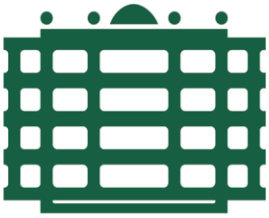

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Doctoral Thesis

entitled

Sensory and methodological aspects in biomechanical research of postural control and clinical fields of application

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Submitted by: Daniel Schmidt
born on January 9, 1985 in Goerlitz (Germany)

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Abstract

The human senses constitute a highly complex system based on various sensory organs, afferent pathways, and central processing locations, which allow us to interact with the environment, but also with ourselves. A further domain is important to achieve this interaction: the motor system, which allows linguistic communication and locomotion, for example. It becomes evident that sensory receptors work as a source of information to initiate, optimize, or cease motor activity. One generic term for such sensory sources is the somatosensory system, which is mainly based on receptors located in muscles, tendons, and the skin (cutaneous sensitivity). In this regard, it has been shown that cutaneous sensitivity contributes to human balance regulation. However, there are still debates concerning the exact role of plantar (foot sole) receptor inputs in particular, and how their isolated contribution to, e.g., balance regulation may be assessed accordingly.

To investigate the interaction between plantar cutaneous sensitivity and human balance capabilities, several aspects need to be considered which are still controversial and inconclusive in the scientific community. For example, when assessing cutaneous vibration sensitivity, it is well-known that increasing vertical forces of the contactor toward the skin usually result in improved sensitivity. However, it has not been profoundly investigated whether assessing plantar vibratory sensitivity differs when comparing a standing or sitting posture, which obviously involves different contactor forces. In addition, many studies implementing cutaneous sensitivity show certain limitations with respect to adequate data analyses. A similar aspect also applies when assessing balance performance: devices allowing an investigation of dynamic balance performance (induced by unexpected platform perturbations while standing, for example) have only been partially investigated with regard to their biomechanical quality criteria, such as reliability.

With these considerations in mind, the present doctoral thesis is based on five published studies. Study 1 investigates if plantar sensitivity is influenced by different body positions when collecting data. Study 2 asks how to appropriatly analze plantar sensitivity data. Study 3 examines the reliability of dynamic balance responses using the so-called Posturomed device, and Study 4 identifies the isolated role of plantar

inputs on balance responses, when an acute sensory manipulation is induced that exclusively affects plantar aspects. Ultimately, clinical fields of application (based on the previous four studies) are highlighted in Study 5.

The main findings of the first four studies can be summarized as follows. First, higher contact forces when standing compared to sitting did not influence plantar sensitivity. This is an important finding, as plantar sensitivity tests (often performed during sitting) may, hence, be brought into context with balance tests usually performed during standing. Second, plantar sensitivity data are shown to exhibit heteroscedasticity, meaning that the measurement error increases as the values increase. In Study 2, we provided an easy-to-follow example for how to account for heteroscedasticity by logarithmizing the raw data, and how to control whether this approach was successful in eliminating heteroscedasticity. Third, dynamic balance responses assessed via the Posturomed device exhibit an overall good reliability. Occasional significant differences were shown to be clinically non-relevant, identified by root mean square error calculations. Fourth, a permanent plantar sensory manipulation (hypothermia) was successfully achieved and maintained throughout data collection. Study 4 showed that the reduced plantar sensory input due to the hypothermic manipulation was compensated during more unchallenging balance conditions (standing still). There was no full compensation during more challenging balance conditions (unexpected platform perturbations during standing), however, with the body reacting with cautious motor behavior. This became evident by decreased outcome measures following hypothermic plantar sensory manipulation. These four studies shed further light onto investigations combining sensory and motor tests, especially with regard to physiological and methodological aspects that should be considered when analyzing and interpreting associated data.
Finally, this doctoral thesis also provides an example of identifying clinical fields of application concerning sensory-focused research. In Study 5, we highlight the role of sensory research in the (early) diagnosis of diseases associated with cognitive decline. For this purpose, various instruments such as sensory tests or coordinative motor tests are implemented. Preliminary results suggest that not only classical cognitive parameters and questionnaires should be used to identify and better-understand cognitive decline.

Zusammenfassung

Die menschlichen Sinne stellen ein sehr komplexes System dar, welches auf verschiedenen sensorischen Organen, afferenten Leitungsbahnen und zentralen Verarbeitungsstellen basiert und es uns ermöglicht, mit der Umwelt, aber auch mit uns selbst, zu interagieren. Dahingehend ist eine weitere wichtige Domäne wichtig, um diese Interaktion zu bewerkstelligen: das motorische System, welches etwa eine sprachliche Kommunikation oder auch die Fortbewegung ermöglicht. Es wird somit offensichtlich, dass sensorische Rezeptoren eine Informationsquelle darstellen, um motorische Aktivität zu initiieren, zu optimieren oder zu beenden. Ein grundlegender Terminus für solch sensorische Quellen ist das somatosensorische System, welches überwiegend auf Rezeptoren in Muskulatur, Sehnen und der Haut (kutane Sensibilität) beruht. Diesbezüglich wurde bereits aufgezeigt, dass die kutane Sensibilität einen Beitrag bei der menschlichen Gleichgewichtsregulation leistet. Allerdings existieren dabei nachwievor Diskussionen in Bezug auf die genaue Bedeutung plantarer (die Fußsohle betreffend) Rezeptor-Inputs und inwieweit deren isolierte Bedeutung bei der Gleichgewichtsregulation entsprechend ermittelt werden kann.

Um die Interaktion zwischen der kutanen Sensorik der Fußsohle und der menschlichen Gleichgewichtsfähigkeit zu erforschen, sollten verschiedene Aspekte berücksichtigt werden, welche nachwievor kontrovers und nicht eindeutig in der Wissenschaft diskutiert werden. Bei Erhebungen der kutanen Vibrationssensibilität, als Beispiel, ist bereits bekannt, dass erhöhte Vertikalkräfte, mit denen der Vibrationsstößel gegen die Haut appliziert ist, generell zu einer verbesserten Sensibilität/Sensorik führen. Allerdings wurde noch nicht klar erforscht, ob sich die plantare Vibrationssensibilität zwischen einer stehenden und sitzenden Haltung der Probanden/innen unterscheidet, wobei hier natürlich unterschiedliche Vertikalkräfte der Stößel wahrscheinlich sind. Darüber hinaus zeigen viele Studien, welche die Hautsensibilität untersuchen, gewisse Limitierungen in Bezug auf eine adäquate Datenanalyse. Ein sehr ähnlicher Aspekt trifft auch auf die Evaluierung der Gleichgewichtsfähigkeit zu: Messgeräte, welche dabei eine Erfassung der dynamischen Gleichgewichtsfähigkeit zulassen (z.B. eingeleitet durch unerwartete

Plattform-Perturbationen während des Stehens), wurden bisher nur teilweise auf die biomechanischen Gütekriterien hin untersucht, wie etwa die Reliabilität.

Aufgrund dieser Überlegungen basiert die vorliegende Dissertation auf fünf publizierten Studien, welche folgende Aspekte untersuchten: Wird die plantare Sensibilität durch verschiedene Körperpositionen während der Datenaufnahme beeinflusst (Studie 1)? Wie können plantare Sensibilitätsdaten angemessen analysiert werden (Studie 2)? Darüber hinaus wurde ebenso untersucht, inwiefern das sogenannte "Posturomed"-Messgerät bei der Beurteilung dynamischer Gleichgewichtsantworten reliable Messwerte liefert (Studie 3). Ferner wurde in Studie 4 untersucht, inwiefern isoliert plantare Inputsignale bei Gleichgewichtsantworten relevant sind (anhand einer akuten sensorischen Manipulation, welche ausschließlich die Fußsohle betrifft). In Studie 5 werden konkrete klinische Anwendungsbeispiele aufgrund der vier hier vorgestellten Studien aufgezeigt.

Die Hauptergebnisse der ersten vier Studien können wie folgt zusammengefasst werden: Erstens, höhere vertikale Kontaktkräfte während des Stehens verglichen mit sitzenden Positionen führten zu keinen Unterschieden bzgl. der plantaren Sensibilität. Dies ist eine wichtige Erkenntnis, da plantare Sensorikmessungen (oft während des Sitzens durchgeführt) dadurch in Kontext mit Gleichgewichtstests gebracht werden können, welche normalerweise im Stehen erfolgen. Zweitens, Daten der plantaren Sensorik zeigten Heteroskedastizität, was bedeutet, dass sich der Messfehler mit Größenzunahme der Messwerte ebenso erhöht. Wir konnten in Studie 2 ein leicht zu erschließendes Beispiel aufzeigen, wie das Problem der Heteroskedastizität durch eine Logarithmierung der Rohdaten behandelt werden konnte und wie kontrolliert werden konnte, ob diese Behandlung erfolgreich war. Drittens, die dynamischen Gleichgewichtsantworten, welche mittels des "Posturomed" ermittelt wurden, zeigen insgesamt eine gute Reliabilität. Gelegentlich auftretende signifikante Unterschiede wurden anhand von Berechnungen der Wurzel der mittleren Fehlerquadratsumme (root mean square error, RMSE) als klinisch nicht relevant eingestuft. Viertens, eine anhaltende plantar-sensorische Manipulation (Hypothermie) wurde erfolgreich eingeleitet und während der Datenerhebung aufrecht erhalten. Studie 4 zeigte ferner, dass die hypothermisch eingeleiteten

reduzierten plantaren Sensorik-Inputs während der eher nicht herausfordernden quasi-statischen Gleichgewichtsbedingungen (einfaches aufrechtes Stehen) kompensiert werden konnten. Während der herausfordernden Gleichgewichtskonditionen (unerwartete Perturbationen der Plattform während des Stehens) hingegen wurde keine vollständige Kompensation erreicht. Allerdings reagierten die Probanden mit einem vorsichtigen motorischen Verhalten. Dies wurde durch die reduzierten Ergebnisparameter infolge der plantaren hypothermischen Manipulation ersichtlich. Die vier hier genannten Studien zeigen weitere Erkenntnisse in Bezug auf Forschungsaktivitäten, welche sensorische und motorische Tests vereinen. Dies trifft speziell in Hinblick auf physiologische und methodologische Aspekte zu, welche bei der Analyse und Interpretation derartiger Daten in Betracht gezogen werden sollten.

Zuletzt bietet diese Arbeit auch ein Beispiel dafür, welche klinischen Anwendungsfelder im Bereich der sensorisch-fokussierten Forschung identifiziert werden können. In Studie 5 wird dafür die Bedeutung sensorischer Forschung bei der (Früh-) Diagnose von Erkrankungen aufgezeigt, welche mit kognitiven Einschränkungen in Verbindung gebracht werden. Für diesen Zweck werden verschiedene Instrumente eingebracht, wie etwa sensorische oder koordinativ-motorische Tests. Vorläufige Ergebnisse deuten dabei bereits an, dass nicht nur die klassischen kognitiven Parameter und Fragebögen bei der Identifizierung oder zum Zwecke des besseren Verstehens kognitiven Verfalls einbezogen werden sollten.

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List of abbreviations (sections 1, 2, 4, 5)

CNS	Central nervous system
COP	Center of pressure
EMG	Electromyography
FAI	Fast adapting type I unit(s)
FAII	Fast adapting type II unit(s)
Hz	Hertz
MCI	Mild cognitive impairment
MoCA	Montreal Cognitive Assessment
m/s	meter(s) per second
µm	Micrometer
SAI	Slowly adapting type I unit(s)
SAII	Slowly adapting type II unit(s)
SEM	Standard error of measurement
VPT/VPTs	Vibration perception threshold/s

Section 1 - Outline, introduction, and background

1.1 Document outline

The present doctoral thesis constitutes a cumulative work based on five scientific studies (overview in Table 1), which were published in international, peer-reviewed journals between the years 2015 and 2020. Please note that Study 5 is not part of the main study presentation and discussion, but is a central element in the section "Perspectives and future direction" (section 5).

Table 1: Overview of the five published works representing the main studies within this cumulative doctoral thesis. Corresponding authors are marked with an asterisk ("*").

Study	Title	Authors	Publication details
1	Plantar sensory vibration thresholds are not influenced by body position	Andresa M.C. Germano*, Daniel Schmidt, Guenther Schlee, Thomas L. Milani	Cogent Medicine, 2016, 3: 1238600, 6 pages. DOI: 10.1080/2331205X.2016.1238600
2	Subjective sensitivity data: Considerations to treat heteroscedasticity	Daniel Schmidt*, Andresa M.C. Germano, Thomas L. Milani	Cogent Medicine, 2019, 6: 1673086, 10 pages. DOI: 10.1080/2331205X.2019.1673086
3	Aspects of dynamic balance responses: inter- and intra-day reliability	Daniel Schmidt*, Andresa M.C. Germano, Thomas L. Milani	Plos One, 2015, 10: e0136551, 13 pages. DOI: 10.1371/journal.pone.0136551
4	Effects of hypothermically reduced plantar skin inputs on anticipatory and compensatory balance responses	Andresa M.C. Germano*, Daniel Schmidt, Thomas L. Milani	BMC Neuroscience, 2016, 17: 41, 14 pages. DOI: 10.1186/s12868-016-0279-2
5	Sensor-based systems for early detection of dementia (SENDA): a study protocol for a prospective cohort sequential study	Katrin Müller*, Stephanie Fröhlich, Andresa M.C. Germano, Jyothsna Kondragunta, Maria Fernanda del Carmen Agoitia Hurtado, Julian Rudisch, Daniel Schmidt, Gangolf Hirtz, Peter Stollmann, Claudia Voelcker-Rehage	BMC Neurology, 2020, 20: 84, 15 pages. DOI: 10.1186/s12883-020-01666-8

The first section of this work includes a general introduction, providing access to the overall topic of the thesis and highlighting its relevance (1.2 General introduction). A brief introduction to each of the five studies is presented, including key theoretical basics and references. This is to help the reader better understand the scientific questions that have emerged and shall be addressed in the main studies.
Sub-section 1.3, Theoretical background and literature, 1.3 Theoretical background and literaturepresents a brief theoretical and literature background, including a description of the human cutaneous receptors and their properties and function. This chapter also presents the basics of human balance regulation. These aspects are then linked to key literature on the topics mentioned above.

The second section presents the overall relevance and goals of this doctoral thesis (2.1), whereas a brief introduction is also provided to improve clarity and understanding. This is performed based on four of the five research studies integrated in this work. Finally, chapter 2.2 "Hypotheses of this thesis" summarizes the hypotheses of the present thesis.

Section 3 presents the four scientific papers implemented in this work (see table 1 above). The presentation of the four published papers is followed by a short section highlighting the logical connection between them.

Section 4 begins with a summary of the hypotheses (4.1 Summary of the hypotheses based on the study results) and is followed by a holistic discussion including the four scientific studies (4.2 General findings and discussion). An overall summary is also presented (4.3 Summary of this thesis). In section 5, perspectives and future directions are presented based on the results of the four studies conducted as part of this doctoral thesis. Study five plays an important role in emphasizing potential fields of application. This thesis concludes with the reference list from sections 1, 2, 4, and 5, the appendix, acknowledgements, the curriculum vitae, and the statement (e.g., of independence).

1.2 General introduction

The phrase "You are what you eat" is probably known to almost everyone. It was the German philosopher Ludwig Feuerbach who made this statement back in 1850. What about "You are what you feel"? In this regard, it is also well-known that sensing not only our own body but also our environment is essential for daily activities we experience and/or perform. The current importance of our senses becomes clear considering that the 2021 Nobel Prize in Physiology or Medicine was awarded to Ardem Patapoutian and David Julius for their work related to discoveries of cutaneous (skin) receptors for touch and temperature. This area of work still occupies scientific journals and public interest, and it will continue to do so in the future. Thanks to our wide range of senses and sensory organs, we receive (internal and external) afferent information from receptors, which are then transmitted toward the central nervous system (CNS) where they are processed accordingly. Consequently, we not only experience perceptions, but also perform various motor actions, both consciously and unconsciously.

Among the human senses, there are several (sub-)domains which contribute to a variety of motor actions executed by the skeletal muscles. Human posture and balance are two important components of these motor actions, that allow us to walk or stand without thinking about it. The sensory sub-domains contributing to human balance include the visual, vestibular, and somatosensory systems (Horak et al. 1990). The term "somatosensory system" includes several sensory sources, namely enteroception (sensory capacity of inner organs), proprioception (e.g., muscle spindles or Golgi tendon organs), and cutaneous sensitivity. The latter informs us about external stimuli touching the skin (Handwerker 2006), whereas plantar skin afferents (electrical signals stemming from mechanoreceptors located in the skin of the soot sole) play an important role in human posture and movement (Chua et al. 2002; Kennedy and Inglis 2002; Meyer et al. 2004). Thus, plantar sensitivity is of special importance within this doctoral thesis, as will be discussed in detail below.

The assessment of cutaneous sensitivity is an important research area in many ways. Prior to relating skin sensitivity to human posture and balance, learning about

the afferent nerve endings (receptors) innervating the skin is necessary, for example, to satisfy basic research questions. Such research is related to learning about fundamental properties of these receptors, for example, in terms of their functional and adaptation behavior (Wilska 1954; Bolanowski et al. 1994; Strzalkowski et al. 2017; Birznieks et al. 2019), spatial and temporal summation behavior (Bolanowski et al. 1994; Gescheider et al. 1999, 2002; Schmidt et al. 2020), electrochemical behavior (Ide and Saito 1980), or behavioral properties when applying varying external conditions (such as temperature variations (Inman and Peruzzi 1961; Schmidt et al. 2017; Alexander et al. 2019) or blood flow reductions (Schlee et al. 2009)). Thus, there are physiological aspects of research related to cutaneous sensors that are part of recent and current investigative activities.

One of these aspects is that assessing plantar vibratory sensitivity is usually performed with participants lying or sitting. As mentioned earlier, plantar sensitivity contributes to human posture and balance, but balance tests are usually performed when standing upright. Based on these postural differences, questions emerge, especially when considering the following two aspects: relatively early studies documented that sensory afferent signal processing can be altered by varying postures (Hayashi et al. 1992; Koceja et al. 1993; Mynark and Koceja 1997; Mildren et al. 2016). Balance-relevant sensory inputs stemming from plantar and other receptors (e.g. proprioceptors) are mediated by the posterior funiculus. It is therefore reasonable to assume that the net plantar sensory input changes, especially because different or additional sensory activity is likely to be required when standing compared to sitting. The second aspect is related to the fact that, in contrast to the findings by Hagander et al. (2000), other studies have shown that cutaneous sensitivity depends on the amount of vertical force the contactor probe exerts on the skin (Lowenthal et al. 1987; Cassella et al. 2000; Zippenfennig et al. 2021b). Based on these two aspects, it is unclear: a) whether the differences in vertical probe forces comparing sitting and standing might affect plantar sensitivity / information similarly; and b) whether the postures (standing versus sitting) might modulate subjective plantar sensory output differently. ***Study 1 "Plantar sensory vibration thresholds are not influenced by body position"*** was performed to answer these questions.

Outcomes from this study would benefit sensory-motor research, particularly in the context of balance tasks.

Another aspect of assessing plantar sensitivity, especially when analyzing vibration perception thresholds (VPTs), is related to a more methodological issue. VPTs constitute values often given in micrometers, whereas such data are collected on the so-called ratio scale. Such values naturally accumulate close to zero (without any negativity), e.g. in young and healthy populations with intact cutaneous sensitivity, with amplitude thresholds far below 1 µm (Schmidt et al. 2017, 2018). It is common for such ratio-scaled data to exhibit heteroscedasticity, which means that the amount of measurement error increases as the measured values increase (Nevill and Atkinson 1997; Atkinson and Nevill 1998). Interestingly, most (inferential) statistical tests, such as tests to detect bias or correlation analyses, should not be used on heteroscedastic data, as they usually do not account for heteroscedastic patterns (Atkinson and Nevill 1998). Consequently, their power and accuracy may be limited. In such cases, the data should not only be treated to allow the afore-mentioned tests, but it should also be investigated whether the treatment could eliminate or at least reduce heteroscedasticity. With respect to VPTs, it is unfortunate to note in the literature that in many cases such data are still analyzed as homoscedastic. Even if the treatment was performed, in other cases no further information is presented regarding its benefit and/or justification. VPTs are an important tool not only for purely basic research questions, but also for a clinically-therapeutic environment due to the link between cutaneous sensitivity and its effects on human balance capabilities (Chua et al. 2002; Kennedy and Inglis 2002; Meyer et al. 2004) or diseases (Drechsel et al. 2021; Zippenfennig et al. 2021a). The aim of this study was to provide an easy-to-follow example of how to solve the problems of homoscedastic data, particularly for environments, in which personnel with a limited statistical background might be involved. ***Study 2 "Subjective sensitivity data: Considerations to treat heteroscedasticity"*** was performed to address this. Results from this study have a basic positive impact on adequately interpreting heteroscedastic data.

As already mentioned, plantar skin sensitivity is one contributor to human posture and balance (Chua et al. 2002; Kennedy and Inglis 2002; Meyer et al. 2004). In

addition to other movement analyses systems, such as motion analysis or electromyography (EMG), force platforms are frequently used to assess human balance. A previous study suggests that quasi-static balance tasks (e.g., standing still on one or both legs) might be less useful to determine balance strategies (Vrieling et al. 2008). In addition, such quasi-static tests do not appear to be a good representative for assessing functional postural control (Taube et al. 2014). Hence, investigating dynamic balance (e.g., standing on moveable platforms allowing unexpected perturbations) is appealing. The Posturomed device (Haider Bioswing GmbH, Germany) allows such investigations. We modified the Posturomed by implementing an electro-magnet which enabled the entire bottom platform to be deflected, thereby allowing unexpected perturbations. However, the Posturomed is also known as a (rehabilitative) training device (Kramer et al. 2014). Therefore, methodological questions arise, such as whether learning effects occur when performing balance tests on the Posturomed. Such knowledge is essential, as there is a growing requirement for reliable balance assessment methods (Bower et al. 2014), particularly with regard to dynamic balance. ***Study 3 "Aspects of Dynamic Balance Responses: Inter- and Intra-Day Reliability"*** was performed to address the lack of literature, particularly in terms of initial dynamic balance responses following unexpected perturbations. Such an investigation constitutes a key prerequisite for conducting research on human balance capabilities.

The direct connection between plantar inputs and human balance (Chua et al. 2002; Kennedy and Inglis 2002; Meyer et al. 2004) is the basis for an additional aspect. This connection becomes evident in clinical settings, as patients suffering from diseases like diabetic neuropathy, for example, usually exhibit impaired plantar sensitivity (Simmons et al. 1997; Drechsel et al. 2021; Zippenfennig et al. 2021a). It has even been shown that vibratory plantar sensitivity constitutes a suitable tool to predict the occurrence of neuropathic foot ulceration (Young et al. 1994). However, there is still debate about the extent to which plantar afferents contribute to human balance, in both healthy and diseased populations. The reason is that investigating the special role of plantar afferents on human balance requires the isolation of their function without affecting other sensory systems (e.g., proprioceptors located in the foot). Only then can effects on balance performance be attributed solely to altered

plantar afferent activity. However, when considering diseased populations, such as patients with diabetic neuropathy, the multifactorial nature of the disease means that not only plantar afferents are affected (Taylor et al. 2004). Hence, various "artificial" and acute sensory manipulation approaches and interventions have been developed solely to diminish plantar receptor activity. However, these reveal (methodological) limitations in some instances. For example, submerging the feet in ice water (hypothermia) or applying ischemia likely result in an interaction of other than merely plantar afferent inputs. In particular, balance tests performed after a hypothermic intervention are usually performed on force platforms. However, these are not temperature-controlled in many cases, hence, a quick re-warming of the tissue is likely, preventing the maintenance of the hypothermically diminished receptor activity level. Of course, this might also mask important effects. ***Study 4 "Effects of hypothermically reduced plantar skin inputs on anticipatory and compensatory balance responses"*** was conducted to address these limitations. The results of this study will help to better understand this relationship and minimize potential methodological limitations that would bias or distort such relationships.

Assessing plantar sensitivity is an important and fundamental tool in related science. As mentioned above, VPTs may be used to identify peripheral neuropathy (Inglis et al. 1994), or even to predict neuropathic foot ulceration (Young et al. 1994). Additionally, it has been shown that plantar sensitivity is decreased in Morbus parkinson patients (Prätorius et al. 2003). The assessment of VPTs is also the subject of recent anthropological studies (Holowka et al. 2019). However, cutaneous sensitivity also plays a growing role in areas not generally considered. The key words here are cognitive disorders and (pre-stages of) dementia, which are a major part of Section 5 "Perspectives and future directions". Dementia is one form of such cognitive disorders representing a neurodegenerative disease, in which important cerebral functions are lost as the disease progresses (Sütterlin et al. 2011). It is well-known that dementia causes deterioration in the cognitive domain, referring to memory, attention, or executive functions, for example (American Psychiatric Association 2013). Mild cognitive impairment (MCI) is considered an in-between or potential pre-stage between changes occurring during the normal aging process and

dementia (Petersen and Negash 2008), with a 10-fold likelihood of developing dementia later in life (Petersen 2011).

Since dementia is not curable, early diagnosis is essential. This also becomes evident as early interventions were shown to slow down disease progression (Hansen et al. 2008; Groot et al. 2016). Interestingly, studies have also shown that dementia exhibits non-cognitive symptoms, which might even be present prior to the onset of the generally accepted cognitive symptoms (Raudino 2013), as commonly assessed via questionnaires. In fact, anatomical structures associated with the processing of e.g. cutaneous sensitivity are affected in dementia or MCI (Rapoport 1991; Doran et al. 2003; Dugger et al. 2013) and the tolerance to cutaneous pain was shown to be changed in dementia patients with Alzheimer (Benedetti et al. 1999). Additionally, quasi-static balance was already proven to be a prodromal marker for dementia (Bahureksa et al. 2017), and certain gait variables foster the differentiation between healthy controls and MCI patients (Bahureksa et al. 2017; Belghali et al. 2017). Note that there is almost no literature investigating cutaneous vibratory sensitivity and dynamic balance performance in cognitively impaired populations. Therefore, ***Study 5 "Sensor-based systems for early detection of dementia (SENDA): a study protocol for a prospective cohort sequential study"*** was included in this doctoral thesis. Due to its innovative character, Study 5 is part of the conclusion and future work section, as it aims to vividly demonstrate how assessing sensory-motor data (cutaneous sensitivity and motor tasks, e.g., quasi-static and dynamic balance) can be implemented in concrete clinical research settings with a significant socio-cultural and demographic role. Preliminary results of current research associated with this aspect and future directions are also part of section 5 (Perspectives and future directions).

1.3 Theoretical background and literature

In this section, theoretical information and literature are presented to mediate appropriate knowledge to better prepare the reader for the studies presented in Section 3. A major issue presented within this sub-section is the cutaneous mechanoreceptors as part of the somatosensory system. As this is a cumulative thesis nature, and as each of the studies presented already contains information on theoretical background and literature, Section 1.3 deliberately provides a very brief and general overview without yielding an overly extensive design.

1.3.1 The somatosensory system

The human somatosensory system is complex and contains several sensory sub-systems. Per definition, the somatosensory system is composed of the cutaneous sensory system (ecteroception), the sensory system of the locomotor system (proprioception), and the sensory system of the inner organs (enteroception). The sensory organs located in the head associated with vision, flavor, audition, olfaction, and balance (vestibular organs) are not part of the somatosensory system (Handwerker 2006). The somatosensory array is responsible for the detection of various qualities, namely touch, proprioception, temperatures, and pain (Fahlbusch 2006). Two sub-systems of the somatosensory system are presented below, with a focus on cutaneous mechanoreceptors. Please note that enteroception will not be part of this section, as its role in the current thesis is negligible.

1.3.1.1 The proprioceptive system

The term proprioception describes the ability of the body to self-perceive. This allows us to perceive not only how our limbs are oriented to each other or in reference to the environment, but also how much muscular effort is actually present or necessary to overcome certain burdens, such as pulling a sleigh. The first step for this is the registration of the (mechanical) stimulus by proprioceptive mechanoreceptors, which are mainly located in the muscles, tendons, joint structures, or fascia, for example. There are three major receptor types associated with proprioception: muscle

spindles, Golgi tendon organs, and receptors located in joints and ligaments. It should also be noted here that the vestibular organs are also part of the proprioceptive system (Zalpour 2006), but they will not be presented here.

1.3.1.1.1 Muscle spindles

Muscle spindles are located within spindle-like capsules of connective tissue, parallel to the skeletal muscles (extrafusal fibers), see Figure 1. Muscle spindle fibers (intrafusal fibers) are present in two major types: nuclear bag fibers and nuclear chain fibers. These fibers are innervated by a) afferent (sensory) fibers to allow high sensitivity when the extrafusal muscle is stretched/lengthened (type Ia and II afferents, alternatively named 1° and 2° or primary and secondary endings, resp.), and by b) motor (efferent) fibers, which allow a shortening of the muscle spindle fibers (induced by gamma (γ)-motoneurons). When the muscle is stretched, the afferent signals travel toward the CNS and elicit an efferent response to contract the extrafusal muscle tissue via alpha (α)-motoneurons located in the anterior horn of the spinal cord. Due to the so-called α-γ-co-activation, γ-motoneurons (also located in the anterior horn) are simultaneously activated. This causes an identical shortening of the extrafusal and intrafusal fibers to match the reduced length of the extrafusal fibers due to the alpha-motoneuronal drive. This equilibrium allows an optimal sensitivity of the muscle spindles. This is an important prerequisite to enable afferent spindle signals to fire even at the slightest amounts of muscle stretch. These stretch reflexes play an important role in protecting the muscle from possible damage due to overstretching. Because of this and other reflex pathways, muscle spindles also play an important role in human posture, locomotion, coordination, and balance control (Weiß and Ullmann 2003; Premkumar 2004; Zalpour 2006; Müller-Wohlfahrt et al. 2010; Guyton and Hall 2011).

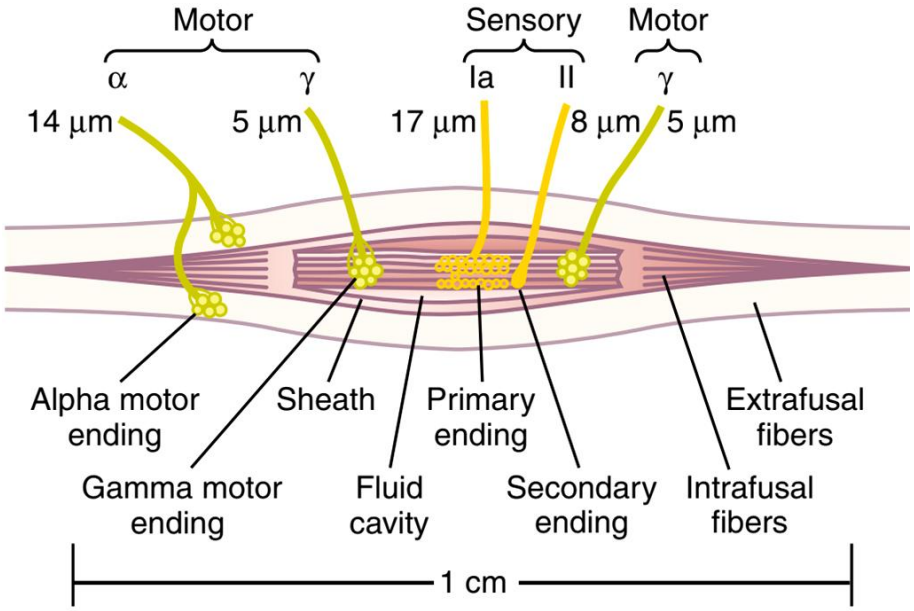

Figure 1: Illustration of the structure of a muscle spindle (from Guyton & Hall, 2011, p. 656).

1.3.1.1.2 Golgi tendon organs

These encapsulated organs are located in the transition zone between the skeletal muscle and tendon tissue, see Figure 2. They constitute a receptor with afferent fibers (type Ib afferents) registering tension and stress which is actively and/or passively exerted from the muscle fibers via the tendon toward the bone. In contrast to muscle spindles, Golgi tendon organs do not possess efferent innervations. In case of activations at high stimuli intensities, afferent signals cause the agonist muscle to relax and the antagonist muscle to contract to protect the agonist muscle from potential overload and tissue damage (Zalpour 2006). However, there are also other important functions associated with these organs at low and intermediate stimuli intensities. Due to their convergence at the spinal cord inter-neuronal level (which in turn modulates the activity pattern of alpha-motoneurons), Golgi tendon organs also contribute to force and stance regulation, for example during locomotion (Deetjen et al. 2004).

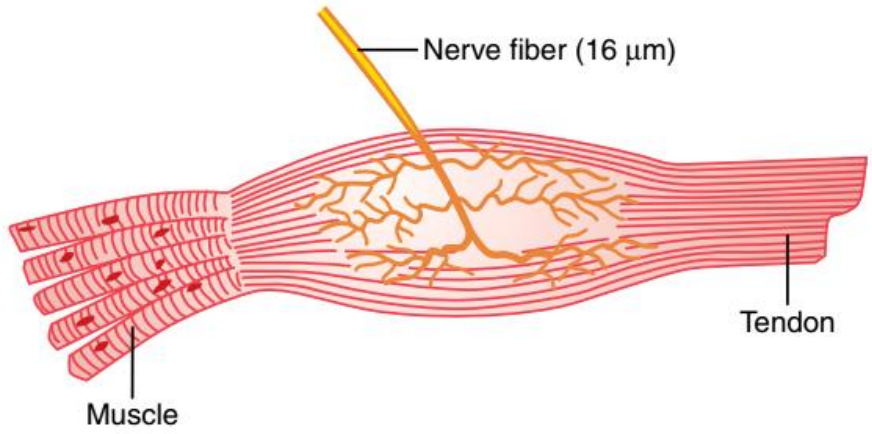

Figure 2: Illustration of the Golgi tendon organ (from: Guyton & Hall, 2011, p. 661).

1.3.1.1.3 Joint and ligament receptors

Receptors located in joints and ligaments are, in terms of their structure and function, similar to cutaneous mechanoreceptors. There are four receptor sub-types described in the literature (see Figure 3): type I constitutes small receptors. They are similar to Ruffini corpuscles, as they are sensitive to stretch. Furthermore, type I exhibits thin but myelinated afferent fibers, and slow adapting behavior. Type I units are present in the anterior cruciate ligament, menisci, and the external joint capsule. Type II is described as being larger with thicker myelinated afferent fibers and fast adaptation behavior. Hence, type II receptors show similarities to the Vater-Pacini corpuscle. Type II are found in the anterior cruciate ligament, the internal joint capsule, or in the menisci. They are sensitive to general movements, particularly to quick position changes. Type III receptors are made of a thick and myelinated afferent tissue, responding at high stress thresholds similar to the Golgi tendon organs with slow adaptation behavior. Their functional role is to protect the organism from potential tissue damage. Type III is located in ligaments or tendon insertions. The last type (IV) refers to unencapsulated, free nerve endings with unmyelinated afferents and slow adaptation behavior. They are usually far more active in extreme joint positions compared to normal, physiological angles. This receptor type is located in structures associated with fibrous joint capsules, and their role is to mediate pain (Sheperd 1993; Häfelinger and Schuba 2002).

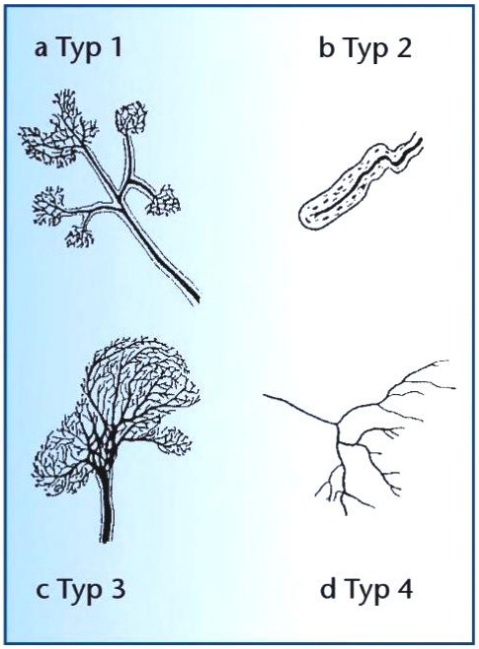

Figure 3: Illustration of the four types (type 1-4) of joint receptors as shown in Häfelinger and Schuba (2002), p. 34.

1.3.1.2 Cutaneous mechanoreceptors

With a surface of about 1.6 - 2 square meters, skin is the largest organ of the human body (Rassner 2002). In addition to its sensory tasks, skin fulfills numerous other functions, such as protecting against radiation, evaporation/dehydration, or heat loss. This section focuses on cutaneous mechanoreceptors.

Cutaneous mechanoreceptors constitute specialized structures (an overview can be found in Figure 4 and Figure 5) registering mechanical stimuli, such as pressure and/or vibrations. They represent the "first step" within the physiological process of the perception of external cutaneous mechanical stimuli. In addition to other sensory systems (e.g. proprioceptors), cutaneous mechanoreceptors are important to recognize the environment and to support motor actions by providing sensory afferent information and feedback. As this thesis deals with mechanoreceptors located in the foot sole (glabrous plantar skin), the focus of the subsequent paragraphs will be on four types of plantar mechanoreceptors and their basic properties, namely Vater-Pacini corpuscles, Meissner corpuscles, Merkel discs, and Ruffini endings.

RECEPTOR	RECEPTOR TYPE	FIELD DIAMETER	POSITION IN THE SKIN	FUNCTION OR PERCEPTION
Meissner's corpuscle	FA	small (I)	Dermis: Stratum papillare	Touch and vibration (20-50Hz)
Merkel cell	SA	small (I)	Epidermis: Stratum basale	Pressure
Pacinian corpuscle	FA	large (II)	Dermis: Deep layer and tela subcutanea	Pressure and vibration (approx. 250Hz)
Ruffini corpuscle	SA	large (II)	Dermis: Stratum reticulare	Pressure, Stretching

Figure 4: Brief overview of the properties of cutaneous mechanoreceptors. Modified from Schneider (2006) and Speckmann, Hescheler, and Köhling (2008).

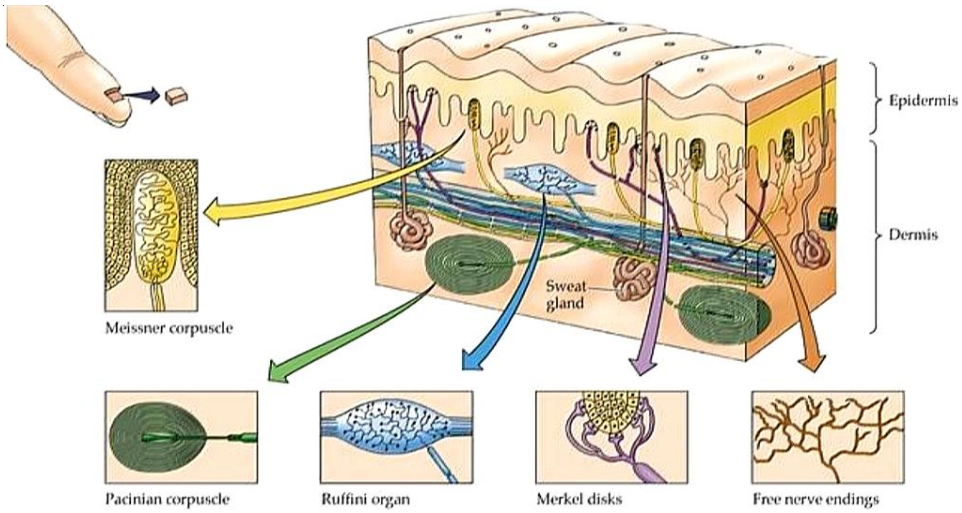

Figure 5: Overview of receptors located in the glabrous skin, here the finger tip. Modified by Purves et al. (2001).

1.3.1.2.1 Vater-Pacini corpuscles

These mechanoreceptors exhibit an onion-like structure with a size of up to 5 mm (Latash 1998). In glabrous skin, these receptors are located in deep regions of the sub-cutis. They are innervated by Aß-axons, are fast adapting type II (FAII) and exhibit large receptive fields (Sheperd 1993). The optimal mechanical stimulus (vibrations) to elicit afferent discharge activity from Vater-Pacini corpuscles was at a frequency of approx. 200 Hz (Strzalkowski et al. 2017). However, the same study also found activity at frequencies of 30 Hz and even lower. Finally, Birznieks et al. (2019) found that vibrations as low as 6 Hz at the fingertips resulted in an actual perception of these vibratory stimuli, apparently mediated by the FAII system.

1.3.1.2.2 Meissner corpuscles

Meissner corpuscles are round or egg-shaped and located at the border between the dermis and epidermis of glabrous skin. Their adaptation behavior is fast (fast adapting type I, FAI), their afferent innervation is type Aß, and their receptive fields are small with sharp boundaries enabling a high spatial resolution capability, which is essential to provide feedback when palpating items using the fingertips. Their optimal frequency range is between 30-40 Hz, which usually occurs when palpating with the fingers (Sheperd 1993; Handwerker 2006; Zalpour 2006).

1.3.1.2.3 Merkel discs

These mechanoreceptors are disc-shaped and are located at the border between the dermis and the epidermis of glabrous skin. They adapt slowly (slow adapting type I, SAI) and therefore continue to fire when the stimulus is constant and long-lasting. Merkel discs are sensitive to vertical deformation (pressure) and register the depth as well as the duration of an indentation. Likewise, their afferent innervations constitute thick, myelinated Aß fibers and their receptive fields are small with sharp borders (Sheperd 1993; Latash 1998; Zalpour 2006).

1.3.1.2.4 Ruffini endings

Ruffini endings exhibit a spindle or piston-shaped structure and are located in upper dermis regions. Their adaptation behavior is slow (slow adapting type II, SAII), their receptive fields are large with vague boundaries, and they have type Aß afferent innervations. Ruffini endings are sensitive to pressure and stretch (Sheperd 1993; Birbaumer and Schmidt 2003).

The next section presents a brief overview of the cutaneous mechanoreceptors, and the afferent signal transmission toward the central nervous system.

1.3.1.2.5 Afferent pathways of cutaneous mechanoreceptors

All four cutaneous mechanoreceptors described above are innervated by large-diameter (myelinated), type Aß fibers. These exhibit a thickness of 6-12 µm, with a transmission velocity of 30-70 m/s (Sheperd 1993). The first-order afferent neuron is located in the dorsal root ganglion with afferent inputs from the cutaneous receptors, transmitting these toward the spinal cord by entering the dorsal horn. For cutaneous

mechanoreceptors, but also for proprioceptors, the corresponding pathway is called the dorsal column medial lemniscal (DCML) pathway. After entering the spinal cord, signals are transmitted toward the brain stem (Medulla oblongata) via the Funiculus dorsalis. In the Medulla oblongata, signals are switched to the second-order afferent neuron with subsequent transmission toward the contra-lateral side. The next target region is the thalamus (via the Lemniscus medialis). In the thalamus, third-order neurons are targeted that are located in the Nucleus ventralis persterior thalami. The primary somatosensory cortex (located within the parietal lobe) is targetet via the Capsula interna network (Schneider and Fink 2007).

The somatosensory system contains three regions involved in afferent processing of (cutaneous) mechanoreceptors and other inputs: the Gyrus postcentralis (containing the primary somatosensory cortex), the secondary somatosensory cortex, and the posterior parietal cortex (Schneider and Fink 2007). These three regions are highly interlinked. The posterior parietal cortex in particular is responsible for processing various afferent information at the highest cortical level, and is responsible for integration processes to allow perception. It is also active when planning, executing, and controlling motor actions, and with regard to higher cognitive processes (Schneider and Fink 2007). Finally, this region represents the first station in which sensory inputs begin transformation into an actual movement plan. There are signal transmissions toward the pre-motor cortex (located in the frontal lobe), which in turn target the primary motor cortex located in the Gyrus precentralis of the frontal lobe. The primary motor cortex targets alpha-motoneurons in the anterior horn of the spinal cord which finally innervate skeletal musculature (Fahlbusch 2006).

The next section contains a brief summary including relevant literature on the occurrence of mechanoreceptors in certain glabrous skin areas, with a focus on plantar aspects.

1.3.1.2.6 Plantar cutaneous mechanoreceptors

As the present thesis includes work focusing on cutaneous mechanoreceptors located in the foot sole (mainly Studies 1, 2, and 4), it is essential to provide a brief overview of these receptors in terms of their properties.

One frequently cited study (Kennedy and Inglis 2002) examines plantar mechanoreceptors in 13 healthy individuals using a microneurographic approach. Tungsten microelectrodes were inserted into the tibial nerve (participants lying prone) to record afferent signals stemming from the corresponding cutaneous receptors. The signals were evoked by vertical pressure from filaments (Kennedy and Inglis 2002). Considering the entire plantar aspect of the foot, 104 single-unit recordings related to cutaneous mechanoreceptors were identified. Of these, 14% were associated with SAI units, 15% with SAII units, 14% with FAII units, and 57% with FAI units. The distribution of the corresponding receptive fields of these mechanoreceptors is depicted in Figure 6.

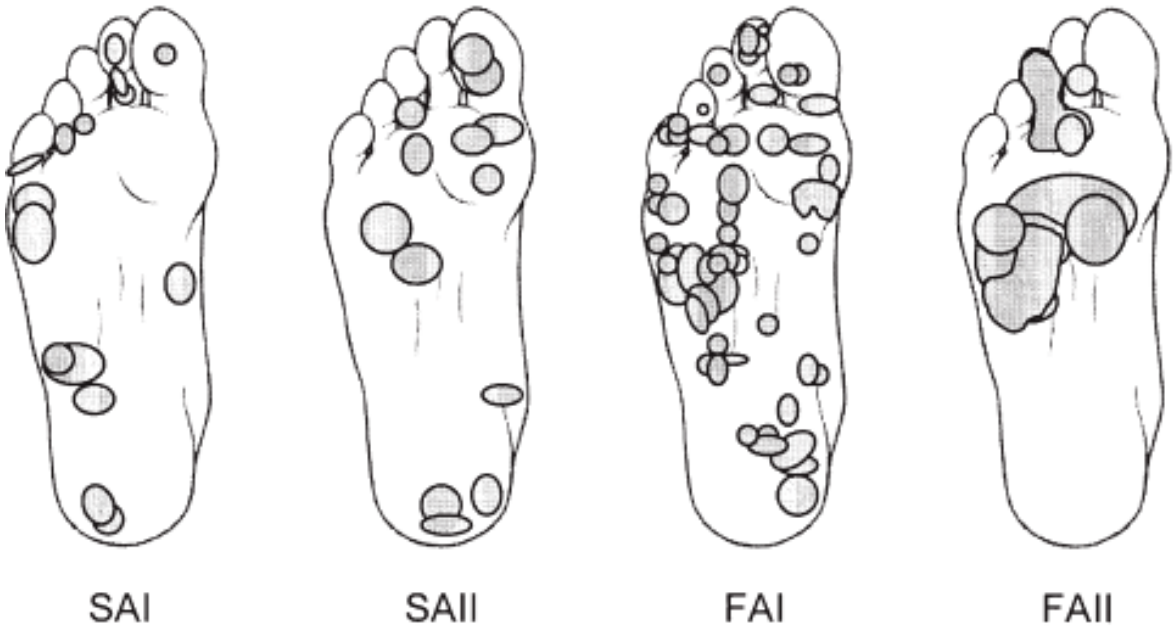

Figure 6: Illustration of the receptive fields of the mechanoreceptors located in the plantar aspect of the foot, modified from Kennedy and Inglis (2002).

Another study found similar results considering relative comparisons: Of 102 plantar afferents successfully identified, 20 % corresponded to SAI, 20 % to SAII, 13 % to FAII, and 47 % to FAI (Strzalkowski et al. 2015). Using vibrational stimuli (3-250 Hz at varying amplitudes) at the plantar foot, another study found slightly different absolute numbers of afferent classes: Of 52 identified afferents (clearly less than in the previous two studies), 27 % corresponded to SAI, 19 % to SAII, 17 % to FAII, and 37 % to FAI afferents (Strzalkowski et al. 2017). Another investigation also confirmed the (relative) ratio between the four plantar afferent unit channels, especially the predominance of FA (particularly FAII) units (Strzalkowski et al. 2018).

Another interesting question regarding these plantar mechanosensitive units is of course whether there is a certain pattern of receptor distribution. In general, there seems to be a proximal-to-distal and a medial-to-lateral increase of plantar innervation densities, especially for FAI units (Viseux 2020). A graphical overview is provided in Figure 7.

