, younger age and OSA were found to have a combined effect to increase the risk of suffering from either moderate or severe EDS. Conversely, older age together with OSA was associated with a deteriorated ability to sustain attention. In addition, a one-point increase in ESS was associated with poor PVT performance in all analyses (range of odds ratios: 1.05 - 1.07, \( p < 0.01 \)). None of the comorbidities were found to display any association with deteriorated vigilance. The only statistically significant association was found between depression and belonging to Q4 based on Sample Entropy (\( \beta = 0.906, p = 0.01 \), standard error = 0.362) (Table 6.5).

Table 6.5: Analysed demographic factors in studies I-IV and the ranges of statistically significant odds of having either moderate or severe EDS and odds ranges of belonging to the worst-performing quartiles (Q4) based on all PVT outcomes.

<table>
<thead>
<tr>
<th></th>
<th>EDS based on MSLT</th>
<th>Q4 quartiles in PVT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male Sex</td>
<td>1.58 - 2.56</td>
<td>No significance</td>
</tr>
<tr>
<td>Female Sex</td>
<td>No significance</td>
<td>2.21 - 6.02</td>
</tr>
<tr>
<td>Age (y)</td>
<td>0.97 - 0.99*</td>
<td>1.01 - 1.05**</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>1.00 - 1.03***</td>
<td>No significance</td>
</tr>
<tr>
<td>ESS</td>
<td>Not applicable</td>
<td>1.05 - 1.07</td>
</tr>
<tr>
<td>Smoking</td>
<td>Not applicable</td>
<td>No significance</td>
</tr>
<tr>
<td>Depression</td>
<td>Not applicable</td>
<td>2.47*</td>
</tr>
<tr>
<td>COPD</td>
<td>Not applicable</td>
<td>No significance</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Not applicable</td>
<td>No significance</td>
</tr>
</tbody>
</table>

* indicates that the odds were statistically significant (\( p < 0.05 \)) in all analyses except those considering the probability to have mean daytime sleep latency (MSL) less than 8 minutes for mild OSA patients. ** indicates that the odds were statistically significant in all analyses except analyses concerning the fastest and the slowest 10% reaction times. *** indicates that the odds were statistically significant in all analyses except analyses concerning of belonging to the group with MSL < 8 min within moderate OSA patients. + indicates that the odds were significant only in comparing Q4 and Q1 based on Sample Entropy. Abbreviations and symbols: EDS = excessive daytime sleepiness, MSLT = multiple sleep latency test, PVT = psychomotor vigilance task, BMI = body mass index, ESS = Epworth sleepiness scale, COPD = chronic obstructive pulmonary disease, MSL = mean daytime sleep latency.
Sub-group analyses in studies considering MSLT outcomes showed that patients with severe EDS had a higher median body mass index (32.8 vs. 30.6, \( p = 0.06 \)), a higher median amount of N2 sleep (56.7\% vs. 46.2\%, \( p < 0.05 \)) and less N3 sleep (9.0\% vs. 16.4\%, \( p < 0.05 \)), compared to patients without EDS. For comparison, sub-group analyses between the best and the worst performing quartiles based on lapses and Sample Entropy indicated that neither higher BMI nor differences in sleep stage percentages were associated with a deterioration in vigilance. A comparison between OSA patients in Q4 and Q1 based on lapses demonstrated, that the men in Q4 were older (median age 56.9 vs. 51.1, \( p = 0.02 \)) and had shorter TST in PSG (median TST 4.9h vs. 5.4h, \( p = 0.02 \)). In addition, the number of hypertensive (43.8\% vs. 29.6\%, \( p = 0.05 \)) and depressed (16.3\% vs. 9.1\%, \( p = 0.16 \)) men was higher in lapses Q4 compared to those in Q1, but the difference did not reach statistical significance. For comparison, women in Q4 based on lapses had higher ESS scores (median ESS score 13 vs. 9, \( p = 0.01 \)) as compared to those in Q1. Furthermore, Q4 based on lapses comprised a higher number of hypertensive women (49.2\% vs. 33.3\%, \( p = 0.07 \)) and they were older (median age 58.8 vs. 54.3, \( p = 0.06 \)) than women in lapses Q1, statistical significance being at the borderline. In both men and women, Q1 and Q4 based on Sample Entropy were very similar and there were no statistical differences in demographics, conventional OSA severity, or sleep quality parameters.
7 Discussion

