MACHINE LEARNING & DATA ANALYTICS

FRIEDRICH-ALEXANDER UNIVERSITÄT ERLANGEN-NÜRNBERG
TECHNISCHE FAKULTÄT

Towards Vertigo Assessment at Home: Evaluation of Orthostatic Reaction in Free-living Environments

Bachelor's Thesis in Medical Engineering

submitted
by

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Started: 03.02.2020

Finished: 07.08.2020

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Übersicht

Aufgrund der steigenden Lebenserwartung nimmt das Durchschnittsalter der Bevölkerung, vor allem in den Industrieländern, stetig zu. Dadurch werden altersbedingte Krankheiten, wie z.B. neurodegenerative Erkrankungen, zu einer zunehmenden Belastung für das Gesundheitswesen. Neurodegenerative Krankheiten zeichnen sich durch Funktionsstörungen des autonomen Nervensystems (ANS) aus, was unter anderem zu einer Einschränkung der Herzratenvariabilität (HRV) führt. Die Untersuchung der HRV kann daher zur Diagnose von neurodegenerativen Erkrankungen beitragen. Zur Messung des HRV werden orthostatische Reaktionstests, wie die Kipptischuntersuchung oder der Schellong-Test, eingesetzt. Die Tests werden meist im klinischen Umfeld durchgeführt. Dies führt jedoch dazu, dass die Untersuchungsergebnisse durch den sogenannten Weißkitteleffekt beeinflusst werden können. Ziel dieser Arbeit ist es daher, die durch Lagewechsel verursachten Veränderungen der HRV im häuslichen Umfeld der Probanden zu untersuchen. Zusätzlich werden die orthostatischen Reaktionen zwischen Aufzeichnungen im Labor, standardisierten Tests zu Hause und kontinuierlichen Aufnahmen im häuslichen Umfeld verglichen. Zur Datenerfassung wurde eine viertägige Studie mit sieben gesunden Probanden durchgeführt. Die Studie beinhaltete EKG-Messungen in jeder der genannten Umgebungen. Aus den aufgezeichneten EKG-Daten wurde anschließend die Herzfrequenz und die HRV berechnet.

In allen Umgebungen nahm die Herzfrequenz nach dem Aufstehen signifikant zu, wohingegen die HRV-Parameter eine Tendenz zur Abnahme zeigten. Lagewechsel während der Tests zu Hause verursachten die größte Zunahme der Herzfrequenz mit einem durchschnittlichen Anstieg von 12 Schlägen pro Minute. Darüber hinaus war der Anstieg der Herzfrequenz bei Tests zu Hause durchgehend stärker ausgeprägt, als im freien häuslichen Umfeld, unabhängig von der Tageszeit oder dem Wochentag der Aufnahme. Somit lässt sich feststellen, dass eine kontinuierliche Aufzeichnung von EKG-Daten nicht erforderlich ist, sondern dass standardisierte Tests zu Hause für die Beurteilung der HRV ausreichen. Zudem wurde innerhalb des Studienverlaufs eine hohe Intrasubjektvarianz festgestellt. Um den Einfluss von Schwankungen zwischen den Tagen zu verringern, ist es deshalb notwendig, eine mehrtägige Datenerfassung durchzuführen.

Die in dieser Arbeit vorgestellten Methoden, könnten in zukünftigen Forschungen durch die Integration von Blutdruckmessungen ergänzt werden, um eine zuverlässigere Analyse der orthostatischen Reaktion zu erreichen. Das entwickelte System wurde bislang nur an gesunden Probanden erprobt. Da das System jedoch darauf abzielt, fehlerhafte Funktionen des ANS zu erkennen, ist es notwendig, die Studie auch mit Patienten durchzuführen, die tatsächlich an Störungen des ANS leiden.

Abstract

As global life expectancy is constantly increasing, the size of the elderly population will also continue to increase in the future, particularly in industrialized countries. Therefore, age-related diseases, such as neurodegenerative disorders, will become an increasing burden for the healthcare system. Neurodegenerative diseases are characterized by dysfunctions of the *Autonomic Nervous System (ANS)*, leading to a limitation of *Heart Rate Variability (HRV)*. The investigation of *HRV* can therefore be used for early diagnosis of neurodegenerative diseases. To assess *HRV*, orthostatic reaction tests, such as the Tilt Table Test or the Schellong Test, are applied. Since the tests are performed in clinical settings, the examination results are often influenced by the white-coat effect. Therefore, this work aims to investigate changes in heart rate and *HRV* induced by posture change in peoples' free-living environments. Furthermore, differences in cardiovascular reactions to postural changes between recordings at the laboratory, standardized tests at home, and in free-living data are evaluated. For data collection, a four-day study procedure was conducted with seven healthy subjects. The study comprises *Electrocardiogram (ECG)* recordings in the above mentioned recording settings. Derived from the recorded *ECG* signals, heart rate and *HRV* were evaluated.

In all recording settings, subjects showed a significant increase in heart rate after posture changes, whereas *HRV* parameters tended to decrease. Postural changes during tests at home caused the highest change in heart rate with a mean increase of 12 bpm. Moreover, the increase in heart rate was always more pronounced in tests at home than in the free-living environment, regardless of the time of day or the day of recording. Consequently, continuous recording of *ECG* data might not be necessary, but performing tests at home is sufficient for assessing the *HRV*. Last, a high variance within the subjects was found throughout the study procedure, indicating the need for collecting data over several days to reduce the influence of day-by-day variation.

The methods presented in this work could be extended in future research by integrating blood pressure measurements to achieve a more reliable analysis of the orthostatic reaction. The developed system has so far only been applied to healthy subjects. However, since the system is designed to detect abnormal functions of the *ANS*, it is necessary to conduct the study with patients who actually suffer from *ANS* disorders.

Contents

Chapter 1

Introduction

Given the fact that the population in western countries is getting older and older, early detection and treatment of age-related diseases will become increasingly important in order to respond to the needs of the elderly and to prevent a rapid deterioration in peoples' health conditions [Suz15]. Within these age-related diseases, neurodegenerative diseases have attracted much attention because of their irreversibility, the lack of effective treatment, and the social and economic burdens associated with them [Hun10].

One of the most prominent examples within this group of diseases is *Parkinson's Disease (PD)*. *PD* is the second most common neurodegenerative disorder affecting between two and three percent of the population aged 65 or older [Poe17]. In early stages, impaired subjects usually suffer from discomfort, subtle fatigue, or shakiness. With advancing disease, symptoms like tremor, muscle stiffness (rigor), and slow movement (bradykinesia) become common [RO09]. However, the clinical manifestations of *PD* are not restricted to these motor symptoms. A multitude of non-motor features such as cognitive impairments, sleep disorders, loss of smell, and dysfunctions of the *ANS* can also be part of the disease [Poe17].

In healthy persons, the *ANS* adapts the cardiovascular system to situations like increased physical activity or postural changes by constricting veins and arteries and increasing the heart rate to counteract a drop in blood pressure and maintain blood supply to the brain [Bra03]. People with impaired function of the *ANS* often show suppressed *HRV*. This autonomic dysfunction results in a drop of blood pressure after a posture change into a standing position that cannot be compensated by the ANS. Hence, *Orthostatic Hypotension (OH)* may occur, which is defined as a reduction in systolic blood pressure of at least 20 mmHg or a reduction in diastolic blood pressure of at least 10 mmHg during the first three minutes of standing [Fre08]. Therefore, measuring

HRV and blood pressure in response to a posture change can be used as a noninvasive marker for assessing the functionality of the *ANS* and identifying corresponding disorders [Szt04].

A standardized and widely used procedure for the diagnosis and assessment of *OH* is the Tilt Table Test. It enables the reproduction of presyncopal and syncopal events under controlled conditions in a clinical environment [Koc98]. However, examination results are often influenced by the white-coat effect, which is defined as a transient elevation of blood pressure and increased activity of the *Sympathetic Nervous System (SNS)* in clinical situations [Man08]. Since an increased sympathetic control of the heart leads to a reduced *HRV* [Cyg13], the *HRV* assessment should be performed in an environment familiar to the patient, such as the home environment, to reduce the influence of the white-coat syndrome. However, by continuously collecting data throughout the day, a considerable amount of irrelevant data related to the examination of the orthostatic reaction is captured, too. Thus, points of interest (i.e., events of postural transitions from lying or sitting into standing position), have to be identified before evaluating the ECG signal. For this purpose, a posture change detection algorithm developed in a previous work by Daniel Krauß [Kra19] was applied in this thesis. Afterwards, the *HRV* can be assessed specifically within the detected periods. For data acquisition, two wearable sensors, including an *Inertial Measurement Unit (IMU)*, were attached to the chest and to the leg. The chest-worn sensor further was able to record a 1 lead ECG signal. The main goal of this bachelor's thesis is, therefore, to evaluate the feasibility of assessing orthostatic reactions in free-living environments and to compare *HRV* measurements performed at home with snapshot measurements in clinical settings.

The thesis is structured as follows: Chapter 2 presents the state of research on the assessment of vital signs in home environments, orthostatic intolerance, and different approaches for assessing postural changes. Afterwards, the medical background necessary for understanding the following analysis is outlined in Chapter 3. Chapter 4 gives a detailed description of the methods used for data processing, followed by a presentation of the developed study procedure in Chapter 5. The results of the conducted study are presented in Chapter 6 and are subsequently discussed in Chapter 7. Finally, Chapter 8 concludes the thesis by summing up the key outcomes and providing an outlook on possible further research questions.

Chapter 2

Related Work

2.1 Home Monitoring of Vital Signs

Due to the ever-increasing demand for home monitoring systems, the market for existing wearable devices has grown rapidly in recent years [Rem]. In typical home monitoring applications, wireless sensors, attached to the patient's body, are used to acquire vital signs such as heart rate, blood pressure, or body motion signals [Hun04]. The sensors for capturing biomedical signals must be miniaturized devices that enable real-time data acquisition, high reliability, and a low energy consumption [Zat09]. To enhance comfort, usability, and convenience for users, different sensor configurations for the patient's clothing and body were introduced in literature [Yil10].

One setup was presented in the patent of Almen who developed a wrist-worn home monitoring system to evaluate the user's *HRV US7460899B2* [A.1]. Similar setups were also introduced by other research groups [AL16] [Jar18] [Mor18]. The comfortable design of such wristbands, similar to a normal watch, allows them to be constantly worn, which enables a continuously monitoring of vital signs [Dia18]. Another set-up for sensor configuration was discussed by Mendoza et al. who used transducers embedded into the patient clothing for data acquisition at home [Men02], as well as Leonov et al. who integrated a wireless electrocardiography system in an office-style shirt [Leo09]. A third approach to assess vital signs is the use of wearable patch sensors attached directly to the user's skin as presented in the work of Chan et al. [Cha13]. The system declared in the patent of Sun et al. also use electrodes placed on the user's skin for monitoring functional changes of the *ANS* caused by side effects of drugs *US6811536B2* [A.2]. Lee et al. developed a smart *ECG* patch which includes three electrodes for *ECG* assessment [Lee16] as well as Shennib who presented a disposable programmable *ECG* sensor patch for the non-invasive detection of risk patterns *US8688189B2* [A.3]. Moreover, chest straps are also

frequently deployed to collect data on heart activity [Dia18]. Weder et al. developed a skin-friendly and non-irritating embroidered textile electrode [Wed15]. Two of these electrodes were embedded into a breast belt, which enables *ECG* assessment at rest as well as during movement. A comparison of four different chest belts concerning their usability and acceptance was performed by Ehmen et al. [Ehm12]. Results indicated a relatively high acceptance, but none of the four belts was completely usable. In the context of this work, a chest-worn belt is likewise used for assessing heart rate and *HRV*.

2.2 Orthostatic Intolerance

Orthostatic intolerance is a collective term for various characteristic symptoms that lead to difficulties with upright posture, especially when standing [Oka12]. One form of orthostatic intolerance is neurogenic *OH*, which can be caused by peripheral and central *ANS* disorders [Fre08].

Various papers discussed the relation between different central *ANS* disorders, such as *PD* or multiple sclerosis, and *OH*, such as the work of Velseboer et al. In their paper they investigated the prevalence of *OH* in *PD*. Results indicated an estimated prevalence of 30%. They further stated that *OH* is one of the main non-motor symptoms of *PD* [Vel11]. However, Allcock et al. reported a prevalence of 47% of *OH* in patients with *PD* [All04]. *OH* in patients with multiple sclerosis has been analyzed in the work of Seze et al. *OH* was found in 18% of the patients and only in progressive forms of multiple sclerosis [dS01]. Goldstein conducted a study to investigate whether *OH* can be an early indicator for *PD*. Results indicated that 60% of *PD* patients with *OH* had an early onset of *OH* [Gol06]. Another work of Centi et al. examined the effects of *OH* on cognition in *PD*. The authors found that especially in upright position patients with *PD* and *OH* had a worse memory encoding than *PD* patients without *OH* [Cen17]. Since *HRV* can normally buffer changes in blood pressure, a limited *HRV* can also lead to an orthostatic dysfunction. Therefore, *HRV* can be used to determine *OH* in *PD* patients, as presented in the work of Vianna et al. [Via16]. They found that *PD* patients with *OH* do not show significant changes in heart rate and *HRV* parameters in response to postural changes, but the values remain largely unchanged [Via16]. In healthy subjects, however, *HRV* decrease and heart rate increase after standing up, as investigated by Dantas et al. [Dan10]. For *HRV* analysis there are several techniques which have been evaluated by Kallio et al. In their paper they compared different analysis methods for revealing *HRV* differences between patients affected by *PD* and healthy controls. The authors

found that time- and frequency-domain analysis showed a reduced cardiovascular autonomic regulation in *PD* patients, whereas non-linear and geometrical measures did not [Kal02].

The relation between peripheral autonomic nervous disorders, such as diabetes mellitus or Sjögren's syndrome, and *OH* was also discussed in multiple papers. Barkai et al. examined the correlation between cardiovascular autonomic dysfunctions and diabetes mellitus in children and adolescents. It was found that diabetic children had a significantly higher resting heart rate and a decreased heart rate response to standing [Bar95]. In the work of Gaspar et al., the prevalence of *OH* in diabetic patients was investigated. Results indicated a prevalence of 31.7% of *OH* in patients with diabetes type 1 and a prevalence of 32.3% in patients with diabetes type 2 [Gas16]. The functionality of the *ANS* in patients with primary Sjörgen's syndrome was evaluated by Mandl et al. In their work they revealed a significantly reduced orthostatic systolic and diastolic blood pressure response in people affected by primary Sjörgen's syndrome [Man07].

However, *OH* is not only a symptom of disorders of the *ANS* but can also be caused by aging, which has been examined by Kawaguchi et al. In their paper they showed a more blunted variation of *HRV* in response to a change in posture in elderly than in younger subjects. Furthermore, they reported that changes in *HRV* are greatest during the first 30 seconds after standing up [Kaw01]. Belmin et al. discussed the variability of blood pressure response to orthostasis at different times of the day. The authors found that there were significant differences in resting blood pressure in the supine position throughout the day. Systolic blood pressure at 10-11 a.m. and at 1-2 p.m. was significant lower than resting blood pressure at 8-9 a.m. The orthostatic change was most pronounced between 8-9 a.m. Furthermore, they showed that the response of systolic blood pressure to orthostatism significantly varies in elderly people between days, indicating poor reproducibility of results and possible diagnoses [Bel00].

2.3 Posture Change Detection

Many different techniques for body position assessment have already been presented in recent years. One approach to evaluate a subject's body position is with the use of computer vision as demonstrated by Cucchiara et al. They monitored and analyzed human behavior at home to identify potential alarm situations such as falling [Cuc04]. Other research groups also applied computer vision techniques for posture change detection [Cuc05] [Jua08]. Venetianer et al. introduced a video-based surveillance system for detecting a person falling or getting up in their patent *US7613324B2* [A.5].