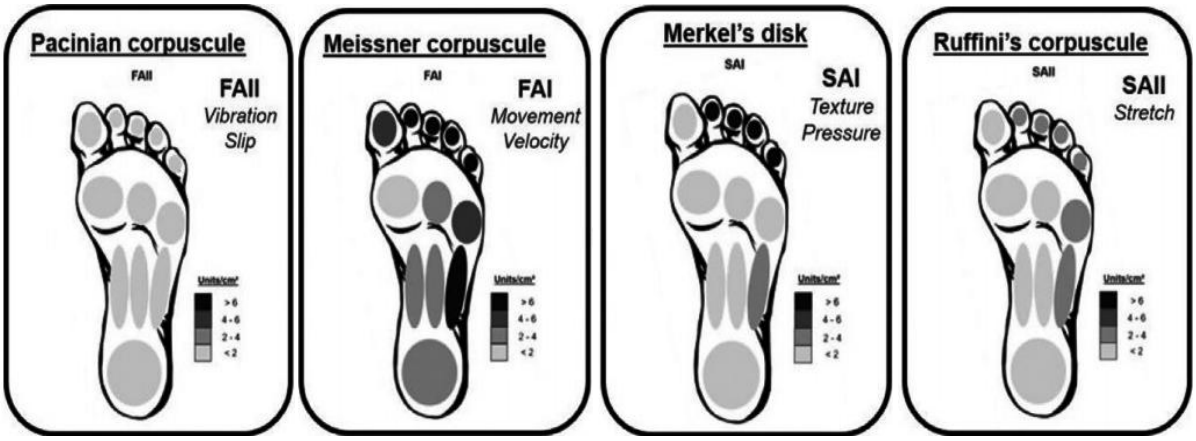

Figure 7: Organization of plantar mechanoreceptors with respect to their density (units/cm^2) distribution. There are four scaling divisions from black to light grey: >6, 4-6, 2-4, and <2 units/cm^2. Modified, from Viseux (2020).

Another study investigated the presence of plantar mechanoreceptors in a different fashion. Following amputation of the lower leg limb of two patients, histological specimens of the foot soles were investigated using an optical microscope (Schneider 2006). In contrast to Kennedy and Inglis (2002), the study performed by

Schneider (2006) was not able to identify Ruffini corpuscles (corresponding to the SAII system). Furthermore, there were 1.171 Meissner (FAI system) and 393 Pacini corpuscles (FAII) found in the entire foot sole (Schneider 2006). One possible explanation for these quantitative differences is that the stimulus probes (filaments) used by Kennedy and Inglis (2002) might simply have been too large to elicit just a single cutaneous mechanoreceptor (Schneider 2006). Furthermore, Merkel discs aligned in neighboring groups may be innervated by one single axon (Latash 1998). Hence, a quantitative underestimation of Merkel receptors seems possible. On the other hand, the cutting procedures (cutaneous cutting distance: 1 mm) used by Schneider (2006) may have limited the informative value of the absolute numbers of mechanoreceptors in his work.

Based on these considerations, a direct comparison between microneurographic and histological studies remains complicated. Therefore, the question of how many receptors the human foot sole actually hosts is difficult to answer and conclusions should be drawn with these circumstances in mind. Despite this, the above-mentioned studies reveal interesting insights and commonalities, such as the predominance of fast adapting units (particularly FAI) located in the human foot sole.

1.3.1.2.7 Factors influencing cutaneous mechanosensitivity

Assessing cutaneous sensitivity is of great importance in Studies 1, 2, and 4 of this thesis. Two main influencing factors were identified: the vertical force the vibrating contactor exerts toward the skin, and the skin temperature at which VPTs are assessed. Hence, a brief overview of literature focusing on these two factors is provided below to better prepare the reader for the rationale of the corresponding studies.

Vertical contactor force

The effect of varying vertical contactor forces on VPTs has been the subject of numerous investigations. The majority of such studies confirms that VPTs decrease with higher vertical contactor forces (e.g. Lowenthal et al. 1987; Cassella et al. 2000; Zippenfennig et al. 2021b), which corresponds to an improvement of vibrotactile sensitivity. These studies include various body parts (glabrous and hairy skin) and

various vibration frequencies. Similarly, Gu and Griffin (2012) found decreased plantar VPTs when increasing the surround / contactor force, albeit this was described as merely a trend. Era and Hänninen (1987) also found an effect of vertical forces on vibratory sensitivity, however, only at the lowest frequencies. Interestingly, the effect of improved sensitivity following an increase of vertical contactor forces was also confirmed in terms of proprioceptive perception (Ferrari et al. 2019). Vibrations applied to the muscles and tendons are known to result in illusions of movement. The minimum stimulation amplitude necessary to elicit such illusional perceptions was shown to be dependent on the pre-determined vertical force level (Ferrari et al. 2019).

In contrast, Hagander et al. (2000) found no relevant differences of VPTs at the index finger and great toe when testing over a band of probe pressures (30 and 50 g/1.22 cm^2). Another study found similar results, however, the same study also proposed that equal cutaneous sensitivity might not be given at very low and very high contactor forces (Gregg 1987).

In summary, the vertical contact force is likely to play an important role when assessing cutaneous sensitivity. Hence, it should be integrated and controlled in such measurements. In this thesis, the central research question of Study 1 is based on these considerations. However, an extension toward a novel research question (comparison between two postures with high and low contact forces) is presented.

Skin temperature

Similar to vertical contact force, skin temperature is also an important factor that is widely investigated in relation to the assessment of cutaneous sensitivity.

Most scientific publications confirm that skin temperature affects subjective sensitivity in such a way that increasing temperatures are associated with improved sensitivity and decreasing temperatures lead to a deterioration of cutaneous sensitivity (Nurse and Nigg 2001; McKeon and Hertel 2007a, 2007b; Schlee et al. 2009b; Germano et al. 2016b; Schmidt et al. 2017). However, also with regard to an early processing stage of vibratory stimuli (at the receptor and afferent nerve level), it has been shown that cooling the skin results in a decreased afferent firing response (Lowrey et al.

2013). Interestingly, another investigation also found a negative effect of skin cooling on cutaneous sensitivity (pressure sensitivity) at hairy skin locations around the knee (Alexander et al. 2019). These temperature-dependent effects can mainly be explained by the activity level of enzymes, which are also temperature-dependent (Ide and Saito 1980), and by processes related to properties of receptor potentials (Inman and Peruzzi 1961).

However, there are also a few reports of only weak or no effects of temperature changes on subjective sensitivity (Gerr and Letz 1994; Thyagarajan and Dyck 1994), or with contradictory outcomes in a sense of deteriorated sensitivity following skin warming (Meh and Denislic 1995). Some possible limitations regarding previous studies include, for example, the study by Gerr and Letz (1994), which did not alter skin temperatures to investigate effects on sensitivity. In their study, skin temperature was a co-variable integrated into the statistical analyses using general linear models. Second, testing frequency and anatomical locations used must also be considered. In some cases, these were quite different from the parameters used in the studies mentioned in the previous paragraph. Other potential limitations include that cooling (and subsequent sensory testing) was sometimes administered directly prior to warming the skin (Thyagarajan and Dyck 1994). This approach could be problematic, as sensory capabilities persisted even after re-warming close to the initial baseline temperature occurred (Kunesch et al. 1987).

In conclusion, although some investigations have contrary findings, the general understanding is that skin temperature affects cutaneous vibratory sensitivity and therefore should be controlled. Study 4 of this thesis investigates the relationship between plantar afferent inputs and human balance (Chua et al. 2002; Kennedy and Inglis 2002; Meyer et al. 2004) in further detail.

1.3.2 Human balance

The term "human balance" is symbolic of the fascinating and complex motor capabilities of the human body. This subsection provides basic information with regard to Study 3 and 4.

1.3.2.1 Definitions of the term balance

The general definition of the balance of forces (or an equilibrium of forces) says that balance is given when the sum of all acting forces and torques toward a body or object equal zero. Subsequently, the object is either not moving or maintains its current and constant movement (Zalpour 2006). In terms of upright human posture in particular, balance is described as those cases in which the vertical projection of the center of mass is located within the area of support (Latash 1998). The area of support may be larger or smaller, which challenges the postural system to a greater or smaller extent, respectively. A large area of support is provided when standing on both feet, shoulder-width apart. In this case, the area of support corresponds to the surface underneath the feet plus the area between both feet. In contrast, when standing on one foot on a narrow beam, the area of support is as small as the surface of the beam covered by the foot.

Human balance may be classified into two categories: quasi-static balance and dynamic balance. The former is defined as a relative resting position of the human body (Meinel and Schnabel 2007; Baumhoer 2010). This includes activities such as standing upright, standing and leaning forward, brushing the teeth, or having a shower, for example (Knuchel and Schädler 2004). The term static balance is sometimes used instead of quasi-static balance. However, this view is too simplistic, as small oscillations and movements always occur when standing upright (Nigg et al. 2000). Hence, the term quasi-static balance is appropriate (Chow et al. 1999). The motor actions executed during quasi-static balance conditions are corrective in nature. Displacement of the body´s center of gravity is controlled and kept in equilibrium via muscular activities (Knuchel and Schädler 2004).
In contrast, dynamic balance is described as the condition in which the body leaves its position; in other words, the body is in movement but balance is maintained

(Baumann and Reim 1989). Such movements are, for example, larger-scaled positional changes, rotations of the body (Meinel and Schnabel 2007), or simple locomotion like walking (Baumhoer 2010). What these all have in common is that the current position is left so that balance must be continually re-established (Ackermann and Oswald 2009). The corresponding motor actions are protective in nature (Knuchel and Schädler 2004). After the balance system is disturbed (e.g. a jostle while standing), protective measures become active by innervating muscles generating a stepping reaction to maintain balance. Without this muscular activity and stepping reaction, balance would be lost and a fall might occur.

1.3.2.2 Anticipatory and compensatory balance responses

After providing a general understanding of what defines human balance, the focus will now be on the two main strategies of how the human body maintains or re-establishes (e.g. dynamic) balance. Both strategies aim to keep or re-position the vertical projection of the center of mass within the area of the base of support (Latash 1998). They are known as anticipatory and compensatory balance responses and constitute two different mechanisms of postural strategies (Latash 1998; Santos et al. 2010).

The following example might be adequate to explain anticipatory balance responses (or activity). Let us imagine a passenger standing in a bus that is approaching the next bus station. After the bus stops, the passenger already knows that the bus will start driving again in a moment, hence, inducing an external perturbation. In this situation, the passenger might grasp a bus holder and/or might widen the standing width to enlarge the area of the base of support. All of these actions aim to be better prepared for the upcoming perturbation, that is, to minimize its destabilizing effect (Santos et al. 2010). Of course, the anticipatory activity may also affect the type and intensity of compensatory responses (Santos et al. 2010). These anticipatory actions are accessed prior to the actual perturbation and induce muscular pre-activations (Santos et al. 2010).

Compensatory actions are executed when anticipatory activities are found to have been incorrect or insufficient (Latash 1998), meaning that balance is at risk or even

lost when the bus starts moving again. These actions occur after the perturbation onset and are a direct consequence of the perturbation. These motor responses often activate pre-programmed reactions causing muscular responses after a certain latency. The resulting reflex-like, muscular activity aims to re-establish balance (Latash 1998; Patel and Bhatt 2015). The origin of such motor activities lies in the various human sensory systems which register a balance perturbation (Park et al. 2004; Alexandrov et al. 2005).

With respect to the sensory systems contributing to human posture and balance, the following subsection provides a brief summary of the particular role of plantar cutaneous inputs.

1.3.2.3 Human balance: the role of plantar cutaneous inputs

As previously mentioned, several sensory systems contribute to human balance. These include visual, vestibular, and somatosensory cues (Horak et al. 1990; Kavounoudias et al. 1998). In particular, Study 4 focuses on the influence of plantar cutaneous mechanoreceptors (as a part of the somatosensory system, see 1.3.1.2 Cutaneous mechanoreceptors) on human balance.

Diseases like diabetes or a diabetes-associated peripheral neuropathy are known to diminish plantar sensitivity (Goddard et al. 2018; Lindholm et al. 2019; Zippenfennig et al. 2021a) and balance capabilities (Akbari et al. 2012; Ghanavati et al. 2012; Ernandes et al. 2020; Thukral et al. 2021). However, such populations are not adequate to investigate the isolated role of plantar afferent inputs on human balance. This is because such diseases usually negatively affect other sensory or anatomical domains, which in turn also affect posture and balance. For example, diabetes-associated peripheral neuropathy is multi-factorial: many structures of the peripheral nervous system are affected, which can lead to far-reaching consequences such as joint immobility or foot deformations (Taylor et al. 2004). Hence, it is necessary to “isolate” the various levels of plantar cutaneous activity and observe their effects and contribution to human balance.

To achieve this, various manipulation approaches are used to reduce plantar afferent activity. These include, for example, anesthesia, ischemia, or cooling procedures (Perry et al. 2000; Eils et al. 2002; Schlee et al. 2009a, 2009b). With regard to hypothermic treatments, the foot is mainly cooled via ice or ice pads (Nurse and Nigg 2001; Hong et al. 2007; Schlee et al. 2009b), cooled water immersion (Yasuda et al. 1999; Perry et al. 2000; Eils et al. 2002; McKeon and Hertel 2007a; Billot et al. 2013), or cooling platforms (Germano et al. 2018; Germano et al. 2016). It is generally accepted that diminished plantar sensory activity induced by hypothermic treatment results in an impaired balance or postural performance (Magnusson et al. 1990; Yasuda et al. 1999; Nurse and Nigg 2001; Hong et al. 2007; McKeon and Hertel 2007a, 2007b; Germano et al. 2018). This was also confirmed in a more recent study, in which no acute (plantar hypothermic) treatment was performed, but impaired plantar sensitivity clearly resulted in poorer physical function of the lower extremity (Santos et al. 2021). Similarly, it has been shown that elderly participants shift their plantar pressure toward more sensitive regions of the foot sole during upright standing, which constitutes a balance strategy (Machado et al. 2016).

However, some nuances must be considered. For example, not all parameters and/or conditions investigated in publications necessarily show the same behavior following (plantar) hypothermia. In one study, for example, hypothermic effects were only evident during the first trial of the balance tests (Billot et al. 2013). In another study, hypothermic effects were only evident under more challenging balance tasks, and not when performing double leg stance with the eyes open (McKeon and Hertel 2007a). It was also reported that plantar hypothermia did not affect balance performance in young adults (Machado et al. 2017).

In addition to these considerations, some of the above-mentioned protocols and studies may also exhibit further limitations: when not exclusively cooling the foot soles, other sensory systems are likely to be co-affected. Furthermore, body parts quickly re-warm once the hypothermic treatment has stopped. Therefore, subsequent data collection performed on (non-tempered) force platforms, for example, may exhibit limitations. All of these aspects constitute the basis for conducting Study 4, which was published in 2016. In a more recent paper, we were able to confirm that

balance tests performed without permanent plantar hypothermic control result in fading effects (Germano et al. 2018). This complements the comments above referencing the studies by Billot et al. (2013) or McKeon and Hertel (2007a).

Section 2 - Relevance, goals, and hypotheses

2.1 Relevance and goals of this thesis

To provide better access to the hypotheses listed in 2.2, the relevance and objectives of this work shall be briefly described again.

Assessing (plantar) vibratory sensitivity is a fundamental scientific tool in many aspects, especially when it comes to its sensory contribution to motor performance, e.g. in clinical settings (Young et al. 1994; Simmons et al. 1997). In Study 1, we refer to the fact that plantar sensitivity measurements are usually taken during sitting, while balance tests are usually performed in a standing position. It is unclear, however, whether different postures modulate the cutaneous sensitivity differently, for example. Hence, the overall ***goal of Study 1 was to compare vibration perception thresholds (VPTs, as an indicator of cutaneous vibratory sensitivity) assessed in standing versus sitting postures***.

Following assessment of VPTs, data must be analyzed appropriately. Such data exhibit an increased likelihood of heteroscedasticity, meaning that there is an increased error rate as the magnitude of the values increases (Nevill and Atkinson 1997; Atkinson and Nevill 1998). Since heteroscedastic data should not be analyzed with most (inferential) statistical tests (Atkinson and Nevill 1998), treating the data and analyzing the success of this treatment are necessary. However, many studies either do not take into account whether data is heteroscedastic, and/or provide little or no justification of whether the treatment of heteroscedasticity was successful. Therefore, ***Study 2 aimed to demonstrate whether VPT data exhibits heteroscedasticity. Furthermore, it was the aim to provide an example of how heteroscedasticity can be treated properly, including a demonstration of whether this treatment was successful***.

The direct connection between plantar sensitivity and human posture (Chua et al. 2002; Kennedy and Inglis 2002; Meyer et al. 2004) leads to another important research field: (quasi-static and) dynamic balance performance. Similar to improving

the quality of VPT data collection and analyses, setups to acquire balance data also need to fulfill the biomechanical quality and criteria, such as reliability. One approach to quantify early dynamic balance responses after unexpected perturbations is using the Posturomed device. Since the Posturomed is also known as a training device (Kramer et al. 2014), and since there is a lack of literature in this specific context, ***Study 3 aimed to examine the intra- and inter-day reliability of dynamic balance responses using the Posturomed device***.

Combining physiological and methodological knowledge on the assessment / treatment of cutaneous sensitivity data (Studies 1 and 2) with the results on reliability from the dynamic balance setup (Study 3), another interesting research question with a rather physiological background emerges. What is the exact role of plantar afferents in human balance control? To answer this question, studies have aimed to manipulate plantar sensitivity, for example, by acute hypothermia, which reduces sensitivity. As mentioned in the introduction, there are some limitations in related studies. Therefore, ***Study 4 investigated the effect of plantar hypothermia on dynamic balance performance and how to maintain the desired level of plantar hypothermia during the entire data collection process***.

The final study included in the present thesis provides examples of areas of clinical application, where sensory-motor assessments might be implemented. This application is directed toward cognitive disorders, such as dementia. One might ask: Can non-cognitive parameters help to detect cognitive disorders (early)? Previous literature not only demonstrates that early diagnosis and interventions can slow cognitive disease progression (Hansen et al. 2008; Groot et al. 2016), but also that non-cognitive symptoms of dementia might have their onset prior to cognitive symptoms (Raudino 2013). Cognitive symptoms are usually and widely identified via questionnaires. Finally, there is a lack of literature investigating non-cognitive parameters in cognitive disorders, although there is (circumstantial) evidence supporting this approach (Rapoport 1991; Benedetti et al. 1999; Doran et al. 2003; Dugger et al. 2013; Bahureksa et al. 2017; Belghali et al. 2017). Therefore, ***Study 5 aims to develop a widely founded instrument enabling the early-detection and prediction of cognitive decline prior to its clinical manifestation***. This will be

achieved using non-cognitive parameters, such as neurophysiological, sensory, and motor measures. Please note again that Study 5 is part of the perspectives and future directions section, and not part of the hypotheses and discussion sections.

2.2 Hypotheses of this thesis

Based on the findings and literature from Section 1, as well as on the overall relevance and objectives of this thesis, there are several hypotheses (H) on which the four studies focus. These hypotheses are presented below.

2.2.1 Study 1: "Plantar sensory vibration thresholds are not influenced by body position"

Study 1 investigated whether plantar vibratory sensitivity (assessed via VPTs) and the corresponding probe forces are affected by two different body positions (standing, sitting).

It was hypothesized that:
1_H1: There are higher vertical forces applied against the probe when standing compared to sitting.
1_H2: Lower VPTs are present when standing compared to sitting.

2.2.2 Study 2: "Subjective sensitivity data: considerations to treat heteroscedasticity"

Study 2 emphasized demonstrating how to identify and deal with heteroscedastic data to allow a more appropriate data analysis.

For Study 2, it was hypothesized that:
2_H1: Plantar sensitivity data exhibit heteroscedasticity.

2.2.3 Study 3: "Aspects of dynamic balance responses: inter- and intra-day reliability"

Study 3 investigated the reliability of a dynamic balance setup (unexpected horizontal perturbations using a modified Posturomed device).

Based on previous literature and the fact that the Posturomed is used as a training device, the hypothesis is:
3_H1: The Posturomed device exhibits a low intra- and inter-day reliability in terms of initial motor responses during dynamic balance performance.

2.2.4 Study 4: "Effects of hypothermically reduced plantar skin inputs on anticipatory and compensatory balance responses"

Study 4 investigated a plantar hypothermic effect (via a self-developed customized thermal platform) on dynamic balance performance.

The hypotheses were:
4_H1: Plantar hypothermia results in impaired balance performance, evident by increased center of pressure (COP) excursions and electromyographic (EMG) activity.

Section 3 - Published studies

Section 3 presents Studies 1 through 4. There is a brief paragraph following each study to highlight the meaning of that study within the overall scope and aims of this doctoral thesis. Please note again that Study 5 (full view in Appendix 1) is part of the perspectives and future directions section.

3.1 Study 1

Plantar sensory vibration thresholds are not influenced by body position

Andresa M.C. Germano[1]*, Daniel Schmidt[1], Guenther Schlee[1] and Thomas L. Milani[1]

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[1]Department of Human Locomotion, Chemnitz University of Technology, Reichenhainer Straße 29a, 09126 Chemnitz, Germany

Abstract

Monitoring skin sensitivity is studied to clarify its relationship on balance. Measuring skin sensitivity is performed when subjects are sitting or lying, whereas balance tests are measured during standing. However, afferent signal processing and subsequent efferent responses can be altered by different body positions. Therefore, this study investigated whether vibration perception thresholds (VPTs) are influenced by body positions. Sixty-six healthy subjects (41♀; 25♂) participated in this study. Five measurements of VPTs were performed at each of the three analyzed anatomical locations (heel, first metatarsal head, hallux) of the right plantar foot under two randomized conditions: during sitting and standing. The contact force applied to the probe was measured and controlled within the five trials. Contact forces between the probe and the foot were higher during standing. However, no differences in VPTs were found between conditions. This indicates that VPTs are not different during standing compared to sitting, contrary to our expectations. We conclude that higher forces did not induce increased receptor activity. Since no differences were found

between thresholds, future clinical studies can implement plantar VPT tests during sitting in association with balance tests during standing.

Subjects: Bioscience; Health and Social Care; Physiotherapy and Sports Medicine; Rehabilitation Medicine; Research Methods

Keywords
foot sensitivity; sitting; standing; vibration; VPT

1. Introduction

It is known that afferent signal processing can be altered by different postures, which also affects efferent responses. For example, previous studies showed that the amplitude of the muscle reflex (H reflex) during standing was lower compared to other conditions (seated, lying, or prone) (Hayashi, Tako, Tokuda, & Yanagisawa, 1992; Koceja, Trimble, & Earles, 1993; Mynark & Koceja, 1997). Studies have reported the particular importance of plantar somatosensory information for balance control. For example, reduced somatosensation is associated with poorer balance abilities (Kavounoudias, Roll, & Roll, 1998; Perry, McIlroy, & Maki, 2000). In particular, various diseases, like diabetes mellitus, lead to reduced plantar sensitivity and deteriorated balance abilities (Leonard, Farooqi, & Myers, 2004). This emphasizes the importance of balance and sensory tests in clinical settings (Berg & Norman, 1996). However, sensory tests are usually performed when subjects are sitting or lying, whereas balance tests are measured during standing. In sensory vibration tests, the forces between the oscillating probe and the anatomical location are apparently greater during standing than during sitting conditions. In this regard, previous studies demonstrated that higher contact forces (by additionally applied masses) reduce vibration perception thresholds (VPTs) during sitting (Cassella, Ashford, & Kavanagh-Sharp, 2000; Hagander, Midani, Kuskowski, & Parry, 2000; Lowenthal & Derek, 1987). In contrast, another study did not find effects of increasing contact forces on VPTs when measuring dorsal foot areas during sitting (Hagander et al., 2000). However, these results may not directly be applied to standing conditions. First, contact forces might be higher when standing compared to sitting. Second, other than plantar aspects were investigated in the above mentioned studies.

Furthermore, when standing, additional afferent inputs are required. Since those inputs are projected in the same afferent pathway, an alteration of the priority of plantar inputs is supposable, which may result in different VPTs. A recently published study (Mildren, Strzalkowski, & Bent, 2016) compared plantar VPTs during sitting and standing and found significant differences only at the metatarsal areas at 250 Hz. Note that they did not measure contact forces, and stimuli were applied by an array of many probes at the plantar metatarsal and heel areas. However, studies and clinical tests relating plantar sensitivity to balance usually investigate sensitivity thresholds using one single contact point and not an array.

Taking into account the above mentioned considerations, the purpose of this study was to compare plantar VPTs measured with subjects in a sitting and standing position. It was hypothesized that (a) contact forces against the probe are greater while standing compared to sitting and (b) consequently, VPTs measured during standing are lower than during sitting. These findings would certainly include observations of fundamental importance for future research as well as clinical diagnosis, in which perception of vibration is associated with body balance.

2. Materials and methods

2.1 Subjects

Sixty-six healthy subjects participated in this study (♂ 178.3 ± 4.7 cm; 75.1 ± 7.1 kg; 24.2 ± 4.1 years; ♀ 170.4 ± 5.9 cm; 62.3 ± 7.2 kg; 22.9 ± 3.2 years). The subjects had no history of lower leg injury or lower-extremity pain six months prior to testing and no peripheral neuropathy or other disorders that could affect sensitivity. Before the study began, the subjects were informed about the purpose of this study, gave informed written consent and were free to withdraw from it at any time. All procedures were conducted according the recommendations of the Declaration of Helsinki and were approved by the faculty's ethics committee.

2.2 Equipment

A modified Tira Vib vibration exciter (model TV51075, Schalkau, Germany) powered by a Voltcraft oscillator (model FG 506, Hirschau, Germany) was used to measure

vibration thresholds. The vibration from the exciter to the foot location was conducted by a metal probe (rounded, 7.8 mm diameter) protruding through a hole in a wooden box, which was internally covered by an acoustic insulation material. The tip of the probe was adjusted 2 mm higher than the level of the box (Nurse & Nigg, 1999). The measurements were performed at 200 Hz, since the optimal response of the vibration receptors (Vater–Pacini corpuscles) is reported to be at frequencies between 200 and 250 Hz (Verrillo, 1985). The vibration exciter was duly calibrated resulting in a constant with which the data was converted from V to μm. Room temperature was measured and controlled at 23 ± 2 °C (EN ISO/IEC17025) using a thermometer (C28 Hand Held Digital Type K, Comark, UK) and the plantar foot temperature was measured using an infrared-thermometer (Mini Flash, TFA, Germany).

2.3 Testing procedure

Prior to measuring, the participants were allowed a period of ten min barefoot, during which they could adapt to the room temperature. The temperature of the foot (heel) and room were measured before each test.

Vibration thresholds were measured in two conditions: sitting and standing. While seated, the subjects should keep their feet rested on the box, knees and hips at 90° angles, not exert any pressure against the probe, and keep their upper limbs hanging down. During standing, the subjects should distribute the body weight evenly on both feet, stand with feet shoulder-width apart and upper limbs hanging down. Subjects were barefoot throughout the measurements and were instructed to wear their individual sports clothes (shorts and t-shirt) in order to feel most comfortable. Additionally, subjects used hearing protectors to avoid distracting noise. Five measurements were performed at each of the three analyzed anatomical locations of the right plantar foot: heel, first metatarsal head (Met I), and hallux. The vibration amplitude was gradually increased (at different speeds) from zero until vibratory stimulation was perceived by subjects. Body position (sitting and standing) and anatomical locations were randomized between the subjects.

Due to a possible influence of contact force between the foot and the probe during data collection, forces were controlled throughout the measurements, whereby it should not vary more than 1 N (Cassella et al., 2000).

2.4 Statistical analysis

The mean value of the five measurements was used to determine the VPT for each subject at each condition. By virtue of non-parametrical data tested using the Shapiro–Wilk test, differences between genders were compared with a Mann–Whitney test ($\alpha = 0.05$) and differences between the conditions were analysed with a Wilcoxon-Test. Bonferroni correction was used in order to adjust the initial level of significance (from $\alpha = 0.05$ to $\alpha = 0.05/3 = 0.016$), by taking account of the three analyzed anatomical locations. SPSS version 18.0 was used for all statistical tests. Based on data from a previous study (Schlee, Sterzing, & Milani, 2009), differences between the conditions were considered relevant when >2.5 µm.

3. Results

Plantar temperatures at the heel were 26.8 ± 2.1 and 26.8 ± 2.0 °C for standing and sitting conditions, respectively. Statistical analysis revealed no significant differences.

The contact forces between the probe and the location were measured for both body positions, and were higher for standing in comparison to sitting for all analyzed locations. As shown in Figure 1, the contact forces increase in the standing position (%) compared to the sitting position. The contact force on the heel during standing was 62.6 % higher than during sitting. On the first metatarsal head (Met I) and hallux the contact forces for the standing position were also higher than while sitting.

There were no significant differences in vibration thresholds when comparing men and women at all analyzed anatomical locations and both conditions. Therefore, the results were analyzed over the whole group ($n = 66$) (Figure 2). The comparison of VPTs between standing and sitting conditions showed no significant differences in any of the analyzed anatomical locations (Figure 2).

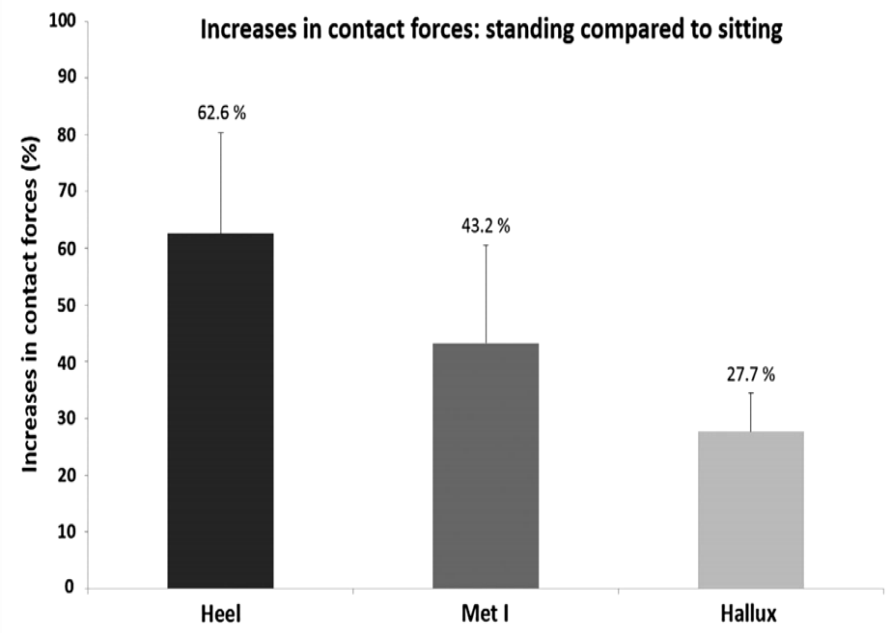

Figure 1. Increase in contact forces in the standing position compared to sitting. Note: Met I = first metatarsal head.

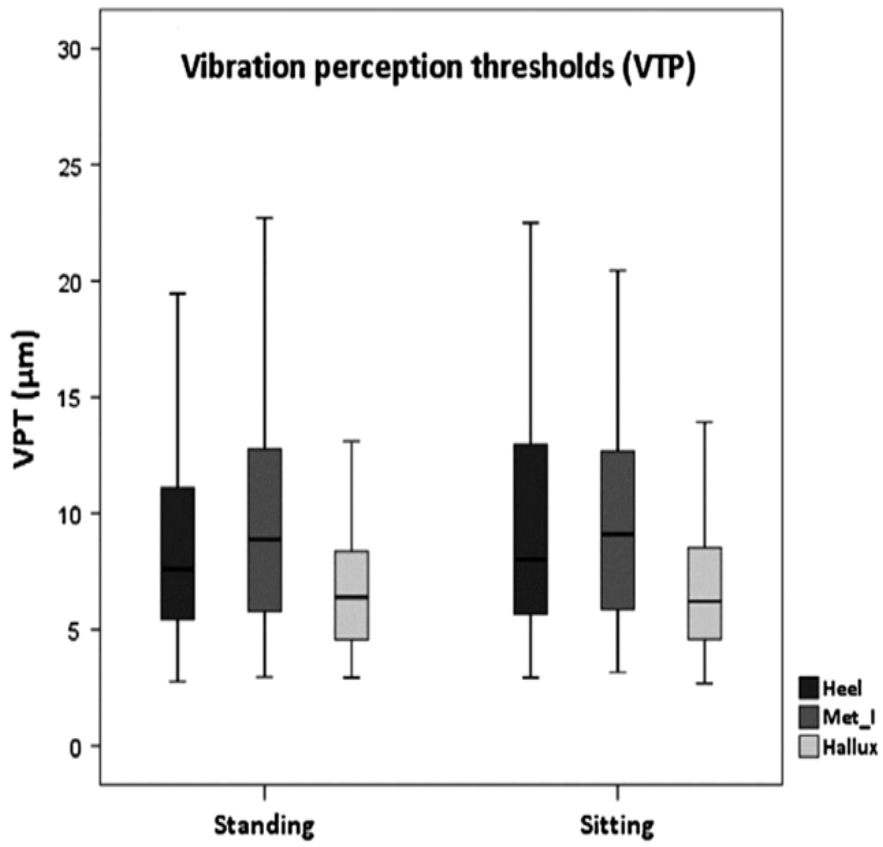

Figure 2. VPTs (µm) between standing and sitting (n = 66). Note: Met I = first metatarsal head.

4. Discussion

Plantar temperatures pre and post trials only varied by 0.4 °C on average. Guaranteeing this uniformity is important since skin sensitivity depends on skin temperature (Schlee et al., 2009).

Not surprisingly, contact forces during standing were higher compared to sitting. During standing, the body weight resulted in higher force applied against the probe, especially at the heel, which carries 60% of the weight-bearing load (Cavanagh, Rodgers, & liboshi, 1987).

Contact force is an influencing factor for VPT measurements. Hagander et al. (2000) investigated the effects of vertically applied masses (30–100 g) on dorsal VPTs at 100 Hz and did not find any differences. Cassella et al. (2000) varied masses (0–100 g) applied to the head of a neurothesiometer and found lower VPTs as masses increased. Likewise, using 200 and 400 g, the VPTs of healthy subjects and subjects with diabetic neuropathy showed reduced values as contact forces increased (Lowenthal & Derek, 1987). However, neither study analyzed plantar aspects. Another issue is that the neurothesiometer lacks repeatability due to non-linear behavior when expressing VPTs in micrometer (Schlee, Schleusener, & Milani, 2012). Although Casella et al. (2000) presented VPTs in volts, comparing this data is still difficult since the common and preferred unit of VPTs is micrometer (Schlee et al., 2012).

In our study, with even higher forces applied towards the probe during standing, VPTs showed no significant or relevant (<2.5 µm) differences between conditions. This means that the perception of vibratory stimuli was not better during standing compared to sitting, which contradicts our hypothesis. Therefore, higher forces do not seem to induce increased receptor activity.

To our knowledge, the study by Mildren et al. (2016) is the only investigation that compared plantar VPTs during standing and sitting. Similar to our study, they also did not find significant differences at the heel array at 250 Hz, but rather increased VPTs at the metatarsal array during standing. This contrary finding may

result from the different probe configurations. Their probe alignment led to a greater area of stimulated skin. Possibly, this changed skin properties like stiffness (Fontanella, Carniel, Forestiero, & Natali, 2014), inducing alterations of the transmission of mechanical stimuli towards the receptor (Mildren et al., 2016). We presumably did not find the same effects as Mildren et al. (2016) did due to the smaller area of stimulated skin in our study.

5. Conclusions

In conclusion, no differences between VPTs were present in our study, despite higher forces for standing compared to sitting. These results have potentially important implications for future research as well as for clinical diagnosis, in which plantar perception and balance control are closely related and implemented in various measuring setups, especially for patient populations or older adults. Future studies should objectively investigate whether vibrational firing rates are the same already at the receptor level when comparing various measuring positions.

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Competing Interests

The authors declare no competing interest.

Author details

Andresa M.C. Germano
E-mail: andresa.germano@hsw.tu-chemnitz.de

Daniel Schmidt
E-mail: daniel.schmidt@hsw.tu-chemnitz.de

Günther Schlee
E-mail: guenther.schlee@hsw.tu-chemnitz.de

Thomas L. Milani
E-mail: thomas.milani@hsw.tu-chemnitz.de

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References

Berg, K., & Norman, K. (1996). Functional assessment of balance and gait. Clin Geriatr Med, 12, 705–723.

Cassella, J. P., Ashford, R. L., & Kavanagh-Sharp, V. (2000). Effect of applied pressure in the determination of vibration sensitivity using the neurothesiometer. The Foot, 10, 27–30. http://dx.doi.org/10.1054/foot.2000.0575.

Cavanagh, P., Rodgers, M., & liboshi, A. (1987). Pressure distribution under symptom-free feet during barefoot standing. Foot & Ankle International, 7, 262 278. http://dx.doi.org/10.1177/107110078700700502.

Fontanella, C., Carniel, E., Forestiero, A., & Natali, A. (2014). Investigation of the mechanical behaviour of the foot skin. Skin Research and Technology, 20, 445–452. http://dx.doi.org/10.1111/srt.2014.20.issue-4.

Hagander, L., Midani, H., Kuskowski, M., & Parry, G. J. (2000). Quantitative sensory testing: Effect of site and skin temperature on thermal thresholds. Clinical Neurophysiology, 111, 17–22. http://dx.doi.org/10.1016/S1388- 2457(99)00192-3.

Hayashi, R., Tako, K., Tokuda, T., & Yanagisawa, N. (1992). Comparison of amplitude of human soleus H-reflex during sitting and standing. Neuroscience Research, 13, 227–233. http://dx.doi.org/10.1016/0168-0102(92)90062-H.

Kavounoudias, A., Roll, R., & Roll, J. P. (1998). The plantar sole is a “dynamometric map” for human balance control. NeuroReport, 9, 3247–3252. http://dx.doi.org/10.1097/00001756-199810050-00021.

Koceja, D. M., Trimble, M. H., & Earles, D. R. (1993). Inhibition of the soleus H-reflex in standing man. Brain Research, 629, 155–158.

http://dx.doi.org/10.1016/0006- 8993(93)90495-9.

Leonard, D., Farooqi, M., & Myers, S. (2004). Restoration of sensation, reduced pain, and improved balance in subjects with diabetic peripheral neuropathy: A doubleblind, randomized, placebo-controlled study with monochromatic near-infrared treatment. Diabetes Care, 27, 168–172. http://dx.doi.org/10.2337/diacare.27.1.168.

Lowenthal, L., Derek, T., & Hockaday, R. (1987). Vibration sensory thresholds depend on pressure of applied stimulus. Diabetes Care, 10, 100–102. http://dx.doi.org/10.2337/diacare.10.1.100.

Mildren, R. L., Strzalkowski, N. D. J., & Bent, L. R. (2016). Foot sole skin vibration perceptual thresholds are elevated in a standing posture compared to sitting. Gait Posture, 43, 87–92. http://dx.doi.org/10.1016/j.gaitpost.2015.10.027.

Mynark, R. G., & Koceja, D. M. (1997). Comparison of soleus H-reflex gain from prone to standing in dancers and controls. Electroencephalography and Clinical Neurophysiology/Electromyography and Motor Control, 105, 135–140. http://dx.doi.org/10.1016/S0924-980X(96)96096-8.

Nurse, M., & Nigg, B. (1999). Quantifying a relationship between tactile and vibration sensitivity of the human foot with plantar pressure distributions during gait. Clinical Biomechanics, 14, 667–672. http://dx.doi.org/10.1016/S0268-0033(99)00020-0.

Perry, S. D., McIlroy, W. E., & Maki, B. E. (2000). The role of plantar cutaneous mechanoreceptors in the control of compensatory stepping reactions evoked by unpredictable, multi-directional perturbation. Brain Research, 877, 401–406. http://dx.doi.org/10.1016/S0006-8993(00)02712-8.

Schlee, G., Schleusener, M., & Milani, T. L. (2012). Repeatability of vibration thresholds measured with the neurothesiometer: Is it a valid and reliable research tool? Clinical Neurophysiology, 123, 1053–1054. http://dx.doi.org/10.1016/j.clinph.2011.09.021.

Schlee, G., Sterzing, T., & Milani, T. L. (2009). Foot sole skin temperature affects plantar foot sensitivity. Clinical Neurophysiology, 120, 1548–1551. http://dx.doi.org/10.1016/j.clinph.2009.06.010.

Verrillo, R. (1985). Psychophysics of vibrotactile stimulation. The Journal of the Acoustical Society of America, 77, 225–232. http://dx.doi.org/10.1121/1.392263.

3.1.1 Study 1: Summary and classification in the context of this thesis

The first study in this cumulative work provides further important insights in terms of factors that must be considered when evaluating VPTs. These physiological and/or methodological factors include, for example, skin temperature, the vertical force of the measuring probe, probe dimensions, diseases and other (medical) conditions of the participants, and so forth. Furthermore, the posture of the participants might play an important role, as literature has shown that afferent signal processing and conduction can be modified by different body positions. In particular, Study 1 demonstrates that VPTs do not differ when comparing a seated and a standing body position, although probe probe contact forces were significantly higher in the latter position. This was evident for all three analyzed plantar locations (frequency: 200 Hz).

These findings add new insights and suggest that vibratory afferent information stemming from plantar mechanoreceptors when sitting are comparable to the information obtained when standing, as it is usually the case when conducting balance tests. As plantar afferent inputs are an important contributor to human balance, Study 1 suggests that -at least from a subjective point of view- studies may integrate plantar VPTs during sitting in conjunction with balance tests during standing.

With the knowledge gained from Study 1, supplemented by earlier work and related literature, VPT data was collected to the best of our knowledge. Therefore, the focus will be on another, methodological aspect: How can VPT data be adequately analyzed? Study 2 was performed to answer this question.

3.2 Study 2

Subjective sensitivity data: Considerations to treat heteroscedasticity

Daniel Schmidt[1]*, Andresa M.C. Germano[1] and Thomas L. Milani[1]

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[1]Department of Human Locomotion, Chemnitz University of Technology, Institute of Human Movement Science and Health, Reichenhainer Straße 31/33, Chemnitz 09126, Germany

Abstract
In many clinical disciplines, especially in subjective sensitivity research, data are collected on the ratio scale. This is also true for vibration perception thresholds (VPTs). Hence, such data may be of heteroscedastic nature, where the amount of measurement error increases as the values increase. Heteroscedastic data is a great scientific concern, since many standard inferential statistical tests assume homoscedasticity and may, therefore, lead to incorrect interpretations. Unfortunately, only few studies even address heteroscedasticity, and even if they do, in many cases this is achieved inappropriately. Therefore, in this paper, we first show a simple approach for how to detect heteroscedasticity in VPTs measured at the plantar aspect of the hallux. Second, we show how to correct for heteroscedasticity by means of logarithmizing the raw data. Finally, we also demonstrate the importance of how data benefits from this transformation. Hence, if data takes benefit from the transformation, we recommend using logarithmized data to conduct further statistical approaches. We also interpret the results presented here. Furthermore, we briefly

mention alternatives in case the transformation is not successful in eliminating heteroscedasticity.

Subjects: Neuroscience; Statistics & Probability; Health & Society; Health Conditions; Medicine

Keywords
heteroscedasticity; log transformation; vibration perception thresholds; VPTs; skin sensitivity; ratio scale

1. Introduction

Skin is the largest organ in the human body and enables various external stimuli, such as touch or vibration, to be detected. This is achieved by mechanoreceptors located in the skin. For example, plantar mechanoreceptors are known to contribute to human balance regulation (Horak, Nashner, & Diener, 1990; Kavounoudias, Roll, & Roll, 1998; Peterka, 2018). Plantar sensitivity, however, depends on various factors like age (Gescheider, Bolanowski, Hall, Hoffman, & Verrillo, 1994) or skin temperature (Germano, Schmidt, & Milani, 2016; Schmidt, Germano, & Milani, 2017). Furthermore, the ability of balance regulation is impaired in various groups, such as patients with peripheral neuropathy, in which plantar sensitivity deteriorates (Inglis, Horak, Shupert, & Jones-Rycewicz, 1994). This highlights the clinical importance of skin sensitivity in order to detect certain diseases. Of course, the interpretation of the outcomes of skin sensitivity measurements must be correct in order to meet clinical requirements. Skin sensitivity may be assessed invasively inserting microelectrodes into afferent nerve fibers (microneurography). Other, more common approaches are known as subjective methods, such as determining vibration sensitivity (vibration perception thresholds, VPTs).

For vibration sensitivity, as well as in many other research disciplines, data are collected on the ratio scale. Such data may not only be expressed as whole numbers, but also as any number of decimal points (Safrit, 1989). In ratio scaled data, the amount of measurement error (or measurement difference, e.g. in a test-retest scenario) increases as the measured values increase (Atkinson & Nevill, 1998): The

measurement error depends on the size of the measured parameter (Nevill & Atkinson, 1997). Such data will accumulate close to zero (without negativity). On the other hand, this kind of data is theoretically unbounded towards the positive direction, likely resulting in heteroscedastic patterns (Nevill & Atkinson, 1997). In contrast to homoscedastic data (especially when following normal distribution), heteroscedastic data should not be analyzed using most conventional statistical methods (Atkinson & Nevill, 1998), as the power and ability to control type I error probability might then be negatively affected (Wilcox, Peterson, & McNitt-gray, 2018). Conducting statistical tests on raw data may lead to substantial misinterpretations and error-prone conclusions.

Although VPT data are subjective and measured on the ratio scale, most VPTs are a) either still analyzed as homoscedastic data (e.g. Alfuth & Rosenbaum, 2011; Flondell et al., 2017; Jansson, Hakansson, Reinfeldt, Fröhlich, & Rahne, 2017; Meyer, Oddsson, & De Luca, 2004, to name a few), or b) sometimes transformed, however, without giving information regarding a validation of its benefit, or with incorrect justifications for performing a transformation. The aim of the pre sent study, therefore, is first to examine whether VPTs exhibit heteroscedasticity in an appropriate and easy-to-understand way. We hypothesized the presence of heteroscedasticity in our vibration data. Second, in the case of heteroscedasticity, we also provide an example of how to correct for this in a simple way, and we demonstrate the necessity to check whether or not the correction was appropriate. Since the main clientele working with ratio-scaled data may not have a strong background in statistics, we deliberately focus on a simple and easy-to-conduct approach. However, we will briefly touch on current recommendations for alternatives in case the elimination of heteroscedasticity is not satisfactory with the simple approach we refer to in this study.

2. Methods

2.1 Subjects

Twenty-eight healthy and injury-free subjects of both genders (16 males, 12 females) participated in this study (mean±SD: 23.2 ± 2.6 yrs, 173.5 ± 8.0 cm, 66.9 ± 9.8 kg).

Subjects had no signs of lower extremity pain during this study and were free of injuries for at least 6 months prior to testing. All participants were also free of neurological diseases (e.g. diabetic neuropathy or Parkinson´s disease). Prior to testing, all subjects were informed about the aim and procedures of this study and gave their written informed consent. Participants were free to withdraw from the experiments at any time. This study was conducted according to the recommendations of the Declaration of Helsinki and was approved by the Ethics Committee of the faculty of the corresponding university.

2.2 Instrumentation

Cutaneous vibration perception thresholds (VPTs, in µm) were determined using a Tira Vib vibration exciter (model TV51075, Schalkau, Germany), powered by a Voltcraft oscillator (model FG 506, Hirschau, Germany). Before the measurements, the vertical movement of the contactor of the vibration exciter was laser calibrated in order to enable direct readings of the vibrating amplitude. The probe diameter was 7.8 mm, and its tip was placed 2 mm above the surrounding surface (Nurse & Nigg, 1999). The frequency of the vibrating contactor was 200 Hz, which is known to be the optimal stimulus to elicit Vater-Pacini-corpuscles (Gescheider et al., 1994; Verillo, 1985). Since skin temperature influences skin sensitivity (Germano et al., 2016; Schlee, Sterzing, & Milani, 2009; Schmidt et al., 2017), the surface of the vibration exciter could be heated to keep plantar temperatures constant. The vertical force applied from the subject’s foot towards the contactor was monitored via a force transducer and was kept within a range of ±0.5 N. Plantar temperatures (hallux) and room temperature were measured using a digital type-K-thermocouple (PeakTech 5135, Ahrensburg, Germany).