This thesis consists of four original publications assessing the connection of obstructive sleep apnea (OSA) to excessive daytime sleepiness (EDS) and a deterioration in vigilance. These studies focused on investigating methods to exploit a more detailed quantification of pulse oximeter data, as nocturnal hypoxemia and physiological stress have been associated with EDS and vigilance deterioration [18, 20, 81, 82]. The present results indicate that the severity of nocturnal intermittent hypoxemia, large fluctuations in heart rate, and increased arterial pulsation frequency (APF) are significant predictors of daytime symptoms in large patient populations. Especially, an increase in Desaturation Severity (DesSev) associated more strongly with a higher risk of having objective EDS and deteriorated vigilance as compared to the gold standard AHI. Furthermore, the investigated novel PSG parameters, incorporating the severity of desaturations, have been previously shown to have a stronger connection to cardiovascular mortality and comorbidity in OSA patients than the AHI [16, 17]. These findings emphasize the urgent need of developing alternative and more informative methods and metrics for severity assessment of OSA and polysomnographic phenotyping of the patients.

7.1 POLYSOMNOGRAPHIC PARAMETERS AND THEIR ASSOCIATION WITH EDS AND IMPAIRED VIGILANCE

Based on the results obtained in studies I and II, the severity of desaturations is one of the strongest predictors of EDS and vigilance deterioration in OSA patients (Table 6.2). A relative 10% increase either in DesSev or $t_{90\%}$ elevated the odds of having severe EDS by over twofold. Increases in both of these parameters elevated significantly the odds of having moderate EDS as well. Similarly, a 10% increase in either DesSev, $t_{90\%}$ or $m_{DD}$ elevated odds for impaired PVT performance and prolonged reaction times (Table 6.2). Moreover, this association strengthened when the model was additionally adjusted with the duration and number of the apneas and hypopneas.

Interestingly, increases in the values of parameters that describe only the duration of apneas, hypopneas, and desaturations were not associated with EDS or poor PVT performance. This might be due to OSA patients having varying physiological responses to apneas and hypopneas [24]. On average, longer apneas and hypopneas cause longer desaturations [24, 83]. However, there exists also extensive inter-subject variation in the physiological responses during a similar airflow limitation. These responses include the depth of the desaturation, how rapidly the decrease in peripheral oxygenation occurs, and conversely, how fast is the reoxygenation rate. All of the aforementioned properties of desaturation events affect both the size of the desaturation areas and the magnitude of $t_{90\%}$. Moreover, hypoxemia induces endothelial dysfunction that causes inflammation [84], which is considered to be a major pathological cause for EDS [18]. Thus it is reasonable,
that DesSev and $t_{90\%}$ had the strongest connection to EDS and impaired vigilance: they both describe the hypoxic load in a detailed manner as compared to parameters that only describe the number or the duration of apneas, hypopneas, and desaturations.

It is however noteworthy, that in studies I and II the desaturation areas were computed differently due to a different scoring protocol. In study I, the recovery area was not considered as a part of the desaturation area whereas in study II the desaturation area also contained the recovery area. This can in part explain the difference in the magnitude in computed odds for DesSev when assessing the probability for belonging to a moderate or severe EDS group in study I and to Q4 based on PVT outcomes in study II (Table 6.2). However, the odds for $t_{90\%}$ were also smaller in PVT-related analysis as compared the EDS analysis. This indicates that hypoxemia is connected to deteriorations in vigilance but to a lesser extent than EDS i.e. it suggests that there are different mechanisms behind EDS and vigilance deterioration. Intermittent hypoxemia can induce micro bleeding and changes comparable to an ischemic injury in the brain in addition to inflammation [20]. Peripheral hypoxemia can translate to cerebral hypoxemia when a certain threshold is exceeded [59]. Therefore, deeper peripheral desaturations can cause a repeated failure of the cerebral autoregulation system. This in turn can lead to intermittent cerebral hypoxemia and thus, neuronal brain damage causing a vigilance deterioration. This could, in part, explain the magnitude difference in the hypoxemia-based odds of EDS and vigilance deterioration as inflammation is much more of an acute consequence of intermittent hypoxemia in comparison to neuronal brain damage.