Another approach for detecting postures is to use body-worn sensors as described in the patent of Wang et al. The system declared in there use a combination of gravitational and motion sensors for posture classification *US7471290B2* [A.6]. Foerster et al. also examined different postures by placing four sensors on the sternum, wrist, thigh, and lower leg [Foe99]. In another work of Yi et al. a system architecture for monitoring remote users' physiological data and detecting movements was presented. For data collection and processing an Android smartphone attached to the chest and an external tri-axial accelerometer attached to the leg were used. Classification of body position was achieved by applying thresholding on the 3-axis output of the accelerometer data. For fall detection, a threshold on the Signal Vector Magnitude was applied. Using this configuration the system was able to determine three body orientations including standing straight, lying down, and sitting down [Yi14].

The classification of postures can also be used as an indicator of soldiers well-being in a battlefield. Detecting a soldier lying on his back would indicate a worrying situation and would permit the early dispatch of help [Bis08]. Biswas et al., therefore, introduced a remote monitoring system for soldier safety by body posture identification. However, they did not use accelerometer-based approaches but instead collected relative proximity information between wireless sensors placed over the subject's body [Bis08].

The groundwork of this bachelor's thesis is the bachelor's thesis of Daniel Krauß about 'Heart Rate Variability Analysis for Unsupervised Tilt Table Testing during Daily-life Activities'. In his work, he developed an algorithm for detecting posture changes using accelerometer data from a smartphone worn in the trousers' front pocket and an *IMU* sensor attached to the chest. To align the sensors to the body and to eliminate the influence of different sensor orientations he first performed a functional calibration. For classifying the postures, he then computed the angle between chest and leg sensor [Kra19]. However, this approach has several drawbacks, which are to be improved in this work. First of all, the sampling rate of the smartphone was inconstant and varied over time. Hence, the sampling rates of the smartphone and the leg sensor had to be manually adjusted. Furthermore, start and endpoints of the functional calibration were also labeled manually whereby automation is desired. The system has so far only been used in laboratory and has not been applied to home monitoring yet. The main goal of this bachelor's thesis is, therefore, to transform this approach to an actual home monitoring setting to reduce the influence of the white coat syndrome on the examination results.

Chapter 3

Medical Background

3.1 Neurodegenerative Diseases

Neurodegenerative diseases, such as Alzheimer's disease, *PD*, and amyotrophic lateral sclerosis, are among the most common diseases in old age [Kre00]. Since the population in western countries is getting older and older, early detection and treatment of neurodegenerative diseases will become increasingly important in order to prevent a rapid deterioration in people's health conditions [Ira14]. In the EU, an increase by 50% of people between 60 and 80 years and an increase by 200% of the over 80 years is predicted by 2030. Therefore, it is expected that one third of the population will be over 65 years and one quarter over 80 years and thus will have an increased risk of suffering from neurodegenerative diseases and dementia [Jel14].

Neurodegenerative disease is a collective term for several different diseases that primarily affect the neurons in the human brain. Nearly all neurons are postmitotic cells, meaning they are unable to perform mitosis after their development in pre-natal neurogenesis is completed [AA12]. Consequently, the brain cannot easily replace damaged or dead nerve cells, which is why neurodegenerative diseases are so fatal [Hor00].

The majority of neurodegenerative diseases are characterized by the accumulation and deposition of one or more specific neuronal proteins either inside the neural cytoplasm or in the extracellular matrix. In every neurodegenerative disease, the deposition consists of a specific major protein component. Thus, neurodegenerative diseases can be classified according to the deposited protein (Table 3.1) [Kre00].

Table 3.1: Classification of neurodegenerative diseases according to the deposited protein [RL19].

Protein-based classification	Disease
Tautopathies	Alzheimer's disease
α-Synucleinopathies	*PD*
	Dementia with Lewy bodies
	Multisystem atrophy
TDP-43 & FUS Proteinopathies	Amyotrophic lateral sclerosis
	Frontotemporal lobar degeneration
Polyglutaminopathis	Huntigton disease
	Spinocerebellar ataxias 1,2,3,6,17
	Dentatorubral-Pallidoluysian Atrophy (DRPLA)
	Spinal and Bulbar Muscular Atrophy (SBMA)
Prion disease	Creutzfeldt-Jakob disease

The most common neurodegenerative disorder is Alzheimer's disease [Pru01]. Today, according to an estimation of Alzheimer's Disease International, around 47 million people in the world suffer from Alzheimer's disease [Rad]. It also represents the most common form of dementia and manifests itself through memory disorders as well as orientation disorders and aphasia [Che11].

The second most common neurodegenerative disease is *PD* with about one to two percent of the general population over the age of 65 affected [Goe01]. The typical known signs of *PD* are a tremor, mainly occurring at rest, muscle stiffness (rigor) and slow movement (bradykinesia) [RO09]. In addition to these typical movement disorders, patients can suffer from a large number of non-motor symptoms such as cognitive impairment, sleep disorders, and depression [Che11]. Furthermore, a dysfunction of the *ANS* may also occur and can be used as an important diagnostic tool to detect *PD*. Symptoms of *ANS* dysfunctions include disorders of cardiovascular regulation, particularly *OH*, which may lead to dizziness and presyncope [Mih06]. For the non-invasive assessment of *ANS* function, the *HRV* is evaluated [Qui12], which describes a measure of the variation in time interval between successive heartbeats.

3.2 Dizziness

Dizziness is an overarching term that describes a variety of abnormal or disturbing sensations related to the stability, movement, or orientation of the human body in its environment. It is one of the most common medical complaints and its lifetime prevalence is about 20% to 30% [Str08].

The likelihood of experiencing dizziness increases by 10% every 5 years with increasing age [Cha13]. For maintaining the postural stability, a variety of different body systems are involved, including the visual system, the vestibular system, the proprioceptive fibers in peripheral joints, the cerebral cortex, the brainstem, and the cerebellum [Ham14], as shown in Figure 3.1. A malfunction of one of these systems can lead to dizziness. Since so many different body systems are involved in the correct functionality of the balance system, it is often difficult to find an accurate diagnosis of dizziness [Ham14].

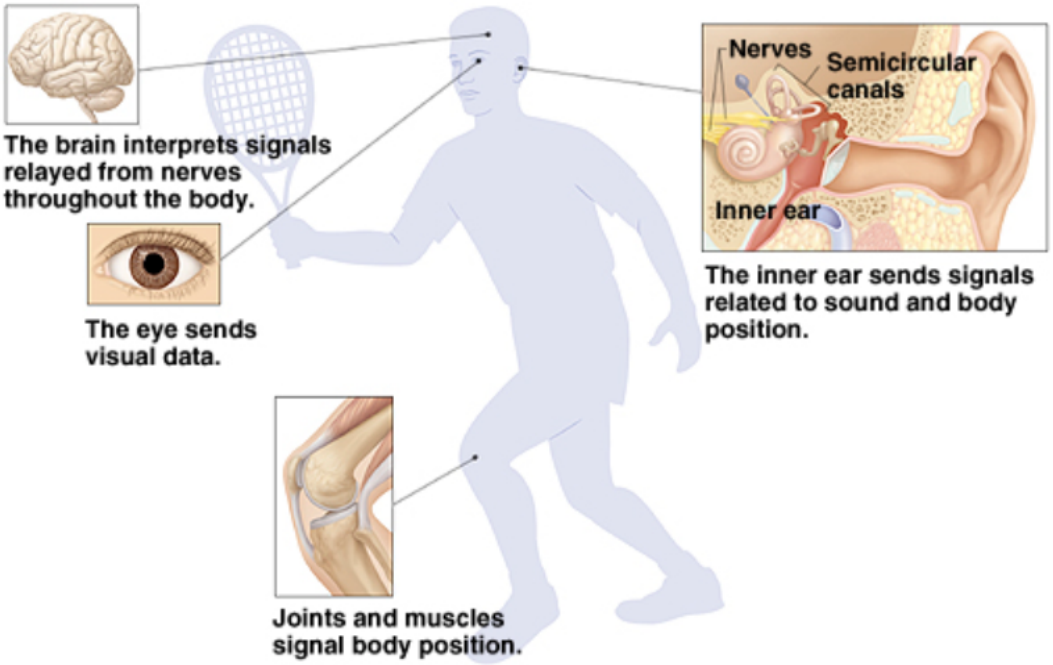


Figure 3.1: Illustration of the different components of the balance system [Sai].

Dizziness can be divided into four types: vertigo, disequilibrium, presyncope/syncope, and nonspecific dizziness [Jun15]. *Vertigo* is the illusion of translational or rotational movement. It can also be described as a spinning sensation in the absence of a stimulus. Most often it is caused by the vestibular system or its connecting pathways [Som12]. *Disequilibrium* can be defined as a loss of stability, creating the sensation of an impending fall. Patients often describe the need for external support for proper locomotion [Kon90]. *Presyncope* is the sensation of weakness, light-headedness, or cognitive symptoms without loss of consciousness. Typically, recovery commences within a few minutes. Syncope, on the other hand, is truly the sudden loss of consciousness [Kra01]. In this work, a closer look at the presyncope and syncope will be taken.

Researches showed that 19% of the population in the United States experience syncope at some point in life. The majority of syncopal events occur either in the early adult years or after the age of 70 [Whi19]. The reasons for syncope can be manifold, as shown in Figure 3.2. Baron-Esquivias et al. investigated different types of causes leading to syncope in emergency departments in Spain. The authors found that syncope was triggered most often by neural causes.

In the context of this bachelor's thesis the connection between dizziness and orthostatic reactions will be examined more precisely, since dizziness caused by orthostatic reactions can be an early indicator for disorders of the *ANS* and neurodegenerative diseases [BE10].

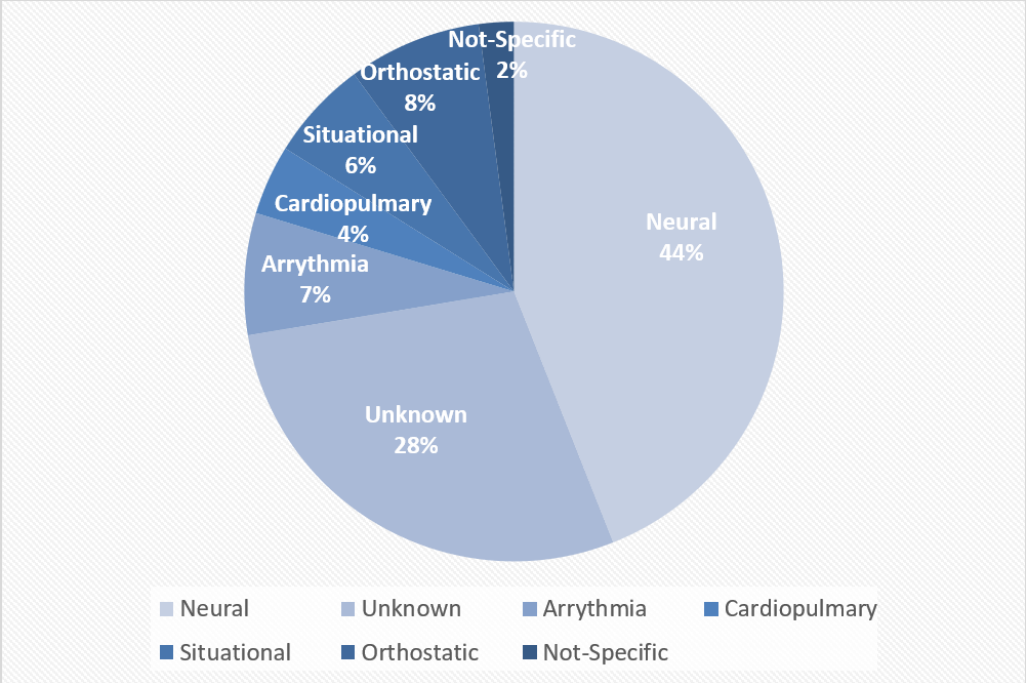


Figure 3.2: Statistical representation of the different causes of syncope [BE10].

3.3 Orthostatic Reaction

3.3.1 Physiological Principle

Orthostatic reaction refers to the ability of the human body to counteract a drop in blood pressure caused by postural changes [Mun20]. By changing the posture from horizontal to vertical position the hydrostatic pressure in the veins increases. As result, the blood volume is being redistributed into the body part below the hydrostatic indifference point, preferably in the leg veins. The

hydrostatic indifference point, which is located at the level of the diaphragm in the abdomen, describes the point at which the posture does not influence the venous pressure [Pet14]. The venous reflux to the heart chambers decreases as the blood sags into the legs, causing a sudden drop in blood pressure. In healthy person, the human body reacts by increasing the activity of the *SNS*, thus inhibiting parasympathetic activity. This leads to a rise in heart rate and in total peripheral resistance, which largely normalizes the blood pressure.

After about a minute, stable conditions have emerged, with diastolic blood pressure having risen by 5-10 mmHg and the heart rate having increased by approximately 10 bpm. The younger the patient, the more pronounced this response [Was00].

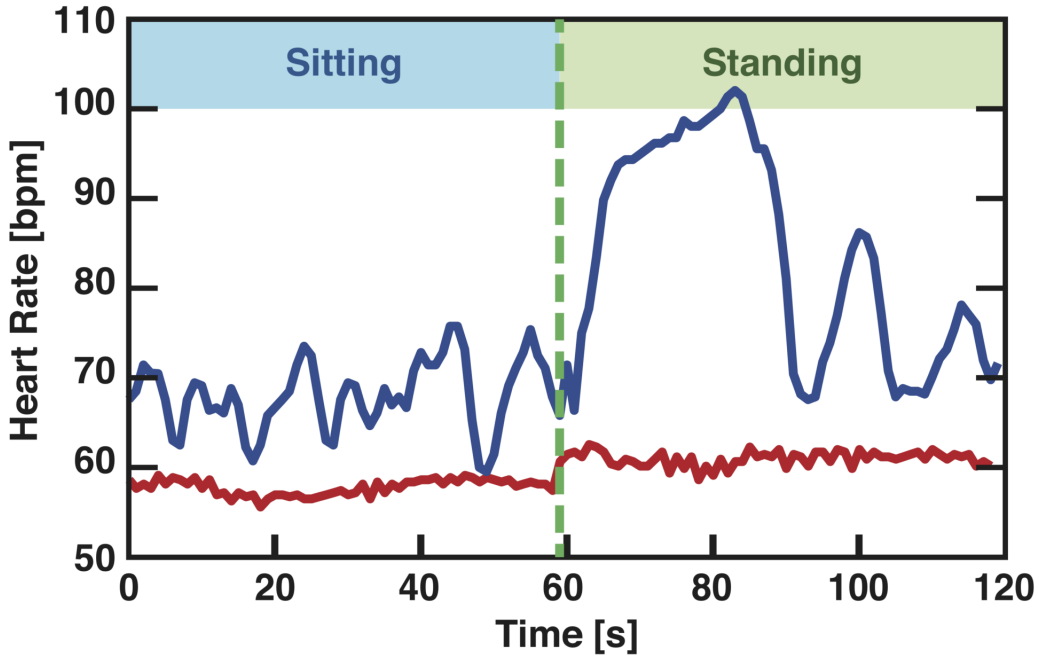


Figure 3.3: Comparison of the orthostatic reaction to a posture change between patients suffering from *PD* (red) and healthy controls (blue) [Ric16].

In people suffering from disorders of the *ANS*, this effect may be impaired, as heart rate and blood pressure cannot be properly regulated to the chancing demands during posture changes. Resulting, the brain is no longer supplied with sufficient oxygen, which can lead to symptoms like dizziness and syncope. Furthermore, *OH* may appear, which is defined as a reduction in systolic blood pressure of at least 20 mmHg or a reduction in diastolic blood pressure of at least 10 mmHg during the first three minutes of standing [Fre08]. Figure 3.3 shows the mentioned difference in orthostatic reaction between patients with *PD* and healthy controls. In healthy subjects, an

increase of about 30 bpm after the posture change can be observed, whereas there is no remarkable difference in heart rate in patients suffering from *PD*. Therefore, heart rate and *HRV* assessment can be used as an investigation tool to quantify the functionality of the *ANS*.

3.3.2 Measurement of the Orthostatic Reaction

For the clinical investigation of the orthostatic response to posture changes, there are two commonly used techniques, which are briefly introduced in the following section.