2.3 Testing procedure

Prior to testing, subjects went through an acclimatization period of 10 min to adjust to the room temperature (23 ± 2 °C, according to EN ISO/IEC 17,025). During the sensitivity tests, subjects closed their eyes and wore noise cancelling earphones (Quiet comfort 20i, Bose, Framingham, USA) in order to avoid distracting noise from the environment. All participants sat with ankle, knee, and hip-angles of approx. 90°, and rested their arms on top of their thighs, close to the abdomen. Subjects were

instructed to sit as described above, but also to be comfortable to enable them to concentrate on detecting vibration stimuli but not on maintaining a certain posture. VPTs were measured similarly to a Method of Limits approach introduced by Mildren, Strzalkowski, and Bent (2016). First, three VPT-trials were collected at the Hallux (barefoot) of the dominant foot (test). After this, subjects waited for 45 min while sitting with their feet on top of the heatable aluminum platform. Finally, VPTs were measured in the same manner (retest). Plantar temperatures only slightly decreased from 26.5 ± 2.8 °C (test) to 25.5 ± 2.1 °C (retest).

2.4 Data analysis and statistics

In terms of VPTs, the mean±SD of the three trials was calculated. All further analyses were performed using R (The R Foundation for Statistical Computing, Vienna, Austria). To check for potential outliers, we used an adjusted boxplot rule as recommended by Wilcox (2013). As suggested (Nevill & Atkinson, 1997), heteroscedasticity was identified by plotting VPT differences (test-retest, raw data) against their mean. The Spearman-correlation (raw data) was also calculated between the absolute differences of the VPTs and their mean. Data was then treated by taking the natural logarithm of the raw data (Nevill & Atkinson, 1997; Wilcox et al., 2018). Bland-Altman plots were created, whereas the limits of agreement were calculated by multiplying 1.96 times the standard deviation of the mean difference.

3. Results and discussion

No outliers were detected by the adjusted boxplot rule. This is important when using means, as in our study, since outliers may considerably lower the power of e.g. difference tests (Wilcox et al., 2018). Raw VPTs (mean±SD) of the test and retest are presented in Table 1. A first quite simple sign towards heteroscedasticity was evident when plotting VPT differences (test-retest) against their mean (Figure 1). Smaller mean VPTs were associated with smaller error (differences), whereas greater mean VPTs were associated with greater error. Data points seem to be “funnel-shaped”, indicating that the measurement error increases as the measured values increase. Another indicator of heteroscedasticity was that differences (not necessarily

Table 1. Raw vibration perception thresholds (VPTs, mean±SD) measured at the hallux for all 28 subjects, before (test) and after (retest) the 45 min waiting period.

Subject	VPT Test [µm] (mean±SD)	VPT Retest [µm] (mean±SD)
1	2.68±0.86	2.40±1.15
2	0.68±0.22	0.85±0.05
3	2.39±0.12	1.20±0.08
4	0.48±0.11	0.47±0.08
5	0.70±0.04	0.97±0.19
6	2.11±0.45	1.73±0.15
7	1.53±0.82	2.65±0.31
8	1.80±0.11	1.93±0.46
9	2.26±0.57	2.59±0.24
10	0.21±0.04	0.40±0.08
11	0.56±0.11	0.37±0.04
12	1.29±0.03	1.30±0.98
13	1.47±0.21	1.39±0.20
14	0.50±0.19	0.65±0.33
15	1.98±0.44	2.06±0.53
16	1.71±0.17	2.47±0.33
17	1.87±0.52	2.31±0.61
18	2.25±0.28	2.51±0.14
19	2.74±0.90	3.67±0.18
20	0.44±0.22	0.84±0.40
21	2.14±0.43	2.33±0.48
22	2.13±0.33	1.13±0.12
23	0.56±0.16	1.14±0.07
24	1.48±0.50	2.42±0.33
25	0.61±0.07	0.53±0.13
26	1.33±0.22	4.01±0.38
27	1.07±0.47	1.13±0.47
28	0.44±0.04	0.43±0.04
All	**1.41±0.78**	**1.64±0.99**

individual data from the test and retest, respectively) were not normally distributed (Shapiro-Wilk test: $p = 0.002$). As the ultimate criterion, the Spearman-correlation between the absolute differences and their mean (Nevill & Atkinson, 1997) was significant ($p = 0.004$), with a correlation coefficient of $r = 0.530$, indicating a

moderate correlation (Mukaka, 2012). We used a Spearman correlation, since it does not require normally distributed data (Mukaka, 2012). This means that the error correlates with the magnitude of the VPT values, constituting heteroscedasticity. The correlation is not required to be significant or to present a high correlation coefficient. A small sample size may account for the lack of significance, but may still correspond to heteroscedastic data when the correlation is found to be positive (Nevill & Atkinson, 1997), even if of lower magnitude. It is then generally recommended to take the natural logarithm (hereafter referred to as log) of the raw data (Nevill & Atkinson, 1997).

To provide a first example regarding the benefit of transforming heteroscedastic data, we created a Bland-Altman plot (Figure 1) based on the raw data from Table 1.

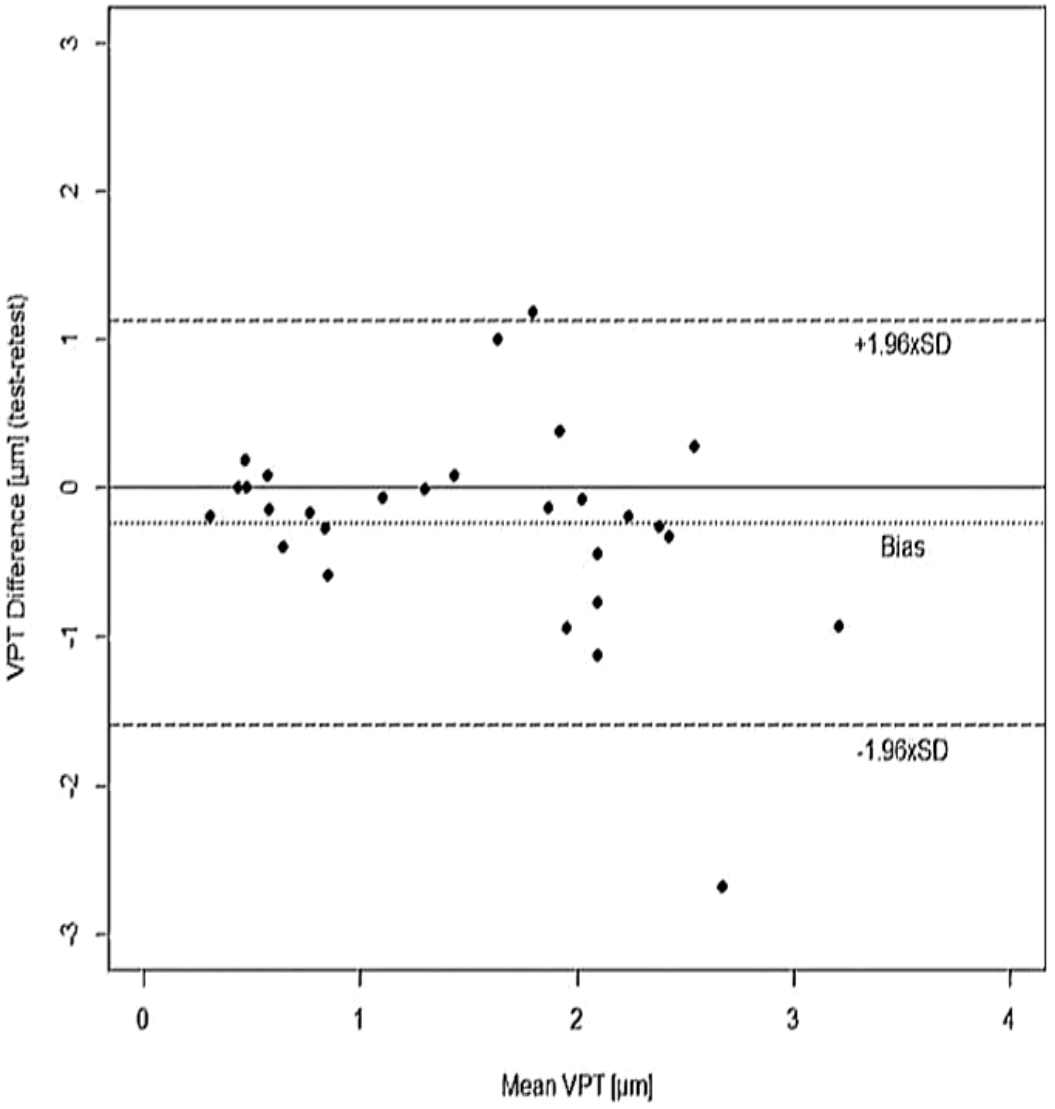

Figure 1. Bland-Altman plot of raw, untransformed vibration perception thresholds (VPTs) based on data from Table 1. The upper limit of agreement (ULOA: 1.131 µm) equals the bias (−0.231 µm) plus the random error component (1.362 µm). The lower limit of agreement (LLOA: −1.593 µm) equals the bias (−0.231 µm) minus the random error component (1.362 µm).

Bland-Altman plots are an important tool to quantify absolute reliability (Bruton, Conway, & Holgate, 2000). In accordance with Bland and Altman (Bland & Altman, 1986), and as can be observed in Figure 1, the limits of agreement were unacceptably far apart for small values, and unacceptably narrow for large values: For example, subject 28 obtained a VPT of 0.44 µm at the test (Table 1), hence data from this subject could range between 1.6 and -1.2 µm (0.44 + 1.131 µm and 0.44–1.593 µm, respectively). This is not possible due to the ratio scale, which does not

allow negative values. In conclusion, the absolute and fix limits of agreement in Figure 1 do not consider ratio properties of data. Therefore, an appropriate interpretation of Bland-Altman plots based on heteroscedastic and untransformed data is not possible and may lead to overestimation of apparently poor reliability.

Therefore, we calculated the natural logarithm (log transformation) of raw data from Table 1. When we then plot VPT differences (test-retest) against their mean, data no longer appear “funnel-shaped” (Figure 2). Instead, differences between tests and retests are then normally distributed (Shapiro-Wilk test: $p = 0.724$). Furthermore, the Spearman correlation coefficient decreased to close to zero ($r = -0.020$), indicating a negligible correlation (Mukaka, 2012). Additionally, the correlation turned out to be non-significant ($p = 0.919$). Hence, the error does not correlate with the magnitude of the values, and data is now of homoscedastic nature (Atkinson & Nevill, 1998). Please note that if the correlation coefficient is numerically reduced by the log transformation, irrespective of the sign, it is usually recommended to transform data logarithmically (Nevill & Atkinson, 1997). This was the case for our data. In other data sets (not related to this paper), we found that a log transformation did not always eliminate heteroscedasticity, as evident by an increasing (absolute) value of the Spearman correlation coefficient. In such cases, other approaches may be adequate (see last paragraph of discussion). Note, however, that most articles using log transformed data do not demonstrate whether or not the transformation induced any benefit toward eliminating heteroscedasticity. This is a clear limitation, and merely (log) transforming data prior to conducting statistical tests should not be regarded as a rigid or proper template. On the other hand, there are recent studies which define a certain r^2-value as the “threshold” between homoscedastic vs. heteroscedastic data (Pérez-Castilla, Feriche, Jaric, Padial, & García-Ramos, 2017; Plautard et al., 2017). However, not considering other parameters to identify heteroscedasticity may lead to restrictions when interpreting data.

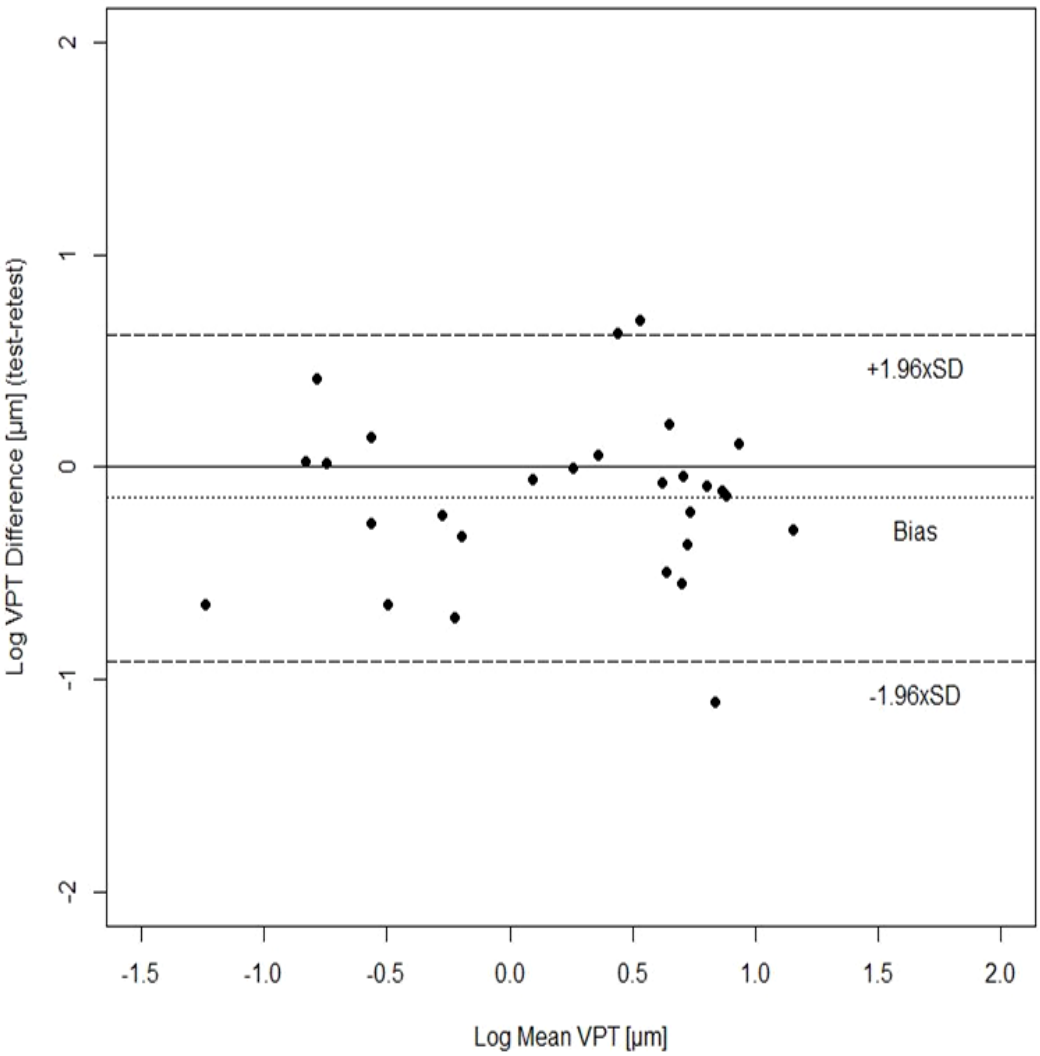

Figure 2. Bland-Altman plot using naturally logarithmized (log) vibration perception thresholds (VPTs).

Based on the log data (Figure 2), we again created a Bland-Altman plot. To be able to calculate on a ratio scale, we followed the recommendation as described in Nevill and Atkinson (1997) and calculated the antilogs:

log(bias) = –0.144 µm

antilog(bias) = 0. 66 µm

log(random error) = 0. 1 µm

antilog(random error) = 2.162 µm

After this, we calculated the ratio upper and lower limits of agreements (rULOA and rLLOA, respectively) as follows:

r LOA = antilog(bias) antilog(random error) = 0. 66 µm 2.162 µm = 1. 2 µm

$$\text{rLLOA} = \frac{\text{antilog(bias)}}{\text{antilog(random error)}} = \frac{0.\ 66\ \mu\text{m}}{2.162\ \mu\text{m}} = 0.401\ \mu\text{m}$$

Going back to our example, subject 28 (0.44 µm at test) could vary between 0.44 × 1.872 µm and 0.44 × 0.401 µm, which is between 0.82 and 0.18 µm (in 95 %). The limits of agreement are now more accurate, since they constitute a percentage change and account for the ratio properties. Therefore, a correct interpretation is now possible.

As mentioned earlier, many other standard inferential statistics assume homoscedasticity (Wilcox et al., 2018), something researchers may not always be aware of. These also include common statistical tests to detect differences (bias), such as t-tests (Atkinson & Nevill, 1998; Markowski & Markowski, 1990; Zimmerman, 2004). When considering different statistical procedures, the general class of analysis of variance (ANOVA), for example, assumes equality of variances within the groups (Zimmerman, 2004). In other words, it assumes that data is homoscedastic (Keselman et al., 1998; Kirchman, Sigda, Kapuscinski, & Mitchell, 1982). Nonparametric tests, like the Mann-Whitney-U test, account for violations of normal distribution, but not if the assumption of homoscedasticity is violated (Zimmerman & Zumbo, 1993). This is in line with other investigations (Keselman, Rogan, & Feir-Walsh, 1977; Pratt, 1964; Tomarken & Serlin, 1986). When executed on both raw and log-transformed data, the same tests for bias result in different p-values, which makes appropriate interpretations more difficult. Furthermore, conducting statistical tests (which assume homoscedasticity) on heteroscedastic data, may indeed alter type I error rates (Zimmerman, 2004). In our data set (Table 1), p-values of the Wilcoxon test were slightly different from each other: 0.046 for log, and 0.045 for raw data (test vs. retest). In addition, conventional correlation analyses (e.g. Pearson correlation, intra-class-correlation (ICC)) are judged to be inappropriate when

conducted on heteroscedastic data (Nevill, 1997). Chinn (1991) states that when data are analyzed on a log scale, all calculations should be performed on the log values. For our data set, the ICC coefficient was 0.821 based on raw, and 0.914 based on log data (both $p<0.001$, model 3,k). Heteroscedasticity also affects measures of variability and absolute reliability: The coefficient of variation (CV) assumes the presence of heteroscedasticity, whereas the standard error of measurement (SEM) assumes the absence of heteroscedasticity (Atkinson & Nevill, 1998). This highlights the importance of carefully analyzing data to be able to conduct adequate statistical tests and to interpret these tests appropriately.

Note again that it is important to check data for outliers. Since we detected no outliers in our data set, we did not include robust statistical methods. Many statistical measures or procedures are not robust against outliers (Wilcox, 2013). This includes the use of means and standard deviations, as well as conventional correlation analyses, such as Pearson or Spearman correlations. In such cases, it is recommended to use trimmed means and the standard error of trimmed means (Wilcox, 2013). An alternative to Spearman´s correlation, which may be distorted by properly placed outliers, are type O correlations. One type of these are e.g. skipped correlations, which downweight or eliminate values of low depth within the data cloud (Wilcox, 2013). Conducting a skipped correlation (center estimator: MCD) on our data resulted in the same interpretation and conclusion regarding the benefit of the logarithmic transformation.

As already mentioned, the present study shows one simple-to-conduct possibility to treat heteroscedasticity. This treatment is easy to understand, which is a clear advantage for the wide range of potential “users”. These may include clinicians, (general) practitioners, or physiotherapists who need to compare means of different groups, for example. Such a versatile clientele might exhibit restricted knowledge in terms of more sophisticated statistical analyses, or, access to appropriate software may simply be difficult. Therefore, we focused on a simple log transformation to treat heteroscedasticity.

In this regard, however, we must also mention that this simple approach may exhibit limitations. A logarithmic transformation does not always yield homoscedastic data. This might be true particularly when correlation coefficients decrease only slightly after logarithmic transformation. Additionally, recent studies showed that sometimes there is no normal distribution (of differences) after logarithmization, or that there are still outliers/a skewed distribution (Rasmussen, 2013; Wilcox et al., 2018). In these cases, when comparing group means, one recommendation is to test the assumption of equal variances by using e.g. the F-test. If there is no significance, one is usually guided to use Student´s t-test. However, this approach is not advisable, since in some instances the F-test fails to detect violations of the assumption of equal variances, or may falsely recommend of using the t-test (especially when sample sizes are not equal) (Hayes & Cai, 2007; Markowski & Markowski, 1990; Wilcox et al., 2018; Zimmerman, 2004). Instead, a rank-based test as introduced by Conover (1980) constitutes a more robust method. When comparing group variances, Levene´s test is also commonly implemented. However, in a more recent study this test was found not to be very robust (Hayes & Cai, 2007). Alternatively, the Brown-Forsythe test and the O´Brien test were found to constitute fairly robust tests (e.g. (Howell, 1996)), although they also have their weaknesses (Hayes & Cai, 2007). In an extensive simulation study performed by Hayes and Cai (2007), they found that so-called unconditional tests performed as good as or even superior to the conditional tests mentioned above (Brown-Forsythe test, O´Brien test, etc.). In particular, bootstrapping the sampling distribution of the separate variance t statistic (UBS), as an unconditional test, resulted in an overall superior performance in most of the simulated conditions (Hayes & Cai, 2007). The superior performance of unconditional separate-variance tests is particularly pronounced when the sample sizes are not equal (Zimmerman, 2004). Hence, these methods are recommended when treating heteroscedasticity and when detecting differences between groups. As already mentioned, however, such approaches and recommendations require more in-depth statistical knowledge. Additionally, the fact that most statistical textbooks still recommend preliminary conditional tests to investigate the equality of variances contributes to this “dilemma”.

4. Conclusion

In this paper, we demonstrated that vibration perception thresholds (VPTs) measured at the plantar aspect of the hallux exhibit heteroscedasticity. Heteroscedastic data is a great scientific concern, since many standard inferential statistical procedures and measures assume homoscedasticity and may, therefore, lead to incorrect interpretations and conclusions. Such measures include, for example, parametrical and non-parametrical tests to detect differences, correlation analyses, or Bland-Altman plots. Based on an existing data set, we corrected for heteroscedasticity by calculating the natural logarithm (log transformation) of raw data. We further provided examples of how our data set benefitted from this correction. In general, we recommend: First, to examine any type of data for heteroscedasticity, especially when measured on the ratio scale. Second, to use log data and to check if data took benefit of the log transformation. Finally, to use log transformed data for conducting further statistical approaches if data benefitted from the transformation. In case the log transformation does not yield homoscedastic data, other more sophisticated approaches based on unconditional tests are recommended.

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Competing interests

The authors declare no competing interest.

Author details

Daniel Schmidt

E-mail: daniel.schmidt@hsw.tu-chemnitz.de

Andresa M.C. Germano
E-mail: andresa.germano@hsw.tu-chemnitz.de

Thomas L. Milani
E-mail: thomas.milani@hsw.tu-chemnitz.de

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References

Alfuth, M., & Rosenbaum, D. (2011). Long distance running and acute effects on plantar foot sensitivity and plantar foot loading. Neuroscience Letters, 503, 58–62. doi:10.1016/j.neulet.2011.08.010.

Atkinson, G., & Nevill, A. (1998). Statistical methods for assessing measurement error (reliability) in variables relevant to sports medicine. Sports Medicine, 26, 217–238. doi:10.2165/00007256-199826040-00002.

Bland, J. M., & Altman, D. G. (1986). Statistical methods for assessing agreement between two methods of clinical measurement. The Lancet, 1, 307–310. doi:10.1016/S0140-6736(86)90837-8.

Bruton, A., Conway, J. H., & Holgate, S. T. (2000). Reliability: What is it, and how is it measured? Physiotherapy, 86, 94–99. doi:10.1016/S0031-9406(05)61211-4

Chinn, S. (1991). Repeatability and method comparison. Thorax, 46, 454–456. doi:10.1136/thx.46.6.454.

Conover, W. (1980). Practical nonparametric statistics (2nd ed.). New York: John Wiley.

Flondell, M., Rosén, B., Andersson, G., Schyman, T., Dahlin, L. B., & Björman, A. (2017). Vibration thresholds in carpal tunnel syndrome assessed by multiple frequency vibrometry: A case-control study. Journal of Occupational Medicine and Toxicology, 12, 34. doi:10.1186/s12995-017-0181-6.

Germano, A., Schmidt, D., & Milani, T. (2016). Effects of hypothermically reduced plantar skin inputs on anticipatory and compensatory balance responses. BMC Neuroscience, 17, 1-14. doi:10.1186/s12868- 016-0279-2.

Gescheider, G. A., Bolanowski, S. J., Hall, K. L., Hoffman, K. E., & Verrillo, R. T. (1994). The effects of aging on information-processing channels in the sense of touch: I. Absolute sensitivity. Somatosensory & Motor Research, 11, 345–357. doi:10.3109/ 08990229409028878.

Hayes, A. F., & Cai, L. (2007). Further evaluating the conditional decision rule for comparing two independent means. British Journal of Mathematical and Statistical Psychology, 60, 217–244. doi:10.1348/000711005X62576.

Horak, F. B., Nashner, L. M., & Diener, H. C. (1990). Postural strategies associated with somatosensory and vestibular loss. Experimental Brain Research, 82, 167–177. doi:10.1007/BF00230848.

Howell, D. (1996). Statistical methods for psychology (4th ed.). Belmont, CA: Dux bury. Inglis, J. T., Horak, F. B., Shupert, C. L., & Jones-Rycewicz, C. (1994). The importance of somatosensory information in triggering and scaling automatic postural responses in humans. Experimental Brain Research, 101, 159–164. doi:10.1007/BF00243226.

Jansson, K.-J. F., Hakansson, B., Reinfeldt, S., Fröhlich, L., & Rahne, T. (2017). Vibrotactile thresholds on the mastoid and forehead position of deaf patients using radioear B71 and B81. Ear and Hearing, 38, 714–723. doi:10.1097/AUD.0000000000000456.

Kavounoudias, A., Roll, R., & Roll, J. P. (1998). The plantar sole is a “dynamometric map” for human balance control. Neuroreport, 9, 3247–3252. doi:10.1097/00001756- 199810050 00021.

Keselman, H., Rogan, J., & Feir-Walsh, B. (1977). An evaluation of some nonparametric and parametric tests for location equality. British Journal of Mathematical and Statistical Psychology, 30, 213–221. doi:10.1111/bmsp.1977.30.issue-2.

Keselman, H. J., Huberty, C. J., Lix, L. M., Olejnik, S., Cribbie, R. A., Donahue, B., … Levin, J. R. (1998). Statistical practices of educational researchers: An analysis of their ANOVA, MANOVA, and ANCOVA analyses. Review of Educational Research, 68, 350–386. doi:10.3102/00346543068003350.

Kirchman, D. L., Sigda, J., Kapuscinski, R., & Mitchell, R. (1982). Statistical analysis of the direct count for enumerating bacteria. Applied and Environmental Microbiology, 44, 376-382.

Markowski, C. A., & Markowski, E. P. (1990). Conditions for the effectiveness of a preliminary test of variance. American Statistics, 44, 322–326.

Meyer, P. F., Oddsson, L. I. E., & De Luca, C. J. (2004). Reduced plantar sensitivity alters postural responses to lateral perturbations of balance. Experimental Brain Research, 157, 526–536. doi:10.1007/s00221-004-1868-3.

Mildren, R. L., Strzalkowski, N. D. J., & Bent, L. R. (2016). Foot sole skin vibration perceptual thresholds are elevated in a standing posture compared to sitting. Gait & Posture, 43, 87–92. doi:10.1016/j.gaitpost.2015.10.027.

Mukaka, M. M. (2012). A guide to appropriate use of Correlation coefficient in medical research. Malawi Medical Journal, 24, 69–71.

Nevill, A. (1997). Why the analysis of performance variables recorded on a ratio scale will invariably benefit from a log transformation. Journal of Sports Sciences, 15, 457–458.

Nevill, A., & Atkinson, G. (1997). Assessing agreement between measurements recorded on a ratio scale in sports medicine and sports science. British Journal of Sports Medicine, 31, 314–318. doi:10.1136/bjsm.31.4.314.

Nurse, M., & Nigg, B. (1999). Quantifying a relationship between tactile and vibration sensitivity of the human foot with plantar pressure distributions during gait. Clinical Biomechanics, 14, 667–672. doi:10.1016/S0268-0033(99)00020-0.

Pérez-Castilla, A., Feriche, B., Jaric, S., Padial, P., & García-Ramos, A. (2017). Validity of a linear velocity transducer for testing maximum vertical jumps. Journal of Applied Biomechanics, 33, 388–392. doi:10.1123/jab.2016-0142.

Peterka, R. J. (2018). Sensory integration for human balance control. In Handbook of clinical neurology - Balance, Gait, and Falls (1st ed.) (pp. 27–42). Elsevier B.V.

Plautard, M., Guilhem, G., Fohanno, V., Nordez, A., Cornu, C., & Guével, A. (2017). Comparison of two methodological approaches for the mechanical analysis of single-joint isoinertial movement using a customised isokinetic dynamometer. Sports Biomechanics, 17, 1–16. doi:10.1080/14763141.2016.1269187.

Pratt, J. (1964). Robustness of some procedures for the two-sample location problem. Journal of the American Statistical Association, 59, 665–680.

Rasmussen, J. (2013). Data transformation, type I error rate and power. British Journal of Mathematical and Statistical Psychology, 42, 203–213. doi:10.1111/bmsp.1989.42.issue-2.

Safrit, M. (1989). An overview of measurement. In M. Safrit & T. Wood (Eds.), Measurement concepts in physical education and exercise science (pp. 3–20). Champaign: Human Kinetics.

Schlee, G., Sterzing, T., & Milani, T. L. (2009). Foot sole skin temperature affects plantar foot sensitivity. Clinical Neurophysiology, 120, 1548–1551. doi:10.1016/j.clinph.2009.06.010.

Schmidt, D., Germano, A. M. C., & Milani, T. L. (2017). Effects of active and passive warming of the foot sole on vibration perception thresholds. Clinical Neurophysiology Practice, 2, 38–43. doi:10.1016/j.cnp.2016.12.005.

Tomarken, A., & Serlin, R. (1986). Comparison of ANOVA alternatives under variance heterogeneity and specific noncentrality structures. Psychological Bulletin, 99, 90–99. doi:10.1037/0033-2909.99.1.90.

Verillo, R. (1985). Psychophysics of vibrotactile stimulation. The Journal of the Acoustical Society of America, 77, 225–232. doi:10.1121/1.392263.

Wilcox, R., Peterson, T. J., & McNitt-gray, J. L. (2018). Data analyses when sample sizes are small: Modern advances for dealing with outliers, skewed distributions, and heteroscedasticity. Journal of Applied Biomechanics, 34, 258–261. doi:10.1123/jab.2017-0269.

Wilcox, R. R. (2013). Introduction to robust estimation and hypothesis testing (3rd ed.). San Diego: Academic Press.

Zimmerman, D. W. (2004). A note on preliminary tests of equality of variances. British Journal of Mathematical and Statistical Psychology, 57, 173–181. doi:10.1348/000711004849222.

Zimmerman, D. W., & Zumbo, B. D. (1993). Rank transformations and the power of the student T-Test and Welch T-Test for non-normal populations with unequal variances. Canadian Journal of Experimental Psychology, 47, 523–539. doi:10.1037/h0078850.

3.2.1 Study 2: Summary and classification in the context of this thesis

The term heteroscedasticity means that the amount of measurement error increases as the values increase. VPT data is often, but not always, heteroscedastic. However, several publications do not take this into account, or, if so, do not provide information about whether or not heteroscedasticity was eliminated prior to conducting inferential statistical analyses. This constitutes a problem, as many standard inferential tests do not assume heteroscedasticity.

Study 2 provides a practical methodological example of how heteroscedastic data can be appropriately analyzed. The study shows how to identify, how to eliminate/reduce, and how to control whether or not the data benefitted from this approach. It is important taking these considerations into account, as only appropriate data analyses allow valid data interpretation and placement in the scientific and/or clinical context.

Studies 1 and 2 focus on how to accurately assess and analyze plantar VPT data. As previously mentioned, VPT data is an important contributor to human balance capability. Often, human balance is measured using force platforms. One particularly interesting and promising "type" of human balance is dynamic balance, e.g., unexpected platform perturbations which challenge the balance system. As with VPT data, there is also a high demand for accurate evaluation and analysis of the (dynamic) balance data. This methodological consideration is particularly evident when devices used to asses balance performance are also used as training devices in clinical or therapeutic settings. It is evident that these might be prone to learning effects, for example. Therefore, Study 3 addresses these methodological issues to guarantee reliable data. Only then can the relationship between sensory inputs and balance performance be investigated appropriately.

3.3 Study 3

Aspects of Dynamic Balance Responses: Inter- and Intra-Day Reliability

Daniel Schmidt[1]*, Andresa M.C. Germano[1], Thomas L. Milani[1]

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[1]Department of Human Locomotion, Institute of Human Movement Science & Health, Technische Universitaet Chemnitz, Chemnitz, Saxony, Germany

Abstract

The Posturomed device is used as a scientific tool to quantify human dynamic balance ability due to unexpected perturbations, and as a training device. Consequently, the question arises whether such measurements are compromised by learning effects. Therefore, this study aimed to analyze inter- and intra-day reliability of dynamic balance responses using the Posturomed. Thirty healthy young subjects participated (24.3±3.2 years). The Posturomed was equipped with a triggering mechanism to enable unexpected, horizontal platform perturbations. A force platform was used to quantify Center of Pressure (COP) excursions for two time intervals: interval 1 (0–70 ms post perturbation) and interval 2 (71–260 ms post perturbation). Dynamic balance tests were performed in single leg stances in medio-lateral and anterior-posterior perturbation directions. Inter- and intra-day reliability were assessed descriptively using Bland-Altman plots and inferentially using tests for systematic error and intra-class-correlations. With regard to the mean COP excursions for every subject and all intervals, some cases revealed significant differences between measurement sessions, however, none were considered relevant. Furthermore, intra class correlation coefficients reflected high magnitudes,

which leads to the assumption of good relative reliability. However, analyzing inter- and intra-day reliability using Bland-Altman plots revealed one exception: intra-day comparisons for the anterior-posterior direction in interval 2, which points towards possible learning effects. In summary, results reflected good overall reliability with the exception of certain intra-day comparisons in the anterior-posterior perturbation direction, which could indicate learning effects in those particular conditions.

Introduction

The ability to successfully balance the human body is required in almost all everyday situations, and is important to avoid falls and restrictions of daily activities [1]. Mechanisms of human balance regulation are highly demanding, including three cooperating systems: the visual, vestibular and somatosensory system [2]. Interactions between these three systems vary considerably when comparing quasi-static to dynamic balance conditions [3]. Dynamic balance tests might be more useful to detect possible balance strategies [4], whereas quasi-static balance tests do not seem to be the optimal indicator for functional postural control [5]. Regarding dynamic balance, postural adjustments may be divided into anticipatory and compensatory responses [6]. Anticipatory responses are associated with strategies to preserve postural balance, hence preparing the body for a forthcoming perturbation [7]. Compensatory responses appear as direct muscular reactions responding to sensory feedback signals which are evoked by a perturbation that has already occurred.

Compensatory balance response patterns are present when on a train or a bus, which are induced by sudden accelerations or decelerations. Another example is when walking over ice-covered or wet, slippery surfaces. In all these examples, unexpected translational perturbations occur which are realistic balance challenges of daily life. These examples were taken as the basis of examining postural control strategies [8].

An extensive variety of such perturbation setups are implemented in experimental designs to cause a temporary disequilibrium. These are, for example, horizontal platform movements or video-linked force platforms [9–11]. Some of these devices, e.g. the Wii Balance Board (Nintendo, Kyoto, Japan), were shown to be both useful to quantify dynamic balance and reliable [11]. Another tool to induce

standardized translational platform perturbations is the widely used Posturomed (Haider Bioswing GmbH, Germany) [12], which is also known to quantify dynamic postural control [12–17]. In this context, Taube et al. [5] used the Posturomed to assess dynamic balance ability after four weeks of slackline training using perturbed and unperturbed conditions. On the other hand, this device is also implemented for balance training and balance tasks [18], [19]. When training on the Posturomed, subjects or patients stand on one or two legs, or they perform different simultaneous tasks, like moving limbs etc. In one study, subjects stood on the Posturomed on their right leg for 40 s to evaluate postural stability [20]. In another study this device was used as a postural stabilization task, after subjects were asked to perform series of 3 trials of unexpected perturbations, with measuring intervals of 10 s [21]. Mierau et al. [18] used the Posturomed as a balance task device to analyze cortical activity in healthy subjects. They recorded three consecutive trials, each lasting 20 seconds with a resting period of one minute between trials. Kramer et al. [19] used the Posturomed as a training device in patients with multiple sclerosis. Training sessions lasted three weeks with a total of 9 training sessions, each lasting 30 minutes. Patients a) simply stood on the moveable platform or b) performed tasks with increasing difficulty on the Posturomed, e.g. standing on both legs, on toes or heels, on one leg or with external perturbations.

Due to the application of the Posturomed as a training tool, improvements of dynamic balance can be expected. Therefore, studies using this device to quantify dynamic balance ability might be prone to provoking balance improvements during data collection. In other words, potential learning effects may occur.

Despite these considerations, reliability aspects of the Posturomed have still not been extensively explored, although there is demand for reliable balance assessment tools [11]. To the knowledge of the authors, our study is the first which aimed to analyze the reliability of first dynamic balance responses after unexpected translational perturbations. Another study which dealt with a reliability analysis of the Posturomed was performed by Boeer et al. [22], but they did not induce unexpected perturbations. They concluded that the Posturomed exhibits slight learning effects, but still shows reproducible results to quantify balance ability. Due to its widespread range of application, a better understanding of reliability aspects is of fundamental importance. For this reason, the objective of the present study was to investigate the

intra- and inter-day reliability of dynamic balance responses after unexpected perturbations using the Posturomed device, whereas low intra- and inter-day reliability was hypothesized.

Materials and Methods

Subjects

Thirty healthy, young subjects (15 females, 15 males) participated in this study (mean±SD: 24.3±3.2 yrs, 71.4±12.5 kg, 173.8±9.1 cm). Participants with a history of lower extremity pain or lower leg injury for at least six months before the measurements were excluded from this study. None of the subjects had any peripheral neuropathy or other similar disorders. Subjects gave their written informed consent. In case of any discomfort, participants were instructed to stop measurements. All procedures were executed in accordance with the recommendations of the Declaration of Helsinki. This study was approved by the Ethics Committee of the Faculty of Behavioural and Social Sciences of the corresponding university.

Instrumentation and Testing Procedure

The Posturomed consists of a horizontally moveable bottom-platform which is vertically suspended. More recent versions of this device are equipped with a lever-based provocation unit to enable unexpected horizontal perturbations. Since the version of the Posturomed used in this study did not provide such a provocation unit, it was equipped with an electro-magnet which fixed the bottom-platform after shifting it 20 mm out of its neutral position. This kind of perturbation unit was also used in other previous studies [5], [21], [23]. Unexpected perturbations were induced by manually triggering the electro-magnet causing the bottom platform to swing until it reached the neutral position again. A force-platform (IMM Holding GmbH, Germany; 1 kHz) was installed directly on top of the bottom-platform. Furthermore, a single axis accelerometer ADXL78 (Analog Devices Inc., USA) was integrated into the setup to calculate the reversal points of the platform. Room temperature was controlled in accordance with EN ISO/IEC 17025 (23±2 °C) and was monitored using a digital C28 type K thermocouple (Comark Instruments, U.K.). To guarantee foot temperature variations of less than ±5 to 6°C, which influence plantar sensibility and

consequently movement coordination [24], a miniflash infrared thermometer (TFA Dostmann GmbH & Co KG, Germany) was used to measure the temperature of the dominant foot sole before and after trials. Dynamic balance tests were performed in single leg stance (dominant leg) for two conditions: medio-lateral (ML) and anterior-posterior (AP) perturbation direction. For ML, subjects stood on top of the setup in such a way that the lateral aspect of the dominant foot was pointed towards the electro-magnet, causing an ML perturbation after its release. For AP, subjects were instructed to turn 90° so that the heel was pointed towards the electro magnet, causing an AP perturbation. The exact foot position on top of the setup was marked with tape to ensure higher standardization. For each condition (ML, AP), 12 trials were collected in a randomized order (randomization routine programmed in R, The R Foundation for Statistical Computing, Austria), resulting in a total of 24 trials for one complete measurement session. For data analysis, both conditions were then separated and brought into temporal order (AP 1, . . ., 12; ML 1, . . ., 12). In order to become accustomed to the apparatus, each subject performed six trials (three in each condition) before starting data collection. During the measurements, participants were asked to look straight ahead with their arms hanging loosely down at their sides. To analyze intra-day reliability, the entire testing procedure mentioned above was performed twice a day for each subject, in the morning and afternoon, with a break period of at least four hours, resulting in two data collections per day (1_1 and 1_2). The same procedure was repeated another day (2_1 and 2_2) with 48 hours off between day one and day two. Consequently, each subject took part in four measurement sessions (4x24 trials).

Data Processing and Statistics

Data processing was conducted using R (The R Foundation for Statistical Computing, Austria) and center of pressure (COP) total excursions were calculated for two time intervals: 0–70 ms post trigger (Int 1) and 71–260 ms post trigger (Int 2). These corresponding first and second reversal points (70 and 260 ms, respectively) of the oscillating bottom-platform were calculated over all subjects resulting in (mean±SD) 70.3±4.6 ms (reversal point 1) and 259.8±15.3 ms (reversal point 2).

Descriptively data are presented as graphs and tables including individual data and means of the 12 trials and standard deviations. Additionally, Bland-Altman plots

are depicted to assess absolute reliability. Since measurement error can be of systematic nature (e.g. bias) [25], a repeated measures Analysis of Variance (ANOVA) was performed with Bonferroni post hoc tests to detect significant bias [25], [26]. The level of significance was corrected due to the number of measurement sessions (n = 4) to $\alpha = 0.05/4 = 0.0125$. The relevance of mean differences was determined by root mean square error (RMSE) calculations. To assess relative reliability, intra-class-correlation (ICC) coefficients were included. As this paper deals with test-retest reliability and averaged COP values, ICC model 3,k was used, as recommended [27]. Furthermore, to quantify data variability, coefficients of variation (COVs) were calculated.

Results

All trials (4 measurement sessions x 12 trials, respectively) were taken into consideration in both perturbation directions (AP, ML) and intervals; Fig 1.

Interval 1 exhibited ranges of COP Total excursions from 10–20 mm (96% of all subject trials) for both perturbation directions. Over the course of all 48 trials, no tendency of increasing or decreasing COP Total excursions was observed, see Fig 1.

For interval 2, measurements ranged from 40–90 mm (88% of all subject trials) for both perturbation directions (Fig 1). Considering individual measurement sessions and their 12 trials, for each condition, no tendency towards increasing or decreasing excursions was found for AP or ML. When comparing intra-day data (day one or day two), decreased COP excursions were evident for seven out of 30 subjects at the retests for AP. In ML, this finding was evident for three out of 30 subjects (e.g. see Fig 1, subject 02: 1_1 vs. 1_2, interval 2) and was not observed for inter-day comparisons.

Fig 2 shows descriptively that inter-subject variations occurred and were greater for interval 2, but also that no trend towards increasing or decreasing intra-subject excursions was present during measurement sessions, especially for interval 2 (e.g. mean excursions from 1_1 were not always greater than for 2_2).

Table 1 shows no significant differences for interval 1 in the AP direction. However, in the ML direction, significantly higher COP excursions were found for 1_1 compared to 1_2 and 2_2. In interval 2, no significant differences were present in the

ML direction. For AP, comparisons with significantly decreased COP excursions at the retest were evident when comparing 1_1 vs. 1_2, 2_1 vs. 2_2 and 1_1 vs. 2_2.

Fig 3 shows exemplary Bland-Altman plots. Summarized data for all comparisons are provided in Table 2. Interval 1 generally demonstrated little bias and random error (Table 2) for both perturbation directions, slightly greater bias was observed for intra-day than for inter-day data.

Bland-Altman parameters for interval 1 revealed that differences were located within the LOAs for 97% of all cases, for AP and ML. In two out of eight Bland-Altman plots, differences were not evenly distributed around the zero line for AP and ML (not graphically illustrated). Exemplary data for interval 1 are shown in Fig 3 (left graphs). For interval 2 (exemplary data in Fig 3, right graphs) in the ML direction, bias was low, although somewhat higher for intraday than for inter-day comparisons (see Table 2). Differences were again mainly distributed within the LOAs, however, intra-day comparisons showed approx. 60% positive differences. For AP, three out of four plots presented large bias and more positive differences for intra-day comparisons, reflecting decreased COP excursions at the respective retest. Random error components were greater than in interval 1 when compared to the grand means (Table 2).

Table 2 summarizes ICC coefficients for intra- and inter-day comparisons and all intervals, ranging between 0.713 and 0.970.

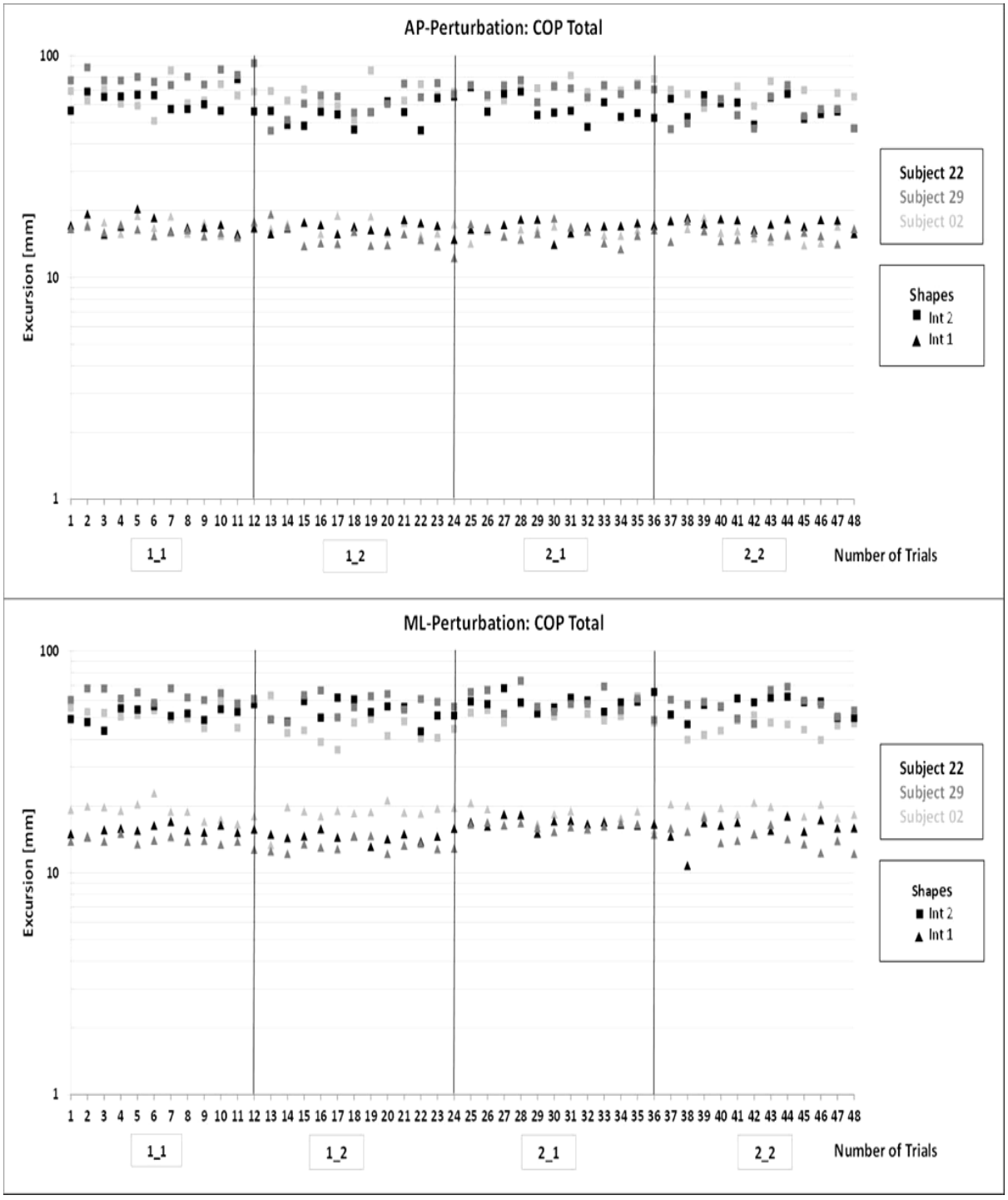

Fig 1. COP Total excursions in both perturbation directions: AP (top), ML (bottom) from six randomly chosen subjects, showing all individual trials (12) for each of the four measurement sessions (1_1, . . ., 2_2).