The correlation analyses and stepwise regression analyses show that DesSev had the highest explaining power towards excessive daytime sleepiness, especially when severe OSA patients were investigated (Table 6.3). Previous findings indicate, that the polysomnographic characteristics of severe OSA patients with EDS differ from those of patients without EDS [39]. For example, these characteristics include a significantly lower minimum nocturnal SpO$_2$ and higher apnea index. As the correlation between MSL and both DesSev and $t_{90\%}$ strengthened significantly in patients with severe OSA as compared to all other groups, it could be speculated that one of the strongest indications of severe EDS together with severe OSA is the severity of nocturnal intermittent hypoxemia. In addition, it can be speculated that frequent but non-desaturating apneas and hypopneas are not as detrimental as apneas and hypopneas causing deep desaturations despite being less frequent. This line of evidence strongly supports the idea of assessing the severity of OSA with other parameters alongside AHI.

Interestingly, the demographic risk factors differed significantly between analyses considering EDS and the deterioration in vigilance (Table 6.5). Whereas younger age and male sex were significant predictors of EDS, female sex and older age were significant predictors of deterioration in vigilance. In addition, BMI showed a significant connection especially to severe EDS but not to a deterioration in vigilance. Based on the findings in studies I-IV, it seems that male OSA patients are more prone to suffer from objective daytime sleepiness, whereas female OSA patients are more likely to lose their ability to sustain attention which is seen as higher within-test variation and a higher number of lapses in PVT. The literature shows, however, that women describe OSA related symptoms rather differently than men, and have in general slower median reaction times and poorer PVT performance [18,85,86]. Similar findings were obtained in this thesis.
Previous studies have shown that younger OSA patients have more complaints of EDS [45, 87, 88]. It could be speculated that younger patients with OSA have more complaints of sleepiness due to life-situation factors such as small children, hectic work schedules, and insufficient sleep in general. These factors could also lead to a higher prevalence of objective sleepiness observed in younger patients. However, in study II, older OSA patients were found to be more prone to have impaired vigilance. All studies included in this Ph.D. thesis investigated suspected OSA patients as a part of the normal clinical inflow. Thus, it could be speculated that older OSA patients have had the untreated OSA for longer and therefore, chronic nocturnal intermittent hypoxemia and sleep fragmentation would have affected them for a longer time than their younger counterparts. This aspect is also in concordance with APPLES-studies, which indicate that the response for CPAP is substantially stronger in the case of sleepiness than neurocognitive deficits [81, 82]. Thus, it could be hypothesized that both subjective and objective sleepiness are more acute symptoms of OSA in comparison to deteriorations in vigilance and ultimately, to cognitive decline. This could be due to the cumulative hypoxemia-related neuronal brain damage discussed above. In order to verify the associations considering gender and age, a large-scale long-term follow-up study should be conducted utilizing PSG, MSLT, ESS, brain MRI as well as PVT and other measures of cognitive functioning with multiple time points during the disease progression.

7.2 ASSOCIATION OF PULSE OXIMETRY-BASED SPECTRAL FEATURES WITH EDS AND IMPAIRED VIGILANCE

The findings emerging from studies III-IV are in concordance with those in studies I-II. The power spectral density (PSD) estimates of pulse oximetry signals were significantly different between EDS categories, especially in the 15 - 35 mHz frequency band (Figure 6.1). OSA causes cyclical heart rate variation due to the apneas, hypopneas, and desaturations during sleep [7, 23]. In study I, a significant relationship was found between severe desaturations and EDS. Therefore, it is reasonable to argue that the spectrum of SpO\textsubscript{2} and heart rate of a patient with a severe EDS show increases in power within the 15 - 35 mHz frequency band that correspond to the fluctuations in oxygen saturation. Moreover, the regression analyses showed that an increase in power within 15 - 35 mHz frequency band in SpO\textsubscript{2} and heart rate PSDs elevates the odds of having severe EDS (Table 6.4). However, no clearly distinguishable differences between the EDS groups were seen in the frequency content of the PPG. Patients with severe EDS had a statistically significant reduction in the mean power in low-frequency range, which could be due in part to the hypoxemia-related vasoconstriction lowering the signal amplitudes. However, all groups demonstrated almost flat and highly similar PSD values within 0.001 to 0.1 Hz band and therefore, no conclusions of these differences can be made.