The first examination method is called Schellong Test, in which patients change their posture by themselves. It can further be split into two sub-tests. During the Schellong Test I, patients lie down on an examination table and remain lying there for about ten minutes. Afterwards, they are asked to get up quickly and to remain in the standing position for about ten minutes as well. During the entire period pulse and blood pressure are measured every two minutes [Win05]. The Schellong Test II also starts in a lying position. Immediately after the resting phase, the patients are asked to get up and climb stairs. Blood pressure and heart rate are measured every minute during the study procedure [Bar05].

The Tilt Table Test is used for simulating posture changes. For this purpose, patients are first comfortably restrained and secured on a tilting table. After about 15 minutes in a lying position, the patient is quickly raised vertically to 60°. After another 10 minutes, they are tilted back into the horizontal position [Köl07]. During the procedure blood pressure and heart rate are measured regularly.

Both tests can be used to investigate the relation between *ANS* reactivity, characterized by *HRV*, and posture changes. However, the Schellong Test proved to be inferior to the Tilt Table Test with regard to the diagnosis of orthostatic dysfunctions [Jun06].

Chapter 4

Methods

This chapter describes the methods developed for assessing *HRV* in the free-living environments. The *HRV* can later be used to evaluate orthostatic reactions evoked by posture changes. First, the procedure for data acquisition is outlined. Secondly, the different methods used for data analysis are presented in more detail, including a section on posture change detection and on *HRV* assessment.

4.1 Data Acquisition

4.1.1 Sensor Data

For data collection two wearable sensors from the company Portabiles GmbH, Erlangen, Germany were used, containing an *IMU*, a barometer, and an *ECG* unit. The *IMU* includes a 3-axis accelerometer for recording translational movements and a 3-axis gyroscope for detecting rotating movements. However, in this bachelor's thesis, only accelerometer data were utilized for posture change analysis. The data obtained from the *IMU* were subsequently processed to identify changes in posture. For *HRV* assessment, the *ECG* sensor was mounted on a chest strap and attached to the chest of the subjects, as demonstrated in Figure 4.1. *ECG* was recorded according to Lead II of Einthoven's triangle during the whole study procedure as reported in previous work [Ric15], [Kra19].

The smartphone application 'PortabilesDemoApp'[1] was used to manage the sensors. A screenshot of the application is presented in Figure 4.2. It allowed the user to start, stop, download,

[1] PortabilesDemoApp, Portabiles GmbH, Erlangen, Germany, `https://play.google.com/store/apps/details?id=de.portabiles.demoapp`

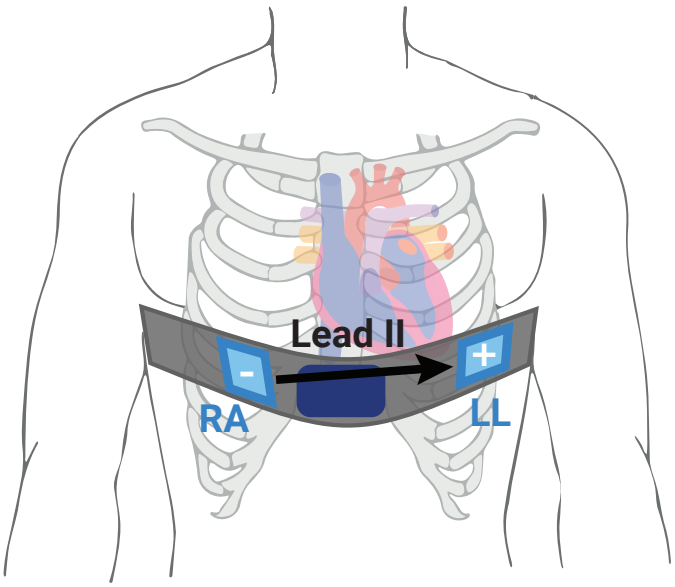


Figure 4.1: Sensor placement according to Lead II of Einthoven's triangle. RA: Right Arm, LL: Left Leg, Modified from [Kra19].

and delete recordings. Furthermore, the application offers the possibility to configure the sensors and provides a real-time plot of the body signals.

All data were recorded with a sampling frequency of 256 Hz and stored on the internal storage of the sensors. After finishing the recording, the data was transferred to the smartphone as binary files via Bluetooth Low Energy. For data analysis, the binary files were then imported using the Python library *NilsPodLib*[2].

4.1.2 Smartwatch Application Data

To test the accuracy of the posture change detection algorithm in free-living environments a smartwatch application was developed that allows to collect additional labels indicating when relevant events such as posture changes and standardized tests occurred. The collected data were saved in a .csv file on the local storage of the smartwatch and transferred to the PC afterwards. Subsequently, the .csv files were imported into Python and used as additional ground truth to test the trustworthiness and accuracy of the posture change algorithm.

[2]NilsPodLib 0.1.0, `https://mad-srv.informatik.uni-erlangen.de/MadLab/portabilestools/nilspodpythonlib`

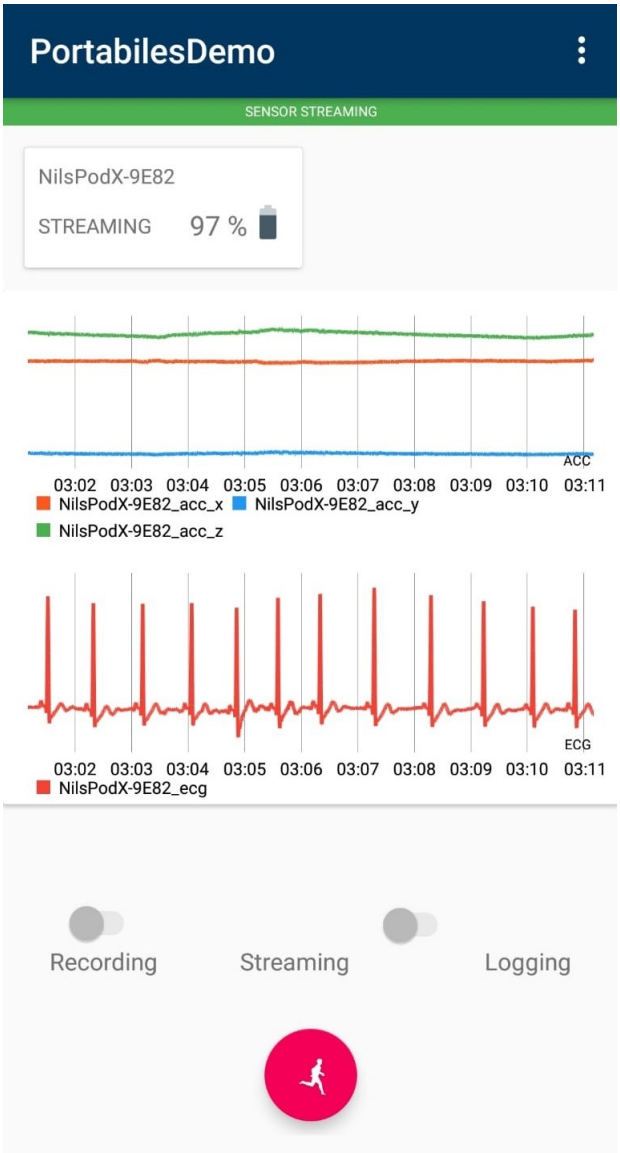


Figure 4.2: Android application for data recording and sensor control. Upper section: Real-time accelerometer data of the chest sensor. Lower section: Real-time *ECG* data of the chest sensor.

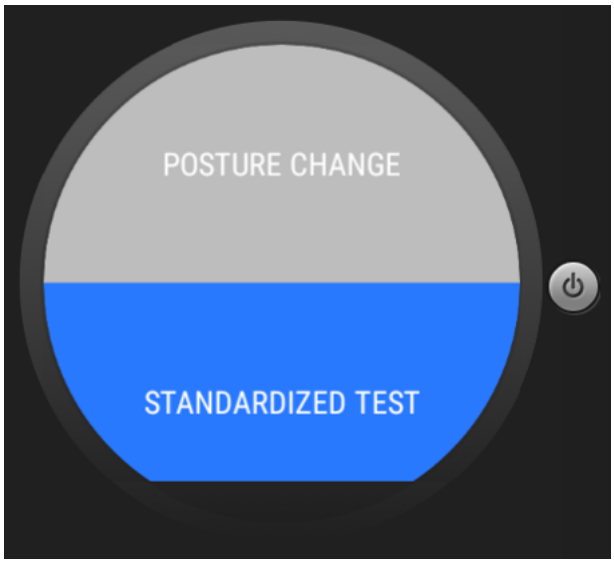


Figure 4.3: Smartwatch application for collecting labels of the times of standardized tests and posture changes.

4.2 Data Processing

4.2.1 Posture Change Detection

The foundation for this bachelor's thesis is the algorithm for detecting posture changes developed in the bachelor's thesis of Daniel Krauß [Kra19]. The proposed algorithm is able to reliably detect different postures, namely standing, sitting, and lying in free-living environments.

As already mentioned in Section 2.3, a drawback of this approach is the requirement of manually labeling the start and end of the functional calibration sequence, whereas automation is desirable to better handle larger amounts of data. For that reason, finding the functional calibration interval was automated within this bachelor's thesis and is introduced in the following section.

The procedure of the functional calibration can be divided into two sections. The first section consists of the alignment of the chest-worn sensor to the chest. For the alignment, the subjects had to bend down their upper body to 90° for about five seconds. During the second section, the leg sensor was aligned by lifting the leg the sensor was attached to by up to 90°. Both calibration steps were recorded as separate sessions on the sensor. For the detection of functional calibration intervals, the recorded accelerometer data were first smoothed by applying a rolling window with a window size of N=50 to the signals in order to reduce noise. The output of the smoothed accelerometer data from the chest sensor is illustrated in Figure 4.4.

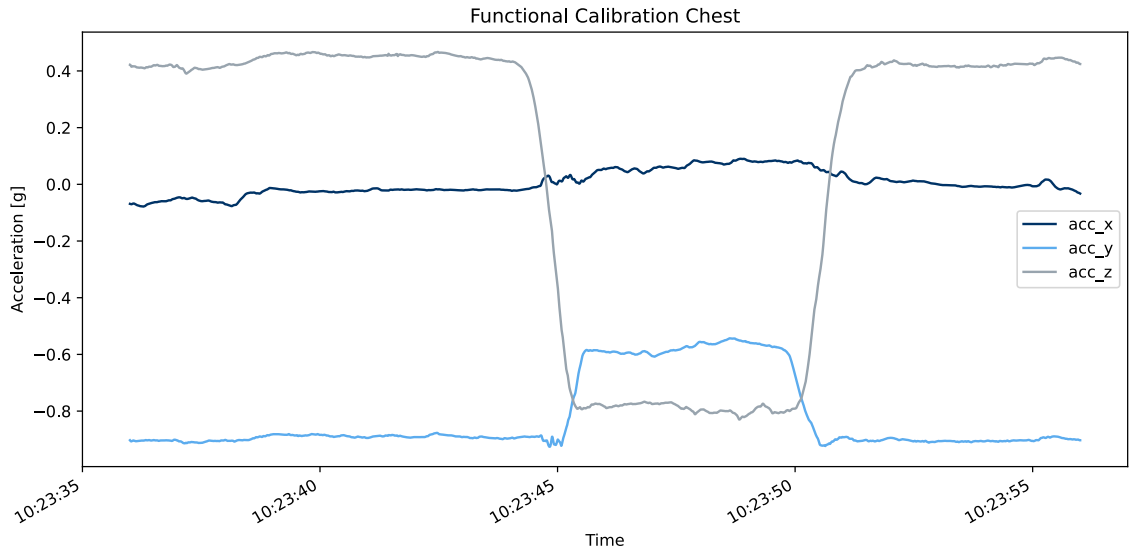


Figure 4.4: Accelerometer data of the chest sensor during functional calibration.

Subsequently, the first derivative of the signal was computed to evaluate changes in acceleration. Python's *NumPy* module[3] was then applied for calculating the euclidean norm of the derivative. The output signal is visualized in Figure 4.5. For detecting the peaks of the output signal the method *find_peaks* of the *SciPy* module[4] was used. The peaks represent the maxima of changes in acceleration, i.e. the middle of body movements (bend upper body down/raise upper body). Since the start and the end of the body movement should be detected, the beginning of the first peak and the end of the second peak, represented in Figure 4.5 by the yellow points, were stored. The calculation of the stored points was performed by applying the function *peak_widths* of Python's *SciPy* module[5]. The function calculates the width of a peak at a relative distance to the peak's height and prominence. For the purpose of detecting the start and end of body movements, the relative distance was determined empirically and set to 0.95. The computed widths were then used to detect the beginning and the end of the peaks.

Afterwards, the accelerometer data of the chest and the leg sensor were cut to the determined interval. The outcome, which is visualized in Figure 4.6, was then processed further by applying the functional calibration as presented in the work of Daniel Krauß [Kra19].

[3]NumPy 1.18.2, numpy.linalg.norm method, `https://numpy.org/doc/stable/reference/generated/numpy.linalg.norm.html`

[4]SciPy 1.4.1, scipy.signal.find_peaks method, `https://docs.scipy.org/doc/scipy/reference/generated/scipy.signal.find_peaks.html`

[5]SciPy 1.4.1, scipy.signal.peak_widths method, `https://docs.scipy.org/doc/scipy/reference/generated/scipy.signal.peak_widths.html`

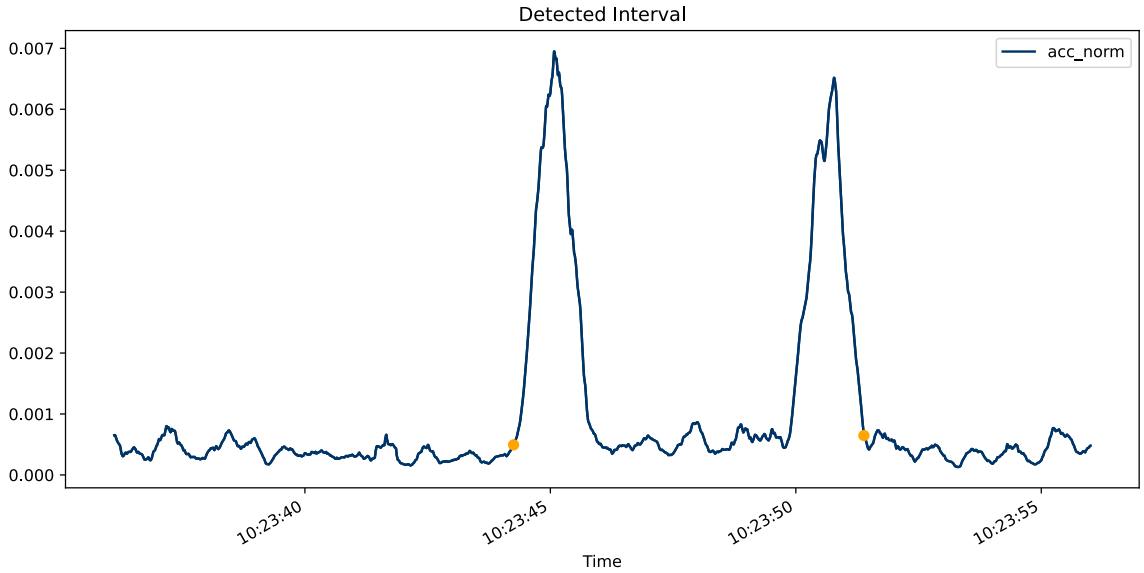


Figure 4.5: Output after calculating the norm of the first derivative of the signal shown in Figure 4.4. The yellow points represent the detected start and endpoint of the functional calibration.