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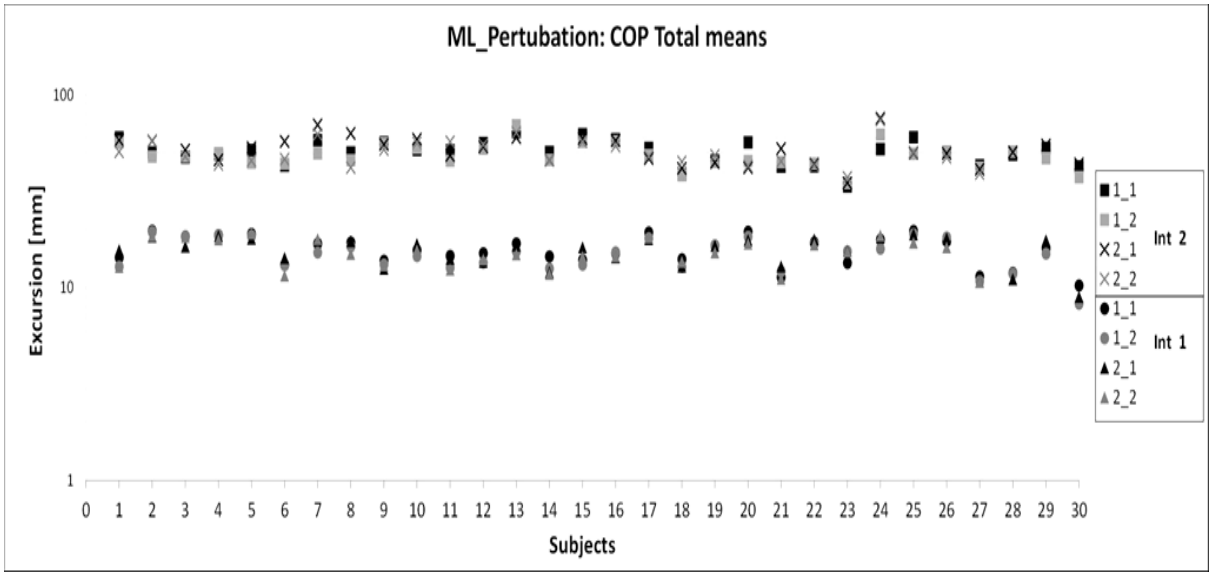

Fig 2. Mean COP Total excursions in the ML direction for all subjects, intervals and measurement sessions (1_1, . . ., 2_2).

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Table 1. COP Total excursions (mean±SD) for both perturbation directions (AP, ML), all four measurement sessions and all analyzed intervals. Significant differences between the four measurement sessions are marked with superscripted symbols; see below (α = 0.0125).

AP COP Total [mm]	**1_1**	**1_2**	**2_1**	**2_2**
Int 1	15.1±1.9	14.8±1.8	15.1±1.8	14.7±2.2
Int 2	61.4±13.3$^{*\#}$	54.2±12.2*	56.5±10.8$^{\Phi}$	52.8±10.6$^{\#\Phi}$
ML COP Total [mm]				
Int 1	15.8±2.7$^{\Psi X}$	15.1±2.8$^{\Psi}$	15.6±2.7	15.1±2.7^{X}
Int 2	51.1±7.3	49.0±7.3	52.4±8.9	50.4±8.0

Significant differences:

*p<0.001

$^{\#}$p=0.001

$^{\Phi}$p=0.003

$^{\Psi}$p=0.003

^{X}p=0.002

doi:10.1371/journal.pone.0136551.t001

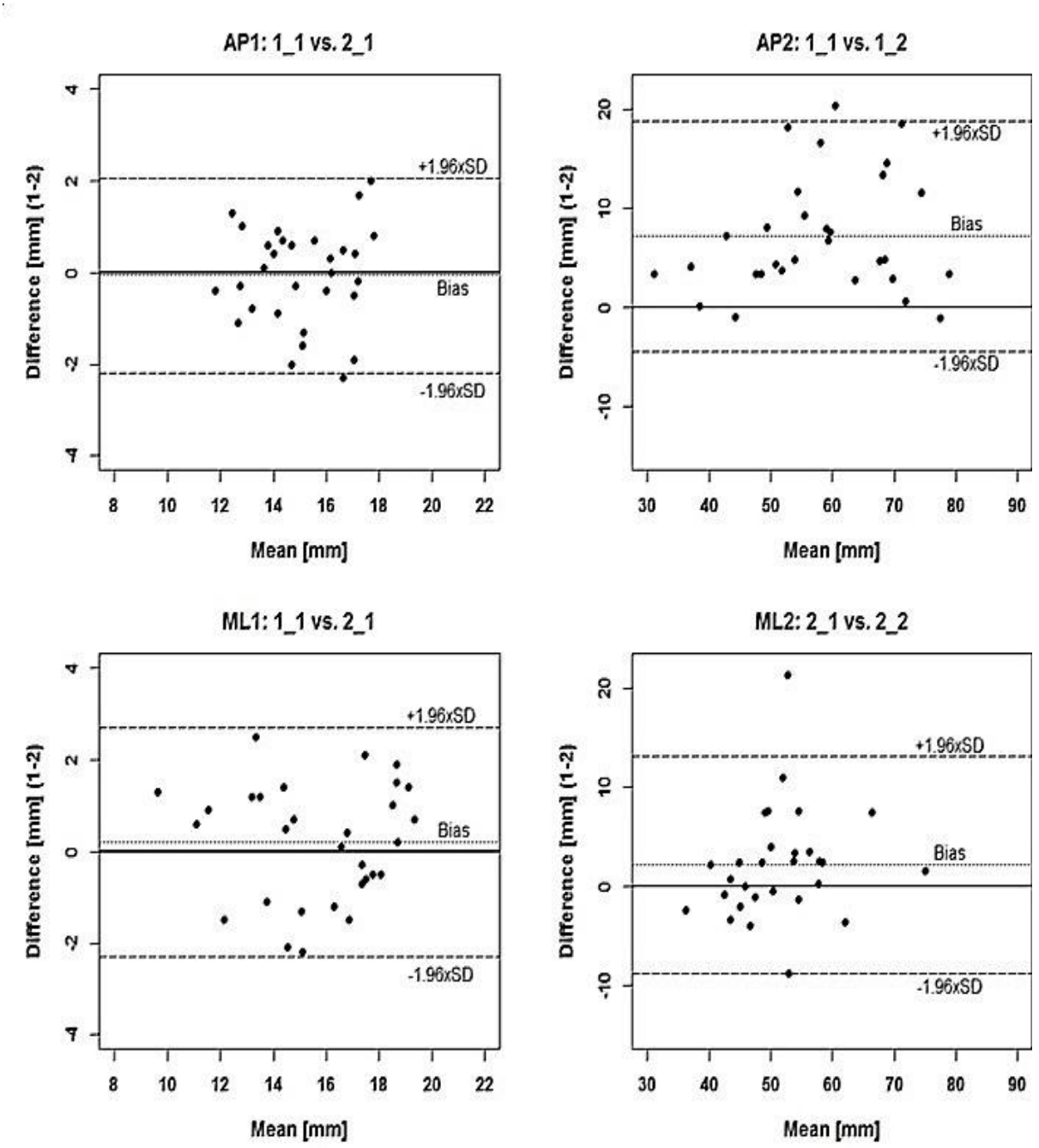

Fig 3. Bland-Altman plots for the AP (top) and ML (bottom) perturbation directions, showing examples for intervals 1 (left plots) and 2 (right plots).

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Table 2. Overview of ICCs and parameters implemented in the analysis of Bland-Altman plots. Depicted are the grand mean (mean of both measurement sessions), bias, random error component and upper/lower limits of agreement (ULOA/LLOA, respectively) for inter- and intra-day comparisons of all intervals in the AP and ML direction.

Int 1	**1_1 vs. 1_2**		**2_1 vs. 2_2**		**1_1 vs. 2_1**		**1_2 vs. 2_2**	
[mm]	**AP**	**ML**	**AP**	**ML**	**AP**	**ML**	**AP**	**ML**
ICC	0.953	0.970	0.937	0.926	0.905	0.941	0.869	0.947
grand mean	14.9	15.5	14.9	15.3	15.1	15.7	14.8	15.1
bias	0.3	0.7	0.5	0.7	-0.1	0.2	0.1	0.2
random error	1.5	1.8	1.9	2.7	2.2	2.5	2.7	2.4
ULOA	1.8	2.5	2.3	3.4	2.0	2.7	2.7	2.6
LLOA	-1.3	-1.2	-1.4	-2.0	-2.2	-2.3	-2.6	-2.2
Int 2	**1_1 vs. 1_2**		**2_1 vs. 2_2**		**1_1 vs. 2_1**		**1_2 vs. 2_2**	
[mm]	**AP**	**ML**	**AP**	**ML**	**AP**	**ML**	**AP**	**ML**
ICC	0.942	0.888	0.934	0.880	0.751	0.713	0.844	0.853
grand mean	57.8	50.0	54.7	51.4	59.0	51.7	53.5	49.7
bias	7.2	2.1	4.0	2.1	4.9	-1.3	1.6	-1.4
random error	11.6	9.1	10.5	11.0	21.2	15.1	16.5	10.9
ULOA	18.8	11.2	14.5	13.1	26.1	13.7	18.2	9.5
LLOA	-4.5	-7.0	-6.5	-8.8	-16.4	-16.4	-14.9	-12.3

doi:10.1371/journal.pone.0136551.t002

Discussion

This study aimed to analyze inter- and intra-day reliability of dynamic balance responses after unexpected perturbations using the Posturomed device. Various statistical approaches were used to assess reliability. In this regard, intra- and inter-day comparisons were made, because different intervention protocols are often conducted between two balance tests. Furthermore, intra-session trials between and within subjects were analyzed. As already shown, the Posturomed is also used as a training device [28], and therefore, consecutive balance tests might be prone to balance improvements at the retest. At the same time, the Posturomed is a standardized device to induce unexpected perturbations [12], hence also used to quantify dynamic balance ability [12]–[17].

The present study showed good relative and absolute reliability for both analyzed intervals and both perturbation directions. However, interval 2 exhibited slight learning effects when considering intra-day comparisons in the AP perturbation direction.

Background on Analyzed Intervals

This section describes the physiological background regarding the time intervals analyzed in this study. As already mentioned, perturbations were implemented unexpectedly, eliciting compensatory motor reactions of muscles [6]. Stelmach et al. [29] examined postural reflexes for different perturbation conditions, similar to ones used in the present study. They found that the tibialis anterior muscle showed activity 100 ms after the onset of the perturbation. Other studies also implemented similar translational perturbations and found muscle latencies to be present at around 100 ms post perturbation [30], [31]. As a consequence of these muscular responses, it is obvious that active COP (Center of Pressure) displacements also occur. In this context, Müller and Redfern [31] examined similar anterior translational platform perturbations and showed that the onset of active COP displacements occurred at approx. 130 ms post perturbation onset. Consequently, active COP displacements in our study are present in interval 2, characterizing first compensatory reflex responses caused by the unexpected perturbation itself. Active balance responses are meaningful to assess dynamic balance, since they are important to control balance after sudden perturbations and hence prevent falls [32]. In contrast, during interval 1

(up to 70 ms post perturbation onset), muscular responses were rather a consequence of quasi-static balance demands of the previous pre-trigger time interval. However, it is possible that previous anticipatory activity still changed postural motor behavior in interval 1.

Interval 1

The subjects' ranges indicate that there were some variations of COP magnitudes between and within subjects. However, these magnitudes did not change within the 12 trials in each of the four measurement sessions (Fig 1). This indicates that there was no learning effect for AP or ML direction and was confirmed when considering inter- and intra-subject variations. In contrast, another study found slight and non-significant decreases of pathways within the course of five trials [22]. This study also used the Posturomed, but the platform pathway was analyzed for six seconds and the setup did not include unexpected perturbations.

Intra- and inter-day observations showed no significant bias for AP. In the ML direction, significant biases were found between 1_1 vs. 1_2 and 1_1 vs. 2_2. However, for both comparisons, differences accounted for only 0.7 mm (4.4%). Furthermore, since the root mean square error (RMSE) term calculated over these comparisons was larger than the mean differences, significant bias found here was not considered relevant regarding improving or deteriorating balance responses.

Considering means of each measurement session for each subject (Fig 2), no trend towards either increasing or decreasing excursions was evident. Additionally, intra- and inter-subject variations were very small (Fig 2). This means, following visual inspection, no learning effects seemed to be present.

ICC magnitudes found in interval 1 were considered to be high (>0.90, [33], [34]) and good (>0.70, [35]). High magnitudes of ICC coefficients show that the ranking of the subjects was similar for both intervals and all measurement sessions. This provides important information of how the measures are associated during several test-retest comparisons. The ICC model of this study (3, k) was only sensitive to random error [27], but the detected significant biases for ML were not relevant, hence ICC magnitudes indeed seem to reflect high relative reliability. Relative reliability describes how data or a score of the individual subject keeps its position with respect to the entire sample throughout repeated measurements [25]. However,

relative reliability does not necessarily provide information on whether measures are close to each other within consecutive trials for individual subjects [25]. Therefore, absolute reliability was also assessed using Bland-Altman plots to indicate to what extent repeated measures change for individuals [25].

Little bias and an even distribution of differences around the zero line were observed in the Bland-Altman plots, pointing towards no learning effects. Bland-Altman parameters were interpreted as follows [36]: if a subject obtained an average COP Total excursion of 13.2 mm on the first test in AP, data could vary within the range of the LOAs (+1.8 and-1.3 mm), which is from 11.9 to 15.0 mm on a retest [36]. The amount of variation within 12 trials ranged from 10.8 to 17.1 mm for this subject. This demonstrates that variation within single trials is of greater magnitude than variation based on calculations using means and LOAs. Hence, the interpretation of the variation should not be based upon whether only a few differences fall outside the LOAs [33], but to evaluate the amount of variation during each of the 12 trials. Some of this variation seems to represent physiological balance patterns, e.g. anticipatory activity, which cannot be avoided. Other studies based on quasi-static balance tests found high intra-subject variations for consecutive days [37], [38] as well as within one day [38]. They suggest the high variability might be due to different balance strategies, and not necessarily due to a low reliability of the setup [38]. This presumption also agrees with Corriveau et al. [39], who estimated test-retest reliability in quasi-static double leg stance. It was assumed that measurement error is mainly linked to the biologic variability [39]. Similarly, Müller [40] found low oscillating frequency variations of the Posturomed, hence also suggesting that platform pathway depends on the subjects neuromuscular strategy. Note, however, that neuromuscular reactions due to the perturbation itself did occur in interval 2 (after approx. 100 ms [31]).

From all intra- and inter-day comparisons, there was only one exception in ML (1_1 vs. 1_2): slightly decreasing COP excursions were present indicating balance improvements at 1_2. The reason for this exception, however, is unknown. Considering the amount of intra and inter-subject variability and the non-relevance of mean differences, differences should not be over-interpreted. Taking into account all analysis during interval 1, which mainly consisted of passive balance demands, data appear to be reliable. This means that the Posturomed indeed seems to be a

standardized perturbation setup to induce unexpected translatoric perturbations, as also proposed by Kiss [12].

Interval 2

No generally decreasing or increasing magnitudes were observed descriptively within all 12 trials per session, indicating neither improving nor deteriorating dynamic balance responses.

Boeer et al. [22] examined balance ability using the Posturomed, however measuring total platform pathway with no perturbation during single leg stance. They performed retests after one to three weeks and found slight but not significant decreases within the course of five consecutive trials. In the present study, when comparing trials from 1_1 with 1_2, no trend was observable for AP or ML. However, especially for AP, decreased excursions at 1_2 (retest) were observed, indicating possible intra-day learning effects (Fig 1, subject 22: 1_1 vs. 1_2).

Mean COP Total excursions exhibited no significant bias for the ML direction, but all intraday considerations and 1_1 vs. 2_2 for AP showed significant bias. Mean differences ranged from 3.7 to 8.6 mm, which corresponds to approx. 6.5 and 10.6% of the grand means, respectively. Similarly to interval 1, calculated RMSE values were larger than mean differences, meaning significant bias found here cannot be regarded as relevant. Therefore, with respect to mean COP excursions, no relevant balance improvements nor deteriorations were observed. This is in accordance with Corriveau et al. [39], who estimated test-retest reliability of center of pressure—center of mass variables. They also detected significant, but not relevant bias in the AP direction. However, they tested older subjects using both legs and measurements lasting for 120 seconds. With respect to the difference between older and younger subjects, Allum et al. [41] found a delayed (approx. 20 ms) onset of muscle responses for older subjects after unexpectedly induced roll and pitch perturbations. Since young subjects participated in the present study, our results might not be directly transferable to older populations. Further studies should investigate this aspect.

With regard to means of each measurement session for each subject, some presented higher COP excursions for AP at 1_1 and 2_1, when compared to the

retests (1_2, 2_2, respectively). This means that those subjects improved their balance, especially within one day. This tendency was not detected for ML (Fig 2).

ICC coefficients of the present study (0.713 to 0.942) indicated good to high relative reliability [33]–[35]. Corriveau et al. [39] found moderate (0.72; 0.74) to excellent (0.89; 0.90) ICC coefficients when assessing quasi-static balance. Importantly, ICCs can be dependent on the variance or variability between single subjects [26], [27], [35], [42], [43] and, therefore, can be context-specific [44]. This means, high inter-subject variability most likely results in high ICC values [25], [27]. To better identify variability, coefficients of variation (COV) were also calculated. Some high ICC coefficients were found, although COVs had lower magnitudes (interval 1 AP, 1_1 vs. 1_2: ICC = 0.953, COV = 0.120) and vice versa (interval 2 AP, 1_1 vs. 2_1: ICC = 0.751, COV = 0.220). These considerations indicate that high ICC coefficients obtained in the present study did not necessarily occur due to high variability between subjects. Hence, good/high ICC magnitudes for interval 2 indeed seem to reflect good to high relative reliability. This indicates that, although during interval 2 there were biological variations due to motor responses, subjects maintained their position within the different test-retest configurations.

Bland-Altman plots for ML also show that the range occurring within 12 trials was larger than the range calculated with means (LOA), indicating high absolute reliability. The same can be claimed for AP, however, the presence of substantial bias became evident. Fig 3 shows that 93 and 80% of the subjects improved balance responses for both intra-day comparisons in AP, which is evident by the smaller COP excursions [45], [46] at both retests. For inter-day comparisons, this finding was not as pronounced. This might be explained in that the central nervous system elaborates a special motor memory program to improve reactive stability [32]. It might be supposable that the large time period between the tests (48 hours) led to a reduced ability of the subjects to recall the acute motor memory program from the pretest.

This means, for AP and especially for intra-day considerations, the present balance data seem to exhibit low absolute reliability, as also confirmed by relatively high random error components. A possible explanation for this is the difference between the limits of the base of support when comparing AP and ML perturbations: in AP, due to the anatomical foot structure, a greater COP path length enables the

generation of greater torque compared to ML. Carpenter et al. [47] confirmed that perturbations in the ML direction are more challenging because they require a more complex muscle response program in comparison to perturbations in the AP direction. This consequently results in a greater demand on information processing in the central nervous system [41]. The less balance-challenging AP direction might induce greater potential to correct and improve balance after unexpected perturbations [40], hence allowing for biological variability. In contrast, Corriveau et al. [39] found lower reliability for the ML direction compared to the AP direction. However, our results may not be directly comparable to their study, since they measured older subjects (minimal age: 60 years) performing double limb stance. As already mentioned, absolute intra-day reliability was somewhat lower in the present study, especially in AP. This finding does not agree with Lin et al. [48], who found better absolute as well as relative reliability for intra-day compared to inter-day considerations. In contrast, their subjects performed quasi-static and upright double leg stance on four different days. A similar study examining balance ability and reliability (retests after 1 to 3 weeks) using the Posturomed found slightly smaller pathways at the retest, indicating possible, although minimal, learning effects [22]. It is also important to note that their study did not mention the relevance of the differences found.

Interval 2 shows high absolute reliability for inter-day comparisons, indicating that individual balance responses are similar for individual subjects during different test-retest comparisons. Lower absolute reliability was found for intra-day comparisons, especially in the AP direction, indicating possible learning effects.

Conclusions

To summarize, when looking at each individual measurement session (12 trials) for all intervals, it is important to note that no increasing or decreasing excursions were observed. This indicates that there was no observable learning effect within the 12 trials performed. Therefore, future investigations using the Posturomed to assess dynamic balance responses should be able to use 12 trials without creating any learning effects. When considering mean COP excursions over those 12 trials for every subject and all intervals, significant differences between measurement sessions were detected in some cases, however, none were considered to be

relevant. Furthermore, ICC coefficients were of high magnitude. Taking these considerations together, one would presume a generally good reliability for the intervals analyzed in this study. This is true for the majority of the present data, but there were some exceptions when analyzing inter- and intra-day reliability using Bland-Altman plots and inspecting individual trial data of the sessions. In this regard it was shown that intra-day reliability for interval 2 in the AP direction presented decreased excursions for the majority of subjects at the retests, corresponding to possible learning effects. For this reason, it is important to be aware of potential learning effects when performing examinations in the morning and afternoon of the same day, as conducted in the present study. These potential learning effects, however, did not occur between inter-day measurements within the intervals of this study. Additionally, it is important to note that our results should be acknowledged in the context of unexpectedly induced perturbations as performed in this study. Further studies should also investigate reliability aspects of muscular activity and when implementing longer test-retest periods. Moreover, it is also suggested to explore reliability aspects of dynamic balance responses of older subjects.

Supporting Information

S1 File. Minimal data set. (XLSX)

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Author Contributions

Conceived and designed the experiments: DS AG TLM.

Performed the experiments: DS AG.

Analyzed the data: DS AG TLM.

Contributed reagents/materials/analysis tools: DS AG TLM.

Wrote the paper: DS AG TL.

References

1. Oancea C, Crişan AF, Timar B, Fira-Mladinescu O, Tudorache V. Balance impairment in patients with COPD. PLoS One. 2015; 10(3): e0120573. doi: 10.1371/journal.pone.0120573 PMID: 25768731.
2. Mergner T, Rosemeier T. Interaction of vestibular, somatosensory and visual signals for postural control and motion perception under terrestrial and micro-gravity conditions—a conceptual model. Brain Res Rev. 1998; 28(1–2): 118–135. PMID: 9795180.
3. Condron J, Hill K. Reliability and validity of a dual-task force platform assessment of balance performance: effect of age, balance impairment and cognitive task. J Am Geriatr Soc. 2002; 50: 157–162. PMID: 12028261.
4. Vrieling AH, van Keeken HG, Schoppen T, Otten E, Hof AL, Halbertsma JPK, et al. Balance control on a moving platform in unilateral lower limb amputees. Gait Posture. 2008; 28(2): 222–228. doi: 10.1016/j.gaitpost.2007.12.002. PMID: 18207407.
5. Taube W, Lorch M, Zeiter S, Keller M. Non-physical practice improves task performance in an unstable, perturbed environment: motor imagery and observational balance training. Front Hum Neurosci. 2014; 8: 1–10.
6. Latash ML. Neurophysiological basis of movement. 1st ed. Champaign: Human Kinetics; 1998.
7. Santos MJ, Kanekar N, Aruin AS. The role of anticipatory postural adjustments in compensatory control of posture: 1. Electromyographic analysis. J Electromyogr Kinesiol. 2010; 20(3): 388–397.
doi: 10.1016/j.jelekin.2009.06.006. PMID: 19660966.
8. Smith G V, Forrester LW, Silver KHC, Macko RF. Effects of treadmill training on translational balance perturbation responses in chronic hemiparetic stroke patients. J Stroke Cerebrovasc Dis. 2000; 9(5): 238–245.
9. Bloem BR, Allum JH, Carpenter MG, Honegger F. Is lower leg proprioception essential for triggering human automatic postural responses? Exp Brain Res. 2000; 130(3): 375–391. PMID: 10706436.
10. Perry SD, McIlroy WE, Maki BE. The role of plantar cutaneous mechanoreceptors in the control of compensatory stepping reactions evoked

by unpredictable, multidirectional perturbation. Brain Res. 2000; 877(2): 401–406. PMID: 10986360.

11. Bower KJ, McGinley JL, Miller KJ, Clark RA. Instrumented static and dynamic balance assessment after stroke using Wii Balance Boards: Reliability and association with clinical tests. PLoS One. 2014; 9 (12): e115282. doi: 10.1371/journal.pone.0115282 PMID: 25541939.
12. Kiss R. A new parameter for characterizing balancing ability on an unstable oscillatory platform. Med Eng Phys. 2011; 33: 1160–1166. doi: 10.1016/j.medengphy.2011.04.017 PMID: 21616699.
13. Bruhn S, Kullmann N, Gollhofer A. The effects of a sensorimotor training and a strength training on postural stabilisation, maximum isometric contraction and jump performance. Int J Sports Med. 2004; 25 (1): 56–60. PMID: 14750014.
14. Hirschmüller A, Konstantinidis L, Baur H, Müller S, Mehlhorn A, Kontermann J, et al. Do changes in dynamic plantar pressure distribution, strength capacity and postural control after intra-articular calcaneal fracture correlate with clinical and radiological outcome? Injury. 2011; 42(10): 1135–1143. doi: 10. 1016/j.injury.2010.09.040 PMID: 21075372.
15. Kiss RM. Effect of the degree of hip osteoarthritis on equilibrium ability after sudden changes in direction. J Electromyogr Kinesiol. 2010; 20(6): 1052–1057. doi: 10.1016/j.jelekin.2010.06.005 PMID: 20656503.
16. Schwab MJ. Chiropractic management of a 47-year-old firefighter with lumbar disk extrusion. J Chiropr Med. National University of Health Sciences; 2008; 7(4): 146–154.
17. Hilberg T, Herbsleb M, Gabriel HHW, Jeschke D, Schramm W. Proprioception and isometric muscular strength in haemophilic subjects. Haemophilia. 2001; 7(6): 582–588. PMID: 11851757.
18. Hülsdünker T, Mierau A, Neeb C, Kleinöder H, Strüder HK. Cortical processes associated with continuous balance control as revealed by EEG spectral power. Neurosci Lett. 2015; 592: 1–5. doi: 10.1016/j. neulet.2015.02.049. PMID: 25724275.
19. Kramer A, Dettmers C, Gruber M. Exergaming with additional postural demands improves balance and gait in patients with Multiple Sclerosis as

much as conventional balance training and leads to high adherence to homebased balance training. Commun Cogn. 2014; 95(10): 1803–1809.

20. Taube W, Gruber M, Beck S, Faist M, Gollhofer A, Schubert M. Cortical and spinal adaptations induced by balance training: Correlation between stance stability and corticospinal activation. Acta Physiol. 2007; 189(4): 347–358.
21. Granacher U, Gruber M, Gollhofer A. Resistance training and neuromuscular performance in seniors. Int J Sports Med. 2009; 30(9): 652–657. doi: 10.1055/s-0029-1224178 PMID: 19569007.
22. Boeer J, Mueller O, Krauss I, Haupt G, Horstmann T. Zuverlässigkeitsprüfung eines Messverfahrens zur Charakterisierung des Standverhaltens und Quantifizierung des Balancevermögens auf einer instabilen Plattform (Posturomed). Sportverl Sportschad. 2010; 24: 40–45.
23. Pfusterschmied J, Buchecker M, Keller M, Wagner H, Taube W, Müller E. Supervised slackline training improves postural stability. Eur J Sport Sci. 2013; 13: 49–57.
24. Schlee G, Sterzing T, Milani TL. Foot sole skin temperature affects plantar foot sensitivity. Clin Neurophysiol. 2009; 120(8): 1548–1551. doi: 10.1016/j.clinph.2009.06.010. PMID: 19616994.
25. Bruton A, Conway JH, Holgate ST. Reliability: What is it, and how is it measured? Physiotherapy. 2000; 86(2): 94–99.
26. Müller R, Büttner P. A critical discussion of intraclass correlation coefficients. Stat Med. 1994; 13(23–24): 2465–2476. PMID: 7701147.
27. Weir J. Quantifying Test-Retest Reliability using the Intraclass Correlation Coefficient and the SEM. J Strength Cond Res. 2005; 19(1): 231–240. PMID: 15705040.
28. Boeer J, Müller O, Krauß O, Haupt G, Horstmann T. Reliability of a measurement technique to characterize standing properties and to quantify balance capabibilities of healthy subjects on an unstable oscillatory platform (Posturomed). Sportverl Sportschad. 2010; 24: 40–45.
29. Stelmach GE, Phillips J, DiFabio RP, Teasdale N. Age, functional postural reflexes, and voluntary sway. J Gerontol. 1989; 44(4): B100–B106. PMID: 2738304.

30. Moore SP, Rushmer DS, Windus SL, Nashner LM. Human automatic postural responses: Responses to horizontal perturbations of stance in multiple directions. Exp Brain Res. 1988; 73: 648–658. PMID: 3224674.
31. Müller M, Redfern M. Correlation between EMG and COP onset latency in response to a horizontal platform translation. J Biomech. 2004; 37: 1573–1581. PMID: 15336932.
32. Patel P, Bhatt T. Adaptation to large-magnitude treadmill-based perturbations: improvements in reactive balance response. Physiol Rep. 2015; 3(2): e12247. doi: 10.14814/phy2.12247 PMID: 25649245.
33. Atkinson G, Nevill A. Statistical methods for assessing measurement error (Reliability) in variables relevant to sports medicine. Sport Med. 1998; 26(4): 217–238.
34. Vincent J. Statistics in Kinesiology. 1st ed. Champaign: Human Kinetics Books; 1994.
35. Bédard M, Martin NJ, Krueger P, Brazil K. Assessing reproducibility of data obtained with instruments based on continuous measurements. Exp Aging Res. 2000; 26(4): 353–365. PMID: 11091941.
36. Nevill A, Atkinson G. Assessing agreement between measurements recorded on a ratio scale in sports medicine and sports science. Br J Sports Med. 1997; 31(4): 314–318. PMID: 9429009.
37. Samson M, Crowe A. Intra-subject inconsistencies in quantitative assessments of body sway. Gait Posture. 1996; 4: 252–257.
38. Benvenuti F, Mecacci R, Gineprari I, Bandinelli S, Benvenuti E, Ferrucci L, et al. Kinematic characteristics of standing disequilibrium: reliability and validity of a posturographic protocol. Arch Phys Med Rehabil. 1999; 80: 278–287. PMID: 10084435.
39. Corriveau H, Hébert R, Prince F, Raîche M. Postural control in the elderly: an analysis of test-retest and interrater reliability of the COP-COM variable. Arch Phys Med Rehabil. 2001; 82(1): 80–85. PMID: 11239290.
40. Müller O, Günther M, Krauß I, Horstmann T. Physical characterization of the therapeutic device posturomed as a measuring device-presentation of a procedure to characterize balance ability. Biomed Tech. 2004; 49: 56–60.

41. Allum JHJ, Carpenter MG, Honegger F, Adkin a L, Bloem BR. Age-dependent variations in the directional sensitivity of balance corrections and compensatory arm movements in man. J Physiol. 2002; 542: 643–663. PMID: 12122159.
42. Shrout PE. Measurement reliability and agreement in psychiatry. Stat Methods Med Res. 1998; 7: 301–317. PMID: 9803527.
43. Vaz S, Falkmer T, Passmore AE, Parsons R, Andreou P. The case for using the repeatability coefficient when calculating test-retest reliability. PLoS One. 2013; 8(9): e73990. doi: 10.1371/journal.pone.0073990 PMID: 24040139.
44. Traub R, Rowley G. Understanding reliability. Educ Meas Issues Pract. 1991; 10: 37–45.
45. Woollacott M, Shumway-Cook A. Attention and the control of posture and gait: A review of an emerging area of research. Gait Posture. 2002; 16: 1–14. PMID: 12127181.
46. Shumway-Cook A, Woollacott M, Kerns K, Baldwin M. The effects of two types of cognitive tasks on postural stability in older adults with and without a history of falls. J Gerontol. 1997; 52: 232–240.
47. Carpenter MG, Allum JHJ, Honegger F. Directional sensitivity of stretch reflexes and balance corrections for normal subjects in the roll and pitch planes. Exp Brain Res. 1999; 129(1): 93–113. PMID: 10550507.
48. Lin D, Seol H, Nussbaum MA, Madigan ML. Reliability of COP-based postural sway measures and age-related differences. Gait Posture. 2008; 28(2): 337–342. doi: 10.1016/j.gaitpost.2008.01.005 PMID: 18316191.

3.3.1 Study 3: Summary and classification in the context of this thesis

The Posturomed device offers a wide range of applications, as it is used for (dynamic) balance measurements, but also serves as a therapeutic training device. Study 3 shows that this device has a good overall reliability when it comes to initial motor responses after unexpected platform perturbations. In fact, there were no clinically relevant differences between the parameters and/or measurement sessions (intra- and inter-day).

Studies 1, 2, and 3 of this thesis deal with aspects associated with plantar vibratory sensitivity and the assessment of human balance. As these two aspects are interrelated, research has focused on investigating the isolated role plantar afferents have on human balance performance. To adequately examine this, researchers need to artificially manipulate (e.g. reduce) the activity of plantar afferents, however, without affecting other sensory systems. This is quite challenging, and indeed, several studies show certain limitations possibly rendering interpretations vague. Study 4 attempts to account for these limitations and to investigate the effect of reduced plantar inputs on (dynamic) balance performance. Thereby, the conclusions and experience gained from Studies 1, 2, and 3 (and other related literature) significantly contribute to current knowledge in this area.

3.4 Study 4

Effects of hypothermically reduced plantar skin inputs on anticipatory and compensatory balance responses

Andresa M.C. Germano[1]*, Daniel Schmidt[1] and Thomas L. Milani[1]

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[1]Department of Human Locomotion, Chemnitz University of Technology, Institute of Human Movement Science and Health, Reichenhainer Straße 31/33, Chemnitz 09126, Germany

Abstract

Background: Anticipatory and compensatory balance responses are used by the central nervous system (CNS) to preserve balance, hence they significantly contribute to the understanding of physiological mechanisms of postural control. It is well established that various sensory systems contribute to the regulation of balance. However, it is still unclear which role each individual sensory system (e.g. plantar mechanoreceptors) plays in balance regulation. This becomes also evident in various patient populations, for instance in diabetics with reduced plantar sensitivity. To investigate these sensory mechanisms, approaches like hypothermia to deliberately reduce plantar afferent input have been applied. But there are some limitations regarding hypothermic procedures in previous studies: Not only plantar aspects of the feet might be affected and maintaining the hypothermic effect during data collection. Therefore, the aim of the present study was to induce a permanent and controlled plantar hypothermia and to examine its effects on anticipatory and compensatory balance responses. We hypothesized deteriorations in anticipatory and compensatory balance responses as increased center of pressure excursions

(COP) and electromyographic activity (EMG) in response to the hypothermic plantar procedure. 52 healthy and young subjects (23.6 ± 3.0 years) performed balance tests (unexpected perturbations). Subjects' foot soles were exposed to three temperatures while standing upright: 25, 12 and 0 °C. COP and EMG were analyzed during two intervals of anticipatory and one interval of compensatory balance responses (intervals 0, 1 and 2, respectively).

Results: Similar plantar temperatures confirmed the successful implementation of the thermal platform. No significant COP and EMG differences were found for the anticipatory responses (intervals 0 and 1) under the hyperthermia procedure. Parameters in interval 2 showed generally decreased values in response to cooling.

Conclusion: No changes in anticipatory responses were found possibly due to sensory compensation processes of other intact afferents. Decreased compensatory responses may be interpreted as the additional balance threat, creating a more cautious behavior causing the CNS to generate a kind of over-compensatory behavior. Contrary to the expectations, there were different anticipatory and compensatory responses after reduced plantar inputs, thereby, revealing alterations in the organization of CNS inputs and outputs according to different task difficulties.

Keywords: Plantar hypothermia, CNS, Spinal cord, Dynamic balance, Sensitivity, anticipatory responses, Compensatory responses

Background

In daily life, we are confronted with various challenges regarding quasi-static and dynamic balance requirements. In both cases, the center of pressure (COP) needs to be corrected to keep or re-establish its position within the base of support. In terms of dynamic balance, postural strategies rely on two different mechanisms: anticipatory and compensatory responses [1, 2]. For example, when getting on a bus it is predictable that the bus will accelerate, causing a translational perturbation. To prepare the body for this upcoming external perturbation, anticipatory responses are accessed and induce pre muscle activation [2]. After the bus accelerates, causing the perturbation, reflexive compensatory reactions are generated resulting in muscular activation to re-establish balance [1, 3]. According to Santos et al. [2], the function of the anticipatory adjustments is to minimize the effect of the forthcoming body

perturbations with some corrections while the function of the compensatory responses is to restore the balance after a perturbation has already occurred. In this way, both anticipatory and compensatory responses start with afferent information and they include activation or inhibition of muscles involved in postural control. All balance control responses are based on afferent inputs arising from visual, vestibular, proprioceptive and cutaneous systems [4, 5].

The relationship between cutaneous receptors in the foot sole and movement control is particularly well-known [6–8]. This relationship is apparent when considering patients suffering from peripheral neuropathy, which is most commonly a consequence of diabetes mellitus [9]. Those patients exhibit decreased plantar foot sensitivity [10] and reduced stability when performing dynamic balance tasks [11]. Since peripheral neuropathy reveals a multi-factorial character, affecting the peripheral nervous system and also resulting in joint immobility or foot ulcerations [12], it is unlikely that certain deteriorations in postural control are exclusively caused by reductions of foot sensitivity.

Therefore, to simulate only diminished cutaneous receptor activity, various methods are implemented, such as anesthesia, ischemia or cooling procedures [13–16]. Yasuda et al. [1] applied hypothermia to cool subjects' feet using ice water for a duration of 20 min and subsequently performed double leg stabilometry. Subjects showed significant increases in sway area and sway velocity. Similarly, Magnusson et al. [18] also confirmed significant increases in sway velocity after hypothermic intervention at the feet during conditions with eyes open and closed. Another study demonstrated significantly greater center of pressure (COP) excursions after foot sole cooling while subjects performed double leg stances with closed eyes [19]. However, the same study found no significant differences when subjects' eyes were open. In contrast, Billot et al. [20] showed that no increased COP excursions were evident after cooling plantar aspects of the feet. Furthermore, they explained these findings through greater EMG activity of the triceps surae muscles. Nurse and Nigg [21] analyzed walking parameters after plantar hypothermia affecting either forefoot or rearfoot areas. They demonstrated that peak pressures and pressure–time integrals were significantly lower in cooled areas, and they observed a shift of the COP towards more sensitive aspects of the foot. Due to these ambivalent findings,

the exact role of plantar cutaneous input on balance control is still not fully understood.

Although the above-mentioned cooling procedures are frequently used as a tool to alter foot sensitivity, it is important to point out some limitations of these interventions. Firstly, when immersing the whole foot into ice water, for example, not only may cutaneous receptor activity be minimized, but joint receptors and muscle spindles may also be affected, as it was already proposed by Meyer et al. [8]. Secondly, after cooling and subsequent data collection, the feet may immediately reheat, for example while stepping on force platforms. As a consequence, the previous hypothermically diminished receptor activity might not be maintained at this level until the end of all trials. Finally, using ice water or ice exhibits difficulties regarding the control and maintenance of a determined temperature during the cooling process itself.

In view of this dilemma, the aim of the present study was to examine the effect of hypothermia of the foot sole during dynamic balance tests. Furthermore, to apply long-lasting and controlled plantar hypothermia and to avoid the involvement of other sensory systems, a self-developed customized thermal plate was integrated into the setup. This thermal plate allows foot soles to be cooled during data collection and enables measurements at intermediate temperatures, which may minimize unpleasant sensations for the subjects. After hypothermia, significant increases in both COP excursions and root mean square (RMS) of the electromyographic (EMG) signal were hypothesized.

Methods

Subjects

The experiments were performed on fifty-two healthy (26 female, 26 male) and injury-free subjects (mean ± SD 23.6 ± 3.0 years, 70.7 ± 13.0 kg, 1.7 ± 0.1 m). Only participants with no history of lower leg injury or lower extremity pain for at least 6 months prior to testing and with no peripheral neuropathy or other related disorders were included in the study. In addition, none of the subjects were taking medication that could affect sensitivity or balance responses. All participants were informed about the purpose of this study and gave informed written consent. They were also instructed to interrupt the measurements if they experienced discomfort. All

procedures were conducted according to the recommendations of the Declaration of Helsinki. The present study was approved (IfS Mil Mai Lastverteilungstypisierung 16052011) by the Ethics Committee of the Faculty of Behavioural and Social Sciences of the corresponding university.

Apparatus

A specialized apparatus was constructed to induce unexpected perturbations, to quantify balance ability, and to apply plantar hypothermia simultaneously (Fig. 1). The commercially available Posturomed device (Haider Bioswing GmbH, Germany) was used to induce unexpected horizontal perturbations [22]. Furthermore, this device is known to quantify dynamic postural control [22–27]. The Posturomed used in this study was equipped with an electro-magnet to attach the bottom platform 20 mm out of the neutral position [28]. After pressing a manual trigger, the bottom platform was released initiating the unexpected perturbation. Subsequently, the bottom platform swung horizontally until it reached the neutral position. Other versions of the Posturomed already include a lever-based provocation unit, which allows for similar perturbations [22]. Participants were secured using a safety belt and the handrail of the Posturomed was covered with insulation material to avoid injuries.

Fig. 1 Picture of the apparatus used. Subjects stood with their dominant leg on top of the thermal plate which was mounted on top of the force platform. The force platform was then placed on top of the bottom platform of the Posturomed.

To quantify balance ability, a force plate (IMM Holding GmbH, Germany; sampling rate 1 kHz) was attached directly on top of the bottom platform. Finally, to induce plantar hypothermia, a self-developed customized thermal platform (Department of Human Locomotion of the corresponding university) was attached to the force plate. This thermal platform (temperature range 0–40 °C; resolution ±1 °C) consists of an upper aluminum plate which can be set to a desired temperature using the Peltier effect. Furthermore, to detect the reversal points of the oscillating bottom

platform after triggering, a single axis accelerometer (ADXL78, Analog Devices Inc., USA; sampling rate 1 kHz) was included in the apparatus.

Electromyography (EMG)

Wireless bipolar surface electrodes (Trigno™ Wireless, Delsys Inc., SA; DC-500 Hz, 160 dB/Dec.) were used to measure muscle activity of the following muscles of the dominant leg: M. tibialis anterior (TA), M. gastrocnemius medialis (GM) and M. fibularis (FIB). EMG data was pre amplified (1000×) and collected at a sampling rate of 1 kHz. EMG electrodes were positioned according to the recommendations of SENIAM [29]. Skin preparation included shaving, abrasion by sandpaper and cleaning with alcohol pads.

Temperature

Before and after the experimental procedures, room temperature was monitored by a digital C28 type K thermocouple (Comark Instruments, U.K.) to maintain the room temperature between 23 ± 2 °C (EN ISO/IEC 17025) to avoid changes in measuring conditions. An infrared thermal camera FLIR E40bx (FLIR Systems Inc., USA) was used to measure the foot sole skin temperature at three anatomical locations (first/fifth metatarsal head (Met1/ Met5) and heel) of the dominant foot. The anatomical locations were chosen since they are in direct contact with the ground when standing upright [30]. Experimental procedures were performed according to the standards of Protocols in Clinical Thermographic Imaging [31].

Plantar hypothermia

Plantar hypothermia was induced by adjusting the thermal platform to three temperature stages in the following order: stage I (25 °C), stage II (12 °C) and stage III (0 °C). Stage I was the initial temperature with an acclimatization time of 3 min in which both feet were in total contact with the thermal platform at 25 °C. For stages II and III, the acclimatization time was 5 min at 12 °C and 10 min at 0 °C, respectively. The above-mentioned acclimatization times were sufficient to achieve and stabilize the desired temperature, avoiding extreme pain or discomfort, as shown in an unpublished pilot study. The temperature for stage II was chosen to examine possible effects regarding balance responses already occurring at the intermediate

temperature. This was meaningful, since Schlee et al. [16] showed that plantar sensitivity is altered when varying plantar temperatures for 5–6 °C compared to the baseline.

Since measuring foot sensitivity is very time consuming, endangering the concentration of the participants, we did not include this issue in our protocol. However, in order to confirm decreased plantar sensitivity using the same hypothermic protocol with the thermal plate and temperature stages, we performed a pilot study: Plantar foot sensitivity (Met I) of ten young and healthy subjects (mean ± SD 25.2 ± 4.7 years, 70.4 ± 13.9 kg, 1.77 ± 0.11 m) was analyzed at 200 Hz. Cooling led to significantly decreased plantar sensitivity for all comparisons (α = 0.05): 25 versus 12, 25 versus 0 and 12 versus 0 °C (Table 1).

Table 1 Mean ± SD plantar temperatures (°C) and vibration perception thresholds (VPT, µm) for the first Metatarsal head (Met I) comparing all three temperature stages (25, 12, 0 °C).

	25 °C		**12 °C**		**0 °C**	
Met I	**VPT [µm]**	**Temp (°C)**	**VPT [µm]**	**Temp (°C)**	**VPT [µm]**	**Temp (°C)**
Mean±SD	$0.7\pm0.4^{\Delta,\square}$	$25.1\pm0.6^{a,b}$	$1.8\pm0.7^{\Delta,\circ}$	$13.5\pm1.0^{a,c}$	$3.1\pm1.8^{\square,\circ}$	$5.5\pm1.8^{b,c}$

Significant differences are marked with superscripted symbols

Significant differences: VPT: $^{\Delta}$ $p < 0.001$; $^{\square}$ $p = 0.001$; $^{\circ}p = 0.049$; Temp: ^{a} $p = 0.006$; ^{b} $p = 0.002$; ^{c} $p = 0.006$

Testing procedure

Prior to the measurements, all subjects performed several trials to become familiar with the apparatus. All trials were performed in four conditions which combined single (S) and double (D) leg stance with perturbations in anterior–posterior (A) and medio-lateral (M) directions: SA, SM, DA and DM (Fig. 2). Three trials were performed for each of the four conditions resulting in 12 trials per subject, which were executed in a randomized order. This series of 12 trials were then performed for each of the three temperature stages, resulting in a total of 36 trials for each subject. Plantar temperatures were measured before and after each series of 12 trials. During all measurements, subjects were instructed to look straight ahead, to keep their knees straightened but not locked, and to keep their upper limbs hanging down at each side of their body. Feet were positioned at the center of the thermal plate

(marked with tape) for all tests. Furthermore, when conducting double leg stance conditions (DA, DM), subjects were asked to evenly distribute their body weight on both feet, keeping them shoulder width apart. While performing single leg stance conditions (SA, SM), subjects had to flex their contra-lateral lower limb backwards. Trials were deemed ineligible when subjects lost their concentration (e.g. talking), held on the handrail, or touched the ground with the contra-lateral foot. After the last temperature stage (0 °C), all participants' feet were reheated using an infrared lamp radiator.

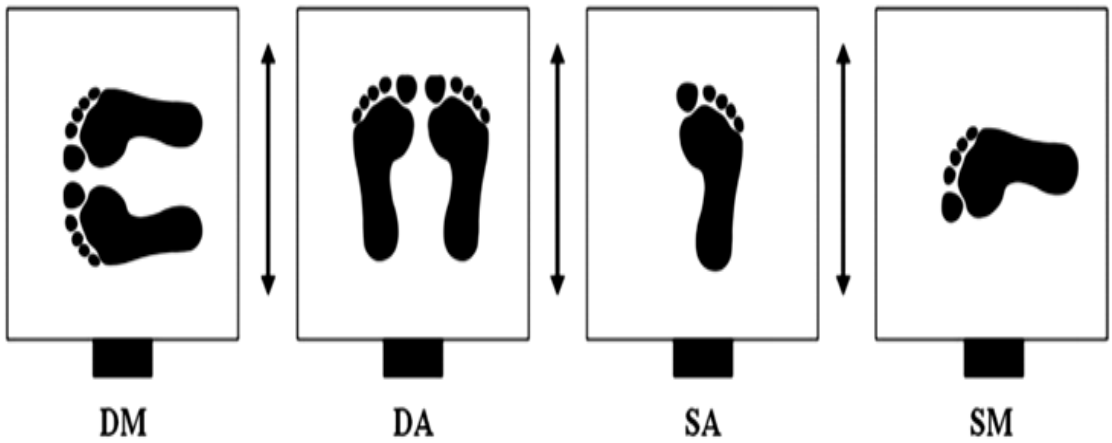

Fig. 2 Illustration of all four balance conditions: double leg in medio-lateral (DM), double leg in anterior–posterior (DA), single leg in anterior–posterior (SA) and single leg in medio-lateral (ML) perturbation directions (black arrows). The electro-magnet is depicted as solid black rectangles.