Findings from study III strengthen the current body of evidence considering the connection between EDS and OSA. Repetitive hypoxemia can lead to hyperactivity of the carotid body which triggers overcompensated responses in heart rate when desaturation occurs [89]. This can be seen as an increase in power within the same frequency range in both SpO\textsubscript{2} and heart rate. Thus, severe intermittent hypoxemia with accompanying large fluctuations in heart rate are significant predictors of EDS.
and could be easily adapted into the assessment of OSA severity via PSD estimates. Despite the aforementioned significant differences in spectral features of pulse oximetry signals between the EDS groups, the neural network-based detection of OSA patients with severe EDS did not reach clinically acceptable values of sensitivity and specificity. However, based on the findings reported in study III, the frequency content of pulse oximeter signals can still provide a potential tool for the estimation of increased risk of EDS.

On the other hand, the frequency domain analyses of the PPG conducted in study IV showed that OSA patients with impaired vigilance have higher nocturnal arterial pulsation frequency (APF) than those who performed well in PVT (Figures 6.2-6.5). Especially in men, the difference was clearly distinguishable in the cumulative distribution of the nocturnal APFs in analyses considering both lapses and Sample Entropy. The 6 pulsations/minute increase in median APF (mAPF) also significantly elevated the odds of having a higher number of lapses in PVT regardless of the sex (Table 6.4). In the recent literature, the glymphatic system of the brain has been shown to have a major role in mediating sleep’s restorative function and the clearance of metabolic waste products [60, 90]. The glymphatic system is driven by a multitude of physiological factors, including slow wave sleep oscillations, arterial pulsations and breathing-related oscillations [61, 63]. OSA distorts the sleep architecture [25], decreases the amount of slow wave sleep [44], increases sympathetic overdrive and is evidently associated with atherosclerosis [91]. These factors increase nocturnal APF, simultaneously increasing nocturnal blood pressure that could lead to a long-term impairment of the functioning of the glymphatic system [62]. Hence, untreated OSA can chronically degrade the protein clearance process and restorative function of sleep, subsequently impairing vigilance and cognitive performance. As the APF estimate is readily obtainable from PPG signal, the probability for impaired vigilance could be evaluated as a part of each diagnostic study without any modifications to current measurement protocols.

Significant differences between men and women were found considering the frequency domain features of PPG and their association to vigilance deterioration. In general, women have a higher resting heart rate and different sensitivities in their cardiac regulation than men [92]. In addition, women have been shown to have poorer PVT results than men in general [86]. Furthermore, in studies II and IV female sex together with OSA was associated with a high probability of poor PVT performance. Based on these findings in both women and men, severe intermittent hypoxemia and higher APF seem to be associated with poor PVT performance. However, the magnitude of the difference in the severity of hypoxemia and APF is significantly higher in men.

7.3 LIMITATIONS

It is acknowledged that the results discovered in this thesis come with certain limitations. First, no comorbidity data were available for the PSG-MSLT patient cohort. Possible confounders such as the presence of COPD, hypertension, and psychiatric disorders can affect both the MSLT results and PSG data. Moreover, there was not a complete record of the medications being used by the patients in studies I-IV. It is acknowledged, that the use of sedative medications or
certain antihypertensive drugs, for example, beta-blockers would exert an effect on nocturnal cardiorespiratory data, nocturnal EEG data, daytime alertness, and daytime sleepiness. In studies II and IV, regression models were adjusted for comorbidities, but it is acknowledged that the lack of information of the medications is a limitation.

Second, the PSG-MSLT cohort suffers from a selection bias related to subjective sleepiness. All patients who had undergone both PSG and MSLT had complained of sleepiness in their clinical interview before diagnostic studies. However, the aim of studies I and III was to focus on investigate objective daytime sleepiness, and therefore it is believed that the interpretation of the results is not jeopardized.

Third, neither in the PSG-MSLT cohort nor the PSG-PVT cohort, data on patients’ habitual sleep patterns was available. It is known that poor long-term sleep hygiene affects both sleepiness and vigilance [55, 93], and most often patients undergoing PSG experience the so-called first night effect: their sleep quality is much worse and the duration of sleep is much lower than under normal circumstances [94]. In all studies, this was taken into account either by excluding those patients who had an abnormally short TST or by using TST as an adjusting factor. In addition, PVTs were conducted prior to PSG; thus, the first night effect did not influence the PVT outcomes. Nevertheless, chronic sleep deprivation affects both vigilance and daytime sleepiness to a significant extent; thus, the lack of actigraphies and sleep diaries is a limitation in all of the studies included in this thesis.