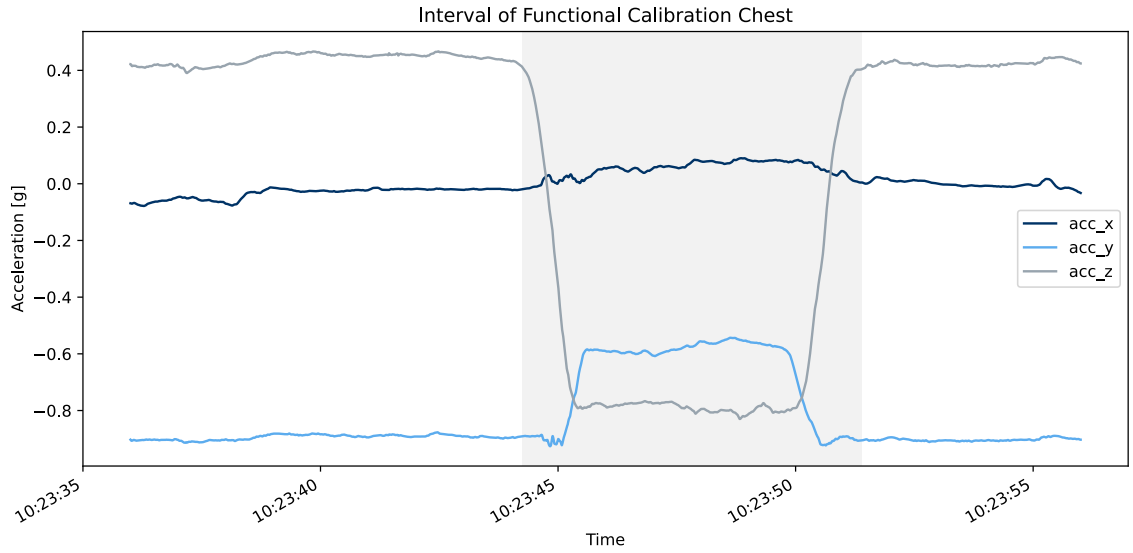


Figure 4.6: Accelerometer data of the chest sensor during functional calibration including the functional calibration interval.

Using Python, the pipeline for detecting the interval of the functional calibration can be implemented as in Listing 4.1.

Listing 4.1: Pipeline for detecting the interval of the functional calibration.

```
import pandas as pd
import numpy as np
import scipy.signal as ss

def cut_to_calib(self, df: pd.DataFrame) -> pd.DataFrame:

    #smooth input signal
    df_filt = df.rolling(50, min_periods=0).mean()

    #calculate the norm of the first derivative of the signal
    df_diff = pd.DataFrame(np.linalg.norm(df_filt.diff(), axis=1),
       columns=['acc_norm'], index=df_filt.index)

    #smooth output of norm calculation
    df_diff = df_diff.rolling(60, min_periods=30).mean()

    #find peaks representing the maxima of the acceleration
    peaks = ss.find_peaks(df_diff['acc_norm'], height=0.004, distance
       =200)[0]

    #calculate width of the peaks to find the start and the endpoint
    peak_widths = ss.peak_widths(df_diff['acc_norm'], peaks,
       rel_height=0.95)

    #store beginning of the first peak and end of the second peak
    #start and end of peaks are store at peak_widths[2]/peak_widths[3]
    peaks[0] = peak_widths[2][0]
    peaks[-1] = peak_widths[3][-1]

    return df.iloc[peaks[0]:peaks[-1], :]
```

After aligning the sensors to the body, the postures were classified by calculating the angle between chest and leg sensor, as described in the work of Daniel Krauß [Kra19]. During phases with high angle variance, such as posture changes, no static postures can be determined (depicted by an interval of NaN values). For that reason, posture changes can be defined at phases between two static postures. The exact time point of a posture change event was defined as the middle of the NaN interval. Since a high angular variance can also be caused by artifacts and noise, the postures before and after the NaN interval had to be compared. If the detected postures differed, the area was classified as posture change, whereas no posture change was detected if they had the same value.

For the examination of the orthostatic reaction, only posture changes from sitting or lying to standing should be considered. Therefore, all posture changes that do not lead to orthostasis, such as standing to sitting, were rejected. Figure 4.7 depicts the accelerometer data with the detected stand-up events.

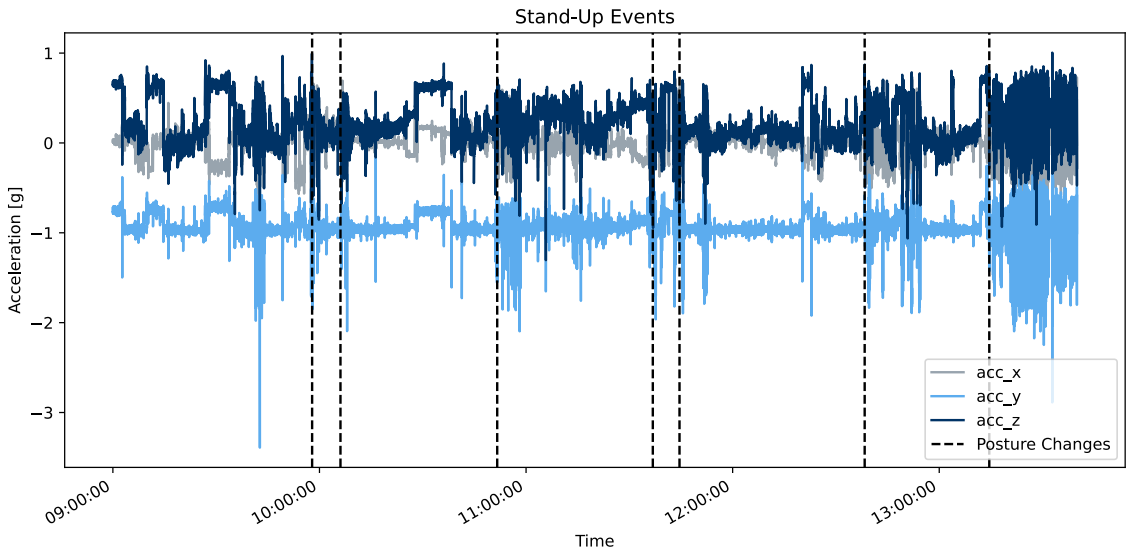


Figure 4.7: Detected stand-up events in free-living accelerometer data.

To induce relevant orthostatic reactions, the body must be initially at rest. Furthermore, after a posture change, the circulatory system needs some time to adapt the body functions to the new load. Therefore, a resting phase of five minutes before and after a posture change was defined, during which the subjects should not change their posture. Otherwise, if the time difference between two posture changes was less than five minutes, the posture change was classified as invalid and, hence, rejected. Figure 4.8 shows the remaining posture changes in the accelerometer data after validating the time differences for the posture changes detected in Figure 4.7.

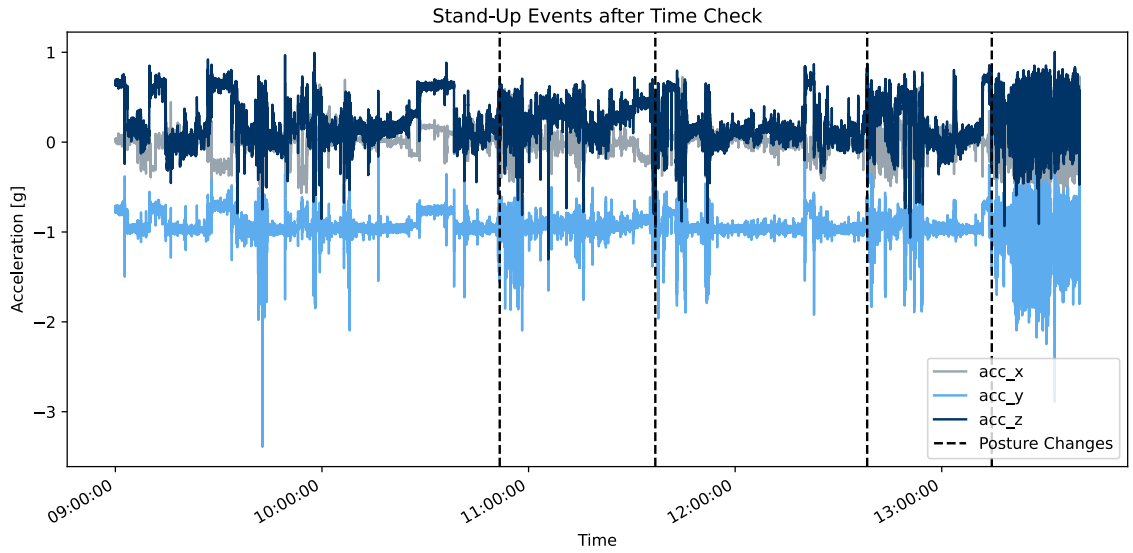


Figure 4.8: Stand-up events in the free-living accelerometer data after applying the rejection rules.

As the *HRV* is a very sensitive measure to artifacts [Sta18], the *ECG* signal must be of sufficient quality in order to ensure a reliable *HRV* analysis. Hence, signal quality was checked by calculating the variance of the *ECG* signal within one minute before and after the posture changes. If the variance was higher than a threshold empirically determined, the posture change was rejected.

4.2.2 HRV Analysis

To investigate the correct functionality of the *ANS*, the change in heart rate and *HRV* before and after a posture change is of particular importance. Therefore, the postural changes were used as basis to assess *HRV* reactivity.

The recorded *ECG* signal was first cleaned by applying the method *ecg_clean* of Python's *Neurokit2* module[6]. The method itself uses a highpass Butterworth filter to remove slow drift and DC offset, to improve signal quality and to reduce the influence of noise, such as movement artifacts and powerline interference. To filter out 50 Hz powerline noise, a moving average kernel with a width of one period of 50 Hz was used. Afterwards, R-peak detection was performed using

[6]Neurokit2 0.0.39, neurokit2.ecg.ecg_clean method, `https://github.com/neuropsychology/NeuroKit/blob/master/neurokit2/ecg/ecg_clean.py`

the *ECG* module of *Neurokit2*[7]. In order to obtain more reliable results, the detected R-peaks are subsequently checked according to different outliers. For removing statistical outliers, the average *ECG* waveform over all detected beats was calculated. Following, the correlation coefficient between each peak and the averaged waveform was determined. If the correlation coefficient was lower than the specified threshold, this R-peak was marked as an outlier. Statistical outliers were defined as the 5% highest and lowest beats and identified as follows if they fell within this range. If the heart rate was lower than 45 bpm or higher than 200 bpm, the R-peak was marked as a physiological outlier. Afterwards, the RR-intervals of the removed beats were linearly interpolated.

For *HRV* assessment, R-peaks were further checked for artifacts and corrected based on outliers in peak-to-peak differences by applying the function *signal_fixpeaks* of the *Neurokit2* Python module[8] as presented in the paper of Lipponen et al. [Lip19]. An example sequence of detected R-peaks is shown in Figure 4.9.

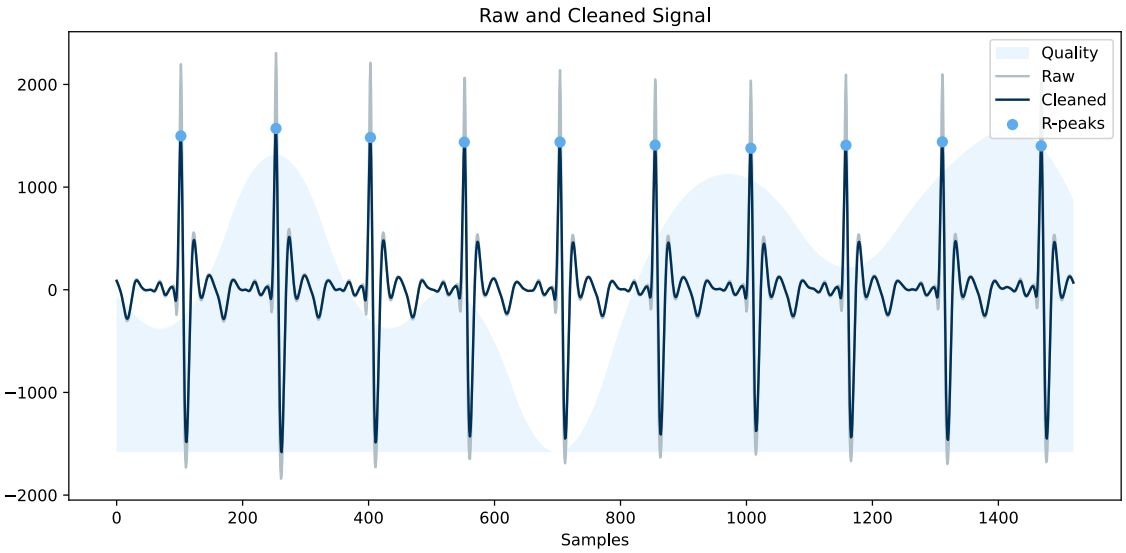


Figure 4.9: R-peak detection performed on a section of the *ECG* signal captured by the chest sensor.

[7]Neurokit2 0.0.39, ECG module, `https://github.com/neuropsychology/NeuroKit/tree/master/neurokit2/ecg`

[8]Neurokit2 0.0.39, neurokit2.signal.signal_fixpeaks method, `https://github.com/neuropsychology/NeuroKit/blob/master/neurokit2/signal/signal_fixpeaks.py`

Based on the corrected R-peaks, the *HRV* was then analyzed before and after valid posture changes. The different *HRV* parameters were calculated on the basis of one-minute time intervals before and after the posture changes to measure their immediate response. However, during the transition period from sitting to standing, the body tries to adapt the heart rate to the changing demands. Therefore, there is a high variance in heart rate, which may undesirably affect the *HRV* assessment. Consequently, 10s before and after the postural changes were left out for the analysis. More detailed information of the examined *HRV* parameters is given in the following sections.

There are several different methods for analyzing the *HRV*, such as time-domain, frequency-domain, and non-linear analysis. Time-domain measures include, among others, *Root Mean Square of Successive Differences (RMSSD)*, *Percentage of Successive RR-Intervals differing more than 50 ms (pNN50)* and *Percentage of Successive RR-Intervals differing more than 20 ms (pNN20)*. Using time-domain analysis, the NN-intervals are evaluated mathematically regarding their variance. Frequency-domain analysis, such as *Low Frequency (LF)* or *High Frequency (HF)* components, required the computation of a power spectrum from the NN-intervals. The most frequently applied methods are Fast Fourier Transformation (FFT) and parametric autoregression. Non-linear methods such as Poincaré plot are used to assess the dynamic of *HRV* by calculating for example *Standard Deviation 1 (SD1)* and *Standard Deviation 2 (SD2)* [Hos13]. Within the context of this bachelor's thesis, the parameters listed in Table 4.1 were examined to quantify *HRV*.

Table 4.1: Selection of HRV features [Jey15]

Abbreviation	Definition	Unit
	Time-Domain Parameters	
RMSSD	Root mean-square of successive differences of adjacent RR-intervals.	ms
pNN20	Percentage of pairs of adjacent RR-intervals differing by more than 20 ms.	%
	Non-Linear Parameters	
SD1	Standard deviation of data against the axis x = y in Poincaré plot	ms
SD2	Standard deviation of data against the axis, which is orthogonal to the axis x = y (crosses this axis at the mean value of the data) in Poincaré plot.	ms
SD1/SD2	Ratio of *SD1*-to-*SD2*	%

Heart Rate

Heart rate is a measure for the number of heart contractions per time interval. The normal resting heart rate ranges from 60 to 100 bpm and can vary from person to person [Wag01]. It is calculated by determining the average of all RR-intervals, i.e. the difference between two consecutive R-peaks. In general, a lower heart rate implies better cardiovascular fitness [Tel88]. Figure 4.10 shows the heart rate before and after a stand-up event.