Data collection and analysis

All force plate, EMG, and accelerometer data were synchronized using the manual trigger (onset of unexpected perturbation) and recorded by a routine written in LabView 8.0 (National Instruments Corp., USA). For further processing, all data was imported into the R program (The R Foundation for Statistical Computing, Austria). EMG data were offset-corrected and band-pass filtered (20–500 Hz; Butterworth 2nd order). Root mean square (RMS) of the measurements of the dominant leg was analyzed in this study. Center of pressure (COP) total excursions of the force plate data were low pass filtered (cutoff frequency 0.1, Butterworth 4th order). All data were analyzed for three time intervals in relation to the trigger (T0): -200 ms to T0 (interval 0), and two post trigger intervals: T0 to 90 ms post trigger (interval I)

and 91–260 ms post trigger (interval II). Intervals I and II were assigned according to the first and second reversal points (90 and 260 ms, respectively) of the oscillating bottom-platform calculated over all subjects resulting in (mean ± SD) 90.0 ± 6.8 ms (reversal point 1) and 260.4 ± 17.0 ms (reversal point 2) which were determined using accelerometer data. Foot sole temperature data were analyzed using the software ThermaCAM™ Researcher Pro 2. SR-1 (FLIR Systems Inc., USA). Mean and standard deviation (SD) temperature values were calculated for each anatomical location (Met 1, Met 5, heel) of the dominant foot.

Statistics

Means of the three trials were used to define the value of the analyzed parameters for each subject at each condition and temperature stage. Testing for normality was performed using the Shapiro–Wilk test ($\alpha = 0.05$). EMG and COP data were analyzed using Friedman's test followed by Wilcoxon-Test. Comparisons were performed between all three temperature stages for each condition. The level of significance was corrected due to the number of different temperature stages ($n = 3$) to $\alpha = 0.05/3 = 0.01$.

Results

Temperature

Room temperature before and after data collection for each subject were (mean ± SD) 22.6 ± 0.6 and 23.3 ± 0.6 °C, respectively.

Figure 3 shows temperature data of the dominant foot sole (Met 1, Met 5 and heel) before and after the 12 trials for each temperature stage (25, 12 and 0 °C). No significant differences were detected within each temperature stage and between all anatomical locations. Comparing plantar temperatures for all three anatomical locations before and after the 12 trials, mean values ranged from: 25.0 to 25.4 °C for stage I, 11.9 to 12.4 °C for stage II and 3.2 to 4.8 °C for stage III.

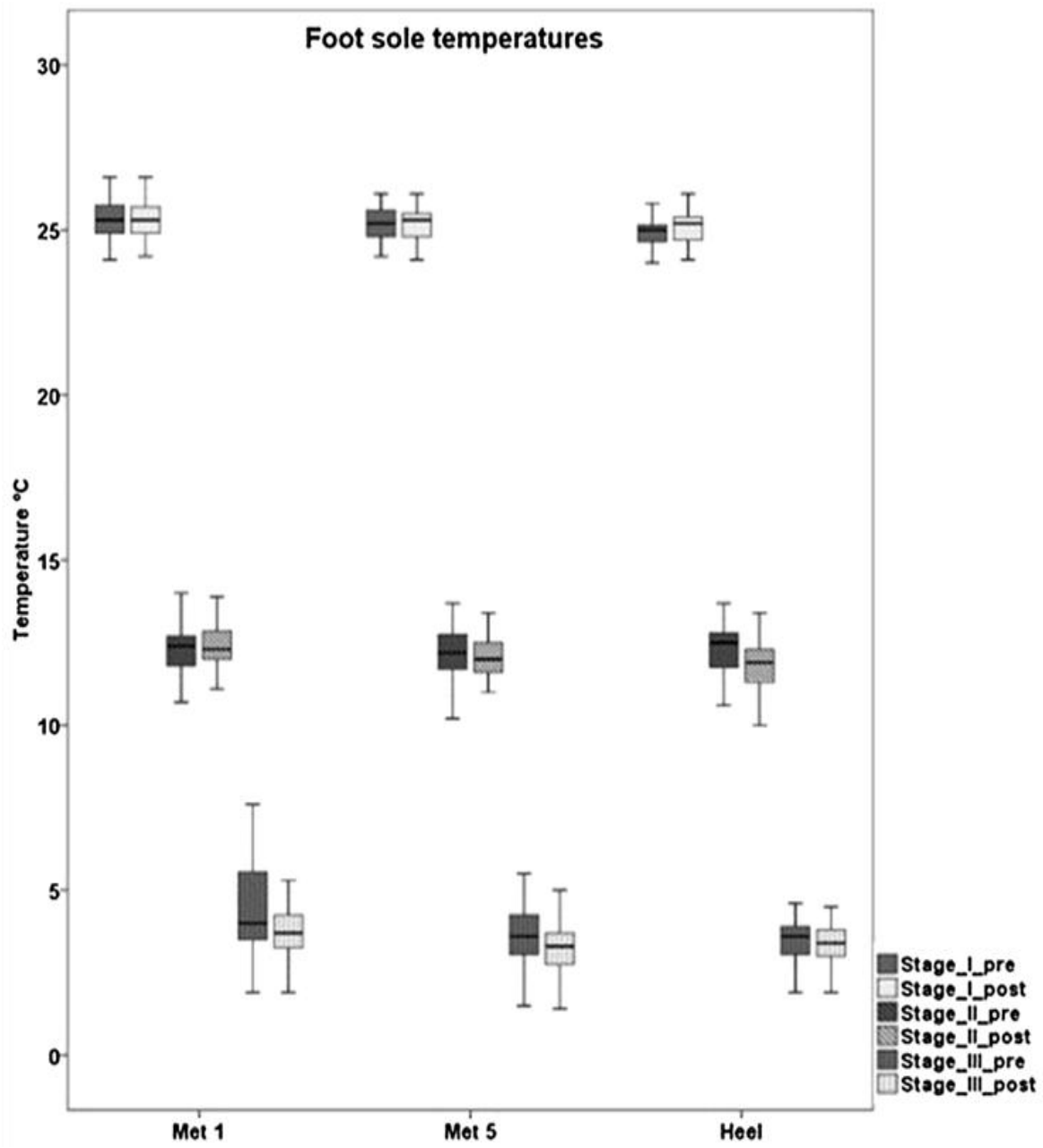

Fig. 3 Boxplots of plantar foot temperatures of each anatomical location (Met 1, Met 5, Heel) and for each temperature stage (stage I, II, III) before and after the 12 trials.

COP data

Table 2 and Fig. 4 exhibit data of COP total excursions for all four conditions and all three temperature stages. For interval 0, no significant differences were found between the temperature stages for all conditions. Similarly, interval 1 did not present significant differences between the three temperature stages in all balance conditions. In interval 2 and for double leg stance conditions, significantly smaller COP total excursions were revealed as plantar temperatures decreased. This was

true for all temperature stages. In single leg stance conditions, significant differences were found when comparing stages I and II as well as stages I and III, with smaller excursions as temperatures decreased. No significant differences were detected when comparing stages II and III for SA and SM conditions.

Table 2 Mean ± SD COP total excursions for each condition (SA, SM, DA, DM) and temperature stage in intervals 0 and 1.

	Interval 0			**Interval 1**			**Interval 0**			**Interval 1**		
Stages	**25 °C**	**12 °C**	**0 °C**	**25 °C**	**12 °C**	**0 °C**	**25 °C**	**12 °C**	**0 °C**	**25 °C**	**12 °C**	**0 °C**
	SA						SM					
COP Total [mm]	9,3 ±2.9	9,0 ±2.5	9,1 ±3.4	29,1 ±4.2	29,2 ±3.7	29,5 ±4.0	9,9 ±3.0	9,0 ±2.8	9,2 ±2.9	33,3 ±3.8	34,0 ±3.8	33,3 ±3.3
	DA						DM					
COP Total [mm]	5,8 ±2.2	5,2 ±1.8	5,6 ±1.8	27,5 ±4.4	27,5 ±4.1	27,1 ±3.9	5,3 ±1.5	5,4 ±1.7	5,8 ±1.8	28,4 ±3.8	28,8 ±3.8	28,9 ±3.8

S Single leg, D double leg, M medio-lateral, A anterior–posterior

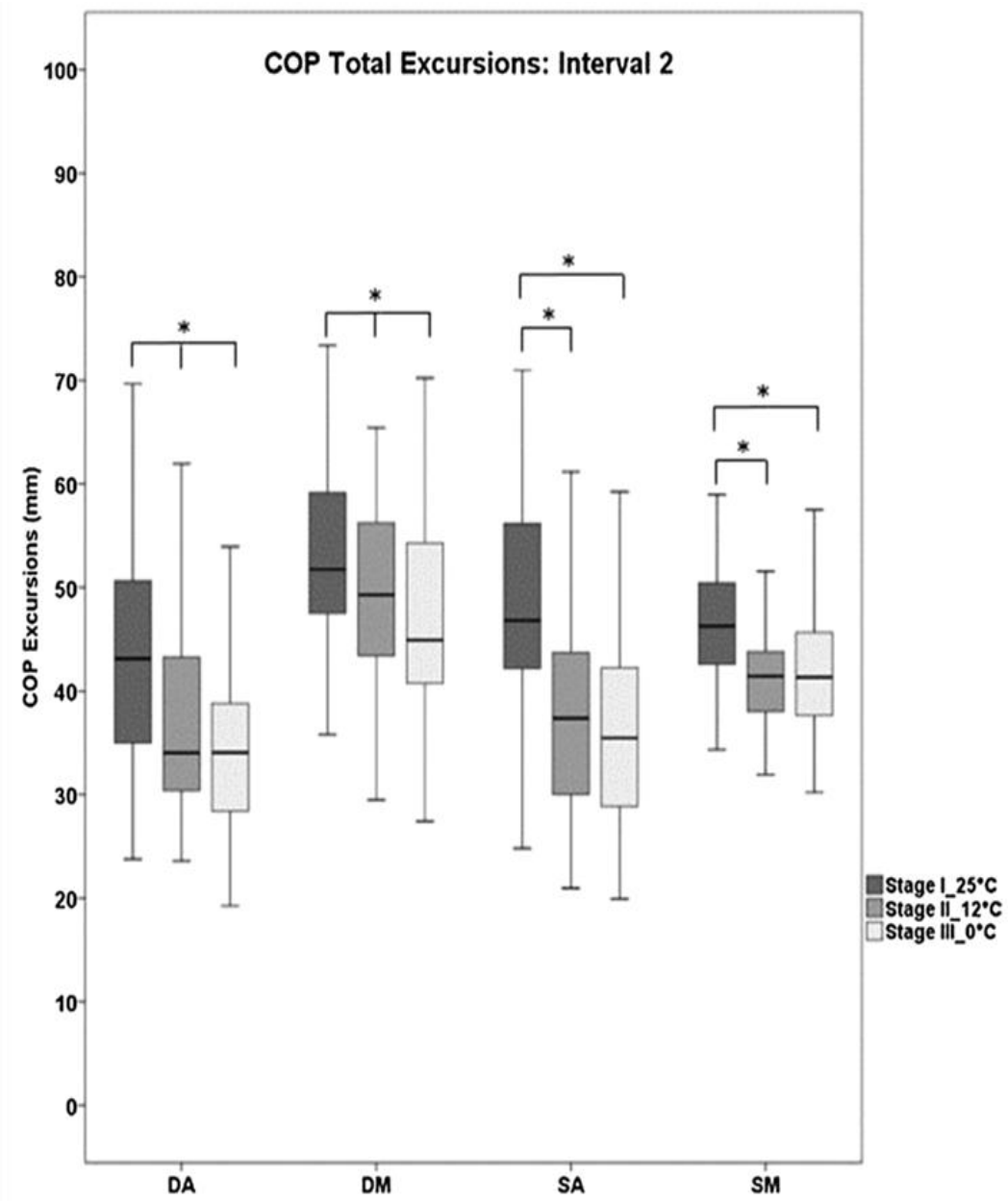

Fig. 4 Boxplots of COP Total excursions for each condition (DA, DM, SA, SM) and each temperature stage for interval 2. Significant differences are marked with asterisks (*p < 0.017).

EMG data

Intervals 0 and 1 did not show significant differences for all analyzed muscles (TA, GM and FIB) in all temperature stages and conditions (see Table 3). In interval 2, no significant differences were detected for DM in any analyzed muscles (see Fig. 5). For DA, significantly lower muscle activity was evident after cooling (stage III) compared to stage I for all analyzed muscles. Additionally, when comparing stage I

with stage II, significantly decreased RMS values were found for TA after cooling. For both SA and SM, muscle activity of TA was significantly lower for stage II compared to stage I. Furthermore, for SM, the tibialis anterior muscle activity showed significantly smaller values in stage III when compared to stage I (see Fig. 5).

Table 3 Mean ± SD EMG values (RMS) for each condition (SA, SM, DA, DM) and temperature stage in intervals 0 and 1.

	Interval 0			**Interval 1**			**Interval 0**			**Interval 1**		
Stages	**25 °C**	**12 °C**	**0 °C**	**25 °C**	**12 °C**	**0 °C**	**25 °C**	**12 °C**	**0 °C**	**25 °C**	**12 °C**	**0 °C**
	SA						SM					
TA	20.3	16.8	19.1	16.2	13.9	16.7	20.0	19.3	21.9	16.2	18.2	18.8
	±13.3	±12.3	±12.0	±11.7	±11.5	±13.3	±13.8	±12.2	±15.1	±11.6	±15.6	±12.7
FIB	40.3	40.5	37.7	39.9	36.0	34.8	46.5	47.8	51.6	47.1	47.3	49.4
	±26.7	±20.1	±19.1	±28.8	±21.9	±19.1	±27.8	±27.8	±30.4	±32.1	±29.9	±34.3
GM	37.7	36.3	37.5	36.4	37.4	35.5	35.9	34.6	35.5	34.0	33.6	34.0
	±16.6	±13.0	±14.9	±18.7	±18.4	±15.2	±17.8	±17.2	±17.0	±17.1	±16.7	±17.7
	DA						DM					
TA	4.7	7.3	4.6	4.4	3.7	4.0	5.5	5.1	6.8	5.4	3.8	6.6
	±5.1	±10.6	±6.3	±8.4	±4.3	±5.5	±5.2	±7.2	±10.1	±7.3	±5.8	±16.7
FIB	7.5	5.8	8.2	5.6	4.6	5.6	7.3	5.4	7.7	6.7	4.5	6.2
	±8.6	±4.6	±7.1	±4.5	±3.1	±4.4	±7.4	±4.0	±7.8	±10.7	±3.0	±9.2
GM	9.7	9.7	7.8	8.2	7.7	10.3	7.4	9.0	6.7	7.1	6.7	6.5
	±6.5	±6.9	±6.4	±6.3	±6.0	±14.6	±4.8	±6.8	±6.5	±7.1	±5.6	±6.7

S Single leg, D double leg, M medio-lateral, A anterior–posterior, TA M. tibialis anterior, FIB M. fibularis, GM M. gastrocnemius medialis

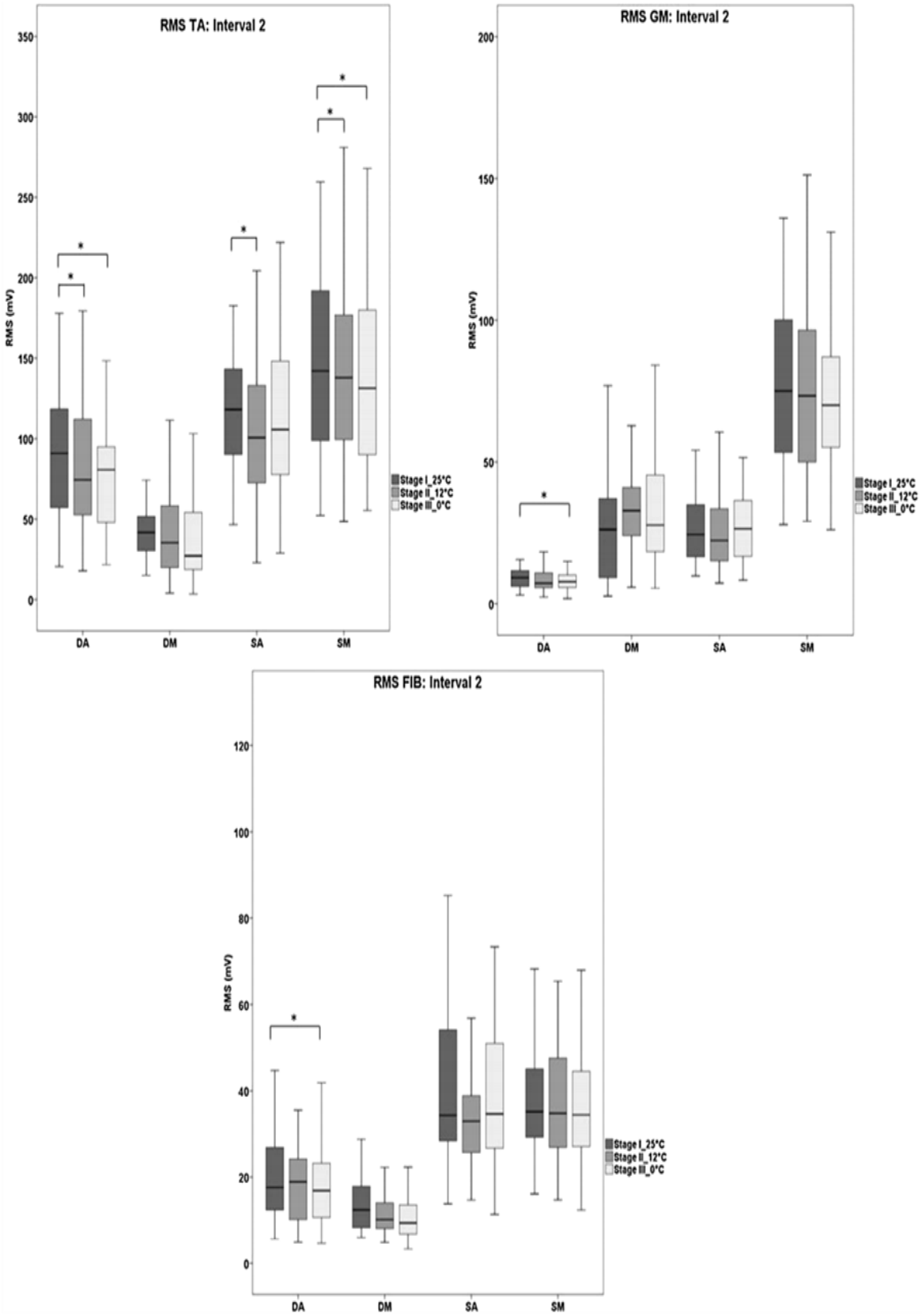

Fig. 5 Boxplots of EMG values (RMS for TA, GM and FIB) for each condition (DA, DM, SA, SM) and each temperature stage for interval 2. Significant differences are marked with asterisks (*$p < 0.017$).

Discussion

Plantar temperatures

Plantar temperatures for all locations in stages I (25 °C) and II (12 °C) showed similar values to the temperatures predetermined by the thermal platform, before and after trials. For stage III (0 °C), plantar temperatures were also similar before and after trials. This shows that the temperature was kept constant throughout the entire balance measurement for each temperature stage. This outcome has large beneficial implications when combining plantar cooling procedures with various balance or gait measures.

It is well accepted that cooling the foot soles reduces plantar sensitivity [16, 19, 21], and it was also proved in our pilot study. However, previous studies examining the effects of plantar hypothermia did not ensure long-lasting cooling during trials, therefore, it is supposable that contact and/or friction to the warmer ground during standing possibly leads to re-warming, improving plantar sensitivity towards the baseline level. For example, a microneurographic study revealed a different finding: In one experiment, ice packets were placed over the receptive fields of a slowly adapting (SA) type II mechanoreceptor on the plantar foot for 15 min [32]. They showed that after 3 and 6 min of natural re-warming, receptor responses returned to 50 and 100 % of baseline firing, respectively. Due to those findings, we recommend ensuring permanent cooling during balance data collection to avoid possible improvements of plantar sensitivity. Another outcome of the present study was that in stage III the overall actual mean plantar temperature was higher (3.7 °C) than the platform temperature (0 °C). This effect is also observable in other studies and is known as cold-induced-vasodilatation to prevent cell death [33].

Background on analyzed time intervals

To preserve balance, the central nervous system (CNS) uses responses which can be classified into anticipatory and compensatory adjustments [1, 2]. There are currently several different theories explaining the time windows in which those adjustments occur. To assess anticipatory responses in this study, a pre trigger interval (interval 0) was defined, similar to Santos et al. [2]. Additionally, they showed that anticipatory adjustments persist until after the trigger onset (T0) [2]. Therefore, interval 1 was chosen to analyze anticipatory adjustments. Since our setup induced

horizontal translational perturbations at the subjects' feet, in which muscle latencies occur at around 100 ms and active COP displacements at around 130 ms post perturbation [34–36], interval 2 was chosen to analyze compensatory responses.

COP and EMG data

Anticipatory responses (intervals 0 and 1)

In intervals 0 and 1, no significant differences were found for all analyzed COP or EMG parameters in all conditions when reducing plantar temperatures. This finding was somewhat surprising, since many studies report reduced foot sensitivity due to cooling [16, 19, 21], which may result in a higher demand on postural activity. The findings of intervals 0 and 1 lead to the first two questions; a) what exact types of mechanoreceptors are being affected and/or b) whether or not these affected receptors are responsible for balance control in intervals 0 and 1. In this context, plantar mechanoreceptors vary considerably in their location, functionality, and frequency dependency. Slowly adapting (SA) mechanoreceptors (Merkel cells and Ruffini endings) are believed to contribute to postural regulation, specifically coding changes in COP parameters [14, 32]. Furthermore, SA receptors participate in responses to prolonged skin indentations [32], hence presumably playing an important role in intervals 0 and 1. Merkel cells are located superficially within the epidermis, whereas Ruffini endings are located slightly deeper within the dermis. Despite this, both SA receptors were shown to be effected by cooling procedures (2–20 min) [32]. This means there must be another explanation for why no significant differences were found in anticipatory COP or EMG responses, although plantar sensitivity was reduced. Regarding postural strategies, Winter et al. [37] r ported that during quiet upright bipedal standing, balance control in the frontal plane is mainly achieved by hip and ankle muscles. Kelly et al. [38] demonstrated that during quiet upright standing with either one or two legs, intrinsic foot musculature shows high activation levels. Although intrinsic foot muscles are smaller than extrinsic foot muscles [39], they function as a unit [38]. Unfortunately, we did not quantify musculature activity associated with the hip strategy, nor did we measure intrinsic foot muscles, which could explain our findings.

Furthermore, there is another possible explanation for non-significant changes for intervals 0 and 1, which can be seen in the consequences of reducing specific

sensory input. It is known that somatosensory, visual and vestibular information contribute to postural control. Peterka [40] argue that when healthy subjects stand on firm surfaces, they rely to 70 % on somatosensory, to 10 % on visual and to 20 % on vestibular input. However, the subsequent processing of that afferent information in the CNS does not follow a simple linear summation [41]. Ernst and Bülthoff [42] describe that senses arising from different modalities are merged in the brain to form a percept, which is achieved by sensory combination and sensory integration. Sensory combination describes the processing of various non-redundant sensory signals, while sensory integration occurs when signals are in the same unit and represent the same aspect of a specific environmental property, describing the processing of redundant signals. According to the concept of Ernst and Bülthoff [42], this can be transferred to our study: Non-redundant sensory signals may stem from visual, vestibular, proprioceptive and plantar skin sensitivity input. Those inputs need to be combined, resulting in redundant signals during postural tasks. That means, e.g. visual information needs to be combined with certain proprioceptive information to enable standardized body coordinates. These combined signals are then integrated to form coherent and robust percepts in the brain to maintain postural control. Interestingly, such sensory combinations have already been shown to exist in early stages of signal processing at the spinal cord level. For example, Lowrey and Bent [43] proved that there is a strong coupling between foot skin sensitivity and vestibular inputs, and that those two inputs influence muscle reflex activity. Another study also proved the relationship between plantar sensitivity and Achilles tendon reflex through induction of hypothermia [44]. Our findings suggest that for anticipatory responses during intervals 0 and 1, combination and integration processes may be responsible for a compensatory mechanism of the reduced plantar skin sensitivity. Hence, no deteriorated balance ability was found which would have been represented by significantly larger COP and/or EMG parameters, as hypothesized. The other intact sensory systems may then be reweighted to a higher degree to maintain balance control. Therefore, the assumption of a simple summation of sensory signals seems rather unlikely, as also affirmed by Mergner and Rosemeier [41]. It shall be acknowledged that a further explanation would be that cutaneous inputs from the foot soles simply play a minor or no role in balance regulation for intervals 0 and 1. However, we find this assumption rather unlikely since the

contribution of plantar sensory inputs towards balance regulation is well proven and accepted [45, 46].

Compensatory responses (interval 2)

It is known that among others, also fast-adapting mechanoreceptors are responsible for such dynamic events, which provide information from the skin surface [32]. Meissner and Vater-Pacini corpuscles are fast-adapting mechanoreceptors, which are located in superficial and deeper skin layers, respectively. Lowrey et al. [32] demonstrated that after similar periods of cooling, mainly a reduced receptor firing rate was evident for both slow and fast-adapting mechanoreceptors of plantar areas. Additionally, they showed that within cooling times of 2–5 min, there was no clear relationship between the receptor location (superficial or in deeper skin layers) and their firing responses. The results of our study support this outcome, since effects were already present when cooling for 5 min at 12 °C; whereas longer cooling periods augmented the effect of a reduced receptor firing response [32].

When comparing 25–12 °C in all conditions, significantly smaller COP total excursions were found with decreasing plantar temperatures. Furthermore, regarding RMS values over all muscles in all conditions, 9 out of 12 (75 %) values showed decreases as the foot sole was cooled, with three values showing significance for TA. When analyzing 25 versus 0 °C, all COP total excursions also showed significantly decreased values after hypothermia for all conditions. EMG activity presented similar behavior, except for two out of 12 comparisons (17 %). These results allowed us to conclude that effects were present in both hypothermic scenarios (25 vs. 12 and 25 vs. 0 °C).

When comparing 12 °C with 0 °C, COP total excursions exhibited significantly smaller values as plantar temperatures decreased, but only during bilateral stance. However, considering mean differences over all conditions for 25 versus 12 and 25 versus 0 °C, values were 4.5 and 6.1 mm, respectively, while mean differences for 12 versus 0 °C were only 1.6 mm. There were no significant differences for EMG activity for all muscles and all conditions. Interestingly, the same behavior for COP mean differences was observed for EMG mean differences. As mentioned above, effects were present, but when comparing 12 versus 0 °C it seems that this final temperature stage presents differences less relevant when considering EMG and COP data of this

study. Hence, it can be presumed that the hypothermic treatment at an intermediate temperature (12 °C) would be enough to elicit effects (comparing 25 vs. 12 °C), which is an important finding for future studies. Although we did not assess the subjects' perceived pain levels, they reported more unpleasant sensations during stage III (0 °C) compared to stage II (12 °C), indicating nociceptor activity. An interesting study conducted by Blouin et al. [47] found that with increasing stimulus temperatures, their subjects perceived pain, which deteriorated the postural control system by an interaction of nociceptor and Ia afferents at the spinal level. Therefore, it could be possible that nociceptive signals elicited in the lower temperature range may interact with α-motoneurons and, consequently, affect balance control in a negative way. This would further emphasize the importance of the effects already achieved at an intermediate temperature, as in our study.

A general finding was that—in the case of significant differences—both COP and EMG parameters always showed decreasing values as foot soles were cooled. Furthermore, most data with non-significant differences showed the same trend. When considering previous literature, decreased COP values were also found in the experiments performed by McKeon and Hertel [19]. Plantar aspects of the subjects feet were immersed into ice water for 10 min. Significant reductions of the COP area were detected, however, only with the eyes closed and in bilateral quasi-static stance conditions. In contrast, Magnusson et al. [18] found increasing parameters (body sway velocity) when the subjects´ feet were placed into ice water for 20 min, however, again in quasi-static conditions. Fukuchi et al. [48] found increased parameters for the SD of COP displacements and for COP velocity, but their subjects where immersed in cold water (approx. 11 °C) up to the umbilical level. After cooling the foot soles, Billot et al. [20] and Billot et al. [49] found no significant differences in COP excursions, but significantly increased muscular activity. Therefore, it becomes evident in previous studies that parameters show no clear behavior, but balance tests were of quasi-static nature which differs from our protocol in interval 2.

As already mentioned, our study demonstrated decreased parameters as plantar temperatures were reduced. Hence, our hypothesis of increased COP and EMG values has to be rejected. This finding was surprising, since decreased values are interpreted as improvements in balance [50–52].

The first explanation for the decreased values are possible learning effects, which seem plausible since we could not randomize the order of the temperature stages. This was because we did not estimate when plantar aspects would reach baseline temperature again after having been cooled. This process may impact the duration of our experiment, therefore, impairing the subjects´ concentration. Future studies should investigate the effects of different randomization approaches of temperature stages on sensitivity/balance parameters. Furthermore, even after sufficient time for re-warming, it is not known whether receptors would behave equally compared to the initial baseline measurement. In this regard, Kunesch et al. [53] demonstrated that even after the initial skin temperature was re-gained, some reduction of receptor sensitivity often persisted for a few minutes. Consequently, stage III was the very last stage and was therefore vulnerable for possible learning effects. Boeer et al. [54] confirmed that the Posturomed shows reproducible results, however, tests were performed in quasi-static balance conditions. In addition, in a previous study implementing a similar protocol with unexpected perturbations, we showed that the Posturomed exhibited good overall reliability [28]. Therefore, we can exclude possible learning effects as the explanation for the decreased COP and EMG parameters in the present study.

The most plausible explanation, therefore, lies in neurophysiological processes during interval 2, which differ from intervals 0 and 1. Although the subjects did not know when exactly the perturbation would occur, they knew that it would occur. Therefore, not only anticipatory adjustments were always present in intervals 0 and 1, but also compensatory responses in interval 2. However, afferent processes are different in interval 2: during dynamic balance tasks there were other still intact afferent channels responsive to a greater amount due to the perturbation (e.g. muscle spindles, joint receptors) and other impaired plantar channels (Meissner and Vater-Pacini corpuscles) contributing to postural control. Therefore, the processes of combination and integration from afferent inputs should be different and more complex than during the two previous intervals. Those aspects may lead to a more cautious behavior compared to intervals 0 and 1, since certain information regarding the base of support are missing or incomplete in addition to the higher demanding task. This would then be integrated into the actual postural motor program in the CNS. Efferent signals from the motor cortex innervate α-Motoneurons in the anterior

horns of the spinal cord which drive musculature [55] via the medial and lateral cortico-spinal tract [56], hence controlling posture. This alpha-neuronal drive is modulated by convergent peripheral sensory input information via spinal inter-neurons with high degrees of “freedom” [5]. We assume that the more cautious behavior produced the necessity for a restricted area of base of support, consequently, preventing loss of balance. Since plantar inputs were impaired, other intact afferents were recruited and reweighted the combination and integration processes within the central nervous system. In the spinal cord, intact afferent information probably influence the actual motor program stemming from the cortex by high prioritized interneurons and intensify this precautious motor program. It is further known that sufficient threat towards posture must exist to induce adaptations in e.g. reflexes [58], which probably occurred in our protocol. Therefore, we presume that a kind of over-compensation due to the cautious behavior occurred which led to the reduced COP and EMG parameters found in this study.

We also expected that significant increases of muscle activity would also lead to significantly increased COP excursions after the hypothermic procedure. However, this relationship between COP and EMG was not always present in our results. This corresponds with Billot et al. [49], who also showed that significant differences in EMG parameters did not necessarily result in significant COP changes within the same trial. However, they investigated COP velocity. These outcomes can be explained in that EMG activity of the muscles we measured are not the only contributors towards COP displacements. In addition, there are delays regarding the onset of EMG activity and the subsequent onset of active COP displacements of approx. 20–40 ms [35]. Therefore, it is possible that the measured EMG and COP onset may not occur at the same time during this interval. Another possible explanation is that the measured muscle activities are not mainly responsible for COP changes. Nardone et al. [59] even argue that muscle strength does not play a major role in sway control when studying patients with peripheral neuropathy (Charcot–Marie–Tooth type 1A). As already mentioned, other intact inputs are integrated already at the spinal level, therefore contributing to balance control.

Finally, a further aspect of studies which reduce afferent information aim to simulate various diseases, like peripheral neuropathy. However, there are different mechanisms of the CNS, depending on whether sensory reductions are of acute or

chronic origin. Our findings suggest that the acute reductions induced a more cautious behavior, in which a sudden re-weighting of afferent inputs was necessary. On the other hand, in many chronic sensory reductions (diseases like diabetes mellitus) these reweighting processes are possibly accomplished more slowly, since sensory impairments also occur continually over long periods of time. Horak [60] even revealed that in patients with certain disorders (e.g. Alzheimer´s disease, peripheral vestibular loss, somatosensory loss from neuropathy), the ability of the CNS to quickly reweight sensory inputs is deteriorated. In agreement with this, Nardone et al. [59] examined patients with the Charcot-Marie-Tooth neuropathy type 1A who were divided into two groups. One group with a neuropathy score (NS) of 13 and the other group with a score <13. They found the sway area to be within a normal range for the less severely affected patients (NS < 13), but moderately elevated for the more severely affected (NS = 13). Therefore, we suggest (1) caution when interpreting COP data, because small excursions/ low EMG activity does not necessarily correspond to improved balance abilities; and (2) reweighting and integration processes are strongly dependent on the type of disease, duration, and type of receptor impairment. Furthermore, the subject´s age and prior physical experience may play an important role within those processes. More studies are needed to clarify these relationships.

Conclusion

The protocol using the thermal platform was successfully implemented since the plantar foot temperatures were similar pre and post trials. Anticipatory responses in intervals 0 and 1 revealed no significant differences as plantar temperatures were reduced. This might be explained by a compensation of the impaired afferent inputs by other intact inputs. In interval 2, compensatory responses of balance in all parameters showed generally decreased values as plantar temperatures were reduced. This is probably due to the balance threat caused by the unexpected perturbations, promoting a more cautious behavior which led to a kind of over-compensations of the CNS´ strategies regarding integration processes. It was further revealed that the intermediate hypothermic temperature stage II (12 °C) already elicited effects. Future studies which aim to induce hypothermia should investigate the influence of cold-induced pain on postural behavior. Further, reweighting

processes of various inputs need to be examined more profoundly, whether intra and inter subject strategies are different, and if so, for what reasons. In this regard, analysis of EMG latencies could also be investigated to better understand dynamic balance responses. Finally, we recommend a cautious interpretation of data when discussing improved or deteriorated balance abilities, according to the particular subjects being examined.

Abbreviations

COP: center of pressure; EMG: electromyographic activity; RMS: root mean square; TA: M. tibialis anterior; GM: M. gastrocnemius medialis; FIB: M. fibularis; SA: single leg stance in anterior–posterior direction; SM: single leg stance in medio-lateral direction; DA: double leg stance in anterior–posterior direction; DM: double leg stance in medio-lateral direction; CNS: central nervous system.

Authors' contributions

AG participated in the design of the study, coordinated data collection, performed the statist cal and data analysis and contributed to the writing of the manuscript. DS participated in data collection, contributed to the data-analysis and contributed to the writing of the manuscript. TLM participated in the design of the study, contributed to the data-analysis and contributed to the writing of the manuscript. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

Consent for publication

All participants were informed about the purpose of this study and gave informed written consent. I, Daniel Schmidt, give my consent for information (picture) about myself to be published in BMC neuroscience, NROS-D-16- 00034R1 (Andresa M. C. Germano).

Ethics approval and consent to participate

All participants were informed about the purpose of this study and gave informed written consent. They were also instructed to interrupt the measurements if they experienced discomfort. All procedures were conducted according to the recommendations of the Declaration of Helsinki. The present study was approved (IfS Mil Mai Lastverteilungstypisierung 16052011) by the Ethics Committee of the Faculty of Behavioural and Social Sciences of the corresponding university.

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References

1. Latash ML. Neurophysiological basis of movement, 1st edn. Champaign, IL: Human Kinetics; 1998.
2. Santos MJ, Kanekar N, Aruin AS. The role of anticipatory postural adjustments in compensatory control of posture: 1. Electromyographic analysis. J Electromyogr Kinesiol. 2010;20:388–97.
3. Patel P, Bhatt T. Adaptation to large-magnitude treadmill-based perturbations: improvements in reactive balance response. Physiol Rep. 2015;3:e12247.
4. Horak FB, Nashner LM, Diener HC. Postural strategies associated with somatosensory and vestibular loss. Exp Brain Res. 1990;82:167–77.
5. Kavounoudias A, Roll R, Roll JP. The plantar sole is a “dynamometric map” for human balance control. NeuroReport. 1998;9:3247–52.
6. Chua R, Inglis T, Kennedy P, Wells C. The role of cutaneous receptors in the foot. Adv Exp Med Biol. 2002;508:111–7.
7. Kennedy PM, Inglis JT. Distribution and behaviour of glabrous cutaneous receptors in the human foot sole. J Physiol. 2002;538:995–1002.

8. Meyer PF, Oddsson LIE, DeLuca CJ. The role of plantar cutaneous sensation in unperturbed stance. Exp Brain Res. 2004;156:505–12.
9. Bron D, Steck AJ. Periphere Neuropathien. Schweiz Med Forum. 2006;6:209–14.
10. Simmons RW, Richardson C, Pozos R. Postural stability of diabetic patients with and without cutaneous sensory deficit in the foot. Diabetes Res Clin Pract. 1997;36:153–60.
11. Inglis JT, Horak FB, Shupert CL, Jones-Rycewicz C. The importance of somatosensory information in triggering and scaling automatic postural responses in humans. Exp Brain Res. 1994;101:159–64.
12. Taylor AJ, Menz HB, Keenan AM. Effects of experimentally induced plantar insensitivity on forces and pressures under the foot during normal walking. Gait Posture. 2004;20:232–7.
13. Eils E, Nolte S, Tewes M, Thorwesten L, Völker K, Rosenbaum D. Modified pressure distribution patterns in walking following reduction of plantar sensation. J Biomech. 2002;35:1307–13.
14. Perry SD, McIlroy WE, Maki BE. The role of plantar cutaneous mechanoreceptors in the control of compensatory stepping reactions evoked by unpredict able, multidirectional perturbation. Brain Res. 2000;877:401–6.
15. Schlee G, Milani TL, Sterzing T. Short-time lower Leg ischemia reduces plantar foot sensitivity. Neurosci Lett. 2009;462:286–8.
16. Schlee G, Sterzing T, Milani TL. Foot sole skin temperature affects plantar foot sensitivity. Clin Neurophysiol. 2009;120:1548–51.
17. Yasuda T, Nakagawa T, Inoue H, Iwamoto M, Inokuchi A. The role of the labyrinth, proprioception and plantar mechanosensors in the maintenance of an upright posture. Eur Arch Oto-Rinho-Laryngol. 1999;256:S27–32.
18. Magnusson M, Enbom H, Johansson R, Pyykkö I. Significance of pressor input from the human feet in anterior–posterior postural control. The effect of hypothermia on vibration-induced body-sway. Acta Otolaryngol. 1990; 110:182–8.
19. McKeon P, Hertel J. Diminished plantar cutaneous sensation and postural control. Percept Mot Skills. 2007;104:56–66.

20. Billot M, Handrigan GA, Simoneau M, Teasdale N. Reduced plantar sole sensitivity induces balance control modifications to compensate ankle tendon vibration and vision deprivation. J Electromyogr Kinesiol. 2014;25:155–60.
21. Nurse MA, Nigg BM. The effect of changes in foot sensation on plantar pressure and muscle activity. Clin Biomech (Bristol, Avon). 2001;16:719–27.
22. Kiss R. A new parameter for characterizing balancing ability on an unstable oscillatory platform. Med Eng Phys. 2011;33:1160–6.
23. Bruhn S, Kullmann N, Gollhofer A. The effects of a sensorimotor training and a strength training on postural stabilisation, maximum isometric contraction and jump performance. Int J Sports Med. 2004;25:56–60.
24. Hilberg T, Herbsleb M, Gabriel HHW, Jeschke D, Schramm W. Proprioception and isometric muscular strength in haemophilic subjects. Haemophilia. 2001;7:582–8.
25. Hirschmüller A, Konstantinidis L, Baur H, Müller S, Mehlhorn A, Kontermann J, Grosse U, Südkamp NP, Helwig P. Do changes in dynamic plantar pressure distribution, strength capacity and postural control after intraarticular calcaneal fracture correlate with clinical and radiological outcome? Injury. 2011;42: 1135–43.
26. Kiss RM. Effect of the degree of hip osteoarthritis on equilibrium ability after sudden changes in direction. J Electromyogr Kinesiol. 2010;20:1052–7.
27. Schwab MJ. Chiropractic management of a 47-year-old firefighter with lumbar disk extrusion. J Chiropr Med. 2008;7:146–54.
28. Schmidt D, Germano AMC, Milani TL. Aspects of dynamic balance responses: inter- and intra-day reliability. PLoS ONE. 2015;10:e0136551.
29. Freriks B, Hermens H. European recommendations for surface electromyography results of the SENIAM project; 2000.
30. Diebschlag W. Die Druckverteilung an der Fußsohle des Menschen im Stehen und Gehen, barfuß und im Schuh. Z Orthop Unfall. 1982;120:814–20.
31. International Academy of Clinical Thermology. Thermography guidelines. Standards and protocols in clinical thermographic imaging; 2002. http:// www.iact-org.org/professionals/thermog-guidelines. Accessed July 2011.

32. Lowrey CR, Strzalkowski NDJ, Bent LR. Cooling reduces the cutaneous afferent firing response to vibratory stimuli in glabrous skin of the human foot sole. J Neurophysiol. 2013;109:839–50.
33. Sendowski I, Launay J-C, Besnard Y, Pequignot J-M, Cottet-Emard J-M, Bittel J, Savourey G. Sympathetic stimulation induced by hand cooling alters cold-induced vasodilatation in humans. Eur J Appl Physiol. 2000;81:303–9.
34. Moore SP, Rushmer DS, Windus SL, Nashner LM. Human automatic postural responses: responses to horizontal perturbations of stance in multiple directions. Exp Brain Res. 1988;73:648–58.
35. Müller M, Redfern M. Correlation between EMG and COP onset latency in response to a horizontal platform translation. J Biomech. 2004;37:1573–81.
36. Stelmach GE, Phillips J, DiFabio RP, Teasdale N. Age, functional postural reflexes, and voluntary sway. J Gerontol. 1989;44:B100–6.
37. Winter DA, Prince F, Frank JS, Powell C, Zabjek KF. Unified theory regarding A/P and M/L balance in quiet stance. J Neurophysiol. 1996;75:2334–43.
38. Kelly LA, Kuitunen S, Racinais S, Cresswell AG. Recruitment of the plantar intrinsic foot muscles with increasing postural demand. Clin Biomech. 2012;27:46–51.
39. Ledoux WR, Hirsch BE, Church T, Caunin M. Pennation angles of the intrinsic muscles of the foot. J Biomech. 2001;34:399–403.
40. Peterka RJ. Sensorimotor integration in human postural control. J Neurophysiol. 2002;88:1097–118.
41. Mergner T, Rosemeier T. Interaction of vestibular, somatosensory and visual signals for postural control and motion perception under terrestrial and microgravity conditions—a conceptual model. Brain Res Rev. 1998;28:118–35.
42. Ernst MO, Bülthoff HH. Merging the senses into a robust percept. Trends Cogn Sci. 2004;8:162–9.
43. Lowrey CR, Bent LR. Modulation of the soleus H-reflex following galvanic vestibular stimulation and cutaneous stimulation in prone human subjects. Muscle Nerve. 2009;40:213 -20.
44. Germano AMC, Schlee G, Milani TL. Effect of cooling foot sole skin receptors on Achilles tendon reflex. Muscle Nerve. 2016;53:965–71.

45. Simoneau G, Ulbrecht J, Derr J, Cavanagh P. Role of somatosensory input in the control of human posture. Gait Posture. 1995;3:115–22.
46. Meyer PF, Oddsson LIE, De Luca CJ. Reduced plantar sensitivity alters postural responses to lateral perturbations of balance. Exp Brain Res. 2004;157:526–36.
47. Blouin J-S, Corbeil P, Teasdale N. Postural stability is altered by the stimulation of pain but not warm receptors in humans. BMC Musculoskelet Disord. 2003;4:23.
48. Fukuchi CA, Duarte M, Stefanyshyn DJ. Postural sway following cryotherapy in healthy adults. Gait Posture. 2014;40:262–5.
49. Billot M, Handrigan GA, Simoneau M, Corbeil P, Teasdale N. Short term alteration of balance control after a reduction of plantar mechanoreceptor sensation through cooling. Neurosci Lett. 2013;535:40–4.
50. Hertel J, Buckley WE, Denegar CR. Serial testing of postural control after acute lateral ankle sprain. J Athl Train. 2001;36:363–8.
51. Tarantola J, Nardone A, Tacchini E, Schieppati M. Human stance stability improves with the repetition of the task: effect of foot position and visual condition. Neurosci Lett. 1997;228:75–8.
52. Shumway-Cook A, Woollacott M, Kerns K, Baldwin M. The effects of two types of cognitive tasks on postural stability in older adults with and without a history of falls. J Gerontol. 1997;52:232–40.
53. Kunesch E, Schmidt R, Nordin M, Wallin U, Hagbarth K-E. Peripheral neural correlates of cutaneous anaesthesia induced by skin cooling in man. Acta Physiol Scand. 1987;129:247–57.
54. Boeer J, Mueller O, Krauss I, Haupt G, Horstmann T. Zuverlässigkeitsprüfung eines Messverfahrens zur Charakterisierung des Standverhaltens und Quantifizierung des Balancevermögens auf einer instabilen Plattform (Posturomed). Sport Sport. 2010;24:40–5.
55. Day BL, Rothwell JC, Thompson PD, Dick JPR, Cowan JMA, Berardelli A, Marsden CD. Motor cortex stimulation in intact man. Brain. 1987;110:1191–209.
56. Guyton A, Hall J. Textbook of medical physiology. 11th ed. Philadelphia: Elsevier Saunders; 2006.

57. Schomburg ED. Spinal sensorimotor systems and their supraspinal control. Neurosci Res. 1990;7:265–340.
58. Haridas C, Zehr EP, Misiaszek JE. Postural uncertainty leads to dynamic control of cutaneous reflexes from the foot during human walking. Brain Res. 2005;1062:48–62.
59. Nardone A, Tarantola J, Miscio G, Pisano F, Schenone A, Schieppati M. Loss of large-diameter spindle afferent fibres is not detrimental to the control of body sway during upright stance: evidence from neuropathy. Exp Brain Res. 2000;135:155–62.
60. Horak FB. Postural orientation and equilibrium: what do we need to know about neural control of balance to prevent falls? Age Ageing. 2006;35:7–11.

3.4.1 Study 4: Summary and classification in the context of this thesis

Study 4 of this thesis deals with inducing and maintaining plantar hypothermia at different intermediate levels throughout data collection. Surprisingly, no hypothermic effect on balance outcomes was detected for the quasi-static balance phases. Contrary to the expectations, balance measures decreased for the dynamic balance responses. Presumably, this corresponds to a possible "over-compensation", causing cautious behavior during the challenging dynamic balance tasks under plantar hypothermia. The results from Study 4 provide new evidence supporting the assumption that plantar hypothermia may be well compensated by other intact sensory systems during unchallenging situations (quasi-static balance in young and healthy adults). However, central processing was affected differently under the more challenging situations (dynamic balance due to unexpected platform perturbations).

In the next section, the summary of the hypotheses is followed by a general and summary discussion based on all four studies already presented. Finally, in the "Perspectives and future directions" section, an interesting example of a clinical application is presented based on the findings from Studies 1 through 4. This example also draws on Study 5, and includes recently been published preliminary work.

Section 4 - Hypotheses, discussion, and summary

This section discusses of the results based on Studies 1 through 4. In contrast to the discussions presented in the individual studies, section 4 aims to discuss the results in a combined and updated context, that is also based on more recent literature. In addition, this section provides a summary of the main findings of this thesis. Prior to that, however, the focus will be on the hypotheses associated with this work.

4.1 Summary of the hypotheses based on the study results

Prior to answering whether or not the hypotheses were rejected, the overall aim(s) of each study are provided for clarity.

Study 1 aimed to compare VPTs assessed in a standing versus sitting posture. The two hypotheses were:
1_H1: There are higher vertical forces applied against the probe when standing compared to sitting.
1_H2: Lower VPTs are present when standing compared to sitting.