Fourth, all of the studies were retrospective in nature and the studied individuals were part of the normal clinical inflow of patients with a suspected sleep disorder. Thus, all studies lack a completely healthy group as a reference group. In all studies, reference groups were separated from the cohorts considering vigilance and EDS. It is acknowledged that the individuals were referred to PSG due to a suspicion of possible sleep disorder which represents a source of bias. Therefore, generalizations to epidemiological populations cannot be made. However, both patient cohorts reflect well the general clinical populations of OSA patients. The purpose of the studies I-IV was to investigate the PSG features that can associate OSA severity with EDS and vigilance deterioration; therefore, the reference groups separated from the initial populations are adequate for evaluating these associations.

### 7.4 FUTURE STUDIES

As studies I-IV included only a limited number of EEG metrics, future studies with similar research questions but more detailed analysis of EEG are warranted. Detailed analysis of EEG includes analyses beyond the conventional 30-second epochs and sleep staging. These investigations should focus on the similarities and dissonance between the features observed in EEG and cardiorespiratory signals in both, time and frequency-domain, to better evaluate the quality of sleep e.g. when recovering from an extensive hypoxemic load. In addition, more stringent analyses of cardiovascular regulation need to be conducted. For example, to evaluate the HRV, pulse transmit times, pulse wave velocities, and stiffness of the arteries as they may better reflect the physiological stress and daytime symptoms associated with OSA-related cardiovascular comorbidities and risk factors. These studies can ultimately lead to a simpler, more affordable, and user-friendly diagnostic sleep studies compared to type I PSG, when the most important nocturnal signals measured in PSG are determined.
Moreover, as both of the investigated cohorts were retrospective, further studies are warranted to prospectively investigate the efficiency of the developed methods in evaluating the connection between daytime symptoms and OSA. This should be extended to various epidemiological populations with healthy control groups, in order to obtain a better overall overview of the causes and biomarkers of the objective sleepiness and vigilance deterioration. Prospective studies should include also structural MRI imaging of the brain to quantify the possible neuronal damage and pathological changes in patients with either severe desaturations, extensive fluctuations in nocturnal heart rate, excessive daytime sleepiness or an impaired ability to sustain attention to better understand the underlying causes of the most detrimental outcomes of OSA.
The first of the two main aims of the thesis was to investigate whether a detailed parametric quantification of apneas, hypopneas, and related blood oxygen desaturations could be linked to objective EDS measured with MSLT as well as to poor psychomotor vigilance in large patient cohorts. The second aim was to examine the usability of frequency-domain features of nocturnal pulse oximetry signals as biomarkers for objective EDS and deteriorations in vigilance. The studies consisted of a novel time and frequency domain characterization of pulse oximetry data alongside conventional PSG parametrization in sub-populations of two large OSA patient cohorts. The association of parameters describing the severity of OSA and frequency domain information of nocturnal pulse oximetry signals with EDS and decreased psychomotor vigilance were evaluated. The following conclusions can be made from the findings emerging from this thesis:

1. More detailed quantification of the characteristic properties of desaturations was able to link the severity of OSA more strongly to EDS and impaired psychomotor vigilance than the conventionally used AHI. This implies that presented novel hypoxemia parameters computed from the pulse oximetry recordings could be used in OSA severity assessment.

2. Low-frequency oscillation in heart rate combined with severe intermittent hypoxemia is a significant predictor of OSA-related objective EDS. Furthermore, higher and more varying peak frequencies in PPG together with increased severity of desaturations provide a marker for prolonged reaction times in PVT. Thus, the increased physiological stress and distorted nocturnal cardiovascular regulation caused by repetitive apneas, hypopneas, and arousals significantly affect daytime sleepiness and vigilance.
BIBLIOGRAPHY


Obstructive sleep apnea (OSA) is one of the most prevalent and detrimental sleep disorders. Conventional severity assessment of OSA, however, relies on the number of airflow limitations, having a weak association with the most prevalent symptoms of OSA: excessive daytime sleepiness and deteriorations in vigilance. In this Ph.D. thesis, novel pulse oximetry-based methods are presented to better associate the severity of OSA with these symptoms.