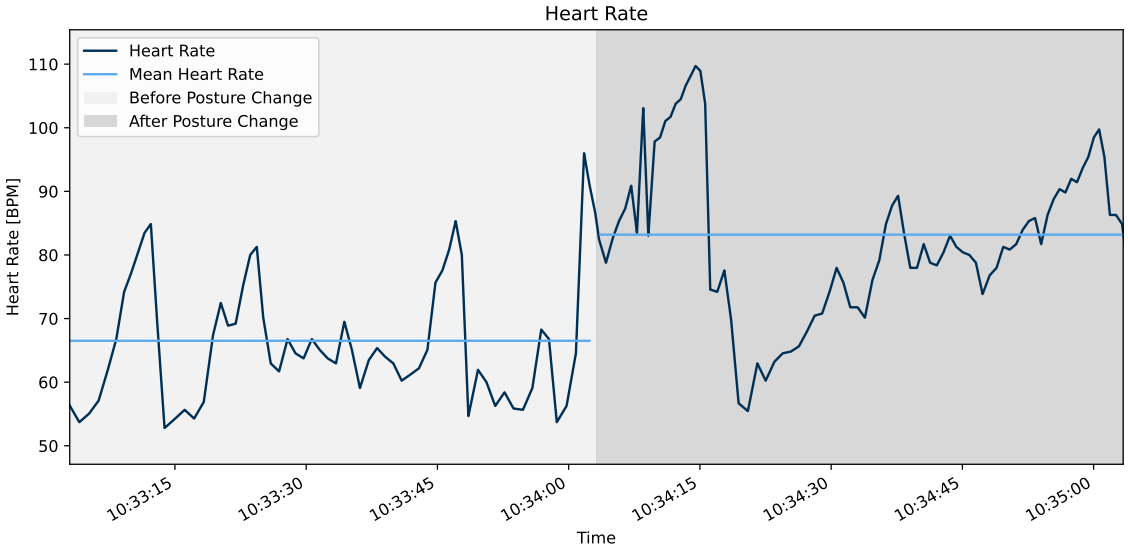


Figure 4.10: Heart rate while standing up. The heart rate increases after a stand-up event.

RMSSD

The *HRV* parameter *RMSSD* describes the root mean square of successive differences between heartbeats. It is a generally accepted measure of the influence of the *Parasympathetic Nervous System (PSNS)* on the heart rate [Mas00]. Therefore, *RMSSD* can also be understood as the body's ability to recover. It is calculated according to Equation 4.1, where N represents the number of R-peaks in the interval and RR_i the time difference between two successive R-peaks. For this work, a moving window with a window size of N=20 was used. As response to a stand-up event the *RMSSD* value decreases as presented in Figure 4.11.

$$RMSSD = \sqrt{\frac{1}{N-1}\sum_{i=1}^{N-1}(RR_{i+1} - RR_i)^2} \tag{4.1}$$

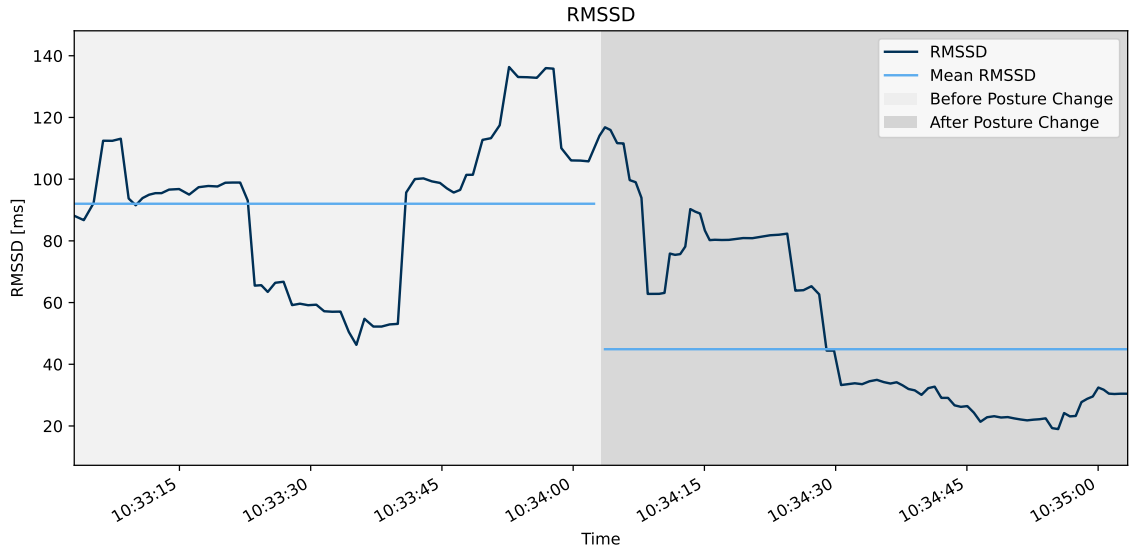


Figure 4.11: *RMSSD* while standing up. The *RMSSD* value decreases after a stand-up event.

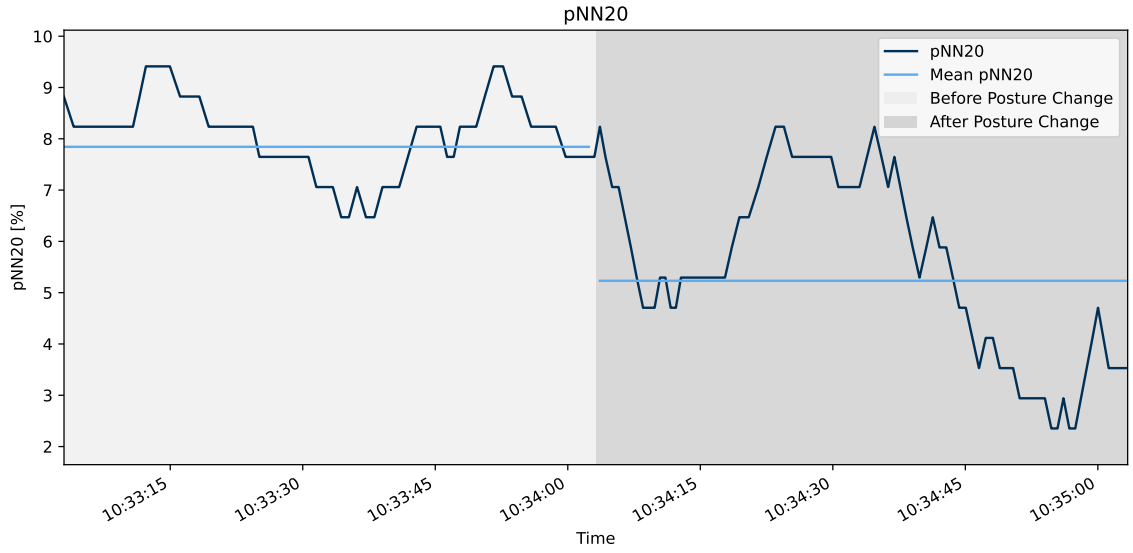
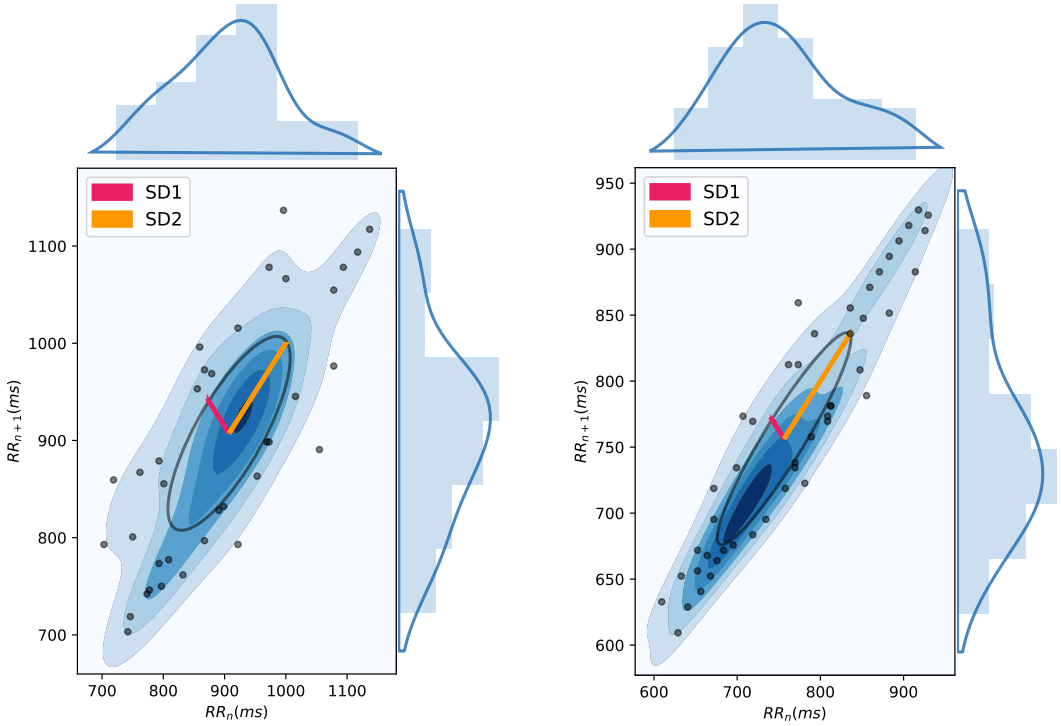


Figure 4.12: *pNN20* while standing up. The *pNN20* value decreases after a stand-up event.

pNN50/pNN20

The *pNN50* value is a measure of the percentage of successive RR-intervals that differ from each other by more than 50 ms and is closely related to the activity of the *PSNS* [Sha17]. While standing up, the *pNN50* value decreases. The same applies to pNN20, as illustrated in Figure 4.12, except that this value indicates the percentage of successive RR-intervals that differ by more than 20 ms. For calculating *pNN20*, a sliding window with N=20 samples was applied.



(a) Poincaré plot before posture change. *SD1*: 46.5 *SD2*: 132.5

(b) Poincaré plot after posture change. *SD1*: 20.1 *SD2*: 111.2

Figure 4.13: Poincaré plot before (a) and after (b) a stand-up event. *SD1*, *SD2*, and *SD1*/*SD2* ratio decrease after standing up.

SD1 and *SD2*

The *HRV* parameters *SD1* and *SD2* are standard descriptors used for quantitatively analyzing the geometry of the Poincaré plot, which is a geometrical and nonlinear method for evaluating *HRV* dynamics [Gol13] [Hsu12].

For the analysis, the point cloud is fitted with the shape of an ellipse to calculate *HRV* indices [Hos13]. Resulting, three parameters can be obtained: *SD1*, *SD2*, and the ratio *SD1*/*SD2*. Geometrically, *SD1* represents the minor axis of the ellipse and is a measure of the standard deviation of the beat-to-beat RR-interval variability. Physiologically, it can be a measure of *PSNS* activity [Hos13]. The *SD2* parameter represents the major axis of the ellipse in the Poincaré plot and includes both sympathetic and parasympathetic aspects. It can further be defined as the standard deviation of the continuous long-term RR-interval variability [Hos13]. Figure 4.13 depicts an exemplary plot of both parameters. It is noticeable that both parameters decreases after a stand-up event. The same applies to the *SD1*/*SD2* ratio, which also tends to decrease after standing up.

All parameters were evaluated using the *HRV* module of Neurokit2[9]. The calculated parameters were subsequently saved in a .csv file and used for the investigation of the orthostatic reaction later.

[9]Neurokit2 0.0.39, HRV module, `https://github.com/neuropsychology/NeuroKit/tree/master/neurokit2/hrv`

Chapter 5

Evaluation

5.1 Study Design

For the evaluation of the presented work, a study protocol for long term data collection was designed. The study design includes a four-day data acquisition. In total, seven healthy subjects (3 male 4 female, aged 22,8 $\pm$ 1,8, height 176,1 $\pm$ 20,9 (M $\pm$ SD)) participated in the study.

The study procedure was divided into three sections: The first session consisted of a supervised recording of standardized tests ('Schellong Test I') at the laboratory (*Lab 1*). Secondly, data were collected for four days in the free-living environment of the participants (*Home-Free*). Additionally, subjects had to perform the same standardized tests in their home environment as they performed at the laboratory three times a day (*Home-Tests*). Lastly, after the recording at home was finished, subjects returned to the laboratory and the procedure of the first section was repeated (*Lab 2*). Figure 5.1 shows a schematic visualization of the study procedure. The different steps are explained more detailed in the next section.

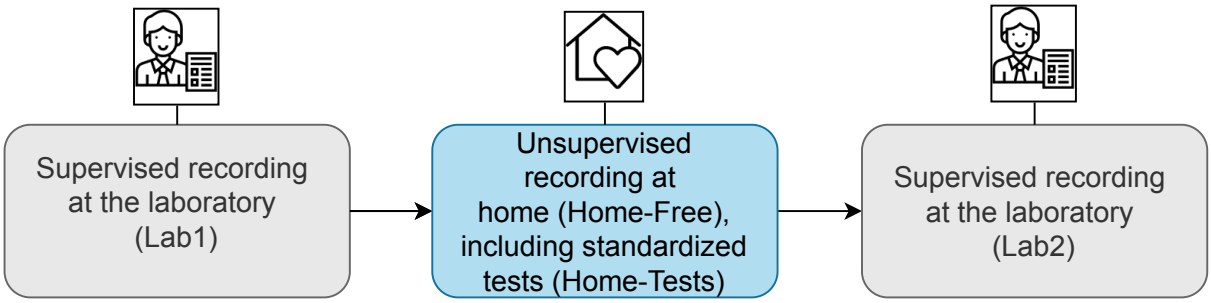


Figure 5.1: Schematic illustration of the study procedure.

5.2 Procedure

5.2.1 Recording at the Laboratory 1

For the beginning of the study, participants were invited to come to the laboratory in the morning between 9:00 a.m. and 10:00 a.m. Prior to the actual study, subjects were asked to fill out a questionnaire for assessing their demographics and the *Physical Activity Readiness Questionnaire (PAR-Q)* [War19] for assessing their general physical condition and to exclude subjects with insufficient physical condition. Furthermore, the participants were introduced to the use of the smartphone application, which is responsible for starting and stopping sensor recordings and downloading sessions. Afterwards, the *ECG* sensor was attached to the chest and the *IMU* sensor to the leg as shown in Figure 5.2. For label support at home, the participants additionally received a smartwatch with the application 'LogYourExercise'.

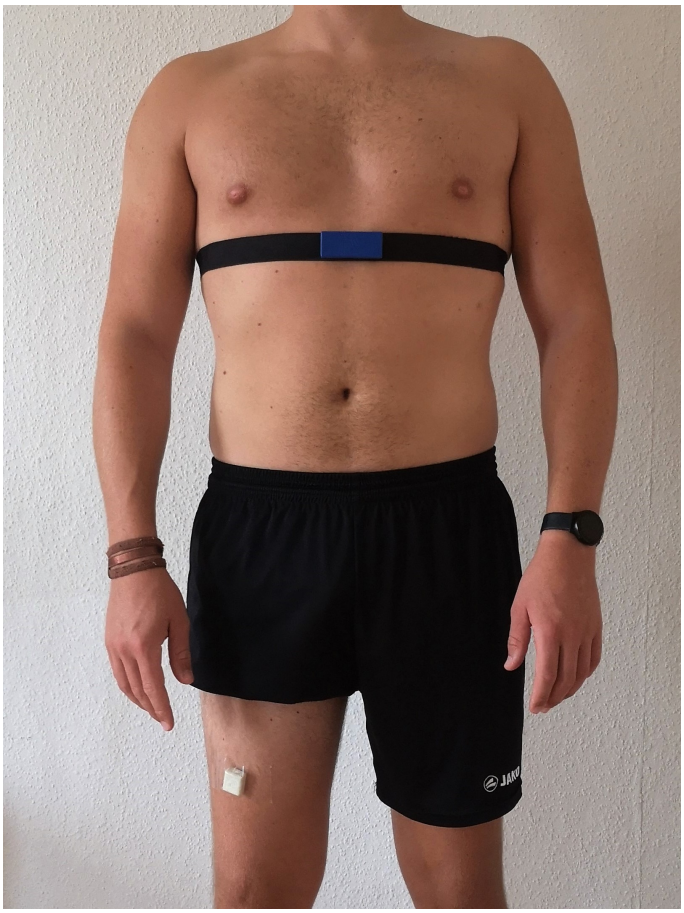


Figure 5.2: Attachment of sensors.

After collecting general information from the participants and completing the introduction, the recording at the laboratory was started. The procedure at the laboratory can be split into three sections as shown in Figure 5.3.

1. First, subjects performed a functional calibration to align both sensors to the respective body segments as described in Section 4.2.1.