Based on the findings of Study 1 "Plantar sensory vibration thresholds are not influenced by body position", hypothesis 1_H1 can be confirmed, as expected. Compared to sitting, the vertical contact forces when standing were 62.6, 43.2, and 27.7% higher for the heel, first metatarsal head, and hallux, respectively. However, the higher vertical contact forces during standing did not alter VPTs. Hence, hypothesis 1_H2 had to be rejected.

Study 2 aimed to demonstrate the presence of heteroscedasticity in VPT data, to provide an example of how to properly treat heteroscedasticity, and to show whether or not his treatment was successful. The hypothesis was:
2_H1: Plantar sensitivity data exhibit heteroscedasticity.

Based on Study 2, "Subjective sensitivity data: considerations to treat heteroscedasticity", we showed that VPT data is indeed heteroscedastic. This was evident when looking at criteria to identify such patterns (Bland-Altman plots, Spearman correlation). As will be further discussed in this section, we also fulfilled the aims of this study mentioned above.

Study 3 aimed to investigate reliability aspects of the Posturomed device. The hypothesis was:
3_H1: The Posturomed device exhibits a low intra- and inter-day reliability in terms of initial motor responses during dynamic balance performance.

Study 3, "Aspects of Dynamic Balance Responses: Inter- and Intra-Day Reliability", showed generally good reliability, whereas intra-day and inter-day reliability were assessed. In terms of reliability, the focus was on tests for bias (differences between the measurements), absolute reliability (Bland-Altman plots), and relative reliability (intra class correlation, ICC). Although there were significant differences in some comparisons, these were not considered clinically relevant. Hence, hypothesis 3_H1 had to be rejected.

Study 4 had the overall aim to investigate the effect of plantar hypothermia on dynamic balance performance. Other aims were to maintain a pre-determined level of plantar hypothermia throughout the experiments without affecting other sensory systems. Based on this, the hypothesis was:
4_H1: Plantar hypothermia results in impaired balance performance, evident by increased center of pressure (COP) excursions and electromyographic (EMG) activity.

The results of Study 4, "Effects of hypothermically reduced plantar skin inputs on anticipatory and compensatory balance responses", showed that participants' balance performance after hypothermia did not deteriorate in any of the parameters / conditions investigated. Hence, hypothesis 4_H1 had to be rejected.

4.2 General findings and discussion

Assessing human cutaneous sensitivity and balance are important research tools in human movement science and biomechanics. As previously mentioned, various sensory systems contribute to the successful maintenance of posture and balance. One significant sub-system is cutaneous sensitivity (Horak et al. 1990; Kavounoudias et al. 1998), often investigated by measuring vibration perception thresholds (VPTs). To adequately draw conclusions from cutaneous sensitivity toward human balance, it is essential to assess VPTs in a way which meets biomechanical quality criteria (reliability, validity, and objectivity). In this context, it is known that a broad range of factors (may) play a decisive role.

Several of these factors have already been discussed in the literature. For example, several studies have shown that decreasing and increasing skin temperatures may deteriorate and improve cutaneous sensitivity, respectively (Nurse and Nigg 2001; Eils et al. 2002; Schlee et al. 2009b; Lowrey et al. 2013; Germano et al. 2016b; Schmidt et al. 2017; Alexander et al. 2019). Other influencing factors include the size and vertical force of the vibrating probe (also known as contactor), as larger contactors and forces usually reduce VPTs, which corresponds with improved sensitivity (Muijser 1990; Gescheider et al. 1999; Morioka and Griffin 2005; Schmidt et al. 2020; Zippenfennig et al. 2021b). In addition, age (Doeland et al. 1989; Gescheider et al. 1994; Wells et al. 2003; Andreato et al. 2020) and diseases (Young et al. 1994; van Deursen and Simoneau 1999; Balducci et al. 2014; Goddard et al. 2018; Lindholm et al. 2019; Zippenfennig et al. 2021a) may affect cutaneous sensitivity, to name some factors. VPTs can also be implemented to help identify (Inglis et al. 1994; Drechsel et al. 2021) or even predict certain diseases (Young et al. 1994).

In the context of this thesis, there are two factors that are not as profoundly embedded in the literature, thus making it more difficult to obtain the necessary methodological standardization. This, in turn, is essential to adequately "apply" VPT data in today´s scientific and clinical application fields / areas. The first factor is part of Study 1, "Plantar sensory vibration thresholds are not influenced by body position",

which is related to the comparison of assessing VPTs during upright standing versus sitting. It was not surprising that increased vertical contact forces were measured during standing compared to sitting. However, these increases did not alter VPTs. Consequently, this study concludes that the two different postures may not influence VPTs. This was contrary to our expectations, because previous studies have shown that increased contact forces usually lower VPTs (Schmidt et al. 2020; Zippenfennig et al. 2021b) and that different postures alter sensory afferent signal processing (Hayashi et al. 1992; Koceja et al. 1993; Mynark and Koceja 1997). Additionally, although related to another sensory modality, one investigation showed that strategies for the subjective perception of verticality seem to vary when comparing standing versus sitting postures (Bergmann et al. 2020). The only known study dealing with a similar methodology as Study 1 found similar results for the heel, but slightly increased VPTs at the metatarsal heads when standing (Mildren et al. 2016). However, one has to bear in mind that Mildren et al. (2016) used a larger probe array, which might explain differences (as already mentioned in Study 1). Additionally, their study did not correct the level of significance. Another point is that Mildren et al. (2016) solely found significant differences in 50% of the comparisons when looking separately at each anatomical location and testing frequency. When merging both locations into one data set, all comparisons became significant (α=0.05). This approach probably has its limitations, as different anatomical locations per se seem to exhibit not only different mechanical or physiological skin properties (Schmidt et al. 2018; Holowka et al. 2019), but also different VPTs (Schlee et al. 2009a; Mildren et al. 2016). Hence, merging such data might mask certain differences or effects.

The new findings from Study 1 are very important, because VPTs do not differ regardless of whether the tests are performed during standing or sitting. Balance tests are usually performed in a standing position, whereas (plantar) sensitivity is often evaluated in a sitting position. The findings of our study show that the results of both tests can be used together. Therefore, a valid interpretation of the relationship between cutaneous sensitivity and balance data seems possible, as will be discussed later.

One important aspect should be mentioned with respect to Study 1. We assessed the subjective VPT, meaning, the perception based on central processes in various parietal cortex areas. However, this does not necessarily reflect the contribution of these afferents when it comes to early, reflex-like motor activity, which also includes balance regulation. In fact, plantar inputs may affect motor pathways quite early in the processing path. This may already occur at the level of the spinal cord (Sayenko et al. 2009; Germano et al. 2016a), which is well before actual subjective perception. In our study, we were clearly not able to assess this. Although the subjective data from Study 1 clearly indicate that there are no differences in vibration perception between the two postures, we cannot provide evidence that early-stage balance modulating and plantar afferent signals behave in the same manner.

In terms of factors that might influence cutaneous (vibratory) sensitivity, the above-mentioned results, including other publications related to the field, led to a comfortable situation: Over the years, new methodological and physiological standards successfully optimized the research quality in our lab, especially with regard to the assessment of VPTs. However, the subsequent (statistical) analysis also plays a fundamental role in appropriate interpretations. That was part of Study 2, "Subjective sensitivity data: Considerations to treat heteroscedasticity", which demonstrated that the VPT data collected was heteroscedastic. This means that the error is in correlation with the magnitude of the VPT data (the larger the values, the higher the error) (Nevill and Atkinson 1997; Atkinson and Nevill 1998).

By calculating the natural logarithm (log transformation) of the raw VPT data in Study 2, we demonstrated how to correct for heteroscedasticity. This approach is not new and is widely described (Nevill and Atkinson 1997; Wilcox et al. 2018). However, even publications performing a log transformation generally do not describe whether the transformation actually eliminated heteroscedasticity. Since many inferential statistical tests and regular measures, e.g. t-test, ANOVA, Mann-Whitney-U test, correlation analyses, or the standard error of measurement (SEM), assume homoscedasticity (Zimmerman and Zumbo 1993; Nevill 1997; Atkinson and Nevill 1998; Zimmerman 2004; Wilcox et al. 2018), this constitutes a problem. Study 2 also found that p-values of the Wilcoxon test and ICC magnitudes differ depending on

whether these tests are performed on raw or log transformed data. Hence, providing such justification is essential prior to drawing conclusions. Study 2 addresses for these considerations, as we provided an easy-to-follow example of how to treat heteroscedasticity, including a verification showing that the treatment successfully resulted in homoscedasticity. Based on personal experience from other (unpublished) VPT data, heteroscedasticity is not always present, and in some cases differences between inferential statistical tests (particularly to detect bias) seem minimal, regardless of whether they are conducted on raw or log transformed data. However, science aims to perform its measures as close to "reality" as possible. Therefore, one conclusion from Study 2 is to follow this aim. As noted above, Study 2 was intentionally presented in an easy-to-understand format, as there is a broad clientele that is concerned with VPTs (and other ratio-scaled subjective data), and, in certain cases, has limited statistical background knowledge. Finally, in some cases heteroscedasticity cannot be (entirely) removed using log transformation. To solve this there are alternative approaches briefly described in Study 2. However, many of them require advanced statistical knowledge, which might constitute a problem for the clientele described above. This highlights the importance of science when it comes to knowledge transfer. The growing demand of scientific input and incooperation in various clinical scenarios further emphasizes this point. Ultimately, accessibility of the results stemming from this incooperation is of utmost importance. A direct and easy-to-understand transfer to the general public still represents an immense challenge in current science.

This thesis previously discussed how cutaneous (plantar) sensitivity contributes to human balance. To appropriately examine and better understand this relationship, it is important to adequately assess and analyze cutaneous sensitivity data. Of course, the same applies for human balance data. In this regard, investigating dynamic balance behavior is appealing, as it is superior to quasi-static balance tests for evaluating functional balance performance (Taube et al. 2014). Dynamic (but also quasi-static) balance can be assessed using the Posturomed device (Hilberg et al. 2001; Bruhn et al. 2004; Schwab 2008; Kiss 2010, 2011; Hirschmüller et al. 2011; Petró and Kiss 2017; Rohof et al. 2020; Rappelt et al. 2021), e.g. by allowing unexpected horizontal platform oscillations. Although it is also used as a training

device, no study had investigated the reliability of dynamic balance tests on the Posturomed, particularly the first dynamic balance responses after unexpected perturbations. Therefore, Study 3, "Aspects of Dynamic Balance Responses: Inter- and Intra-Day Reliability", was performed and proved an overall good reliability of the Posturomed. In this study, reliability was assessed intra (for both testing days) and inter day (day 1 versus day 2). Other investigations only include few parameters (e.g., Morat et al. 2019; Watkhum et al. 2020; Rappelt et al. 2021). In contrast, Study 3 implemented several parameters to calculate and judge reliability: tests for systematic error (bias), relative reliability (intra class correlations, ICC), absolute reliability (Bland-Altman plots), and descriptive data considering the series of all 12 individual balance tests per condition. Although significant bias was observed in rare cases, these differences were not found to be clinically relevant. The clinical relevance of mean differences was assessed by calculating the root mean square error (RMSE) terms of the corresponding data. However, based on Bland-Altman plots, which also include a random error component (not only systematic error), intra-day absolute reliability was poorer in the AP perturbation direction for interval 2. This could indicate possible learning effects. However, there is also likely to be greater biological variability due to a lower balance demand compared to the ML perturbation. Another study (Boeer et al. 2010) investigating the reliability of the Posturomed found quite similar conclusions, that the Posturomed is a reliable device. However, as previously mentioned, this study (Boeer et al. 2010) investigated quasi-static balance performance, not dynamic balance as Study 3 of this thesis.

All in all, intra-day comparisons (morning versus afternoon measurements) under the AP perturbation direction should be treated with caution, as there could be a lower absolute reliability. However, the Posturomed device is suitable to reliably assess quasi-static and dynamic balance performance as achieved in Study 3. Therefore, the frequently expressed demand for reliable balance assessment approaches (Bower et al. 2014) could be met. With respect to evaluating functional balance (Taube et al. 2014), the possible superiority of dynamic balance tasks over quasi-static balance tasks also plays an important role in another context: For example, when predicting or preventing falls in affected populations, such as the elderly and/or diseased.

The overall good reliability of the Posturomed device is, however, only valid for data as analyzed in this study. In unpublished data, we observed that when investigating longer time intervals (lasting e.g. 5 or 20 seconds), there were indeed patterns of pronounced learning effects. Hence, it might be in the nature of the initial, reflex-like motor responses that they do not tend to show such patterns, which should be kept in mind when analyzing data obtained from (therapeutic) training devices. For example, another investigation cited Study 3 to confirm the good overall reliability of the Posturomed, but collected balance data for a duration of 10 s (Rappelt et al. 2021). We clearly stated that the good overall reliability is only valid for the short time intervals used in Study 3 (less than 300 ms). Therefore, the justification for Rappelt et al. (2021) is questionable. The same is also true for another study analyzing data from the Posturomed (Morat et al. 2019). Further, Study 3 focussed on young and healthy participants, and similar reliability cannot be assumed for different populations and/or balance tasks.

Two important objectives were achieved with Studies 1, 2, and 3: First, VPT data can now be properly assessed and analyzed. Second, to the best of our knowledge, a reliable approach to investigate (dynamic) balance performance has been found. On this basis, a further step was taken towards investigating another interesting research question, which was part of Study 4, "Effects of hypothermically reduced plantar skin inputs on anticipatory and compensatory balance responses". In contrast to many studies in this area, Study 4 successfully induced hypothermia exclusively to plantar aspects of the feet. Other foot regions, such as dorsal areas or the ankle, apparently remained unaffected. Furthermore, all pre-determined plantar temperature stages were successfully maintained throughout the entire process of data collection (similar temperatures before and after balance trials). These aspects are of utmost importance, since many other studies (e.g., Magnusson et al. 1990; Yasuda et al. 1999; Nurse and Nigg 2001; McKeon and Hertel 2007b; Billot et al. 2014) were unable to guarantee the maintenance of hypothermia during subsequent balance tests. A previous study showed that after 3 min of natural re-warming, afferent receptor responses already reach 50% of their baseline firing activity (Lowrey et al. 2013). Although this method is based on an (objective) microneurographic approach rather than subjective measures when assessing VPTs, there should clearly be

caution when permanent hypothermia cannot be guaranteed during subsequent motor performance tests.

Despite these methodological outcomes from Study 4, other conclusions can also be drawn. The first is that the exact role or significance of plantar afferent input on human balance is still controversial in the literature, especially considering various co-factors, such as open or closed eyes, or the postural demand of the balance tests per se. Study 4 provides new evidence that integration and combination processes of afferent information lead to compensatory mechanisms during more unchallenging balance settings (as during the quasi-static phases of Study 4, namely intervals 0 and 1). Such mechanisms were already proposed in another study (Ernst and Bülthoff 2004). In Study 4, this would mean that the reduced plantar afferent input was successfully compensated by other available input systems during the unchallenging balance conditions (quasi-static and eyes open), as no differences in the COP data were evident.

In contrast, Santos et al. (2021) found that the co-parameter "decreased plantar sensitivity" resulted in poorer lower extremity physical function. Their study did not artificially induce plantar dysthesia but did include quasi-static balance tests, as in Study 4. However, it is presumable that those participants who exhibited a poor plantar sensitivity also suffered from deteriorations of other sensory domains, which then led in sum to the deteriorated motor performance. Hence, only limited comparisons with our acute and "artificial" protocol to reduce plantar sensitivity are possible, as previously mentioned above. The findings from Study 4 also contrast another recent investigation, in which we found increased quasi-static balance parameters after plantar hypothermia using the same thermal platform, indicating that there was no compensation (Germano et al. 2018). However, the single-leg quasi-static balance tests in this study were performed much longer than in Study 4. Therefore, it remains unclear whether the hypothermically induced increased COP parameters found (Germano et al. (2018)) occurred because of a lack of compensation from a high balance threat. Despite the relatively long period of single-leg stance (25s), the afore-mentioned assumption seems unlikely for the following reasons. The tests were of quasi-static nature, which is usually not associated with a notable balance threat, especially in young and healthy adults. In this context, it has

been shown that sufficient or increased balance threat is associated with no or slight decreases in COP parameters in younger adults (Brown et al. 2002): among four threat stages, the greatest threat condition induced slight COP decreases. This also suggests that the CNS may allow a certain sway as long as balance is not in acute danger. This would explain the non-significant findings for the quasi-static performance (intervals 0, 1) in Study 4. Similarly, another publication found that plantar hypothermia did not alter balance performance of young adults (Machado et al. 2017). There are also other sensory input systems which appear more relevant for balance control than plantar inputs. In this context, in a recent study, we were able to demonstrate that an acute loss of visual inputs could not be compensated under different conditions/groups (young and elderly participants, quasi-static and dynamic balance) (Schmidt et al. 2021a).

For the more challenging balance conditions (dynamic balance due to unexpected horizontal platform perturbations with eyes still open, interval 2) in Study 4, the permanent hypothermic treatment resulted in decreased balance parameters, which is usually interpreted as improved balance performance (Shumway-Cook et al. 1997; Tarantola et al. 1997; Hertel et al. 2001). There are (diseased) populations in which smaller or equal (COP) excursions do not necessarily represent improved or equally good balance capabilities compared to healthy participants. This is true for Parkinson´s disease (Schieppati et al. 1994) and less severely affected patients suffering from Charcot-Marie-Tooth neuropathy type 1A (Nardone et al. 2000). However, it is presumable that this possibility can be excluded, as our participants were healthy and young (mean±SD: 23.6±3.0 yrs). The above-mentioned integration and combination processes may be different compared to intervals 0 and 1, because interval 2 involved an increased postural demand induced by the unexpected perturbation in addition to plantar hypothermia. Hence, we speculate that the actual motor program was based on a more threatening balance situation, resulting in more "cautious" and "alert" behavior to respond to sudden reweighting processes. This would result in decreased parameters. These findings are supported by another investigation (Brown et al. 2002), which also found decreased balance parameters for the most threatening balance condition. Due to the dynamic nature of the balance tests, the feet and legs in particular were confronted with these shifts, which could

have activated other intact afferent sources (e.g. muscle spindles or joint receptors) to a greater extent than easier quasi-static conditions. This assumption is supported by fact that sufficient threat towards balance is able to modulate reflexes (Haridas et al. 2005). In addition, increased afferent input from other intact sensory sources (compared to quasi-static balance) might have modulated alpha-neuronal drive by spinal inter-neurons, which was demonstrated in an earlier study (Schomburg 1990). Similar behavior of "using" available sources has also been observed in the elderly: they shifted their plantar pressure toward more sensitive regions of the foot sole, hence improving sensory input (Machado et al. 2016). Since the entire plantar foot was cooled in Study 4, this strategy does not seem applicable here. However, these considerations provide a possible explanation for the lower magnitudes of the parameters we examined.

A final noteworthy finding from Study 4 is that an intermediate plantar temperature stage (12 °C) was already sufficient to elicit hypothermic balance effects. The lowest temperature stage (0 °C) pronounced this effect further, however, only with moderate expression. Although perceived pain levels were not evaluated during Study 4, personal experience and participant reports confirmed the occurrence of pain during the 0 °C stage. Although related to heat-induced pain, another study found that temperature-induced pain deteriorated postural control due to an interaction of nociceptors and Ia afferents in the spinal cord (Blouin et al. 2003). Since cold-induced pain is also mediated by the same nociceptors, it is essential to determine the point at which pain starts in posturographic studies.

Study 4 also has a limitation that should be discussed. The hypothermic treatment was applied to the plantar aspects only, and we did not record any relevant temperature changes at the ankle or dorsal foot areas, for example. However, due to the overall duration of cooling, we cannot entirely exclude an involvement of (mechano-)receptors located in deeper tissue regions. It is well-known that mechanoreceptors are also located in bone material, ligaments, or fascia (Schleip 2003) - which is - per definition - not part of the cutaneous sensory system. On the other hand, it would be reasonable to assume that cutaneous and deeper (proprioceptive) mechanoreceptors work as a functional unit, which might somewhat

relativize this limitation (provided of course these structures were also affected in Study 4). Another limiting factor is that we did not assess subjects' psychological activities during the interval prior to the onset of external platform perturbation. That is, we did not assess how intensively they were thinking (and, hence, automatically acting) while anticipating the perturbation. Different coping strategies, especially in a laboratory setting, may affect this. After all, it was shown that anticipatory activity indeed affects compensatory motor activity (Santos et al. 2010).

4.3 Summary of this thesis

The studies incorporated in this thesis shed further light onto research questions affecting quality criteria when assessing and analyzing biomechanical data, and regarding their (neuro-physiological) interpretation. In summary, assessing (plantar) skin sensitivity is a broad area of research, for example its contribution to human balance performance. Of course, assessing plantar VPTs requires thorough collection and interpretation of data, as there are numerous internal and external co-factors being identified which must be controlled and analyzed. In this regard, Study 1 aimed to investigate whether VPTs differ during standing and sitting. We clearly demonstrated that this was not the case. Consequently, VPT data collected when sitting can be related to balance data collected during standing.

Another fundamental aspect refers to the correct interpretation of VPT data, which requires the consideration of procedures that account for possible data heteroscedasticity. Study 2 aimed to provide an easy-to-follow example of how to achieve this using a logarithmic transformation. We also provided practical recommendations, as merely performing a transformation may not be sufficient, since the benefit of such measures can vary even within one data set.

The same requirements and standards to adequately assess and analyze data are also valid when examining human balance. One device used to assess human balance performance is the Posturomed. Hence, Study 3 aimed to investigate the intra and inter-day reliability of this device. We demonstrated an overall good reliability with regard to initial motor responses following unexpected perturbations.

Building on the experience and knowledge gained from these three studies, we finally investigated the role of plantar sensory inputs on balance responses in young and healthy individuals (Study 4). We found that plantar afferent input during unchallenging balance tasks seems to be compensated by other sensory systems that were not affected by sensory deprivation. However, the participants primarily seem to have chosen a more cautious behavior under more challenging tasks, which we interpreted as an over-compensation due to the higher balance threat. This

contributes to the idea of non-uniform and non-linear central processing of plantar inputs with regard to human balance, according to the type of balance task. This also highlights the importance of carefully interpreting certain outcomes of balance measures.

5. Perspectives and future directions

The remaining part of this work could put further emphasis on perspectives and future directions directly incorporating Studies 1 through 4. However, this sub-section shall instead provide brief examples, using the four studies presented "merely" as a basic premise. To round off this thesis, and in relation to the last aspect of its title, practical research examples shall be mentioned demonstrating new and innovative fields of scientific research integrating cutaneous sensitivity and motor/balance measurements.

These new and innovative areas of research fields may even be surprising, because of the role of "non-cognitive" parameters in cognitive disorders. Study 5, "Sensor-based systems for early detection of dementia (SENDA): a study protocol for a prospective cohort sequential study", was published for this purpose (Appendix 1).

Study 5 is one of the first studies to examine cognitive, motor, sensory, and neurophysiological markers in combination. In line with the topic of this doctoral thesis, the focus is on the overall aim to identify sensory and motor parameters and their role in the (early) detection of cognitive impairment, such as mild cognitive impairment (MCI) as a possible precursor to dementia. Interestingly, studies have shown that dementia exhibits various non-cognitive symptoms, which might even be present prior to the onset of the generally accepted cognitive symptoms (Raudino 2013). Additionally, structures associated with the processing of cutaneous (vibratory) sensitivity are affected in MCI, early dementia, and dementia (Rapoport 1991; Doran et al. 2003; Dugger et al. 2013). These structures include, for example, the brainstem, spinal cord, and the primary somatosensory cortex (Rapoport 1991; Doran et al. 2003; Dugger et al. 2013), some of which also play a role in balance regulation. Cognitive decline that is already at the MCI stage may affect motor performance, as shown in previous studies (Verghese et al. 2009; Shin et al. 2011; Makizako et al. 2013). Building upon this, preliminary work is briefly presented below highlighting perspectives and future directions for this area of research.

We were able to descriptively demonstrate that participants with MCI tend to exhibit poorer plantar vibratory sensitivity compared to age-matched controls, although statistically non-significant (Schmidt et al. 2021b) (Appendix 2). We were also able to detect a significant correlation between balance performance and cognitive state (assessed using the Montreal Cognitive Assessment (MoCA) questionnaire) of the participants, although no balance-related differences were found between MCI and the age-matched control group (Germano et al. 2021) (Appendix 3). Since small sample sizes may account for limitations regarding statistical significance (Nevill and Atkinson 1997; Wilcox et al. 2018), more work is necessary to investigate the role of cutaneous sensitivity and/or motor-related parameters in the context of cognitive decline. As dementia is not curable (Sütterlin et al. 2011), early diagnosis and intervention are paramount to better detect these conditions and slow disease progression much as possible.

Several aspects remain unanswered, which raises questions for future biomechanical investigations. For example, how might dynamic balance performance after unexpected perturbations (with and without dual-task conditions) help to better understand or diagnose cognitive decline earlier? How might other motor parameters, such as eye-foot or eye-hand coordination tasks with and without dual tasks fit into these considerations? What is the role of the overall physical activity level of the participants? This is an interesting aspect since studies have shown a positive influence of physical activity on sensory integration and balance control (Prioli et al. 2005; Schmidt et al. 2021a), and even a slowing down/reduction of the progression of cognitive decline (Groot et al. 2016; Nuzum et al. 2020). Data analyses are fundamental for drawing valid and appropriate conclusions.

Therefore, together with the Professorship of Research Methodology and Data Analysis in Biomechanics (head: Prof. Christian Maiwald, Chemnitz University of Technology), we are looking further than the “classical” statistical approaches, such as non-linear estimates, to help draw appropriate conclusions from the data. This would clearly help to better understand cognitive decline and to develop early interventions.

The incorporation of cutaneous sensory and balance data into clinical application is also the main purpose of two ongoing third-party exchange projects between the Federal University of Pampa in Brazil (principal investigator: Prof. Felipe P. Carpes) and our team (principal investigator: Dr. Andresa M.C. Germano), with a timeline of 2020-2021 and 2022-2024 (approved as of November 2021). In brief, the projects aim to develop an intervention to enhance plantar sensitivity and balance control in elderly (obese) people, with and without dual-task settings.

Based on the studies of this thesis, further important information for a more adequate and holistic use of various scientific tools is provided. An interesting feature of sensory-motor investigations is the wide implementation for various research questions and settings. Such an implementation serves as a significant contributor for the clinical and health-related scope. Ultimately, there should be an urge to involve important recommendations for various clienteles in order to improve their overall quality of life.

References (sections 1, 2, 4, 5)

Ackermann A, Oswald W. Psychomotorische Aktivierung mit SimA-P - Selbstständig im Alter. Wien: Springer Verlag; 2009.

Akbari M, Jafari H, Moshashaee A, Forugh B. Do diabetic neuropathy patients benefit from balance training? J Rehabil Res Dev. 2012;49:333–8.

Alexander J, Selfe J, Rhodes D, Fowler E, May K, Richards J. Mapping of skin surface sensitivity and skin surface temperature at the knee over a re-warming period following cryotherapy Mapping knee skin surface sensitivity and temperature following cryotherapy. J Quant Res Rehabil Med. 2019;2:1–5.

Alexandrov A, Frolov A, Horak F, Carlson-Kuhta P, Park S. Feedback equilibrium control during human standing. Biol Cybern. 2005;93:309–22.

American Psychiatric Association I. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington, VA: American Psychiatric Association Press; 2013.

Andreato L, de Oliveira D, Follmer B, Bertolini S. The influence of age and overweight or obesity on foot sensitivity and postural control: A systematic review. Australas J Ageing. 2020;00:1–8.

Atkinson G, Nevill A. Statistical methods for assessing measurement error (reliability) in variables relevant to sports medicine. Sport Med. 1998;26(4):217–38.

Bahureksa L, Najafi B, Saleh A, Sabbagh M, Coon D, Mohler MJ, et al. The Impact of Mild Cognitive Impairment on Gait and Balance: A Systematic Review and Meta-Analysis of Studies Using Instrumented Assessment. Gerontology. 2017;63:67–83.

Balducci S, Sacchetti M, Haxhi J, Orlando G, D'Errico V, Fallucca S, et al. Physical Exercise as therapy for type II diabetes. Diabetes Metab Res Rev. 2014;32(30):13–23.

Baumann W, Reim H. Bewegungslehre. 2. Braunschweig: Diesterweg; 1989.

Baumhoer I. Förderung der Kooperationsfähigkeit in einer vierten Klasse durch Erarbeitung und Präsentation einer Zirkusvorstellung für das Schulabschiedsfest. München: GRIN Verlag; 2010.

Belghali M, Chastan N, Cignetti F, Davenne D, Decker LM. Loss of gait control assessed by cognitive-motor dual-tasks: pros and cons in detecting people at risk of developing Alzheimer's and Parkinson's diseases. GeroScience. 2017;63:67–83.

Benedetti F, Vighetti S, Ricco C, Lagna E, Bergamasco B, Pinessi L, et al. Pain threshold and tolerance in Alzheimer's disease. Pain. 1999; 0(1):3 –82.

Bergmann J, Bardins S, Prawitz C, Keywan A, Macneilage P, Jahn K. Perception of postural verticality in roll and pitch while sitting and standing in healthy subjects. Neurosci Lett. 2020;730:135055.

Billot M, Handrigan GA, Simoneau M, Corbeil P, Teasdale N. Short term alteration of balance control after a reduction of plantar mechanoreceptor sensation through cooling. Neurosci Lett. 2013;535(1):40–4.

Billot M, Handrigan GA, Simoneau M, Teasdale N. Reduced plantar sole sensitivity induces balance control modifications to compensate ankle tendon vibration and vision deprivation. J Electromyogr Kinesiol. 2014;25(1):155–60.

Birbaumer N, Schmidt R. Biologische Psychologie. 5. Berlin Heidelberg New York: Springer Verlag; 2003.

Birznieks I, Mcintyre S, Nilsson HM, Nagi SS, Macefield VG, Mahns DA, et al. Tactile sensory channels over-ruled by frequency decoding system that utilizes spike pattern regardless of receptor type. Elife. 2019;8:e46510.

Blouin J-S, Corbeil P, Teasdale N. Postural stability is altered by the stimulation of pain but not warm receptors in humans. BMC Musculoskelet Disord. 2003;4:23.

Boeer J, Mueller O, Krauss I, Haupt G, Horstmann T. Zuverlässigkeitsprüfung eines Messverfahrens zur Charakterisierung des Standverhaltens und Quantifizierung des Balancevermögens auf einer instabilen Plattform (Posturomed). Sport Sport. 2010;24:40–5.

Bolanowski SJ, Gescheider GA, Verrillo RT. Hairy skin: Psychophysical channels and their physiological substrates. Somatosens Mot Res. 1994;11:279–90.

Bower KJ, McGinley JL, Miller KJ, Clark R a. Instrumented static and dynamic balance assessment after stroke using Wii Balance Boards: Reliability and association with clinical tests. PLoS One. 2014;9(12):e115282.

Brown LA, Sleik RJ, Polych MA, Gage WH. Is the prioritization of postural control altered in conditions of postural threat in younger and older adults? J Gerontol A Biol Sci Med Sci. 2002;57(12):M785--M792.

Bruhn S, Kullmann N, Gollhofer a. The effects of a sensorimotor training and a strength training on postural stabilisation, maximum isometric contraction and jump performance. Int J Sports Med. 2004;25(1):56–60.

Cassella JP, Ashford RL, Kavanagh-Sharp V. Effect of applied pressure in the determination of vibration sensitivity using the Neurothesiometer. Foot. 2000;10(1):27–30.

Chow CC, Lauk M, Collins JJ. The dynamics of quasi-static posture control. Hum Mov Sci. 1999;18(5):725–40.

Chua R, Inglis T, Kennedy P, Wells C. The Role of Cutaneous Receptors in the Foot. Adv Exp Med Biol. 2002;508:111–7.

Deetjen P, Speckmann E-J, Hescheler J. Physiologie. 4th ed. Munich: Elsevier, Urban & Fischer; 2004.

van Deursen RW, Simoneau GG. Foot and ankle sensory neuropathy, proprioception, and postural stability. J Orthop Sports Phys Ther. 1999;29(12):718–26.

Doeland HJ, Harriet AM, Heimans JANJ. The relationship of cold and warmth cutaneous sensation to age and gender. Muscle and Nerve. 1989;12:712–5.

Doran M, Du Plessis DG, Enevoldson TP, Fletcher NA, Ghadiali E, Larner AJ. Pathological heterogeneity of clinically diagnosed corticobasal degeneration. J Neurol Sci. 2003;216(1):127–34.

Drechsel TJ, Monteiro RL, Zippenfennig C, Ferreira JSSP, Milani TL, Sacco ICN. Low and high frequency vibration perception thresholds can improve the diagnosis of diabetic neuropathy. J Clin Med. 2021;10:3073.

Dugger BN, Hidalgo JA, Chiarolanza G, Mariner M, Henry- J, Sue LI, et al. The distribution of phosphorylated tau in spinal cords of Alzheimer's and non-demented individuals. J Alzheimers Dis. 2013;34(2):529–36.

Eils E, Nolte S, Tewes M, Thorwesten L, Völker K, Rosenbaum D. Modified pressure distribution patterns in walking following reduction of plantar sensation. J Biomech. 2002;35(10):1307–13.

Era P, Hänninen V. The effects of intensity, frequency, static load, and shore hardness on different parameters in vibration sensitivity measurements. J Neurol Neurosurg Psychiatry. 1987;50:465–70.

Ernandes RDC, Brech GC, Mariana N, Luna S, Bega A. Impact of diabetic neuropathy on quality of life and postural balance in Brazilian older adults. Acta Ortop Bras. 2020;28:275–9.

Ernst MO, Bülthoff HH. Merging the senses into a robust percept. Trends Cogn Sci. 2004;8(4):162–9.

Fahlbusch J. Einfluß unterschiedlich komplexer motorischer Aufgaben auf die Organisation des primären somatosensorischen Kortex. Eberhard Karls Universität Tübingen; 2006.

Ferrari F, Clemente F, Cipriani C. The preload force affects the perception threshold of muscle vibration- induced movement illusions. Exp Brain Res. 2019;237(1):111–20.

Germano A, Schlee G, Milani TL. Effect of cooling foot sole skin receptors on Achilles tendon reflex. Muscle and Nerve. 2016a;53:965–71.

Germano A, Schmidt D, Milani T. Effects of hypothermically reduced plantar skin inputs on anticipatory and compensatory balance responses. BMC Neurosci. 2016b;17(1):1–14.

Germano AMC, Heß T, Schmidt D, Milani TL. Effects of plantar hypothermia on quasi-static balance: Two different hypothermic procedures. Gait Posture. 2018;60:194–9.

Germano AMC, Schmidt D, Masuch N, Milani TL. Limits of stability in cognitively healthy individuals and mild cognitive impairment (MCI). XXVIII Congr Int Soc Biomech (online, July 25-29). Stockholm, Sweden; 2021.

Gerr F, Letz R. Covariates of Human Peripheral-Nerve Function .2. Vibrotactile and Thermal Thresholds. Neurotoxicol Teratol. 1994;16(1):105–12.

Gescheider G, Berryhill M, Verrillo R, Bolanowski S. Vibrotactile temporal summation: probability summation or neural integration? Somatosens Mot Res. 1999;16:229–42.

Gescheider GA, Bolanowski SJ, Hall KL, Hoffman KE, Verrillo RT. The effects of aging on information-processing channels in the sense of touch: I. Absolute Sensitivity. Somatosens Mot Res. 1994;11(4):345–57.

Gescheider GA, Bolanowski SJ, Pope J V, Verrillo RT. A four-channel analysis of the tactile sensitivity of the fingertip: frequency selectivity, spatial summation, and temporal summation. Somatosens Mot Res. 2002;19:114–24.

Ghanavati T, Shaterzadeh Yazdi M, Goharpey S, Arastoo A. Functional balance in elderly with diabetic neuropathy. Diabetes Res Clin Pract. 2012;96:24–8.

Goddard K, Vas P, Purves A, McMillan V, Langford T, Reid F, et al. Comparing the diagnostic accuracy of simple tests to screen for diabetic peripheral neuropathy: protocol for a cross-sectional study. JMIR Res Protoc. 2018;7:e72.

Gregg E. Absolute measurement of the vibratory threshold. Arch Neurol Psychiatry. 1987;66:403–11.

Groot C, Hooghiemstra AM, Raijmakers PG, van Berckel BN, Scheltens P, Scherder EJ, et al. The effect of physical activity on cognitive function in patients with dementia: A meta-analysis of randomized control trials. Ageing Res Rev. 2016;25:13–23.

Gu C, Griffin MJ. Vibrotactile perception thresholds at the sole of the foot: Effects of contact force and probe indentation. Med Eng Phys. 2012;34(4):447–52.

Guyton AC, Hall JE. Textbook of Medical Physiology. 12th ed. Philadelphia: Elsevier Saunders; 2011.

Häfelinger U, Schuba V. Koordinationstherapie - Propriozeptives Training. Aachen: Meyer & Meyer Verlag; 2002.

Hagander L, Midani H, Kuskowski M, Parry G. Quantitative sensory testing: Effect of site and pressure on vibration thresholds. Clin Neurophysiol. 2000a;111:1066–9.

Hagander LG, Midani HA, Kuskowski MA, Parry GJ. Quantitative sensory testing: effect of site and skin temperature on thermal thresholds. Clin Neurophysiol. 2000b;111(1):17–22.

Handwerker HO. Neuro- und Sinnesphysiologie. In: Schmidt F, Schaible HG, editors. Somatosensorik. Heidelberg: Springer Medizin Verlag; 2006.

Hansen RA, Gartlehner G, Webb AP, Morgan LC, Moore CG, Jonas DE. Efficacy and safety of donepezil, galantamine, and rivastigmine for the treatment of Alzheimer's disease: a systematic review and meta-analysis. Clin Interv Aging. 2008;3:211–25.

Haridas C, Zehr EP, Misiaszek JE. Postural uncertainty leads to dynamic control of cutaneous reflexes from the foot during human walking. Brain Res. 2005;1062(1–2):48–62.

Hayashi R, Tako K, Tokuda T, Yanagisawa N. Comparison of amplitude of human soleus H-reflex during sitting and standing. Neurosci Res. 1992;13(3):227–33.

Hertel J, Buckley WE, Denegar CR. Serial Testing of Postural Control After Acute Lateral Ankle Sprain. J Athl Train. 2001;36(4):363–8.

Hilberg T, Herbsleb M, Gabriel HH, Jeschke D, Schramm W. Proprioception and isometric muscular strength in haemophilic subjects. Haemophilia. 2001;7(6):582–8.

Hirschmüller A, Konstantinidis L, Baur H, Müller S, Mehlhorn A, Kontermann J, et al. Do changes in dynamic plantar pressure distribution, strength capacity and postural

control after intra-articular calcaneal fracture correlate with clinical and radiological outcome? Injury. 2011;42(10):1135–43.

Holowka NB, Wynands B, Drechsel TJ, Yegian AK, Tobolsky VA, Okutoyi P, et al. Foot callus thickness does not trade off protection for tactile sensitivity during walking. Nature. 2019;571:261–4.

Hong SL, Manor B, Li L. Stance and sensory feedback influence on postural dynamics. Neurosci Lett. 2007;423(2):104–8.

Horak FB, Nashner LM, Diener HC. Postural strategies associated with somatosensory and vestibular loss. Exp Brain Res. 1990;82:167–77.

Ide C, Saito T. Electron microscopic histochemistry of cholinesterase activity of Vater-Pacini Corpuscle. Acta Histochem Cytochem. 1980;13(3):298–305.

Inglis JT, Horak FB, Shupert CL, Jones-Rycewicz C. The importance of somatosensory information in triggering and scaling automatic postural responses in humans. Exp Brain Res. 1994;101(1):159–64.

Inman BYDR, Peruzzi P. The effects of temperature on the responses of Pacinian corpuscles. J Physiol. 1961;155:280–301.

Kavounoudias a, Roll R, Roll JP. The plantar sole is a “dynamometric map” for human balance control. Neuroreport. 1998;9(14):3247–52.

Kennedy PM, Inglis JT. Distribution and behaviour of glabrous cutaneous receptors in the human foot sole. 2002;995–1002.

Kiss RM. Effect of the degree of hip osteoarthritis on equilibrium ability after sudden changes in direction. J Electromyogr Kinesiol. 2010;20(6):1052–7.

Kiss RM. A new parameter for characterizing balancing ability on an unstable oscillatory platform. Med Eng Phys. 2011;33(9):1160–6.

Knuchel S, Schädler S. Differenzialtests bei Gleichgewichtsstörungen. Drei Systeme in der Balance. Physiopraxis. 2004;2:28–31.

Koceja DM, Trimble MH, Earles DR. Inhibition of the soleus H-reflex in standing man. Brain Res. 1993;629(1):155–8.

Kramer A, Dettmers C, Gruber M. Exergaming with additional postural demands improves balance and gait in patients with multiple sclerosis as much as conventional balance training and leads to high adherence to home-based balance training. Arch Phys Med Rehabil. 2014;95(10):1803–9.

Kunesch E, Schmidt R, Nordin M, Wallin U, Hagbarth K-E. Peripheral neural correlates of cutaneous anaesthesia induced by skin cooling in man. Acta Physiol Scand. 1987;129:247–57.

Latash ML. Neurophysiological basis of movement. 1st ed. Champaign: Human Kinetics; 1998.

Lindholm E, Löndahl M, Fagher K, Apelqvist J, Dahlin L. Strong association between vibration perception thresholds at low frequencies (4 and 8 Hz), neuropathic symptoms and diabetic foot ulcers. PLoS One. 2019;14:e0212921.

Lowenthal LM, Derek T, Hockaday TD. Vibration sensory thresholds depend on pressure of applied stimulus. Diabetes Care. 1987;10(1):100–2.

Lowrey CR, Strzalkowski NDJ, Bent LR. Cooling reduces the cutaneous afferent firing response to vibratory stimuli in glabrous skin of the human foot sole. J Neurophysiol. 2013;109(3):839–50.

Machado Á, Da Rocha ES, Carpes F. Effects of plantar foot sensitivity manipulation on postural control of young adult and elderly. Rev Bras Reumatol. 2017;57(30–36).

Machado ÁS, Bombach GD, Duysens J, Carpes FP. Differences in foot sensitivity and plantar pressure between young adults and elderly. Arch Gerontol Geriatr. 2016;63:67–71.

Magnusson M, Enbom H, Johansson R, Pyykkö I. Significance of pressor input from the human feet in anterior-posterior postural control. The effect of hypothermia on vibration-induced body-sway. Acta Otolaryngol. 1990;110(3–4):182–8.

Makizako H, Shimada H, Doi T, Park H, Yoshida D, Uemura K, et al. Poor balance and lower gray matter volume predict falls in older adults with mild cognitive impairment. BMC Neurol. 2013;13:102.

McKeon P, Hertel J. Plantar hypoesthesia alters time-to-boundary measures of postural control. Somatosens Mot Res. 2007a;24(4):171–7.

McKeon PO, Hertel J. Diminished plantar cutaneous sensation and postural control. Percept Mot Skills. 2007b;104(1):56–66.

Meh D, Denislic M. Influence of age, temperature, sex, height and diazepam on vibration perception. J Neurol Sci. 1995;134(1–2):136–42.

Meinel K, Schnabel G. Bewegungslehre-Sportmotorik. Aachen: Meyer & Meyer Verlag; 2007.

Meyer PF, Oddsson LIE, De Luca CJ. The role of plantar cutaneous sensation in unperturbed stance. Exp Brain Res. 2004;156(4):505–12.

Mildren RL, Strzalkowski NDJ, Bent LR. Foot sole skin vibration perceptual thresholds are elevated in a standing posture compared to sitting. Gait Posture. 2016;43:87–92.

Morat M, Bakker J, Hammes V, Morat T, Giannouli E. Effects of stepping exergames under stable versus unstable conditions on balance and strength in healthy community-dwelling older adults: A three-armed randomized controlled trial. Exp Gerontol. 2019;127:110719.

Morioka M, Griffin MJ. Thresholds for the perception of hand-transmitted vibration: Dependence on contact area and contact location. Somatosens Mot Res. 2005;22:281–97.

Muijser H. The influence of spatial contrast on the frequency-dependent nature of vibration sensitivity. Percept Psychophys. 1990;48:431–5.

Müller-Wohlfahrt H, Ueblacker P, Hänsel L. Muskelverletzungen im Sport. Stuttgart: Thieme Verlagsgruppe; 2010.

Mynark RG, Koceja DM. Comparison of soleus H-reflex gain from prone to standing in dancers and controls. Electroencephalogr Clin Neurophysiol - Electromyogr Mot Control. 1997;105(2):135–40.

Nardone A, Tarantola J, Miscio G, Pisano F, Schenone A, Schieppati M. Loss of large-diameter spindle afferent fibres is not detrimental to the control of body sway during upright stance: evidence from neuropathy. Exp Brain Res. 2000;135(2):155–62.

Nevill A. Why the analysis of performance variables recorded on a ratio scale will invariably benefit from a log transformation. J Sport Sci. 1997;15(5):457–8.

Nevill AM, Atkinson G. Assessing agreement between measurements recorded on a ratio scale in sports medicine and sports science. Br J Sports Med. 1997;31(4):314–8.

Nigg B, MacIntosh B, Mester J. Biomechanics and Biology of Movement. Champaign: Human Kinetics; 2000.

Nurse MA, Nigg BM. The effect of changes in foot sensation on plantar pressure and muscle activity. Clin Biomech. 2001;16(9):719–27.

Nuzum H, Stickel A, Corona M, Zeller M, Melrose RJ, Wilkins SS. Potential benefits of physical activity in MCI and dementia. Behav Neurol. 2020;2020:1–10.

Park S, Horak FB, Kuo AD. Postural feedback responses scale with biomechanical constraints in human standing. Exp Brain Res. 2004;154:417–27.

Patel P, Bhatt T. Adaptation to large-magnitude treadmill-based perturbations: improvements in reactive balance response. Physiol Rep. 2015;3(2):e12247.

Perry SD, McIlroy WE, Maki BE. The role of plantar cutaneous mechanoreceptors in the control of compensatory stepping reactions evoked by unpredictable, multi-directional perturbation. Brain Res. 2000;877(2):401–6.

Petersen RC. Mild Cognitive Impairment. N Engl J Med. 2011;364:2227–34.

Petersen RC, Negash S. Mild Cognitive Impairment: An Overview. CNS Spectr. 2008;13:45–53.

Petró B, Kiss RM. Directional ratio: a proposed new variable of dynamic balance regain. Recent Innov Mechatronics. 2017;4:1–4.

Prätorius B, Kimmeskamp S, Milani T. The sensitivity of the sole of the foot in patients with Morbus Parkinson. Neurosci Lett. 2003;346(3):173–6.

Premkumar K. The Massage Connection - Anatomy and Physiology. 2nd ed. Darcy P, editor. Philadelphia, Pennsylvania: Lippincott Williams & Wilkins; 2004.

Prioli A, Freitas P, Barela J. Physical Activity and Postural Control in the Elderly: Coupling between Visual Information and Body Sway. Gerontology. 2005;51:145–8.

Purves D, Augustine G, Fitzpatrick D, Katz L, LaMantia A-S, McNamara J, et al. Neuroscience. 3rd ed. Sunderland, Massachusetts, USA: Sinauer Associates Inc.; 2001.

Rapoport SI. Positron emission tomography in Alzheimer's disease in relation to disease pathogenesis: a critical review. Cerebrovasc Brain Metab Rev. 1991;3(4):297–355.

Rappelt L, Held S, Donath L. Concentric not eccentric cycling sprint intervals acutely impair balance and jump performance in healthy active young adults : A randomized controlled cross-over study. Gait Posture. 2021;90:55–60.

Rassner G. Dermatologie: Lehrbuch und Atlas. München: Urban und Fischer; 2002.

Raudino F. Non-cognitive symptoms and related conditions in the Alzheimer's disease: a literature review. Neurol Sci. 2013;34(8):1275–82.

Rohof B, Betsch M, Rath B, Tingart M, Quack V. The - Nintendo ® Wii Fit Balance Board can be used as a portable and low ‐ cost posturography system with good agreement compared to established systems. Eur J Med Res. 2020;25:44 (1-8).

Santos A, Manzieri Prado-Rico J, Tasse de Oliveira Cirino N, Rodrigues Perracini M. Are foot deformity and plantar sensitivity impairment associated with physical function of community-dwelling older adults? Brazilian J Phys Ther. 2021;In press.

Santos MJ, Kanekar N, Aruin AS. The role of anticipatory postural adjustments in compensatory control of posture: 1. Electromyographic analysis. J Electromyogr Kinesiol. 2010;20(3):388–97.