2. Subsequently, the participants were asked to carry out two repetitions of a modified 'Schellong Test I' [Win05]. One iteration consisted of five minutes sitting, followed by two minutes standing. The five minutes of sitting before standing up ensured that the body has reached a resting state and is not affected by previous activities.

3. The last test performed at the laboratory was the 'Schellong Test II' [Bar05]. For this, the subjects initially had to rest for also about five minutes in a sitting position. Afterwards, they were asked to climb the stairs at the laboratory three times, which corresponds to 51 steps. The test was completed by sitting again for about five minutes to investigate the time it takes for the heart rate and *HRV* measures to return to their level before the test.

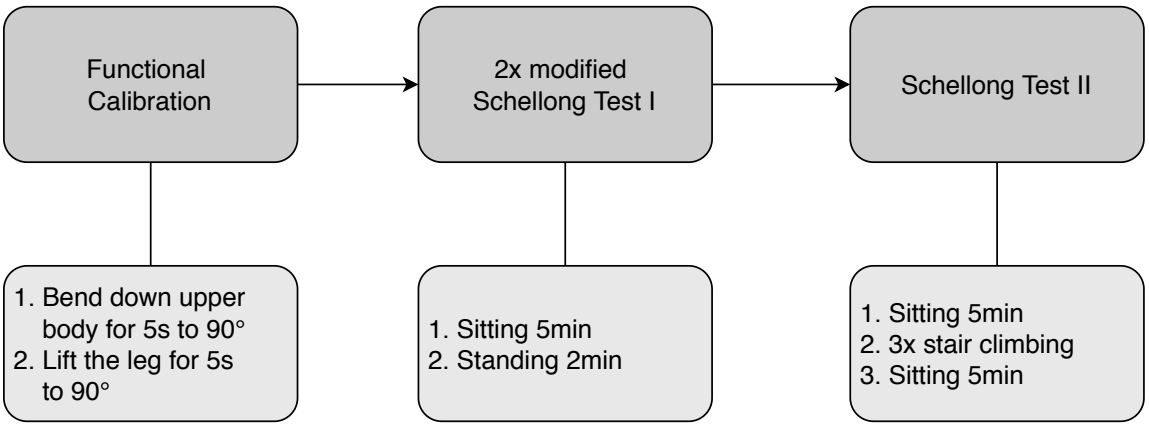


Figure 5.3: Schematic illustration of the study procedure at the laboratory.

5.2.2 Recording at Home

After finishing the recording at the laboratory, the home monitoring recording was started immediately. The data were recorded from noon on the first day of the study until noon on the fourth

day of the study. In order to ensure correct alignment between sensors and body, the participants were instructed to perform a functional calibration each time before starting a recording.

The measurement was performed while subjects continued with their daily-life activities. As mentioned in Section 4.1.2, in supplement to the sensors, the participants wore a smartwatch with the application 'LogYourExercise' for self-label support at home. Self-labeling at home required that participants set a label each time they performed a posture change.

To improve comparability between the data collected at home and those collected at the laboratory, the subjects had to perform the same standardized test in both environments. Furthermore, the test at home was carried out three times a day, which made it possible to compare the reactions depending on the time of day. To ensure good comparability between the tests, the subjects were instructed to always use the same chair for these tests throughout the whole study duration. The first test was carried out between 7:00 a.m. and 9:00 a.m., the second one between 11:00 a.m. and 1:00 p.m. and the last one between 5:00 p.m. and 7:00 p.m. The times at which the standardized tests were performed had to be entered into the smartwatch application. Additionally, the participants were asked to manually note the times on a sheet of paper in their logging diaries. Afterwards, both times were compared. If they differed, the time manually noted on the sheet of paper was taken. Based on the labeled times, the standardized tests were cut out of the long-term home recordings and analyzed separately.

Furthermore, subjects were asked to record the orthostatic reaction after getting out of bed in the morning. For that, they were instructed to attach the sensors in bed before getting up for the first time. Since all body functions are reduced during the night, the functionality of the circulatory system is also lowered. Therefore, it should be verified whether the first orthostatic reaction in the morning differs from those during the day. The whole study procedure at home is depicted in Figure 5.4.

5.2.3 Recording at the Laboratory 2

After four days the participants returned to the laboratory and the recording of free-living data was stopped. Afterwards, the procedure of the first supervised recording, as described in Section 5.2.1, was repeated. This is particularly important if the study is conducted with patients suffering from disorders of the *ANS*, as it gives the possibility to compare the body functionality before and after the study procedure at home. If the tests at the laboratory would show a large change within the study period, the results of the study would not be reliable, as the disease pattern may have changed within the study period.

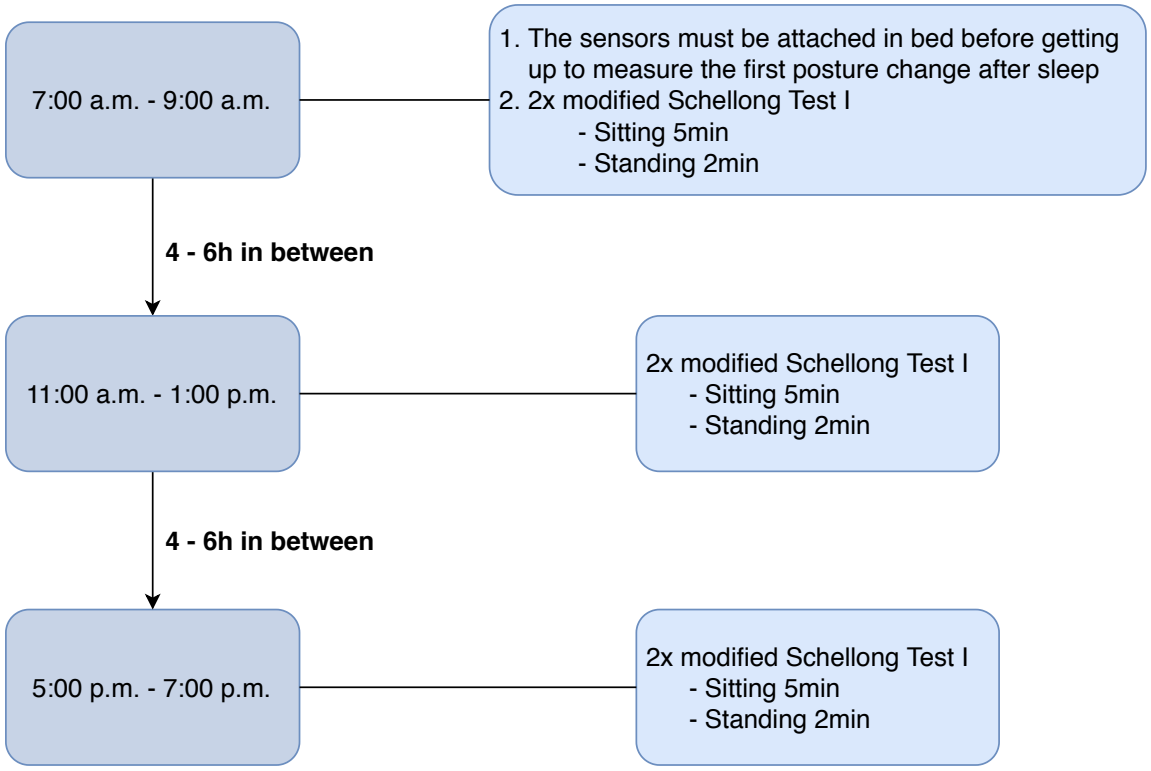


Figure 5.4: Schematic illustration of the study procedure at the home.

5.3 Analysis

ECG Measures

The automatically detected free-living posture changes were checked according to different rejection criteria for valid posture changes, as presented in Section 4.2.2. The resulting valid posture changes were then used to assess orthostatic reactions. To measure the immediate orthostatic response to posture changes, the recorded *ECG* signal was evaluated one minute before and after valid posture changes, respectively. Derived from the *ECG* signal, heart rate and *HRV* measures as *RMSSD*, *pNN20*, *SD1*, *SD2*, and *SD1*/*SD2* ratio were computed. The transition interval between two postures was generally not taken into consideration as this period shows high variations in heart rate and, thus, may undesirably affect the *HRV*. Consequently, 10s before and after the postural changes were left out for the analysis. The measured heart rate and *HRV* parameters were then analyzed regarding their changes before and after stand-up events.

Statistics

Pairwise t-tests were used to determine differences in heart rate and *HRV* measures before and after stand-up events. Moreover, differences in orthostatic reactions between various recording settings were also evaluated by pairwise t-tests. Repeated-measures *Analysis of Variance (ANOVA)* were used to determine differences in orthostatic response at different times of day and between different days during the study. If *ANOVA* showed significant results, pairwise t-tests were used as post-hoc tests to identify individual group differences. The significance level was set at $\alpha = 0.05$. Effect sizes of *ANOVA* are reported as η_p^2 and of pairwise t-tests as Cohen's d with 95% confidence interval. All methods applied for statistical evaluation are provided by Python's *Pingouin* module[1].

[1] Pingouin 0.3.6, `https://pingouin-stats.org/`

Chapter 6

Results

All results obtained in the context of the presented study are illustrated in the following Chapter. For the analysis, one subject had to be completely excluded due to problems with data acquisition. In addition, the free-living data of Subject3 and Subject4 had to be partially removed and Lab2 of Subject2 had to be completely removed. A detailed description of the recording times per subject is given in Table B.1. The remaining 152 hours of recording were analyzed regarding the *HRV* according to the procedure presented in the previous section.

6.1 Detected Posture Changes

A schematic representation of the number of postural changes detected in the free-living data sets is given in Figure 6.1. After applying the posture change algorithm, 1030 posture changes were found within the recorded data. Since only stand-up events should be considered for the analysis, all other posture changes that were not classified as stand-up events were rejected. The remaining 459 posture changes were then checked to ensure whether they are at least 5 minutes apart from other postural changes, resulting in a total of 59 valid postural changes. Finally, after validating the quality of the *ECG* signal, 48 posture changes remained for *HRV* analysis.

6.2 Differences in Recording Settings

The detected posture changes were all categorized according to their recording setting. Table 6.1 lists the change in heart rate and the changes in time and non-linear HRV parameters in each recording setting. In all settings, heart rate showed an increase after posture changes, whereas

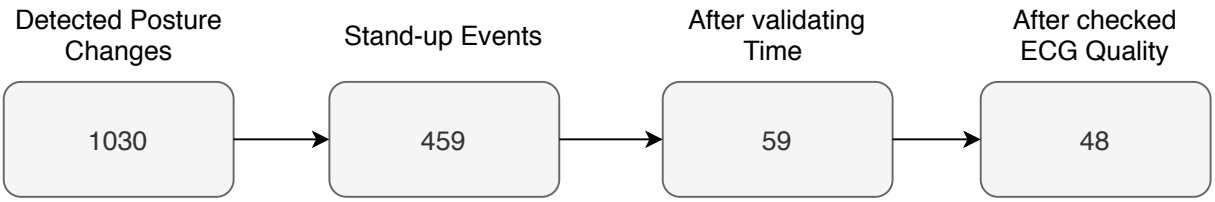


Figure 6.1: Schematic representation of the number of valid posture changes after applying various rejection criteria.

most *HRV* parameters tended to decrease except for *HRV* measures in Lab2. The resting heart rate was lowest during Home-Tests, slightly elevated for Home-Free and Lab1, and highest during Lab2.

Table 6.1: Change in heart rate and *HRV* during posture changes in different recording settings. Resting heart rate is reported as M $\pm$ SD before the posture change. All other values are reported as M $\pm$ SD increase relative to the interval before the posture change.

	Unit	Lab1	Lab2	Home-Tests	Home-Free
Resting Heart Rate	bpm	75 ± 8	89 ± 7	72 ± 11	75 ± 12
Heart Rate	bpm	$+9 \pm 8$	$+8 \pm 4$	$+12 \pm 8$	$+4 \pm 10$
pNN20	%	-38 ± 22	$+6 \pm 50$	-33 ± 36	-5 ± 39
RMSSD	%	-31 ± 26	$+27 \pm 78$	-13 ± 77	$+1 \pm 41$
SD1/SD2	%	-17 ± 29	$+30 \pm 73$	-22 ± 51	-1 ± 59

Table 6.2 shows the post-hoc tests results for differences in heart rate and *HRV* measures before and after posture changes. In all recording settings, t-testing confirmed significantly elevated heart rate values after standing up (Figure 6.2). Additionally, significant decreases of *HRV* measures after posture changes were detected in Home-Tests and during Lab1 (Figure B.1, Figure B.2).

The absolute changes in heart rate caused by posture changes are visualized in Figure 6.3, arranged according to their recording setting. During Home-Tests, the increase in heart rate was highest among all recording settings, whereas it was lowest in Home-Free conditions. Pairwise t-tests of heart rate before and after posture changes between the different recording settings revealed significant differences in heart rate increase between Home-Tests and Lab2 ($t(16.540) = 3.118, p = 0.006, d = 0.985$), Home-Free and Home-Tests ($t(34) = -5.075, p < 0.001, d = -1.692$), and Home-Free and Lab2 ($t(16.952) = -2.627, p = 0.018, d = -0.858$).

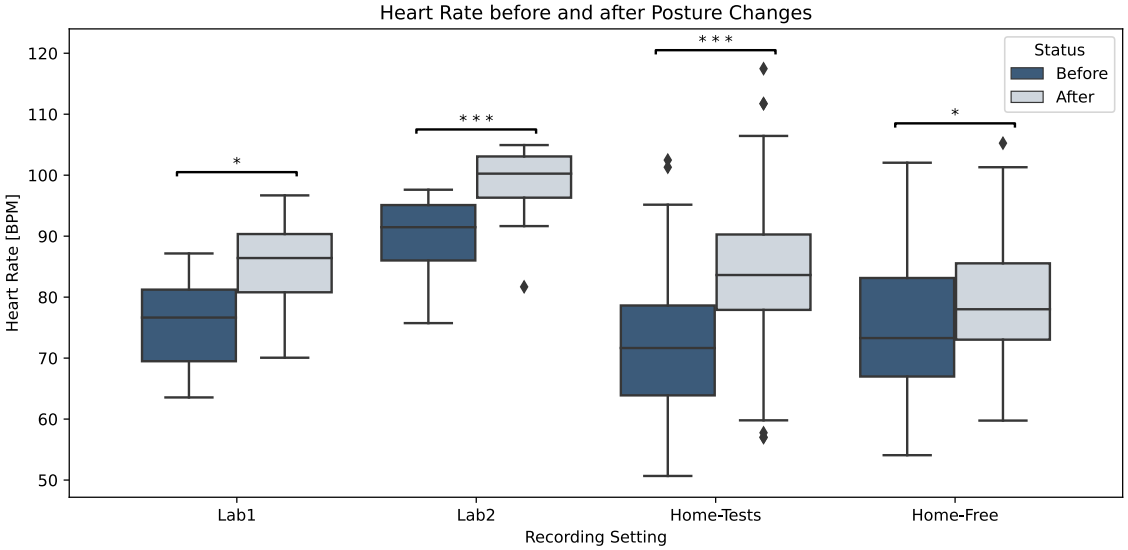


Figure 6.2: Heart rate during posture changes in the different recording settings. *Note:* $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$

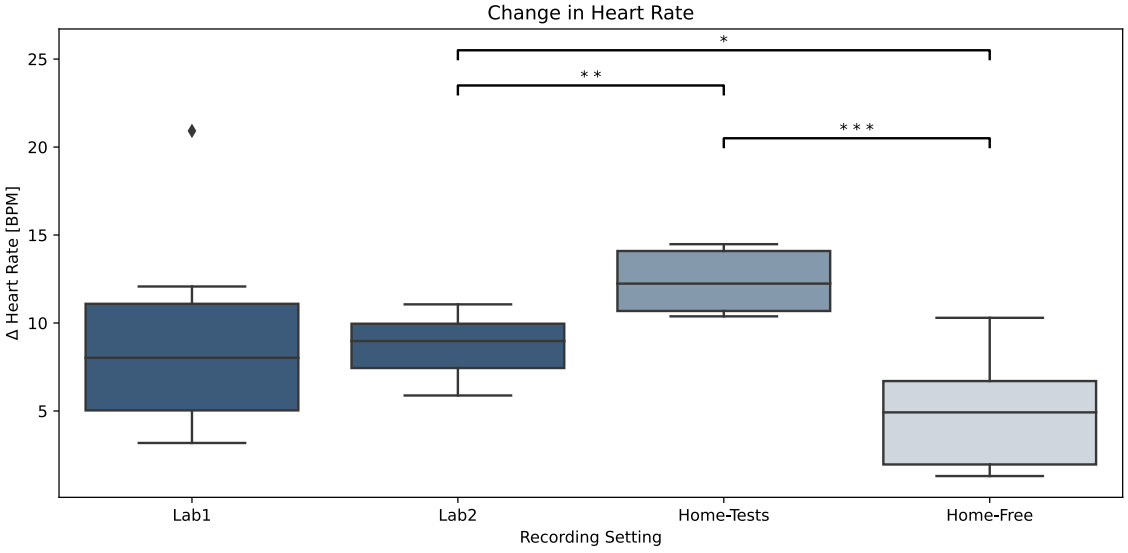


Figure 6.3: Absolute change in heart rate before and after posture changes in the different recording settings. The boxplots display the distribution of the data averaged for each subject. *Note:* $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$

Table 6.2: Pairwise t-testing of heart rate and *HRV* measures before and after posture changes. *Note:* $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$

Measure	Recording Setting	Degrees of Freedom (dof)	t	p	Cohen's d
Heart Rate	Lab1	5	-3.541	0.016 *	-1.196
	Lab2	4	-9.467	< 0.001 ***	-1.246
	Home-Tests	5	-11.022	< 0.001 ***	-1.768
	Home-Free	5	-2.824	0.037 *	-0.601
pNN20	Lab1	5	4.800	0.005 **	1.548
	Lab2	4	0.295	0.782	0.044
	Home-Tests	5	12.570	< 0.001 ***	1.166
	Home-Free	5	1.911	0.114	0.455
SD1	Lab1	5	3.144	0.025 *	1.413
	Lab2	4	-1.086	0.339	-0.210
	Home-Tests	5	3.185	0.024 *	0.641
	Home-Free	5	1.301	0.250	0.220

On average, subjects showed a lower resting heart rate during tests at home and in free-living environment than at the laboratory (see Figure 6.4). Significant differences in resting heart rate were revealed between Home-Tests and Lab2 $(t(7.421) = -4.538, p = 0.002, d = -2.034)$, Home-Free and Lab2 $(t(10.979) = -3.455, p = 0.005, d = -1.318)$, and Lab1 and Lab2 $(t(8.867) = -3.070, p = 0.014, d = -1.844)$ by pairwise t-tests.

6.3 Intraday Differences

The day's trend of the orthostatic reaction averaged over all days and all participants is depicted in Figure 6.5. Subjects showed a more distinctive orthostatic reaction in the morning than at noon or afternoon during Home-Tests. Moreover, the increase in heart rate during Home-Tests was higher than in Home-Free, regardless of the time of day. Repeated-measures *ANOVA* of changes in heart rate during Home-Tests also indicate significant differences between orthostatic reactions at different times of day $(F(2, 10) = 5.986, p = 0.019, \eta_p^2 = 0.545)$. Post-hoc testing showed significant differences between morning and noon $(t(5) = 2.697, p = 0.0429, d = 1.202)$ and between morning and afternoon $(t(5) = 2.601, p = 0.0481, d = 1.594)$, respectively. The comparison of orthostatic reactions during different times of the day in Home-Free showed no significant differences.

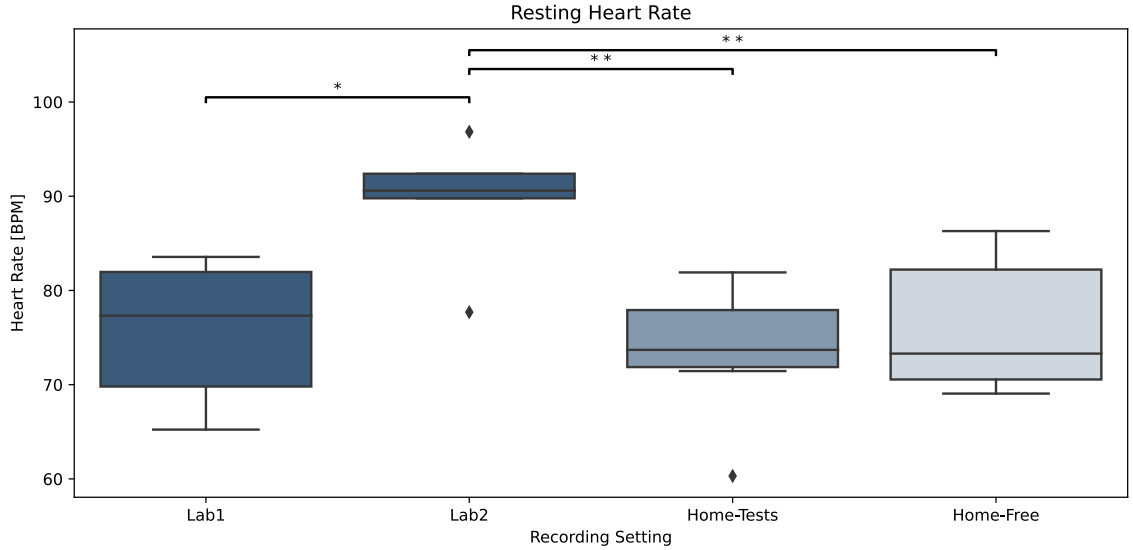


Figure 6.4: Resting heart rate before posture changes in the different recording settings. The boxplots display the distribution of the data averaged for each subject. *Note:* $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$

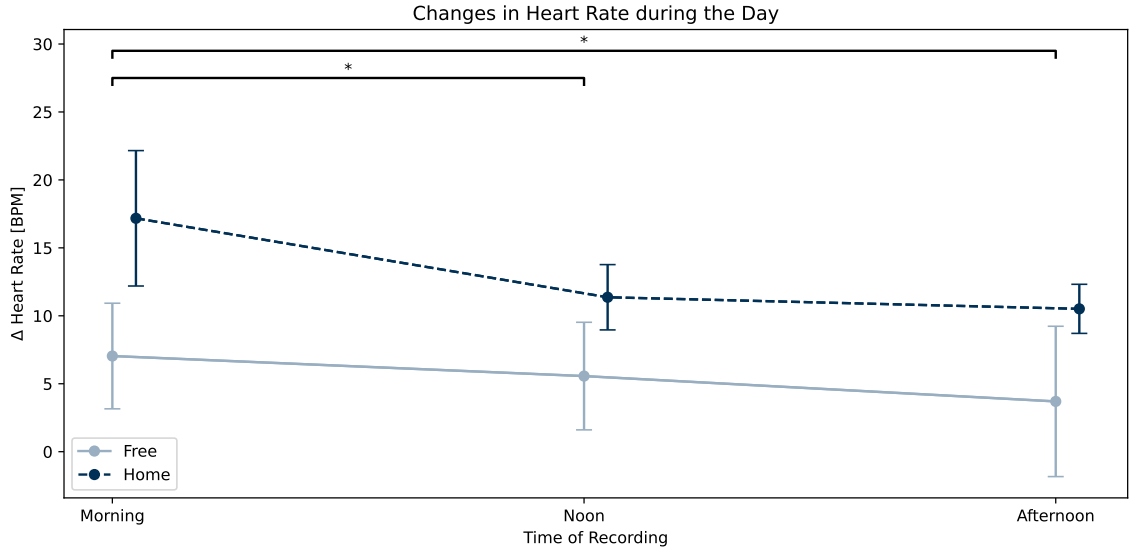


Figure 6.5: Absolute change in heart rate while posture changes during the day. Values are depicted as mean and standard error over all subjects. *Note:* $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$

The number of posture changes causing an increase in heart rate of more than 10 bpm are presented in Table 6.3. Throughout the day, Home-Tests revealed the highest percentage (61%) of such posture changes, whereas only 35% of Home-Free and 36% of Lab1 + Lab2 recordings showed an increase in heart rate of more than 10 bpm. Across all times of the day, the highest percentage (95%) was found in Home-Tests in the morning, while recordings at Lab1 + Lab2 at noon showed the lowest percentage (25%).

Table 6.3: Number of posture changes causing an increase in heart rate of more than 10 bpm. Values are denoted as absolute number of posture changes and percentage number of posture changes based on all posture changes detected within the respective time.

	Home-Free	Home-Tests	Lab1 + Lab2
Morning	5 (45%)	18 (95%)	5 (42%)
Noon	5 (29%)	22 (58%)	2 (25%)
Afternoon	7 (33%)	16 (47%)	1 (50%)
Whole Day	17 (35%)	56 (61%)	8 (36%)

6.4 Interday Differences

Figure 6.6 shows the trend of the orthostatic reaction throughout the whole study procedure. The data is averaged over each day and each subject and divided into Home-Tests and Home-Free conditions. Since recordings at the laboratory cannot be divided into these two categories, the two data points were combined into one point representing the mean value of the recordings at the laboratory. Similar to observations in Figure 6.5, the change in heart rate during Home-Tests is consistently higher than the change in heart rate in Home-Free. Comparing the values between the different days, certain variations during the study procedure can be observed. However, repeated-measures *ANOVA* of Home-Tests data ($F(3, 15) = 1.060, p = 0.395, \eta_p^2 = 0.175$) and Home-Free data ($F(3, 15) = 1.586, p = 0.234, \eta_p^2 = 0.241$) showed no significant difference in orthostatic reaction between the days. Furthermore, high variations in the data are noticeable, especially during the first day at home, where the heart rate partly even decreased after a change of posture.

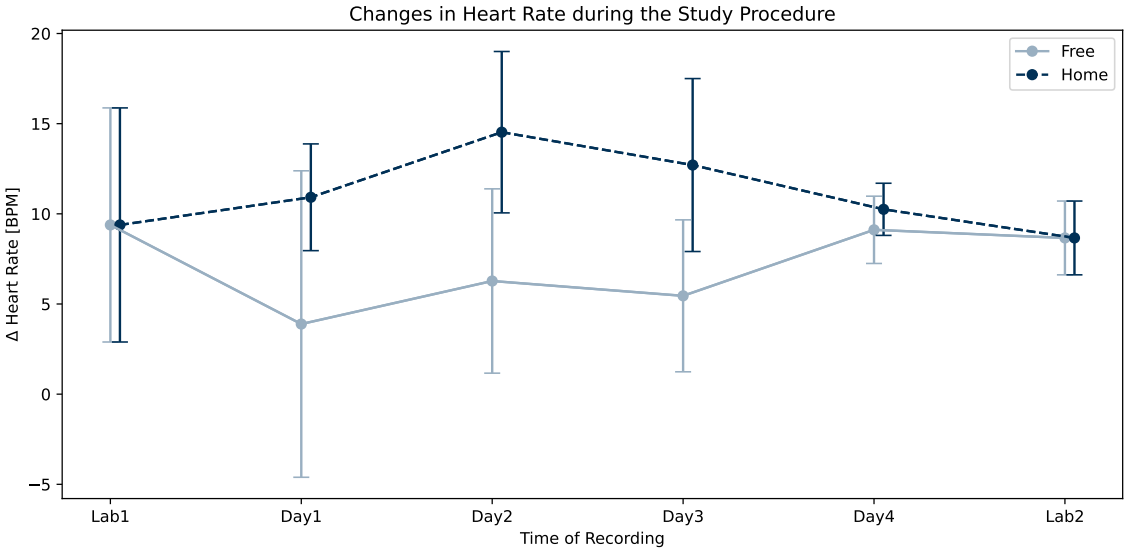


Figure 6.6: Absolute change in heart rate while posture changes during the study procedure. Values are depicted as mean and standard error over all subjects.

Chapter 7

Discussion

The goal of this thesis was to evaluate the feasibility of assessing changes in heart rate and *HRV* evoked by postural changes by monitoring participants in their natural home environment. Furthermore, the differences in body reactions to posture changes were compared between recordings at the laboratory, tests at home, and free-living data. The following section will discuss the presented methods for data acquisition, the obtained results regarding the *HRV*, and the study design.

7.1 *HRV* Analysis

Results of the study evaluation indicate a significant increase in heart rate after posture changes in all recording conditions (cf. Figure 6.3) and, therefore, correlate with results of prior investigations as by Ewing et al. [Ewi80]. Moreover, *HRV* measurements show the tendency to decrease with some exceptions during the second recording at the laboratory (cf. Table 6.2). The increase in heart rate and decrease in *HRV* further reflect increased sympathetic activity, confirming the fact that *HRV* assessment at home can be used for the investigation of the *ANS*.

7.1.1 Differences in Recording Settings

Comparing the heart rate increase between the different recording settings revealed that there was a significantly higher increase in heart rate during Home-Tests than in Home-Free data ($p = 0.018$) or during Lab2 ($p = 0.006$). The fact that posture changes during Home-Tests caused a significantly higher change in heart rate than posture changes during Lab2 can be attributed to the ‘white coat syndrome’. This phenomenon can also be observed when examining the resting

heart rate at different recording settings. On average, subjects showed a higher resting heart rate at the laboratory than during tests at home and in a free-living environment. This may be due to anxiety in clinical situations and can be prevented by performing heart rate and *HRV* assessment in the participants' home environment. However, there was an unexpected difference between the resting heart rate in Lab1 and the resting heart rate in Lab2. This unexpected difference may be attributed to the participants' leisure activities. For example, two subjects stated that they had consumed alcohol the night before the study. In the context of this study protocol, this was not an exclusion criterion, therefore, the data were included in the analysis. Nevertheless, alcohol consumption has a strong influence on heart rate, as shown in the paper of Kentala et al. which stated that people have a significantly higher resting heart rate during the hangover period than before consuming alcohol [Ken76]. Furthermore, other factors such as intense physical activity before the *HRV* assessment can also affect the resting heart rate [Jav02]. Thus, the increase in resting heart rate during Lab2 may be caused by unequal physical conditions of participants between the two recordings at the laboratory.

Moreover, the difference can also be due to the fact that the Lab2 recording had to be excluded for Subject2 and, hence, less data were available for evaluation, which may lead to a distortion in data distribution.

7.1.2 Intraday Differences

The evaluation of changes in heart rate at different times of day led to the finding that changes in the morning at home was significantly higher than changes at noon or afternoon. The observation that orthostatic reactions differ significantly at different times of the day correlates with results obtained in literature [Bel00]. Therefore, heart rate and *HRV* assessment should always be performed at the same time, as results would not be reliable if the assessment was carried out at different times of the day. Furthermore, tests at home always showed a more pronounced orthostatic reaction than measurements in a free-living environment, regardless of the time of day. For unobtrusive *HRV* assessment at home, it might therefore not be necessary to perform a continuous free-living data acquisition, but it is sufficient to conduct regular tests at predefined times. This is further confirmed by comparing the resting heart rates in free-living data and during tests at home. In both settings, they did not show considerable differences, so it can be assumed that no white coat effect occurred during tests at home. This offers several advantages for users, physicians, and developers.

First of all, patients do not have to wear the sensors all the time, but they only have to attach them during the tests. Although sensor technologies have made great progress in recent years,

especially in terms of wearing comfort [Liu20], they are usually still uncomfortable in some way after a certain time. Therefore, the patients' quality of life would be enhanced by wearing the sensors only for the tests. Moreover, by collecting data through standardized tests at home rather than in a free-living environment, data quality can be improved and (movement) artifacts can be minimized as patients only perform predefined movements. For sensor technologies there are also several advantages, as the amount of collected data decreases, and therefore battery life and storage space can be reduced, which gives the possibility for further minimization of the sensors.