Sayenko DG, Vette AH, Obata H, Alekhina MI, Akai M, Nakazawa K. Differential effects of plantar cutaneous afferent excitation on soleus stretch and H-reflex. Muscle Nerve. 2009;39:761–9.

Schieppati M, Hugon M, Grasso M, Nardone a, Galante M. The limits of equilibrium in young and elderly normal subjects and in parkinsonians. Electroencephalogr Clin Neurophysiol. 1994;93(4):286–98.

Schlee G, Milani T, Sterzing T, Oriwol D. Short-time lower leg ischemia reduces plantar foot sensitivity. Neurosci Lett. 2009a;462(3):286–8.

Schlee G, Sterzing T, Milani T. Foot sole skin temperature affects plantar foot sensitivity. Clin Neurophysiol. 2009;120(8):1548–51.

Schleip R. Fascial plasticity – a new neurobiological explanation : Part 1. J Bodyw Mov Ther. 2003;7:11–9.

Schmidt D, Carpes FP, Milani TL, Germano AMC. Different visual manipulations have similar effects on quasi-static and dynamic balance responses of young and older people. PeerJ. 2021a;9:e11221.

Schmidt D, Germano A, Milani T. Effects of active and passive warming of the foot sole on vibration perception thresholds. Clin Neurophysiol Pract. 2017;2:38–43.

Schmidt D, Germano AMC, Milani TL. Effects of water immersion on sensitivity and plantar skin properties. Neurosci Lett. 2018;686:41–6.

Schmidt D, Milani TL, Germano AMC. Longitudinal aspects of foot sensitivity in normal aging and mild cognitive impairment (MCI). Int Foot Ankle Biomech Meet (online, April 11-14). São Paulo, Brazil; 2021b.

Schmidt D, Schlee G, Germano AMC, Milani TL. Larger contactor area increases low-frequency vibratory sensitivity in hairy skin. PeerJ. 2020;8:e8479.

Schneider F. Korpuskuläre und enkapsulierte Nervenendigungen im Bereich der Fußsohle des Menschen. Julius-Maximilians-Universität zu Würzburg; 2006.

Schneider F, Fink G. Funktionelle MRT in Psychiatrie und Neurologie. Heidelberg: Springer Medizin Verlag; 2007.

Schomburg ED. Spinal sensorimotor systems and their supraspinal control. Neurosci Res. 1990;7(4):265–340.

Schwab MJ. Chiropractic management of a 47-year-old firefighter with lumbar disk extrusion. J Chiropr Med. 2008;7(4):146–54.

Sheperd G. Neurobiologie. Berlin Heidelberg: Springer Berlin Heidelberg; 1993.

Shin BM, Han SJ, Jung JH, Kim JE, Fregni F. Effect of mild cognitive impairment on balance. J Neurol Sci. 2011;305(1–2):121–5.

Shumway-Cook A, Woollacott M, Kerns K, Baldwin M. The effects of two types of cognitive tasks on postural stability in older adults with and without a history of falls. J Gerontol. 1997;52:232–40.

Simmons RW, Richardson C, Pozos R. Postural stability of diabetic patients with and without cutaneous sensory deficit in the foot. Diabetes Res Clin Pract. 1997;36(3):153–60.

Speckmann EJ, Hescheler J, Köhling R. Physiologie. 5th ed. München: Elsevier; 2008.

Strzalkowski ND, Ali A, Bent LR. The firing characteristics of foot sole cutaneous mechanoreceptor afferents in response to vibration stimuli. J Neurophysiol. 2017;118:1931–42.

Strzalkowski NDJ, Peters RM, Inglis JT, Bent LR. Cutaneous afferent innervation of the human foot sole: what can we learn from single-unit recordings? J Neurophysiol. 2018;120:1233–46.

Strzalkowski NDJ, Triano JJ, Lam CK, Templeton CA, Bent LR. Thresholds of skin sensitivity are partially influenced by mechanical properties of the skin on the foot sole. Physiol Rep. 2015;3(6).

Sütterlin S, Hoßmann I, Klingholz R. Demenz Report. 2011.

Tarantola J, Nardone A, Tacchini E, Schieppati M. Human stance stability improves with the repetition of the task: effect of foot position and visual condition. Neurosci Lett. 1997;228(2):75–8.

Taube W, Lorch M, Zeiter S, Keller M. Non-physical practice improves task performance in an unstable, perturbed environment: motor imagery and observational balance training. Front Hum Neurosci. 2014;8:1–10.

Taylor AJ, Menz HB, Keenan A-M. Effects of experimentally induced plantar insensitivity on forces and pressures under the foot during normal walking. Gait Posture. 2004;20(3):232–7.

Thukral N, Kaur J, Malik M. A systematic review and meta-analysis on efficacy of exercise on posture and balance in patients suffering from diabetic neuropathy. Curr Diabetes Rev. 2021;17:332–44.

Thyagarajan D, Dyck PJ. Influence of local tissue temperature on vibration detection threshold. J Neurol Sci. 1994;126(2):149–52.

Verghese J, Robbins M, Holtzer R, Zimmerman M, Wang C, Xue X, et al. Gait Dysfunction in Mild Cognitive Impairment Syndromes. J Am Geriatr Soc. 2009;56(7):1244–51.

Viseux FJF. The sensory role of the sole of the foot: Review and update on clinical perspectives. Neurophysiol Clin / Clin Neurophysiol. 2020;50(1):55–68.

Vrieling AH, van Keeken HG, Schoppen T, Otten E, Hof AL, Halbertsma JPK, et al. Balance control on a moving platform in unilateral lower limb amputees. Gait Posture. 2008;28(2):222–8.

Watkhum A, Boonyarom O, Srisupornkornkool K. Effect of Wii Balance Board and motor imagery on balance and muscle strength in football players. Chulalongkorn Med J. 2020;64:185–90.

Weiß O, Ullmann J. Motopädagogik. Wien: Facultas Verlags- und Buchhandels AG; 2003.

Wells C, Ward LM, Chua R, Inglis JT. Regional variation and changes with ageing in vibrotactile sensitivity in the human footsole. J Gerontol A Biol Sci Med Sci. 2003;58(8):680–6.

Wilcox R, Peterson TJ, McNitt-gray JL. Data analyses when sample sizes are small: modern advances for dealing with outliers , skewed distributions, and heteroscedasticity. J Appl Biomech. 2018;34:258–61.

Wilska A. On the vibrational sensitivity in different regions of the body surface. Acta Physiol Scand. 1954;31:285–9.

Yasuda T, Nakagawa T, Inoue H, Iwamoto M, Inokuchi A. The role of the labyrinth, proprioception and plantar mechanosensors in the maintenance of an upright posture. Eur Arch Otorhinolaryngol. 1999;256 Suppl:S27-32.

Young MJ, Breddy JL, Veves A, Boulton AJM. The prediction of diabetic neuropathic foot ulceration using vibration perception thresholds: A prospective study. Diabetes Care. 1994;17(6):557–60.

Zalpour C. Anatomie, Physiologie. 2. München: Urban und Fischer; 2006.

Zimmerman DW. A note on preliminary tests of equality of variances. Br J Math Stat Psychol. 2004;57:173–81.

Zimmerman DW, Zumbo BD. Rank Transformations and the Power of the Student T-Test and Welch T-Test for Nonnormal Populations With Unequal Variances. Can J Exp Psychol. 1993;47(3):523–39.

Zippenfennig C, Drechsel TJ, Monteiro RL, Sacco ICN, Milani TL. The mechanoreceptor's role in plantar skin changes in individuals with diabetes mellitus. J Clin Med. 2021a;10:2537.

Zippenfennig C, Wynands B, Milani TL. Vibration perception thresholds of skin mechanoreceptors are influenced by different contact forces. J Clin Med. 2021b;10:3083.

Appendix

Appendix 1

Study 5

Sensor-based systems for early detection of dementia (SENDA): a study protocol for a prospective cohort sequential study

Katrin Müller[1]*, Stephanie Fröhlich[1], Andresa M.C. Germano[2], Jyothsna Kondragunta[3], Maria Fernanda del Carmen Agoitia Hurtado[4], Julian Rudisch[1, 5], Daniel Schmidt[2], Gangolf Hirtz[3], Peter Stollmann[4] and Claudia Voelcker-Rehage[1, 5]

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[1]Department of Sports Psychology (with focus on prevention and rehabilitation), Institute of Human Movement Science and Health, Faculty of Behavioural and Social Sciences, Chemnitz University of Technology, Thüringer Weg 11, 09126 Chemnitz, Germany.
[2]Department of Human Locomotion, Institute of Human Movement Science and Health, Faculty of Behavioural and Social Sciences, Chemnitz University of Technology, Chemnitz, Germany.
[3]Department of Digital Signal Processing and Circuit Technology, Faculty of Electrical Engi neering and Information Technology, Chemnitz University of Technology, Chemnitz, Germany.
[4]Department of Analysis, Faculty of Mathematics, Chemnitz University of Technology, Chemnitz, Germany. 5Department of Neuromotor Behavior and Exercise, University of Münster, Münster, Germany.

Abstract

Background: Dementia and cognitive decline are serious social and economic burdens. An increase in the population of older people, as well as longer life-spans mean that numbers of dementia cases are exponentially rising. Neuropathological changes associated with dementia are thought to appear before the clinical manifestation of cognitive symptoms, i.e., memory impairments. Further, some older adults (OA) experience cognitive decline before it can be objectively diagnosed. For optimal care of these patients, it is necessary to detect cognitive decline and dementia at an early stage. In this vein, motor, sensory, and neurophysiological declines could be promising factors if found to be present before the onset of cognitive impairment. Hence, the objective of the SENDA study is to develop a multi-dimensional sensor-based instrument that allows early detection of cognitive decline or dementia in OA with the help of cognitive, sensory, motor, and neurophysiological parameters before its clinical manifestation.

Methods/design: In the cohort sequential study, participants are assigned to one of three study groups depending on their cognitive status: 1. cognitively healthy individuals (CHI), 2. subjectively cognitively impaired persons (SCI), or 3. (possible) mildly cognitively impaired persons (pMCI, MCI). All groups take part in the same cognitive (e.g., executive function tests), motor (e.g., gait analyses, balance tests), sensory (e.g., vibration perception threshold test, proprioception tests), and neurophysiological (e.g., electroencephalograms) measurements. Depending on the time at which participants are included into the study, all measurements are repeated up to four times in intervals of 8 months within 3 years to identify associations with cognitive changes over time.

Discussion: This study aims to detect possible motor, sensory, neurophysiological, and cognitive predictors to develop an early screening tool for dementia and its pre-stages in OA. Thus, affected persons could receive optimal health care at an earlier time point to maintain their health resources.

Trial status: The study is ongoing. The recruitment of participants will be continued until May 2020.

Keywords: Dementia, MCI, Early detection, Motor performance, Gait analyses, Sensitivity, Proprioception, EEG

Background

Dementia is a common age-related neurodegenerative disease whose prevalence is increasing globally. According to the German Alzheimer Society e.V. [1], the number of dementia cases in Germany will have risen to three million by 2050. In addition to the personal cost, the disease causes substantial economic and social burdens [2]. Early diagnosis of dementia and its pre-stages could alleviate these by enabling sustainable disease management and optimal health care for affected individuals.

Although no effective treatment of dementia exists yet, early diagnosis has been shown to enable interventions which slow down disease progression (i.e. physical activity interventions [3] or pharmaceutical interventions [4]). Early diagnosis provides the opportunity to start treatment before neurodegeneration has progressed and with only minimal disease pathology present [5]. The deterioration of cognitive functions, e. g., memory, attention, or executive functions, is a typical symptom of this illness [6]. Additionally, patients with dementia show anomalies in their social behavior and activities of daily living (ADL) [6]. Mild cognitive impairment (MCI) is classified on a continuum between cognitive changes of normal aging and symptoms of dementia [7]. In this vein, people with MCI have a 10-fold increased risk of developing dementia [8]. Patients with MCI are characterized by the following criteria: (1) concerns about changes in cognition by themselves or someone else, (2) impairments in at least one cognitive domain, and (3) no problems in ADL [9]. Cognitive impairments most often pertain to memory, but can also include other cognitive domains, such as executive functions, attentional control, language skills, or visuo-spatial skills [9]. Interestingly, a substantial amount of older people report memory loss and other cognitive deficits even in the absence of objective cognitive impairments [10]. The condition has been classed as SCI, meaning subjective cognitive impairment, as people subjectively experience worsening of their cognitive performance compared to prior performance levels while they still perform within normal range on standard clinical assessments of cognition [11]. SCI has been shown to triple the risk of Alzheimer’s disease [12], is associated with underlying

dementia neuropathology [13], and as such could be considered an even earlier pre-clinical stage of dementia [11].

Brain imaging, e.g., computed tomography or magnetic resonance imaging, laboratory tests, and cognitive or neuropsychological tests are standard methods of diagnosing dementia [6, 14]. However, by the time individuals receive the diagnosis, cognitive impairments will generally have progressed [5, 15]. Neuropathological changes associated with dementia have been found to develop before the clinical manifestation of cognitive symptoms, i.e., memory impairments [5], and might be expressed in SCI or even MCI. Since the costs are too high to use neuroanatomical and biological markers for diagnosis [9], it is worthwhile to explore whether behavioral markers, other than cognitive performance, can be used to successfully predict the development of dementia. If successful, it would provide a low cost and easy to apply approach to screening for dementia at the pre-clinical stage, and enable appropriate interventions to be established to delay its clinical manifestations. Consequently, current research aims to determine prodromal markers for early detection of dementia, for example, changes in the motor (e.g. abnormalities in gait) or the sensory systems [16].

With regard to motor control, persons with MCI present a transitional stage between healthy controls and patients with early Alzheimer's disease [1]. For example, identifying abnormalities in gait parameters are a key focus in early screening for dementia [18–20]. A meta -analysis of Bahureska et al. [18] revealed that lower gait velocity, termed senile gait [21, 22], seems to be a marker to discriminate between MCI and healthy controls [19]. Additionally, poor performance walking under more complex conditions, such as dual-task conditions, has been associated with higher risk of developing dementia [19, 23, 24].

Furthermore, other motor changes might be used for predicting dementia, e.g., dynamic balance control, finger dexterity, and cutaneous sensitivity. Many anatomical structures (e.g., the brainstem, spinal cord, or the primary somatosensory cortex [25–29]), associated with processing cutaneous sensations, are negatively affected in dementia, early dementia, or its precursor MCI. To date, however, there are only few studies which investigate cutaneous sensitivity in MCI patients or dementia diseases [30]. Cutaneous sensitivity is essential for motor performance [31], gait [32], and balance [33]. Quasi-static balance [34] has already been identified as a prodromal

marker of dementia [18], whereas dynamic balance with unexpected perturbations has not yet been explored in patients with MCI. Changes in finger dexterity could be predictors for the development of dementia [35], independently from age-related changes [36]. For instance, Rabinowitz and Larner [37] revealed that patients with MCI or dementia show an increase in duration and variability of the finger-touch phase during finger tapping compared to cognitively healthy OA.

Furthermore, neurophysiological techniques, including electroencephalography (EEG), enable detection of functional changes in brain activity at an early stage of dementia [38, 39]. Resting state EEG reveals differences between persons with dementia or pre-clinical dementia and healthy OA [38, 39]. The limited number of longitudinal studies have identified the mean frequency of the total spectrum [40], relative beta power [41], relative alpha power [41–44], relative theta power [40, 42, 45], coherence across all frequencies [40], and coherence in the delta band [46] as possible predictors of cognitive decline. Unfortunately, there is not yet a clear consensus about which parameters best predict dementia or how to translate these findings into cut-offs for individual diagnosis.

In conclusion, early detection of dementia at the presymptomatic stage of disease using prodromal markers is important to detect progressive changes of the central nervous system and to initiate targeted and optimal health care as early as possible. There are, however, only few studies which investigate different markers (e.g., biomarkers, cognitive markers) to detect cognitive decline or the transition from MCI to dementia [47–51]. Gomar et al. [47] examined different biomarkers (e.g., total tau, Aβ1–42), cognitive markers (working memory), and risk factors (APOE genotype) in one study to predict transition from MCI to Alzheimer's disease. They were able to show that cognitive markers predict these transitions more than most biomarkers. This was also shown in a 4 year follow-up data phase [48]. Another longitudinal study (The Sydney Memory and Ageing Study) by Lipnicki et al. [52] revealed that older age, slower walking speed, and APOE ε4 carrier at baseline were associated with MCI or dementia after 6 years. In a current gait and balance platform study (part of the Ontario Neurodegenerative Research Initiative (ONDRI) by MonteroOdasso et al. [53]), motor-cognitive profiles across neurodegenerative diseases, e. g. Alzheimer's diseases or MCI, will be identified over 3 years using gait and balance tests. However, to our knowledge, other than the ONDRI study [54],

there are no other studies investigating cognitive, motor, sensory, and neurophysiological markers in combination to develop a multi-dimensional instrument to predict cognitive decline or dementia.

Therefore, the objective of the current study is to develop such a multi-dimensional sensor based instrument to detect cognitive decline or dementia in older adults with the help of several cognitive, sensory, motor, and electroencephalogical parameters in a longitudinal cohort. The results of this study will lead to a better understanding of the different prodromal markers and their interaction, and might help to predict MCI or dementia.

This study is named “Sensor-based systems for early detection of dementia (SENDA)” and is funded by the European Social Fund and the Sächsische AufbauBankFörderbank (SAB) of the Free State of Saxony (ProjectNumber: 100310502).

Methods

Study aims

The following main research question investigated in this study is:

Which cognitive, sensory, motor, and neurophysiological variables are predictors of the transition from subjective cognitive impairment or MCI to dementia in comparison to age-matched healthy OA?

The objective of the SENDA study is to develop a multi-dimensional sensor-based instrument based on the stated variables or their combination to detect cognitive decline or dementia in OA.

Participants and procedures

Participants were recruited via local newspaper articles and the website of the Chemnitz University of Technology. In addition, we received 1500 names and addresses of men and women aged ≥ 0 years from the registration office of the city of Chemnitz to enable initial contact for potential study participation. A study hotline was set up for anyone interested in study participation to call. Trained project staff determine eligibility for study participation in telephone interviews following the inclusion and exclusion criteria outlined below. People who fulfill the inclusion criteria are invited to participate in the study by mail.

Inclusion and exclusion criteria

Men and women aged ≥ 0 years and with their principal residence in the city of Chemnitz and surrounding areas are included in the study. Participants must be able to visit the lab independently or with the help of an accompanying person. They must be able to walk by themselves, but the use of a walking aid is allowed. Further criteria for inclusion in the study are basic knowledge of German and passing hearing and vision screening tests. Participants are excluded from the study if they present any of the criteria listed in Table 1.

Table 1 Exclusion criteria of the study.

Exclusion criteria
- Medically prohibited to be physically active
- Diagnosed psychological disorders such as major depression or neurocognitive disorders such as dementia (MoCA-score < 19)
- Permanent impairments due to a stroke or a brain surgery
- Other neurological diseases such as epilepsy, Parkinson, neuropathy
- Severe diseases of the cardiovascular system (e.g., cardiac arrhythmia, arterial occlusive disease, heart failure)
- Severe diseases of the respiratory system (e.g., COPD stage 4, severe asthma)
- Severe diseases of the musculoskeletal system (e.g. arthritis, orthopaedic operations in the last 6 months)
- Diabetes with diagnosed neuropathy
- Substance abuse (delirium)
- Difficulties in understanding language or speech
- Participant of other clinical studies e.g. for clinical testing of new anti-dementia drugs

Study design

The SENDA study is designed as a prospective cohort sequential study. After successful screening for study eligibility, participants are assigned to one of three study groups depending on their cognitive status based on their MoCA (Montreal Cognitive Assessment), CERAD-Plus (Consortium to Establish a Registry for Alzheimer's Disease), and the FLei ('Fragebogen zur geistigen Leistungsfähigkeit', questionnaire for complaints of subjective cognitive disturbances) scores: 1.

cognitively healthy individuals (CHI), 2. subjectively cognitively impaired persons (SCI), 3. possible mildly cognitively impaired persons due to inconclusive test results (pMCI), or mildly cognitively impaired persons (MCI). During the study period participants of four cohorts will be recruited at different time points (see Table 2). All participants complete the same cognitive, motor, sensory, and neurophysiological tests. Depending on the time point of study entry, all tests are repeated up to four times (time points: T1, T2, T3, T4) in intervals of 8 months within 3 years to identify associations with cognitive changes over time (see Fig. 1 for the study design and Table 2). The interval of 8 months was chosen according to Chamberlain et al. [55]. Only this frequency of follow-ups enables the measurements to be repeated up to three times in the defined funding period of 3 years. One test consists of three examination days of 1 to 2 h each.

Table 2 Time points of study recruitment of the four cohorts and number of follow-up surveys (T1: Baseline; T2-T4: Follow-up surveys; 'X': participation; '-': no participation).

Cohorts	**T1**	**T2**	**T3**	**T4**
Cohort 1 (begin: February 2018)	X	X	X	X
Cohort 2 (begin: July 2018)	X	X	X	-
Cohort 3 (begin: January 2019)	X	X	-	-
Cohort 4 (begin: January 2020)	X	-	-	-

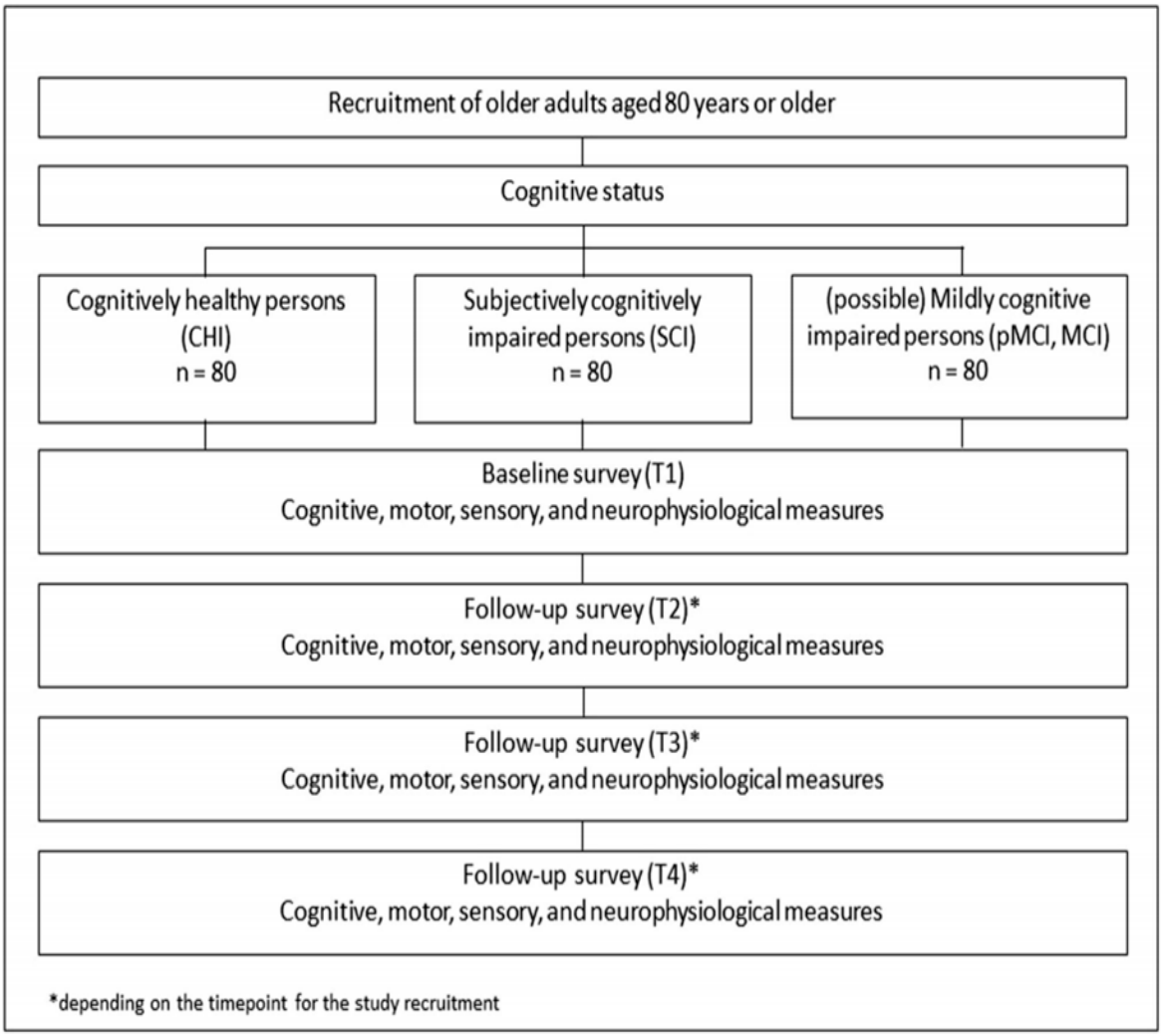

Fig. 1 Study design.

Outcome measures

Participants are invited to the labs of the study center in Chemnitz to complete the baseline (T1) and follow-up measurements (T2, T3, T4) as shown in Fig. 1. At all time points, participants undergo proven and standardized assessments, including different motor, sensory, cognitive, and electroencephalogical assessments.

Cognitive assessments

Montreal Cognitive Assessment/ Consortium to Establish a Registry for Alzheimer's Disease

To identify cognitive decline, we assess global cognition using the MoCA (Montreal Cognitive Assessment [56]) and the CERAD-Plus (Consortium to Establish a Registry for Alzheimer's Disease [5]) tools. MoCA is a short screening tool for measuring

mild cognitive impairment, i.e., in memory, attention, or executive functions. Participants can reach a maximum of 30 points [58]. The cutoff between healthy and mild cognitive impairment is set at 26 in accordance with the recommendations from Nasreddine et al. [56], which means individuals with a score of 25 or lower are considered impaired.

CERAD-Plus is a reliable and valid assessment of Alzheimer's disease and consists of different neuropsychological tests, such as the Mini-Mental State Examination, verbal fluency, Boston Naming, word list learning, recall and recognition, constructional praxis and recall, and trail making tests A and B [57]. To detect objective cognitive impairments according to CERAD-Plus, we will compare scores in each subtest (excluding MMSE) to the age, education, and gender-controlled reference norms. Following recommendations of the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease [9], performances worse than 1.5 SD below the norm in one or more subtests are considered objective cognitive impairments.

Questionnaire for subjective assessment of mental performance (FLei)

We use the FLei ('Fragebogen zur geistigen Leistungsfähigkeit' [59]) to assess subjective cognitive status. The questionnaire employs 30 questions about cognitive challenges in everyday life, including items about executive functions, memory, attention, and 5 control items. Participants are asked to indicate the frequency of these challenges on a scale from 0 ('never') to 5 ('very often') and a sum score is then calculated (range 0–120). Participants with a score of 31 or higher and no objective cognitive impairment are categorized as only subjectively impaired in their cognition. This cut-off was chosen because 30 points are reached when a participant chooses 1 ('seldom') for every item. This is in accordance with data in other studies showing that participants on average score at the lower end of the answer range (for example M = 36.3 for OA with objective impairment [60] and M = 28.2 for a general population representative sample [61]). After completing data collection, we will also use a data driven approach to determine a suitable cut-off for our sample and, if needed, adjust the assessment of subjective cognitive status.

Cognitive status

All prior introduced neuropsychological assessments are used to establish the cognitive status of each participant at baseline and each follow-up. All criteria including cut-offs can be found in Table 3. Cognitive decline is defined as a change from CHI to SCI, pMCI, or MCI, as well as a change from SCI to pMCI or MCI or from pMCI and MCI to dementia. Individuals are categorized as having dementia when they receive a clinical dementia diagnosis outside of the study at any follow-up. Furthermore, participants are categorized as having dementia if they score less than 19 points in the MoCA [62] and perform worse than 1.5 SD below the norm in multiple cognitive domains of the CERAD-Plus. If so participants are advised to visit their general practitioner for further evaluation regarding dementia and to give a feedback to the study coordinator of SENDA as soon as possible. Additionally, functional

limitations in ADL and the presence of depression will also be taken into account (see section ‘Questionnaire battery’).

Table 3 Criteria for cognitive status of the participants.

Group	Cognitive Status	Measures		
		MoCA	CERAD-Plus	Flei
Group 1	CHI	30-26	All tests within normal range (≤ 1.5 SD)	≤ 30
Group 2	SCI	30-26	All tests within normal range (≤ 1.5 SD)	> 30
Group 3	pMCI	30-26	1 or more tests below normal range (≥ 1.5 SD)	not considered
		< 26	All tests within normal range (≤ 1.5 SD)	not considered
	MCI	< 26	1 or more tests below normal range (≥ 1.5 SD)	not considered

Digit Symbol Substitution Test

The Digit Symbol Substitution Test (DSST), as a part of the Wechsler Adult Intelligence Scale, is a neuropsychological test for response speed, sustained

attention, visual spatial skills, and set shifting. The pencil paper task is timed at 90 s. Participants have to write down the correct symbol which is paired to a series of digits from 1 to 9. The correct number-symbol matches are then calculated [63].

Flanker task

We use a modification of the Eriksen flanker task [64] to study attentional control and response inhibition, two executive function skills known to be impaired in patients with MCI and dementia [65, 66]. Stimuli consist of a center disk surrounded by four flanker disks set against a black background. Participants are asked to ignore the flanker disks (blue, red, or green) and react only to the center disk (red or green) by pressing the button of the correct color. The task consists of three blocks of 100 trials. One trial consists of a fixation cross (300 ms), a blank screen (200 ms), stimulus presentation (200 ms), a blank screen during the response interval (terminated by button press, maximal 3000 ms), and a blank screen (randomly chosen between 500 to 800 ms). Outcomes include response times of correct trials and accuracy.

With respect to cognitive testing, standardized methods with known psychometric properties, as well as data available about practice effects were chosen. All have good to excellent test-retest-reliability (r = .92 for MoCA [56], r = .88 for DSST [67], r = .53–.91 for subtests of the CERAD-Plus [68] and ICC = .61–.74 for RT of different trial types in the Flanker task [69]). In addition, practice effects are usually smaller for longer intervals and older participants [70].

Single and dual-task cognitive performance

All participants perform the modified Serial Sevens Test (SST) and Verbal Fluency Test (VFT) during single-task (while seated for 15 s) and dual-task conditions (during gait), to evaluate the cost of dual-tasking for cognitive functioning. To minimize the effects of learning the order of single and dual tasks were randomized compared to Montero-Odasso et al. [23] and Muir et al. [24]. The number of correct answers is recorded.

The modified SST [71] is a test of cognitive function. During the SST, participants are asked to successively count backwards aloud by increments of 7, starting at either 283 or 213. Due to poor cognitive functioning of most participants, a

simpler version of the SST is administered, in which participants have to simultaneously count backwards by increments of 3, starting at either 153 or 183 and by increments of 1, starting at either 200 or 300.

The VFT is an additional test of cognitive function and part of the MoCA [56]. The VFT is a phonemic fluency test, in which participants are asked to generate as many words as possible within a specified time, starting with a specific letter, in this study with ‘K’ or ‘M’. Names or numbers or the same word stem are not allowed. Verbal fluency has been shown to be reduced in elderly persons with mild cognitive impairments as compared to their non-impaired persons [72].

Neurophysiological measures

EEG recording

We record electroencephalograms (EEGs) in all participants with an actiCHamp system (Brain Products GmbH, Gilching, Germany) using 32 electrodes positioned according to the modified 10–20 system (Fp1, Fp2, F7, F3, F4, F8, FC5, FC3, FC1, FC2, FC4, FC6, T7, C3, Cz, C4, T8, CP5, CP3, CP1, CP2, CP4, CP6, P7, P3, Pz, P4, P8, O1, Oz, O2 with reference to Fz and a forehead ground electrode). We keep electrode-skin impedance below 25 kΩ, which is suitable for active electrodes [3]. All data are acquired at 500 Hz sampling rate in continuous recording mode. EEG is recorded during (1) resting with eyes open for 4 min, (2) resting with eyes closed for 2 min, and (3) three fine motor tasks (see below), and (4) a flanker task. Measurements take place in an electrically and acoustically shielded room with lights turned off during rest and dimly lit during task conditions. We monitor participants’ level of consciousness online in real time and annotate changes and artifacts in the EEG protocol. Total recording time is about 60 min and includes individual breaks between tasks.

Resting state EEG

For the rest conditions, participants are instructed to sit relaxed on a chair with both hands resting comfortably on the table in front of them. They are asked to first look at a white fixation cross at the center of a black screen for 4 min and to then close their eyes for 2 min. Similar resting state protocols are often used in aging and dementia research [74–77].

Motor performance

Gait analysis

Spatiotemporal gait parameters (i.e. gait velocity, step length, step width) are collected using a walkway system for optical detection (Optogait®, Microgate, BolzonaBozen, Italy). Each transmitting and receiving bar consists of 96 LEDs communicating on an infrared (visible) frequency with the same number of LEDs on the opposite bar. The walking distance of each walk is 12 m and includes a turning point after 6 m. Width of the track is 1 m. Participants start 1 m before the beginning of the pathway and stop 1 m past the end. All participants perform the following walking blocks in the same order after one test trial: (1) preferred walking speed (two separate walks), (2) fast walking (one walk); and (3) dual-task walking (preferred walking and cognitive task, four separate walks). Gait performance is assessed by measuring, e.g., gait velocity, step length, and step width, as well as the variability of these parameters. All measured data are recorded and saved for analysis by the Optogait software.

Additionally, we use Kinect and XPCV framework (XPCV-Cross Platform Computer Vision Framework; www.xpcv.de) to record the 3D gait data of the participants for all conditions of the different walks. Acquired data is pre-processed to generate heat maps, and annotation assignment is done. This pre-processed data is used to train our deep learning algorithm to estimate the 3D pose of the person with our 3D pose estimation model, by several different architectures of Convolutional Neural Networks (CNN). Gait parameters are defined and abnormalities are ascertained with factors such as mean stride time, mean stride length, mean stance duration, or mean swing duration.

Dual-task walking The modified SST and VFT are performed during preferred walking speed using the Optogait system. During dual-task walking, participants are instructed to keep walking even if they cannot solve the cognitive task. The selection of the dual-task conditions is based on current research [19, 53].

Balance tests

To measure balance tasks, we implement a self-built, customized balance setup test (Fig. 2). The balance setup is made up of a force-platform (IMM Holding GmbH,

Germany; 1 kHz), which is installed directly on top of the bottom-platform of a Posturomed device (Haider Bioswing GmbH, Germany). The force-platform is also equipped with heating elements to keep the surface temperature at 25 °C. The bottom-platform of the Posturomed is mobile in the horizontal direction and suspended vertically. To perform quasi-static tests, the bottom-platform is locked in place, so as to prevent movements. To enable unexpected perturbations (dynamic balance tasks), the Posturomed is equipped with an electro-magnet, which holds the bottom-platform in place after shifting it 20 mm out of its neutral position, according to Germano et al. [33]. Unexpected perturbations are induced by manually triggering the electro-magnet, causing the bottom platform to be released and to swing until it again reaches the neutral position. Moreover, the setup also includes a single axis accelerometer ADXL78 (Analog Devices Inc., USA), which is used to detect the reversal points of the oscillating bottom-platform. Participants are secured with a safety belt during all balance tests, which is a built-in safety feature included to prevent falls or other injuries. The balance setup exhibits a good inter- and intra-day reliability [78].

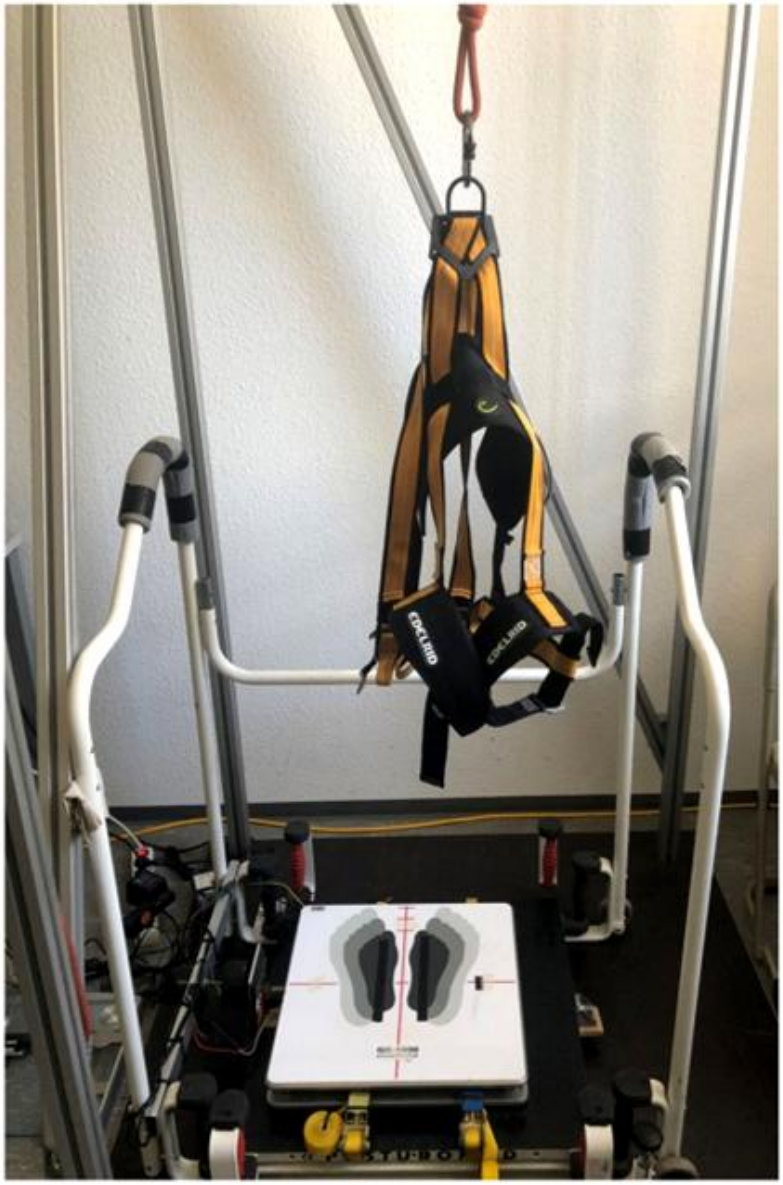

Fig. 2 Balance set-up with Posturomed, force-platform, and safety belt.

Quasi-static balance tests Participants perform two different balance tasks to measure quasi-static abilities. The first balance task tests participants' quasi-static balance ability during three conditions: double leg stance (eyes opened and eyes closed) and single leg stance (eyes open). For the double leg stance tests, trials of 25 s are performed and participants are instructed to keep their knees straightened but not locked, and to keep their arms hanging down. They are also asked to evenly distribute their body weight on both feet, keeping them hip width apart. For single leg stance tests, trials of 12 s are collected and participants are asked to stand on their dominant leg while flexing their contra-lateral lower limb backwards and keeping their

upper limbs hanging down. To become accustomed to the apparatus, participants perform one practice trial per condition. Then, three trials per condition are collected for data analysis in randomized order.

The second quasi-static balance task is the so-called Limits-of-Stability-Test [79]. Participants are asked to stand as still as possible in their normal posture, with their arms by their sides and eyes opened. After an acoustic signal from the experimenter, they lean forward as far as possible and stay inclined for 10 s. Inclinations are accomplished without lifting toes or heels, and with minimal bending at the hip or knees. Furthermore, the trunk is kept almost straight. One practice trial is performed and another three valid trials are included for data analysis.

Dynamic balance tests The dynamic balance tests investigate the ability to withstand unexpected perturbations in the medio-lateral and anterior-posterior directions [33, 78]. Participants are instructed to look straight ahead while keeping their knees straightened but not locked, and to keep their upper limbs hanging down at both sides, eyes opened. Feet are positioned hip-width apart at the center of the plate. After the experimenter presses a manual trigger, the bottom platform is released, initiating the unexpected perturbation. Subsequently, the bottom platform swings horizontally until it again reaches the neutral position. Participants are asked to maintain or regain their balance while the platform is in motion. The dominant foot is positioned towards the electro-magnet during the tests in the medio-lateral direction. For the anterior-posterior direction, participants stand on the plate with their heels pointing toward the electro-magnet. To become accustomed to the apparatus, each participant performs six trials (three in each direction) before data collection begins. Collecting in a randomized order, the three following valid trials per condition are included in the data analysis.

Fine motor tasks

Participants carry out three fine motor tasks: (1) force modulation of a precision grip with thumb and index finger (similar to the set-up of Voelcker-Rehage and Alberts [80]), (2) tapping with the index finger of the dominant hand (based on Rabinowitz and Lavner [38]), and (3) connecting dots on a touchscreen with a touch pen / tracing (as studied by Yan [81]). To collect data for the fine motor task (1), two compression

load cells with a diameter of 29.5 mm, a depth of 8 mm, and a measurement range of 0–22.5 kg (Manufacturer: Measurement Specialties Inc., Hampton, VA, USA; Model: FX-1901-0001-50 L) are used (cf. [82] for comparable unimanual setup). Signals are pre-amplified (using a customized voltage amplifier), digitally converted, and sampled at a frequency of 120 Hz, using a NI-DAQ USB-6002 (National Instruments, Austin, TA, USA). For programming the experimental procedures, i.e., data acquisition and real time visual feedback, a customized LabView 2015 (National Instruments, Austin, TA, USA) script is used. Force transducers are placed on a table in front of the participants, which are seated at a distance of 60 cm in front of a 23.8 in. monitor (hardware resolution 1920 × 1080 pixels). This monitor produces real-time feedback about actual force levels of the participants and target forces that need to be met (see Fig. 3). Fee back about the magnitude of the applied force to both sensors is indicated by two small dots that move up when more force is applied and down when less force is applied. Squares (width and height: 12.5 mm) are displayed on the screen to indicate reference values (see Fig. 3). The scale of the display is adjusted with respect to individual force ranges and the size of the target box corresponds to 0.6% of maximum voluntary contraction (MVC). The aim of the force modulation of a precision grip task is to assimilate the force to a sine wave (ranging from 5 to 12% of MVC of the dominant hand). In our task, the target sine wave is visualized on the screen by the squares which, depending on the condition, are either moving up and down (fre- quency 0.2 Hz) or are held constant. Participants have to modulate their force to try and keep the dot in the box. This task is performed bimanually and unimanually. The bimanual condition consists of 34 trials (20 s each) overall and includes five conditions: (1) inphase – the target sine waves move simultaneously; (2) antiphase – the target sine waves move inversely, when the right sine wave is on the maximum, the left sine wave is on the minimum; (3) constant – a constant symmetric force with both hands at 12% of MVC (boxes do not move), (4) left hand applies a constant force at 12% of MVC and the right hand follows an alternating sine-wave force pattern between 5 and 12% of MVC, and (5) right hand applies a constant force at 12% of MVC while the left hand follows an alternating sine-wave force pattern between 5 and 12% of MVC.

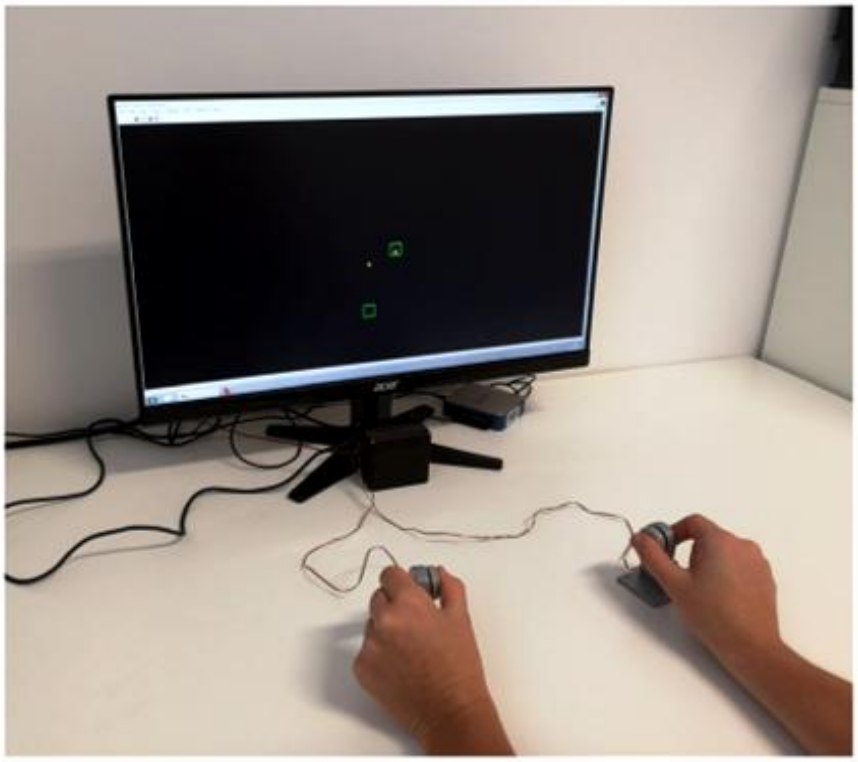

Fig. 3 Set-up for fine motor task “force modulation”.

For the fine motor task (2) “finger tapping”, one of the two force transducers from the previous task is used. The force transducer is fixed in a self-built wooden board which is placed on the table in front of the participants to prevent any movement of the transducer during the task (see Fig. 4). Experimental procedures, i.e., data acquisition, were programmed using a customized LabView 2015 (National Instruments, Austin, TA, USA) script. The task is to tap with the dominant index finger on the force transducer, which participants carry out in two different conditions: as consistently as possible at a self-selected pace, and tapping as fast as possible with disregard to consistency. Each trial lasts 15 s, with three trials in the first condition and two trials in the second condition. There is no visual feedback for the participants.

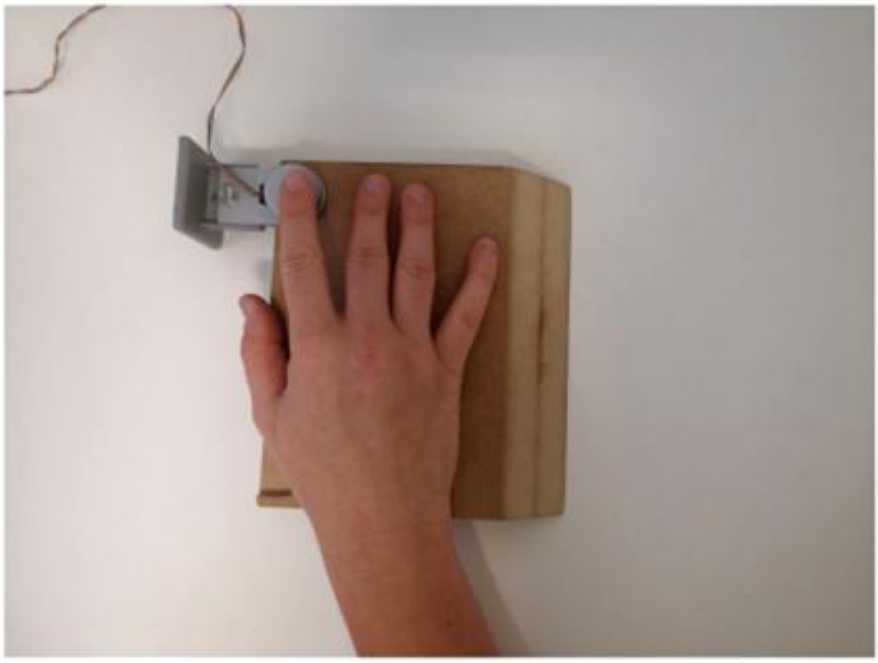

Fig. 4 Set-up for fine motor task “finger tapping”.

For the fine motor task (3) “connecting dots / tracing”, a touch monitor (Manufacturer: Hannstar Display Corp., 23.0 in., hardware resolution 1920 × 1080 pixels, Taipei City, Taiwan; Modell: HSG 1353) and a touch pen (WACOM Bamboo-Stylus Alpha CS-180, length 130 mm, diameter 9 mm, weight 12 g) are used. The monitor is placed horizontally on a table in front of the participants. The pen is held in the dominant hand (see Fig. 5). Experimental procedures, i.e., data acquisition and real time visual feedback, were programmed using a customized LabView 2015 (National Instruments, Austin, TA, USA) script. Participants have to connect dots on the touchscreen (black desktop background) via the touch pen by drawing a white line. There are two tasks: tracing a straight line and tracing a curved line. Two green dots (diameter 15 mm) are shown in the straight line setting, which are marked with 'Start' and 'Target', one above the other (see Fig. 5). Furthermore, there are two different distances (50 mm and 200 mm) between the start and target dots. In addition, a third white in-between-dot (diameter 12.5 mm) is presented half way between the start and target dots in each condition (horizontal distance 25% of that distance (12.5 mm or 50 mm) to the right) in the curved line setting, which the participants have to draw through (see Fig. 5). Overall, four conditions (straight line

short, straight line long, curved line short, and curved line long) with seven trials are completed in randomized order.