7.1.3 Interday Differences

By observing the changes in heart rate throughout the entire study procedure, no significant differences between the recording days were detected. However, high variances in the data were observed. This can be caused by various factors, both of physiological and environmental origin that may directly influence *HRV* [Fat16]. Two main factors include stress and negative emotions, as they reduce parasympathetic activity and thus decrease *HRV* [Kim18]. As the human body is exposed to diverse social and environmental situations, large changes in *HRV* within different days can occur. As mentioned above, alcohol can also affect the heart rate, since the consumption of alcohol is related to a sympathetic activation and a parasympathetic inhibition and can, therefore, lead to altered *HRV* [Ken76]. Physiological factors such as respiration or fever can also impact *HRV* as they are closely related to heart rate, too. [Fat16]. Apart from physical reasons, *HRV* assessment can also be affected by sensor placement, as the participant had to reattach the sensors each morning without supervision. An incorrect sensor placement can cause failures in data acquisition and thus lead to errors in the evaluation of *HRV*. Since the *HRV* is such a sensitive measure, recordings should always be performed for several days in order to reduce the influence of day-by-day variation.

7.2 Limitations

7.2.1 Data Acquisition

As shown in Table 6.1, *HRV* measures show a variance often higher than the measured value itself. This may result from high inter-subject variances, but can also be caused by problems with data acquisition. Furthermore, 9% of valid posture changes had to be rejected due to poor *ECG* quality. Although the sensors used for data acquisition are very advantageous concerning its small size, the system also had several drawbacks. Firstly, the *ECG* sensor was attached under the chest using

a belt. Since the belt did not adhere to the skin, the probability of sensor displacement was higher compared to *ECG* electrodes which are directly attached on the user's body surface. This effect was particularly noticeable when lying down. Therefore, the correct and reliable calculation of *HRV* parameters was not possible under these conditions due to strong artifacts.

Moreover, the recording procedure using the smartwatch application can impose problems for participants who are not familiar with new technologies, as the control of the sensors is partly complicated. In the context of this study, participants had to start, stop and download their recordings by themselves. Furthermore, since the storage of the sensors was limited to recordings of about 14 to 20 hours, the recorded sessions had to be downloaded every night. For this study, only participants aged between 21 and 24 years with a good technical background were included. This minimized problems with technical applications. By conducting the study with people who have a less pronounced technical background, such as elderly patients, who might even suffer from cognitive impairment, solutions should be considered that allow easier control of sensors or give the study supervisor the ability to control the sensors remotely.

7.2.2 Study Design

As depicted in Figure 6.5 the resting heart rate is only increased for Lab2 but there is no large difference between the resting heart rate of Lab1 and the resting heart rate at home. This result is probably based on the fact that the supervised tests were not conducted in a clinical environment under medical supervision, but at the laboratory of the university. Moreover, participants did not have to fear orthostatic dysfunction. Both minimize the experience of anxiety under supervised conditions and thus reduce the influence of the white-coat effect. Hence, to obtain a more reliable difference in *HRV* analysis between recordings at home and clinical settings, it would be preferable to conduct the supervised sections of the study in a hospital or physician's office.

For data collection, a four-days time period was defined in the study protocol. As the time available for the study was limited, the number of participants was set to N = 7. The participants in the study were all students aged 21 to 24 years. Therefore, the results achieved are not transferable to other social groups or society as a whole, but only represent a specific outcome of this age group. To obtain representative data for more social groups, the study has to be conducted with more subjects covering a larger variety of people in terms of age, gender, fitness level, and health conditions. Furthermore, the limited number of participants increases the influence of undesirable outlier to examination results as shown in Figure 6.3. The outlier at Lab1 causes that there is no significant difference in heart rate increase compared to tests at home. By conducting the study with more participants, problems associated with extreme or biased groups can be avoided, as the

influence of a single group or participant on the study results decreases with increasing numbers of participants.

As shown in Figure 6.6 during the first recording day, negative changes in heart rate appeared, meaning the heart rate decreased after standing up. As the study was conducted with healthy subjects, only increases in heart rate were expected. However, negative changes in heart rate may result due to hard physical activity before the posture change. Although a five-minute resting period before posture changes was included, the cardiovascular system sometimes needs more time to recover after hard physical activity [Jav02]. Therefore, the cooling-down effect, which provokes a decrease in heart rate, may outweigh the increase in heart rate caused by the posture change. The combination of both effects will result in a decrease in heart rate. Thus, a longer time of rest period would prevent this undesired effect. On the other hand, increasing the rest period would result in more posture changes being rejected. As there is already a very high number of rejected posture changes due to the defined rest periods, it would be more suitable to exclude posture changes after hard physical activity for a specific time. Literature states that after physical exercise heart rate and *HRV* continually decrease or increase, but does not completely attain rest values within 30 minutes after exercise [Jav02]. Therefore, a period of more than 30 minutes should be chosen to exclude posture changes after physical exercises.

Chapter 8

Conclusion and Outlook

The main goal of this bachelor's thesis was to evaluate the feasibility of assessing othostatic reactions in free-living environments. Furthermore, changes in heart rate and *HRV* parameters between different recording settings, namely at the laboratory, during tests at home, and in free-living data were compared. For this purpose, *ECG* was recorded during a period of four days in the free-living environment of the subjects. In addition, participants had to perform the same standardized test twice at the laboratory and three times a day at home. The evaluation of the *ECG* signal revealed a significant increase in heart rate evoked by posture changes in all recording settings. *HRV* measures, however, tended to decrease after a posture change. Moreover, the presented study showed that the orthostatic reaction was most pronounced during tests at home. This offers several advantages for users, physicians, and developers, such as an enhanced quality of life for patients or improvements in signal quality. Last, a high variance within the data was observed throughout the study procedure, indicating the need for data collection over several days. In summary, the presented study shows that *HRV* assessment at home can be used to evaluate orthostatic reactions in order to assess the functionality of the *ANS*.

Using the presented methods, an orthostatic dysfunction would be classified as a too-small change in heart rate and associated *HRV* parameters. However, orthostatic hypotension is further defined as a drop in blood pressure of at least 20 mmHg systolic or 10 mmHg diastolic when standing up. Therefore, a future investigation goal is the inclusion of blood pressure measurements in the study procedure to enable a more reliable assessment of the orthostatic reaction.

The sensors utilized for *ECG* and accelerometer data recording were attached using an adhesive plaster on the leg and a chest belt. To make home monitoring even more unobtrusive and comfortable, future work should consider further miniaturization, the integration of the sensors into clothing or not requiring the second sensor at all.

Since the presented system aims to detect abnormal functions of the *ANS*, it is important to conduct the study not only with healthy subjects but also with patients suffering from dysfunctions of the *ANS* such as *PD*.

Concluding, this work showed that vertigo assessment at home can be used to improve the early diagnosis of *OH* and neurodegenerative diseases. As early diagnosis of neurodegenerative disorders enables better treatment of the disease, the quality of life of patients can be improved and the burden of age-related diseases on the health care system can be reduced. Vertigo assessment at patients' home should therefore be further developed and specified in future work.

Appendix A

Patents

A.1 Apparatus and method for monitoring heart rate variability

Publication Number	US7460899B2
Date of Publication	Dec. 2, 2008
Inventors	Adam J. Almen
Assignee	Quiescent, Inc.
Abstract	A wrist-worn or arm band worn heart rate variability monitor is provided. Heart rate variability ('HRV') refers to the variability of the time interval between heartbeats and is a reflection of an individual's current health status. Over time, an individual may use the results of HRV tests to monitor either improvement or deterioration of specific health issues. Thus, one use of the HRV test is as a medical motivator. When an individual has a poor HRV result, it is an indicator that they should consult their physician and make appropriate changes where applicable to improve their health. If an individual's HRV results deviate significantly from their normal HRV, they may be motivated to consult their physician. In addition, the inventive monitor is capable of monitoring the stages of sleep by changes in the heart rate variability and can record the sleep (or rest) sessions with the resulting data accessible by the user or other interested parties.

A.2 Non-invasive apparatus system for monitoring autonomic nervous system and uses thereof

Publication Number	US6811536B2
Date of Publication	Nov. 2, 2004
Inventors	Dehchuan Sun, Terry B. J. Kuo
Assignee	Quiescent, Inc.
Abstract	A non-invasive apparatus system for monitoring autonomic nervous system, and its uses in monitoring autonomic nervous system functional change side effects caused by drugs and monitoring the aging of autonomic nervous system and tracing therapeutic effect thereof.

A.3 Programmable ECG sensor patch

Publication Number	US8688189B2
Date of Publication	Apr. 1, 2014
Inventors	Adnan Shennib
Abstract	The invention provides a disposable programmable ECG sensor patch for the non-invasive detection of risk patterns according to programmed criteria. The patch is programmed by a medical professional to select one or more monitoring parameters for detection and alarm indication. One application is to detect changes in the ECG due to cardioactive drugs. Another application is triggering an alarm for a cardiac patient during a stress condition. The programmable patch operates in conjunction with an external programming unit for selecting the detection monitoring parameters.

A.4 System for seamless and secure networking of implantable medical devices, electronic patch devices and wearable devices

Publication Number	US8653966B2
Date of Publication	Feb. 18, 2014
Inventors	Raman K. Rao, Sanjay K. Rao
Assignee	IP Holdings, Inc.
Abstract	A system level scheme for networking of implantable devices, electronic patch devices/sensors coupled to the body, and wearable sensors/devices with cellular telephone/mobile devices, peripheral devices and remote servers is described.

A.5 Detection of change in posture in video

Publication Number	US7613324B2
Date of Publication	Nov. 3, 2009
Inventors	Peter L. Venetianer, Andrew J. Chosak, Niels Haering, Alan J. Lipton, Zhong Zhang, Weihong Yin
Assignee	ObjectVideo, Inc.
Abstract	Input video data is processed to detect a change in a posture of a person shown in the video data. The change of posture may be the result of an event, for example, the person falling or getting up. The input video data may include a plurality of frames. Objects in the frames are tracked and then classified, for example, as human and non-human targets. At least one of the position or location of a human target in the frames is identified. Changes in the location or position of the human target between the frames is determined. When the change in at least of the position or location exceeds a predetermined threshold, a falling down event or a getting up event is detected. The changes in the position or location of the human target can be determined based on a number of different factors.

A.6 Posture detection system

Publication Number	US7471290B2
Date of Publication	Dec. 30, 2008
Inventors	Hua Wang, John Hatlestad, Keith R. Maile
Assignee	Cardiac Pacemakers, Inc.
Abstract	Methods, systems, and apparatus are described for posture detection. Orientations of a body are detected with respect to first and second axes. A movement of the body with respect to a third axis is also detected. Three-dimensional orientations of the body are determined based on the orientations and the movement. The detected posture may be used for applications such as controlling medical devices and detecting patient disorders.

Appendix B

Additional Figures and Tables

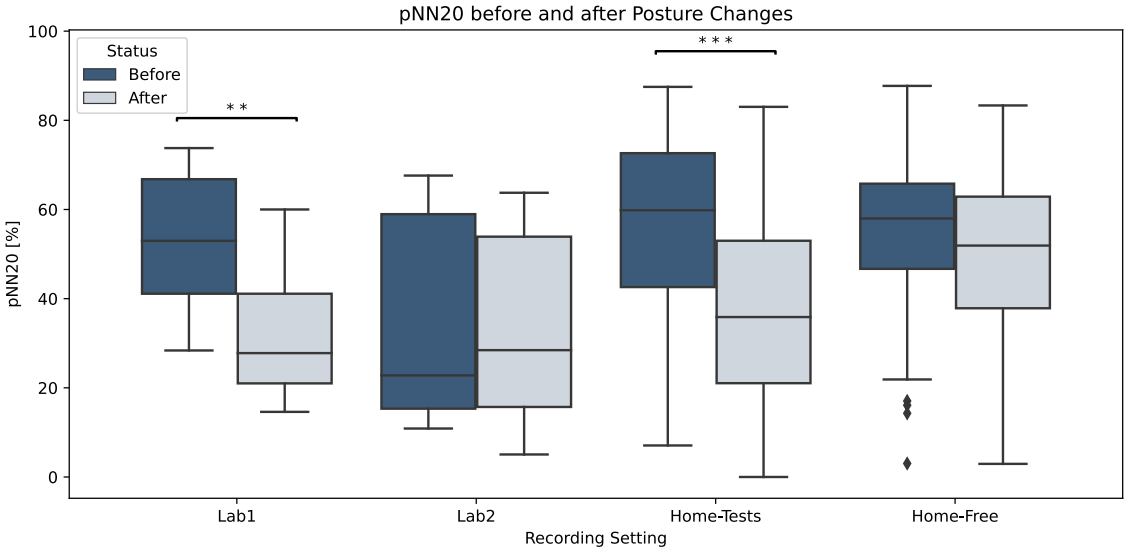


Figure B.1: *pNN20* values before and after posture changes at the different recording settings. *Note:* $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$

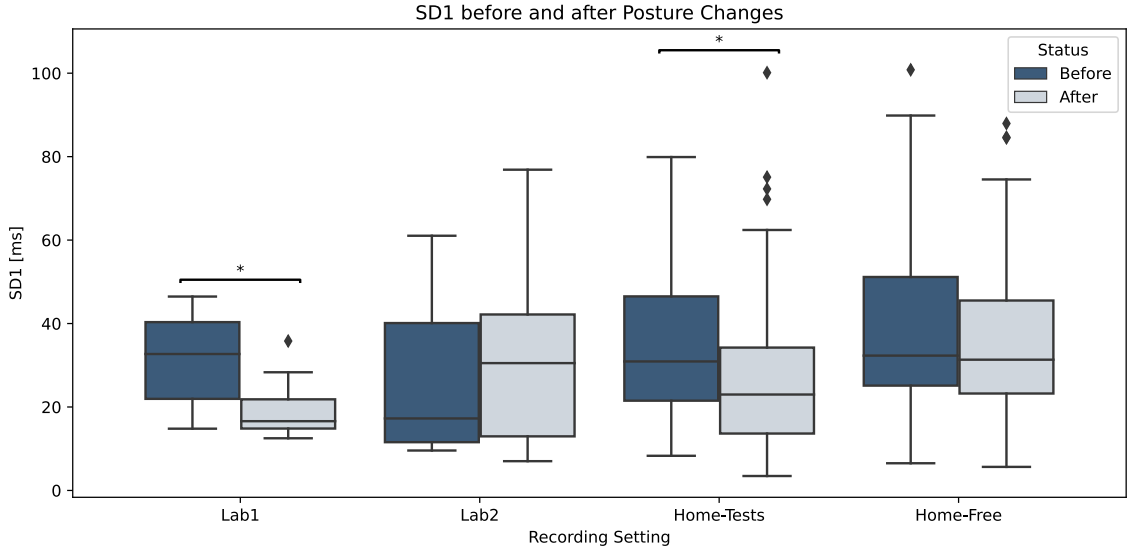


Figure B.2: *SD1* values before and after posture changes at the different recording settings.
Note: $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$

Table B.1: Recording times per subject.

	Recording time at the laboratory	Recording time at home	Total recording time
Subject 1	31 min	42:51 h	43:22 h
Subject 2	15 min	15:43 h	15:58 h
Subject 3	30 min	12:10 h	12:40 h
Subject 4	30 min	19:33 h	20:03 h
Subject 5	0 min	0 min	0 min
Subject 6	30 min	30:05 h	30:35 h
Subject 7	30 min	28:58 h	29:28 h
			152:06 h

Glossary

ANOVA Analysis of Variance.

ANS Autonomic Nervous System.

DRPLA Dentatorubral-Pallidoluysian Atrophy.

ECG Electrocardiogram.

HF High Frequency.

HRV Heart Rate Variability.

IMU Inertial Measurement Unit.

LF Low Frequency.

OH Orthostatic Hypotension.

PAR-Q Physical Activity Readiness Questionnaire.

PD Parkinson's Disease.

pNN20 Percentage of Successive RR-Intervals differing more than 20 ms.

pNN50 Percentage of Successive RR-Intervals differing more than 50 ms.

PSNS Parasympathetic Nervous System.

RMSSD Root Mean Square of Successive Differences.

SBMA Spinal and Bulbar Muscular Atrophy.

SD1 Standard Deviation 1.

SD2 Standard Deviation 2.

SNS Sympathetic Nervous System.

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