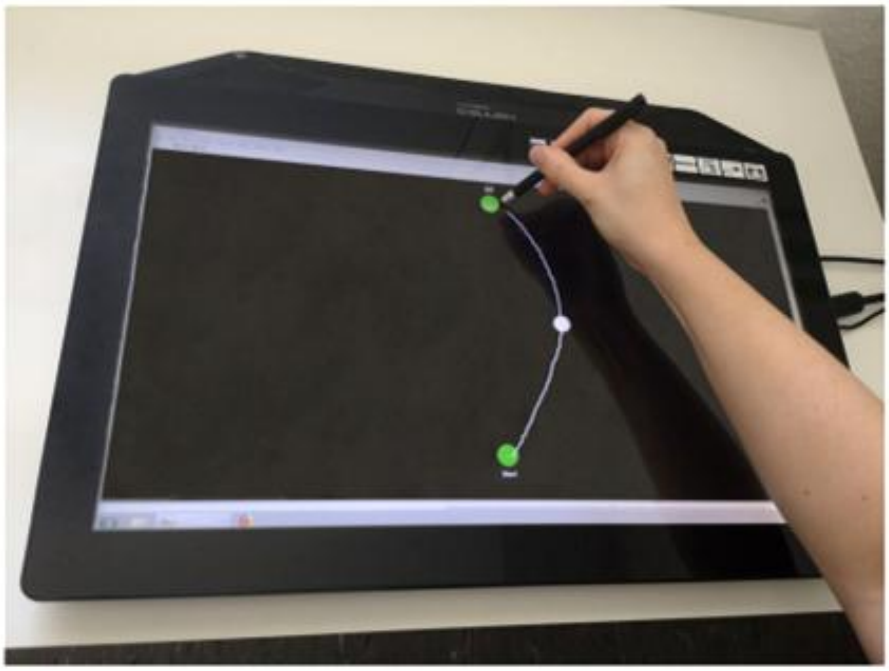

Fig. 5 Set-up for fine motor task “connecting dots / tracing.

Foot-eye coordination tests (pedal)

Foot-eye coordination (foot proprioception) is investigated using self-constructed pedals for the right and left feet (Fig. 6). The pedals are equipped with a gas spring (Febrotec, Nitrider® 0GS-N06AAA0050, Halver, Germany) and a linear potentiometer (Vishay Electronic GmbH, 249FGJS0 XB25, 1kohm, Landshut, Germany). With a starting position of 45° dorsiflexion with respect to the horizontal floor, the pedals can be freely rotated within a range of ±20°. The analog data of the potentiometer is converted to digital signals using an AD card (Measurement Computing, USB- 231, Bietigheim-Bissingen, Germany). A flat computer screen (24 in., 16:9) is positioned approximately 100 cm in front of the participant. The foot-eye coordination task is an accuracy task, in which participants are requested to reproduce given curves using their foot (right and left, separately). Visual feedback is provided on the screen using a routine in LabView 2015 (National Instruments Corp., Texas, USA). During plantar or dorsal flexion, the rotation of the pedals (pressing or depressing the pedal) generates live control of the line on the screen. Participants

are instructed to reproduce the displayed curve as precisely as possible. The visual feedback begins as soon as the pedals are pressed.

Fig. 6 Set-up for foot-eye coordination.

For the foot-eye coordination tests, participants are instructed to sit comfortably, keeping their knees and hips at 90°, placing their feet on the pedals, and adjusting the distance between the chair and the pedals. Participants are instructed to reproduce given curves using their foot (right and left, separately) to operate the

pedals. For each trial, ten sinusoidal curves at two different frequencies are displayed as a continuous graph. One test-trial per foot is performed. After the test-trial, three trials per foot are collected in a randomized sequence. Foot temperatures at the first metatarsal head (Met1) are measured before and after testing. Note that the three trials did not seem to be sufficient to promote long-lasting and relevant practice effects. Even with training sessions, a study of Teasdale et al. [83] exhibited no long-term retention in learning processes for MCI.

Functional status and physical performance

Functional status and physical performance is assessed using the Short Physical Performance Battery (SPPB), a standardized instrument which includes tests for (1) balance (legs closed / feet together, semi-tandem stand, tandem stand), (2) comfortable gait speed over four meters, and (3) chair raising test (five times sit-to-stand transfer) [84]. Each test is scored between 0 and 4, the total score ranges from 0 (low mobility/functionality) to 12 (full mobility / functionality).

Additionally, cardiovascular fitness is measured using the 2-min step test [85]. Therefore, the OA step in place as often as possible in 2 min. All steps with the right leg are scored.

Hand Grip Strength is assessed using the digital grip dynamometer (Grip D®, Takei scientific instruments, Niigata City, Japan). Three assessments are executed with the right and the left hand with a straightened elbow [86].

We also collect data for height, weight, and body fat using a stadiometer (seca213, seca Deutschland, Hamburg, Germany) and a bioimpedance scale (Tanita InnerScanV, Model BC-545 N, TANITA Corporation, Tokyo, Japan).

Sensory measures

Visual acuity

The Freiburg Visual Acuity Test [87] with Landolt C is used to measure visual acuity. The participants are placed exactly 3 m from the screen and complete 18 trials. The measurement is carried out with vision aid to measure corrected vision.

Hearing

To measure corrected hearing ability, four lists of the Freiburg monosyllabic test (part

of the Freiburg speech test [88]) are presented without background noise via headphones. Four different sound levels (35 dB, 47 dB, 24 dB, 53 dB) are used in the same order for all participants.

Vibration perception thresholds

To assess skin sensitivity, vibration perception thresholds (VPTs) are measured using a Tira Vib vibration exciter (model TV51075, Schalkau, Germany) (Fig. 7), which presents good reliability [89]. Vibration from the exciter is applied to the foot location by a metal probe (rounded, 7.8 mm diameter) protruding through a hole (2 mm above surrounding surface level), according to [32, 90]. The surface of the vibration exciter is an aluminum platform equipped with heating elements to maintain the surface at a constant temperature (in this case 25 °C), to avoid skin temperature fluctuations. Vibration amplitude (in µm) is detected using an accelerometer (MMA2241KEG, NXP Semiconductors). The frequency of the vibrating contactor is set at 30 Hz and 200 Hz, which are known to be the optimal stimuli to elicit Meissner corpuscles and Vater–Pacini corpuscles, respectively [91]. The vertical force applied from the participants' feet toward the probe is monitored via a force transducer and kept within a range of ± 0.5 N. Acoustic noise cancelling headphones (Bose® QuietComfort 25) are used to ensure that there is no distraction during the measurements.

Fig. 7 Left: Vibration perception threshold set-up for measuring hand and foot sensitivity. Right: Platform with tip of vibrating probe (black squares).

Vibration perception threshold tests First, sensitivity tests at the fingertip are performed. Participants are instructed to sit in a standardized manner but also comfortably, to be able to concentrate on detecting the vibration stimuli. The fingertips rest on top of the metal probe, without exerting additional pressure. Furthermore, participants wear acoustic noise cancelling headphones. Before starting the tests, test-trials are performed to define the value of the starting amplitude for the consecutive trials. The protocol for measuring VPTs is similar to a method of limits approach introduced by Mildren et al. [92].

In short, vibrations are introduced above the threshold, so that they can be clearly perceived by the participants (start amplitude defined according to test-trials). For each trial, a sequence of vibrations with different amplitudes (with randomized pauses in between) is applied and participants are asked to push a hand-held button as soon as they perceive each vibration stimulus. After pressing the button, the intensity of the previous, perceivable vibration stimulus is halved. When a vibration stimulus is not perceived, the next stimulus is delivered at half the intensity of the unperceived and the previously perceived stimuli. Then, four more stimuli are

delivered to determine the final VPT. In total, three VPT-trials are collected at the fingertip of the index finger (at 30 Hz). Skin temperatures at the fingertip are measured before and after the three trials. After the hand sensitivity tests, the same protocol is performed to test foot sensitivity at the first Metatarsal head (at 30 Hz and 200 Hz).

Questionnaire battery

Participants need to complete a questionnaire battery, which includes the following secondary outcome parameters: frailty, physical activity, social support, social activities, depression, comorbidities, health behavior, quality of life, and handedness. The self-administered questionnaire contains validated instruments and self-generated items which are shown in Table 4. Sociodemographic information includes age, sex, education, and employment.

Table 4 Outcome measures in the self-administered questionnaire.

Outcome measure	Instrument/scale
Physical activity	
Physical activity	Modified Baecke Inventory (similar to [93]) PRISCUS-Physical Activity Questionnaire [94] Nürnberger-Alters-Inventar (NAI) [95]
Social support, social activities	
Social support	Social Support Questionnaire - short form [96]
Social activities	Florida Cognitive Activities Scale (modified [97])
Health behavior	
Objective health	List with diseases and use of medication (modified [98])
Comorbidities	Charlson Comorbidity Index [99]
Chronic medication	Individual medication regimen (name, dosage and frequency of intake for all prescribed medication)
Frailty	Frail Scale [100, 101] Tilburg Frailty Indicator [102, 103]
History of falls	Elderly Fall Screening Test (modified [104])
Falls efficacy	Fall Efficacy Scale [105]
Smoking behavior	Smoking Behavior Questionnaire [106]
Quality of life and well-being	
Quality of life	Satisfaction with Life Scale [107]
Depression	Geriatric Depression Scale [108]
Personality	Big Five Inventory [109, 110]
Handedness	
Handedness	Edinburgh Handedness Inventory [111]
Manual activities	Manual Activities Questionnaire [112]

Data collection and management

Participant information will be recorded by a coded ID number. Hard copy forms will be stored in locked cabinets accessible only by project staffs. Electronic data will be stored on a secured computer that is password-protected. The databases will not

contain subject identifiers and the data linking subject identifiers and the subject ID code will be stored separately.

Data quality will be promoted by double data entry and range checks for data values. Only project staffs will have access to the final trial dataset.

Data monitoring

A data monitoring committee, responsible for data monitoring, interim analyses, and auditing, will not be established, because no adverse events are to be expected. However, study participants will be under the surveillance of trained project staff who will intervene if a negative reaction is observed during the measurements.

Sample size

The sample size calculation was based on the outcome cognitive decline. Based on literature [47, 51] small to moderate effect sizes are expected. Statistical power analysis using G*Power (Version 3.1.9.4, Franz Faul, University of Kiel, Germany) showed that 200 participants are required for analysis with $\alpha = .05$ and power = . 0. Expecting a 20% dropout rate during the study period, 240 participants will be included.

Statistical analyses

A multiple regression model (with e. g. ordinary least squares technique) is used to detect several predictors or mediators of cognitive decline. To identify the most parsimonious model, and with it the final predictors, we analyze the corresponding coefficients of determination and consider the multiple comparisons problem providing a proper method to counteract it. Additionally, we propose an alternative classification taking hand of the k-nearest neighbors algorithm. Furthermore, we analyze changes in motor, sensory, electroencephalogical, and cognitive parameters over time in all three groups using mixed-effects models to explain the correlations in repeated measures in the same subject. Hazard ratios of progressing to dementia for participants with cognitive, motor, sensory, and neurophysiological decline are obtained in the classical way using the Cox semi-parametric proportional hazard model. Several variables are included as potential confounders, such as sex, age, education, co-morbidities, psychological status, and social support. The most

appropriate procedure for handling missing data will be selected after inspecting the amount and pattern of missing data.

Expected results

We expect to find several motor, sensory, electroencephalogical, and cognitive prodromal markers for early detection of dementia and its pre-stages. Our assumptions are based on a current literature overview including international and national study results [18, 19, 23, 113].

Trial registration

The trial was retrospectively registered at German Clinical Trials Register (DRKS) with registration number DRKS00013167 (https://www.drks.de/drks_web/navigate.do?navigationId=trial.HTML&TRIAL_ID=DRKS0001316 7; http://apps.who.int/trialsearch/Trial2.aspx?TrialID=D RKS00013167; Date of registration 11 April 2018).

Conclusion

This study aims to detect possible motor, sensory, electroencephalogical, and cognitive predictors to develop a screening tool for dementia and its pre-stages in older

adults, aged ≥ 0 years. Thus, affected individuals could receive optimal health care at an earlier stage to better maintain their health resources. Nevertheless, some study limitation have to be mentioned. First, cognitive decline will be determined based on the results of cognitive instruments (MoCA and CERAD-Plus) and not based on imaging or cerebrospinal fluid measures [9]. Next, participation in the study is voluntary and the participants have to come to the labs by themselves. This may lead to an inadvertent recruitment of persons with higher cognitive or physical performance levels. Due to the funding period of 3 years and the different time points of study recruitment, it is not possible to observe cognitive decline of the participants over an extended period. Despite of the use of reliable and valid instruments to detect predictors for an early screening tool for cognitive decline, practice effects cannot be excluded completely. In spite of these limitations, a longitudinal design clearly outweighs a cross-sectional one. The present study is one of few studies [53, 54] investigating cognitive, motor, sensory, and neurophysiological markers in

combination to develop a multi-dimensional instrument to predict cognitive decline or dementia.

Abbreviations

ADL: Activities of daily living; CERAD-Plus: Consortium to Establish a Registry for Alzheimer's Disease; CHI: Cognitively healthy individuals; FLei: Fragebogen zur geistigen Leistungsfähigkeit; MCI: Mild cognitive impairment; MoCA: Montreal Cognitive Assessment; OA: Older adults; SCI: Subjective cognitive impairment; SENDA: Sensor-based systems for early detection of dementia; SST: Serial Sevens Test; VFT: Verbal Fluency Test

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Dissemination

All results of the study will be published in open-access and international journals. In addition, the results will be presented at congresses.

Authors' contributions

CVR is the head of the study. KM, SF, AG, JK, MH, JR, DS, GH, PS, and CVR have made substantial contributions to the conception and design of the study. KM and CVR wrote the first draft of the manuscript. All authors read, critically revised, and approved the manuscript and have given approval of the final manuscript.

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Availability of data and materials

All participant information and data will be stored securely and identified by a coded ID number only to maintain participants' confidentiality. Data can be obtained from the corresponding author upon reasonable request.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Chemnitz University of Technology (TU Chemnitz), Faculty of Behavioral and Social Sciences, on December 19, 2017 – number V-232-17-KM-SENDA-07112017.

The study was retrospectively registered with the German Clinical Trials Register on April 11, 2018 – number DRKS00013167. All study participants are fully informed about the study, have been deemed capable of ethically and medically consenting for their participation and give written informed Müller et al. BMC Neurology (2020) 20:84 Page 12 of 15 consent for study participation and data analysis following the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Deutsche Alzheimer Gesellschaft e.V. Informationsblatt 1 Die Häufigkeit von Demenzerkrankungen. 2018. https://www.deutsche-alzheimer.de/fileadmin/alz/pdf/factsheets/infoblatt1_haeufigkeit_demenzerkrankungen_dalzg.pdf. Accessed 05 Oct 2019.
2. Lin PJ, Neumann PJ. The economics of mild cognitive impairment. Alzheimers Dement. 2013;9(1):58–62.
3. Groot C, Hooghiemstra AM, Raijmakers PGHM, van Berckel BNM, Scheltens P, Scherder EJA, et al. The effect of physical activity on cognitive function in patients with dementia: a meta-analysis of randomized control trials. Ageing Res Rev. 2016;25:13–23.

4. Hansen RA, Gartlehner G, Webb AP, Morgan LC, Moore CG, Jonas DE. Efficacy and safety of donepezil, galantamine, and rivastigmine for the treatment of Alzheimer's disease: a systematic review and meta-analysis. Clin Interv Aging. 2008;3(2):211–25.
5. Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guide lines for Alzheimer's disease. Alzheimers Dement. 2011;7(3):280–92.
6. American Psychiatric Association, editor. Neurocognitive Disorders. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Washington, DC: American Psychiatric Association Press; 2013.
7. Petersen RC, Negash S. Mild cognitive impairment: an overview. CNS Spectr. 2008;13(1):45–53.
8. Petersen RC. Clinical practice. Mild cognitive impairment. N Engl J Med. 2011;364(23):2227–34.
9. Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011;7(3):270–9.
10. Jessen F, Wiese B, Cvetanovska G, Fuchs A, Kaduszkiewicz H, Kölsch H, et al. Patterns of subjective memory impairment in the elderly: association with memory performance. Ir J Psychol Med. 2007;37(12):1753.
11. Jessen F, Amariglio RE, van Boxtel M, Breteler M, Ceccaldi M, Chetelat G, et al. A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. Alzheimers Dement. 2014;10(6): 44–52.
12. Ronnlund M, Sundstrom A, Adolfsson R, Nilsson LG. Subjective memory impairment in older adults predicts future dementia independent of baseline memory performance: evidence from the Betula prospective cohort study. Alzheimers Dement. 2015;11(11):1385–92.

13. Amariglio RE, Becker JA, Carmasin J, Wadsworth LP, Lorius N, Sullivan C, et al. Subjective cognitive complaints and amyloid burden in cognitively normal older individuals. Neuropsychologia. 2012;50(12):2880–6.
14. Deuschl G, Maier W. S3-Leitlinie “Demenzen” (Langfassung - Januar 2016): Deutsche Gesellschaft für Psychatrie, Psychotherapie und Nervenheilkunde (DGPPN) & Deutsche Gesellschaft für Neurologie (DGN). 2016. https://www.dgppn.de/_Resources/Persistent/ade50e44afc7eb8024e7f65ed3f44e995583c3a0/S3-LL-Demenzen-240116.pdf. Accessed 12 Apr 2019.
15. Langa KM, Levine DA. The diagnosis and management of mild cognitive impairment: a clinical review. Jama. 2014;312(23):2551–61.
16. Mielke MM, Cha R, Christianson T, Pankratz VS, Roberts RO, Rocca WA, et al. Assessing the temporal relationship between cognition and gait: slow gait predicts cognitive decline in the Mayo Clinic study of aging. J Gerontol A Biol Sci Med Sci. 2012;68(8):929–37.
17. Kluger A, Reisberg B, Franssen E, Ferris SH, Gianutsos JG, Golomb J, et al. Patterns of motor impairment in Normal aging, mild cognitive decline, and early Alzheimer’ disease. J Gerontol B Psychol Sci Soc Sci. 199 ;52B(1):2 – 39.
18. Bahureksa L, Najafi B, Saleh A, Sabbagh M, Coon D, Mohler MJ, et al. The impact of mild cognitive impairment on gait and balance: a systematic review and meta-analysis of studies using instrumented assessment. J Gerontol. 2017;63(1):67–83.
19. Belghali M, Chastan N, Cignetti F, Davenne D, Decker LM. Loss of gait control assessed by cognitive-motor dual-tasks: pros and cons in detecting people at risk of developing Alzheimer’s and Parkinson’s diseases. GeroScience. 2017;39(3):305–29.
20. Kressig RW, Monsch AU, Bridenbaugh SA. Gait analysis as an early marker for Alzheimer's disease. Neurobiol Aging. 2014;35:S13.
21. Gillain S, Petermans J. Contribution of new techniques to study the gait in old populations. Ann Phys Rehabil Med. 2013;56(5):384–95.
22. Verghese J, LeValley A, Hall CB, Katz MJ, Ambrose AF, Lipton RB. Epidemiology of gait disorders in community-residing older adults. J Am Geriatr Soc. 2006;54(2):255–61.

23. Montero-Odasso M, Pieruccini-Faria F, Bartha R, Black SE, Finger E, Freedman M, et al. Motor phenotype in neurodegenerative disorders: gait and balance platform study design protocol for the Ontario neurodegenerative research initiative (ONDRI). J Alzheimers Dis. 2017;59(2):707–21.
24. Muir SW, Speechley M, Wells J, Borrie M, Gopaul K, Montero-Odasso M. Gait assessment in mild cognitive impairment and Alzheimer's disease: the effect of dual-task challenges across the cognitive spectrum. Gait Posture. 2012; 35(1):96–100.
25. Bidelman GM, Lowther JE, Tak SH, Alain C. Mild cognitive impairment is characterized by deficient brainstem and cortical representations of speech. J Neurosci. 2017;37(13):3610–20.
26. Parvizi J, Van Hoesen GW, Damasio A. The selective vulnerability of brain stem nuclei to Alzheimer's disease. Ann Neurol. 2001;49(1):53–66.
27. Xie Q, Zhao WJ, Ou GY, Xue WK. An overview of experimental and clinical spinal cord findings in Alzheimer's disease. Brain Sci. 2019;9(7):168.
28. Ortiz TA, Lopez-Ibor M, Martínez EC, Fernández AL, Maestú FU, Lopez-Ibor J. Deficit in sensory motor processing in depression and Alzheimer's disease: a study with EMG and event related potentials. Electromyogr Clin Neurophysiol. 2000;40(6):357–63.
29. Stephen JM, Montaño R, Donahue CH, Adair JC, Knoefel J, Qualls C, et al. Soma tosensory responses in normal aging, mild cognitive impairment, and Alzheimer's disease. J Neural Transm. 2010;117(2):217–25.
30. Prätorius B, Kimmeskamp S, Milani TL. The sensitivity of the sole of the foot in patients with Morbus Parkinson. Neurosci Lett. 2003;346(3):173–6.
31. Germano AM, Schlee G, Milani TL. Effect of cooling foot sole skin receptors on achilles tendon reflex. Muscle Nerve. 2016;53(6):965–71.
32. Nurse MA, Nigg BM. Quantifying a relationship between tactile and vibration sensitivity of human foot with plantar pressure distributions during gait. Clin Biomech. 1999;14:667–72.
33. Germano AM, Schmidt D, Milani TL. Effects of hypothermically reduced plantar skin inputs on anticipatory and compensatory balance responses. BMC Neurosci. 2016;17(1):41.

34. Leandri M, Cammisuli S, Cammarata S, Baratto L, Campbell J, Simonini M, et al. Balance features in Alzheimer's disease and amnestic mild cognitive impairment. J Alzheimers Dis. 2009;16(1):113–20.
35. de Paula JJ, Albuquerque MR, Lage GM, Bicalho MA, Romano-Silva MA, Malloy-Diniz LF. Impairment of fine motor dexterity in mild cognitive impairment and Alzheimer's disease dementia: association with activities of daily living. Braz J Psychiatry. 2016;38(3):235–8.
36. Vieluf S, Godde B, Reuter E-M, Voelcker-Rehage C. Age-related differences in finger-force control are characterized by reduced force production. Exp Brain Res. 2013;224(1):107–17.
37. Rabinowitz I, Lavner Y. Association between Finger tapping, attention, memory, and cognitive diagnosis in elderly patients. Percept Mot Skills. 2014;119(1):259–78.
38. Babiloni C, Lizio R, Marzano N, Capotosto P, Soricelli A, Triggiani AI, et al. Brain neural synchronization and functional coupling in Alzheimer's disease as revealed by resting state EEG rhythms. Int J Psychophysiol. 2016;103:88–102.
39. Jeong J. EEG dynamics in patients with Alzheimer's disease. Clin Neurophysiol. 2004;115(7):1490–505.
40. Prichep LS, John ER, Ferris SH, Rausch L, Fang Z, Cancro R, et al. Prediction of longitudinal cognitive decline in normal elderly with subjective complaints using electrophysiological imaging. Neurobiol Aging. 2006;27(3): 471–81.
41. Huang C, Wahlund L, Dierks T, Julin P, Winblad B, Jelic V. Discrimination of Alzheimer's disease and mild cognitive impairment by equivalent EEG sources: a cross-sectional and longitudinal study. Clin Neurophysiol. 2000; 111(11):1961–7.
42. Jelic V, Johansson SE, Almkvist O, Shigeta M, Julin P, Nordberg A, et al. Quantitative electroencephalography in mild cognitive impairment: longitudinal changes and possible prediction of Alzheimer's disease. Neurobiol Aging. 2000;21(4):533–40.
43. Moretti DV, Frisoni GB, Fracassi C, Pievani M, Geroldi C, Binetti G, et al. MCI patients' EEGs show group differences between those who progress and those who do not progress to AD. Neurobiol Aging. 2011;32(4):563–71.

44. Luckhaus C, Grass-Kapanke B, Blaeser I, Ihl R, Supprian T, Winterer G, et al. Quantitative EEG in progressing vs stable mild cognitive impairment (MCI): results of a 1-year fo low-up study. Int J Geriatr Psychiatry. 2008;23(11):1148–55.
45. Coben LA, Danziger W, Storandt M. A longitudinal EEG study of mild senile dementia of Alzheimer type: changes at 1 year and at 2.5 years. Electroencephalogr Clin Neurophysiol. 1985;61(2):101–12.
46. Rossini PM, Del Percio C, Pasqualetti P, Cassetta E, Binetti G, Dal Forno G, et al. Conversion from mild cognitive impairment to Alzheimer's disease is predicted by sources and coherence of brain electroencephalography rhythms. Neuroscience. 2006;143(3):793–803.
47. Gomar JJ, Bobes-Bascaran MT, Conejero-Goldberg C, Davies P, Goldberg TE. Alzheimer's disease neuroimaging initiative ft. utility of combinations of biomarkers, cognitive markers, and risk factors to predict conversion from mild cognitive impairment to Alzheimer disease in patients in the Alzheimer's disease neuroimaging initiative. Arch Gen Psychiatry. 2011;68(9):961–9.
48. Gomar JJ, Conejero-Goldberg C, Davies P, Goldberg TE. Alzheimer's disease neuroimaging I. extension and refinement of the predictive value of different classes of markers in ADNI: four-year follow-up data. Alzheimers Dement. 2014;10(6):704–12.
49. Egli SC, Hirni DI, Taylor KI, Berres M, Regeniter A, Gass A, et al. Varying strength of cognitive markers and biomarkers to predict conversion and cognitive decline in an early-stage-enriched mild cognitive impairment sample. J Alzheimers Dis. 2015;44(2):625–33.
50. Livingston G, Sommerlad A, Orgeta V, Costafreda SG, Huntley J, Ames D, et al. Dementia prevention, intervention, and care. Lancet. 2017;390(10113): 2673–734.
51. Ottoy J, Niemantsverdriet E, Verhaeghe J, De Roeck E, Struyfs H, Somers C, et al. Association of short-term cognitive decline and MCI-to-AD dementia conversion with CSF, MRI, amyloid- and (18) F-FDG-PET imaging. Neuroimage Clin. 2019;22:101771.

52. Lipnicki DM, Crawford J, Kochan NA, Trollor JN, Draper B, Reppermund S, et al. Risk factors for mild cognitive impairment, dementia and mortality: the Sydney memory and ageing study. J Am Med Dir Assoc. 2017;18(5):388–95.
53. Montero-Odasso MM, Sarquis-Adamson Y, Speechley M, Borrie MJ, Hachinski VC, Wells J, et al. Association of Dual-Task Gait with Incident Dementia in mild cognitive impairment: results from the gait and brain Study Association of dual-task gait with incident Dementia. Association of dual-task gait with incident dementia. JAMA Neurol. 2017;74(7):857–65.
54. Farhan SM, Bartha R, Black SE, Corbett D, Finger E, Freedman M, et al. The Ontario neurodegenerative disease research initiative (ONDRI). Can J Neurol Sci. 2017;44(2):196–202.
55. Chamberlain SR, Blackwell AD, Nathan PJ, Hammond G, Robbins TW, Hodges JR, et al. Differential cognitive deterioration in dementia: a two year longitudinal study. J Alzheimers Dis. 2011;24(1):125–36.
56. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005;53(4):695–9.
57. Morris JC, Heyman A, Mohs RC, Hughes JP, van Belle G, Fillenbaum G, et al. The consortium to establish a registry for Alzheimer's disease (CERAD): I. clinical and neurops chological assessment of Alzheimer's disease. Neurology. 1989;39(9):1159–65.
58. Julayanont P, Nasreddine ZS. Montreal cognitive assessment (MoCA): concept and clinical review. In: Larner AJ, editor. Cognitive screening instruments - a practical approach. 2nd ed. Switzerland: Springer; 2017. p. 139–96.
59. Beblo T, Kunz M, Brokate B, Scheurich A, Weber B, Albert A, et al. Entwicklung eines Fragebogens zur subjektiven Einschätzung der geistigen Leistungsfähigkeit (FLei) bei Patienten mit psychischen Störungen. Z Neuropsychol. 2010;21(3):143–51.
60. Donix M, Haussmann R, Helling F, Zweiniger A, Lange J, Werner A, et al. Cognitive impairment and medial temporal lobe structure in young adults with a depressive episode. J Affect Disord. 2018;237:112–7.

61. Diener C, Bornschlegl M, Menke B, Petermann F. Subjektive Einschätzung und objektive kognitive Leistung bei psychisch Gesunden. Z Neuropsychol. 2016;27(3):147-57.
62. Trzepacz PT, Hochstetler H, Wang S, Walker B, Saykin AJ. Alzheimer's disease neuroimaging I. Relationship between the Montreal Cognitive Assess ment and Minimental State Examination for assessment of mild cognitive impairment in older adults. BMC Geriatr. 2015;15:107.
63. Wechsler D. The psychometric tradition: developing the Wechsler adult intelligence scale. Contemp Educ Psychol. 1981;6(2):82–5.
64. Eriksen BA, Eriksen CW. Effects of noise letters upon the identification of a target letter in a nonsearch task. Percept Psychophys. 1974;16(1):143–9.
65. Wylie SA, Ridderinkhof KR, Eckerle MK, Manning CA. Inefficient response inhibition in individuals with mild cognitive impairment. Neuropsychologia. 2007;45(7):1408–19.
66. Bélanger S, Belleville S, Gauthier S. Inhibition impairments in Alzheimer's disease, mild cognitive impairment and healthy aging: effect of congruency proportion in a Stroop task. Neuropsychologia. 2010;48(2):581–90.
67. Houx PJ, Shepherd J, Blauw GJ, Murphy MB, Ford I, Bollen EL, et al. Testing cognitive function in elderly populations: the PROSPER study. Prospective study of pravastatin in the elderly at risk. J Neurol Neurosurg Psychiatry. 2002;73(4):385–9.
68. Welsh-Bohmer KA, Mohs RC. Neuropsychological assessment of Alzheimer's disease. Neurology. 1997;49(3 Suppl 3):S11–3. 69. Hedge C, Powell G, Sumner P. The reliability paradox: why robust cognitive tasks do not produce reliable individual differences. Behav Res Methods. 2018;50(3):1166–86.
69. Hedge C, Powell G, Sumner P. The reliability paradox: why robust cognitive tasks do not produce reliable individual differences. Behav Res Methods. 2018;50(3):1166–86.
70. Calamia M, Markon K, Tranel D. Scoring higher the second time around: metaanalyses of practice effects in neuropsychological assessment. Clin Neuro psychol. 2012;26(4):543–70.
71. Folstein MF, Robins LN, Helzer JE. The mini-mental state examination. JAMA Psychiatry. 1983;40(7):812.

72. Nutter-Upham KE, Saykin AJ, Rabin LA, Roth RM, Wishart HA, Pare N, et al. Verbal fluency performance in amnestic MCI and older adults with cognitive complaints. Arch Clin Neuropsychol. 2008;23(3):229–41.
73. Laszlo S, Ruiz-Blondet M, Khalifian N, Chu F, Jin Z. A direct comparison of active and passive amplification electrodes in the same amplifier system. J Neurosci Methods. 2014;235:298–307.
74. Alexander DM, Arns MW, Paul RH, Rowe DL, Cooper N, Esser AH, et al. EEG markers for cognitive decline in elderly subjects with subjective memory complaints. J Integr Neurosci. 2006;5(1):49–74.
75. Toth B, File B, Boha R, Kardos Z, Hidasi Z, Gaal ZA, et al. EEG network connectivity changes in mild cognitive impairment - preliminary results. Int J Psychophysiol. 2014;92(1):1–7.
76. van der Hiele K, Vein AA, van der Welle A, van der Grond J, Westendorp RG, Bollen EL, et al. EEG and MRI correlates of mild cognitive impairment and Alzheimer's disease. Neurobiol Aging. 200 ;2 (9):1322–9.
77. Gaal ZA, Boha R, Stam CJ, Molnar M. Age-dependent features of EEG reactivity - spectral, complexity, and network characteristics. Neurosci Lett. 2 010;479(1):79–84.
78. Schmidt D, Germano AM, Milani TL. Aspects of dynamic balance responses: inter- and intra-day reliability. PLoS One. 2015;10(9):e0136551.
79. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol. 2001;56A(3):M146–M56.
80. Voelcker-Rehage C, Alberts JL. Age-related changes in grasping force modulation. Exp Brain Res. 2005;166(1):61–70.
81. Yan JH. Effects of aging on linear and curvilinear aiming arm movements. Exp Aging Res. 2000;26(4):393–407.
82. Hübner L, Godde B, Voelcker-Rehage C. Older adults reveal enhanced task related beta power decreases during a force modulation task. Behav Brain Res. 2018;345:104–13.
83. Teasdale N, Simoneau M, Hudon L, Germain Robitaille M, Moszkowicz T, Laurendeau D, et al. Older adults with mild cognitive impairments show less

driving errors after a multiple sessions simulator training program but do not exhibit long term retention. Front Hum Neurosci. 2016;10:653.

84. Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol. 1994;49(2):M85–94.
85. Rikli R, Jones J. Development and validation of a functional fitness test for community-residing adults. J Aging Phys Act. 1999;7:129–61.
86. Bohannon RW, Schaubert KL. Test-retest reliability of grip-strength measures obtained over a 12-week interval from community-dwelling elders. J Hand Ther. 2005;18(4):426–8.
87. Bach M. The Freiburg visual acuity test--automatic measurement of visual acuity. Optom Vis Sci. 1996;73(1):49–53.
88. Hahlbrock K. Speech audiometry and new word-tests. Archiv fur Ohren-, Nasen- und Kehlkopfheilkunde. 1953;162(5):394–431.
89. Kempf F. Vergleich plantarer Vibrationswahrnehmungsschwellen von drei Vibrationserzeugern. Master thesis. Chemnitz: Chemnitz University of Tech nology, Department of Human Locomotion; 2018.
90. Schmidt D, Germano AMC, Milani TL. Effects of active and passive warming of the foot sole on vibration perception thresholds. Clin Neurophysiol Pract. 2017;2:38–43.
91. Verrillo RT. Psychophysics of vibrotactile stimulation. J Acoust Soc Am. 1985; 77(1):225–32.
92. Mildren RL, Strzalkowski ND, Bent LR. Foot sole skin vibration perceptual thresholds are elevated in a standing posture compared to sitting. Gait Posture. 2016;43:87–92.
93. Wagner P, Singer R. Ein Fragebogen zur Erfassung der habituellen körperlichen Aktivität verschiedener Bevölkerungsgruppen. Sportwissenschaft. 2003;33(4):383–97.
94. Trampisch U, Platen P, Burghaus I, Moschny A, Wilm S, Thiem U, et al. Reliabilität des PRISCUS-PAQ. Z Gerontol Geriatr. 2010;43(6):399–406.
95. Oswald W, Fleischmann U. Nürnberger-Alters-Inventar (NAI). 3. überarbeitete und ergänzte Auflage. Göttingen: Hogrefe; 1995.

96. Fydrich T, Sommer G, Tydecks S, Brähler E. Fragebogen zur sozialen Unterstützung (F-SozU): Normierung der Kurzform (K-14). [Social Support Questionnaire (F-SozU): Standardization of short form (K-14).]. Z Med Psychol. 2009;18(1):43–8.

97. Schinka JA, McBride A, Vanderploeg RD, Tennyson K, Borenstein AR, Mortimer JA. Florida cognitive activities scale: initial development and validation. J Int Neuropsychol Soc. 2005;11(1):108–16.

98. Hultsch DF, Hertzog C, Small BJ, Dixon RA. Use it or lose it: engaged lifestyle as a buffer of cognitive decline in aging? Psychol Aging. 1999;14(2):245–63.

99. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373–83.

100. Braun T, Gruneberg C, Thiel C. German translation, cross-cultural adaptation and diagnostic test accuracy of three frailty screening tools: PRISMA-7, FRAIL scale and Groninen frailty Indicator. Z Gerontol Geriatr. 2018;51(3):282–92.

101. van Kan GA, Rolland YM, Morley JE, Vellas B. Frailty: toward a clinical definition. J Am Med Dir Assoc. 2008;9(2):71–2.

102. Freitag S, Schmidt S, Gobbens RJ. Tilburg frailty indicator. German translation and psychometric testing. Z Gerontol Geriatr. 2016;49(2):86–93.

103. Gobbens RJ, van Assen MA, Luijkx KG, Wijnen-Sponselee MT, Schols JM. The Tilburg frailty Indicator: psychometric properties. J Am Med Dir Assoc. 2010; 11(5):344–55.

104. Cwikel JG, Fried AV, Biderman A, Galinsky D. Validation of a fall-risk screening test, the elderly fall screening test (EFST), for community-dwelling elderly. Disabil Rehabil. 1998;20(5):161–7.

105. Dias N, Kempen GI, Todd CJ, Beyer N, Freiberger E, Piot-Ziegler C, et al. The German version of the falls efficacy scale-international version (FES-I). Z Gerontol Geriatr. 2006;39(4):297–300.

106. Renner B, Schwarzer R. Risk and health behaviors documentation of the scales of the research project: “risk appraisal consequences in Korea” (RACK). 2nd ed; 2005. http://www.gesundheitsrisiko.de/docs/RACKEnglish.pdf. Accessed 05 Oct 2019.

107. Diener E, Emmons RA, Larsen RJ, Griffin S. The satisfaction with life scale. J Pers Assess. 1985;49(1):71–5.
108. Gauggel S, Birkner B. Validität und Reliabilität einer deutschen Version der Geriatrischen Depressionsskala (GDS). Z Klin Psychol Psychother (Gott). 1999; 28(1):18–27.
109. Rammstedt B, Danner D. Die Facettenstruktur des Big Five Inventory (BFI). Diagnostica. 2017;63(1):70–84.
110. Soto CJ, John OP. Ten facet scales for the big five inventory: convergence with NEO PI-R facets, self-peer agreement, and discriminant validity. J Res Pers. 2009;43(1):84–90.
111. Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia. 1971;9(1):97–113.
112. Staudinger UM, Godde B, Heidemeier H, Kudielka BM, Schömann K, Stamov-Roßnagel C, et al. Den demografischen Wandel meistern: Eine Frage der Passung. Bielefeld: Wilhelm Bertelsmann Verlag; 2011.
113. Dugger BN, Hidalgo JA, Chiarolanza G, Mariner M, Henry-Watson J, Sue LI, et al. The distribution of phosphorylated tau in spinal cords of Alzheimer's disease and non-demented individuals. J Alzheimers Dis. 2013;34(2):529–36.

Appendix 2

Longitudinal aspects of foot sensitivity in normal aging and mild cognitive impairment (MCI)

Daniel Schmidt, Thomas L. Milani, Andresa M.C. Germano*

Poster presentation at i-FAB Congress (online), April 2021, São Paulo, Brazil, abstract book: https://www.i-fab2021.com/wp-content/uploads/2021/04/ifab2021_bookabstracts_site.pdf

TECHNISCHE UNIVERSITÄT CHEMNITZ
Faculty of Behavioural and Social Sciences
Department of Human Locomotion

LONGITUDINAL ASPECTS OF FOOT SENSITIVITY IN NORMAL AGING AND MILD COGNITIVE IMPAIRMENT (MCI)

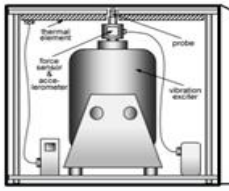
Daniel Schmidt, Thomas L. Milani, and Andresa M. C. Germano*
Department of Human Locomotion, Chemnitz University of Technology, Chemnitz, Germany

Introduction Cognitive disorders, e.g. subjective and mild cognitive impairment (SCI, MCI, resp.) or Alzheimer disease (AD), characterize structural and functional changes of the brain (fig. 1) [1], whereas AD constitutes an incurable progression [2]. AD and preclinical AD were shown to exhibit abnormalities in cortex areas associated with the interpretation of (cutaneous) sensory information [3]. Furthermore, aging also deteriorates skin sensitivity [4]. Therefore, we aimed to compare foot sensitivity in normal aging vs. SCI and MCI in a cross-sectional and longitudinal fashion. We hypothesized decreased sensory capabilities in the cognitively impaired groups (SCI, MCI), both cross-sectionally and longitudinally.

Fig. 1 https://www.serraville.com/

Methods Thirty-six subjects (13 MCI, 8 SCI, and 15 healthy controls (CG); mean±SD: 82.1±2.2 yrs) participated. The Montreal Cognitive Assessment (MoCA) and a questionnaire for complaints of cognitive disturbances (FLei) were used to determine the three groups: MCI: MoCA 19-26, FLei not considered; SCI: MoCA ≥ 26, FLei > 30; CG: MoCA ≥ 26, FLei ≤ 30. Vibration perception thresholds (VPT, µm) were collected at the plantar foot (Met 1) at 30 Hz (fig. 2, 3). Data were collected at time points T1 and T2 with an interval of 8-9 month in between. Statistical analyses were performed based on the mean of three single VPT trials.

Fig. 2 Vibration exciter.



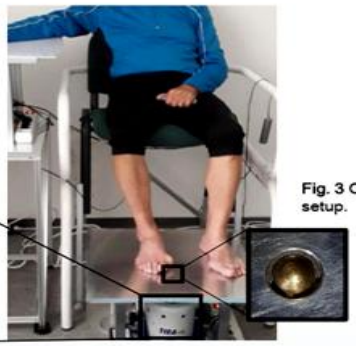


Fig. 3 Overall setup.

Results Descriptively, results show higher VPT with cognitive decline at T1 and T2 (cross-sectional, tab. 1). However, no statistical differences were found. Longitudinally, each group also showed a trend toward increasing VPT after 8-9 months, but again, no statistical differences were found (tab. 1). Percentual VPT increases after 8-9 month are shown in fig. 4.

Tab. 1 . VPT (mean±SD) for each group (CG, SCI, MCI) and both time points (T1, T2, interval: 8-9 months).

VPT (mean±SD)	CG	SCI	MCI
T1	29.5±15.8	33.5±26.7	36.2±15.2
T2	38.0±27.8	42.1±39.5	44.0±28.3

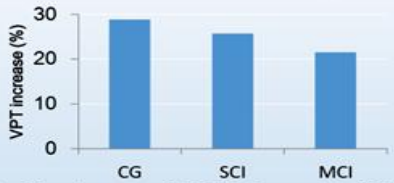


Fig. 4 Mean increases of VPT [%] after a period of 8-9 months for all three groups: CG, SCI, and MCI.

Discussion Aging affects sensitivity [4] and sensitivity-processing structures are already negatively affected in MCI [5] and (pre-clinical) AD [3]. Despite this, literature lacks investigations of skin sensitivity in cognitive disorders. We found no cross-sectional and longitudinal statistical differences between groups. This led us to reject our hypothesis. Hence, plantar skin sensitivity is neither affected by the cognitive status nor by a time period of 8-9 months. Descriptively, however, our data seem to favor the notion of a negative influence of cognitive decline and longitudinal aspects on skin sensitivity. This might have been masked by data heterogeneity and a small sample size. Interestingly, yet in a short period of time, there were clear decreases of skin sensitivity which could have a negative impact on balance control. Hence, further studies should investigate the relation between cognitive disorders and skin sensitivity, especially because of its contribution to motor performance.

Acknowledgement: Special thanks to the European Social Fund (ESF) for funding the project "SENDA".
References: [1] Chen W et al. Shanghai Arch Psychiatry 2013, 25: 119-120. [2] Pietrzak K Med Chem 2018, 14: 34-43. [3] Jacobs HIL et al. Brain Cogn 2011, 75: 154-163. [4] Gescheider GA et al. Somatosensory & Motor Research 1994, 11: 345-357. [5] Kluger A et al. J Gerontol B Psychol Sci Soc Sci. 1997, 52: 28-39.

Email: andresa.germano@hsw.tu-chemnitz.de
Phone: +49 371 531 38939
Chemnitz University of Technology
Department of Human Locomotion
International Foot & Ankle Biomechanics (i-FAB) Meeting
April 11-14, 2021, São Paulo, Brazil (online)

Appendix 3

Limits of stability in cognitively healthy individuals and mild cognitive impairment (MCI)

Andresa M.C. Germano*, Daniel Schmidt, Niclas Masuch, Thomas L. Milani

Poster presentation at ISB Congress (online), July 2021, Stockholm, Sweden, abstract book: https://www5.shocklogic.com/scripts/jmevent/programme.php?Client_Id=%27KONGRESS%27&Project_Id=%2721349%27&System_Id=1

TECHNISCHE UNIVERSITÄT CHEMNITZ

Faculty of Behavioural and Social Sciences
Department of Human Locomotion

Limits of stability in cognitively healthy individuals and mild cognitive impairment (MCI)

Andresa M. C. Germano, Daniel Schmidt, Niclas Masuch, Thomas L. Milani

Department of Human Locomotion, Group Motor Control, Cognition, and Neurophysiology, Chemnitz University of Technology, Chemnitz, Germany

Introduction Aging and disorders, such as dementia and mild cognitive impairment (MCI), are well-known to affect the cognitive domain [1]. Studies also indicate that MCI may affect the motor domain [2,3,4], which is believed to be related to the cognitive decline [5]. In terms of balance control, limits of stability (LoS) tests seem to constitute a promising measure for neurodegenerative disorders [6]. Therefore, we investigated LoS in MCI compared to healthy controls. We hypothesized decreases in balance control in MCI and correlations between balance and cognitive parameters.

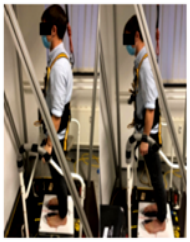


Fig. 1 Conduction of the limits of stability (LoS) test.

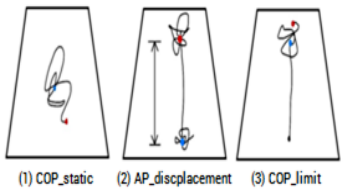


Fig. 2 Graphical description of the parameters evaluated.

Methods 193 participants (90 MCI (82.7±2.4 yrs), 75 older cognitively healthy individuals (OCH) (82.5±2.6 yrs), and 28 young cognitively healthy individuals (YCH) (22.8±3.1 yrs) participated (mean±SD). The Montreal Cognitive Assessment (MoCA) was used to determine groups (MoCA value < 26 corresponds to MCI). The protocol consists of three phases: 1) 20s of quiet stance (COP_static); 2) the distance until maximal forward leaning without losing balance (AP_displacement; normalized by foot length); and 3) maintenance of maximal forward leaning position for 10s (COP_limit) (Fig. 1 and 2). After one practice trial, the mean of three valid trials were included into inferential statistical analyses (α=0.05).

Results Gender differences were found. Differences between the groups were found in all parameters, but only between both older groups and YCH (Exemplary Fig 3). No differences were found between OCH and MCI. Balance correlated with cognitive parameters (Fig. 4).

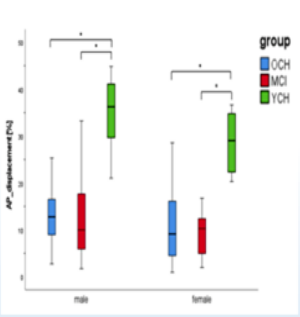


Fig. 3 Exemplary: Boxplot showing the comparison between the three grouos for AP_ displacement (*p<0.05).

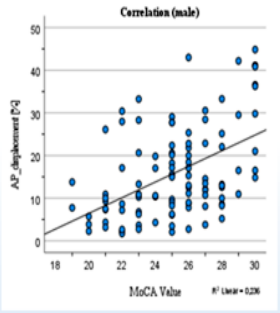


Fig. 4 Exemplary: correlation between AP_displacement and MoCA value (ρ = 0.470, p <0.001).

Discussion Rejecting our first hypothesis, differences between the groups were found in all parameters, but only between both older groups and YCH, probably caused by detrimental aging effects [7]. This contrasts other studies [2,3,4], showing various effects in MCI. However, correlations between balance and cognitive variables support our second hypothesis, showing that motor control is affected as a consequence of brain damage in cognitively impaired individuals. This is in line with a previous study [8], which also reported a low cognitive performance and increased postural instability. However, it remains unclear whether there were simply no differences in our study participants, or whether the LoS test might have been less discriminative for identifying MCI. Hence, further studies are needed to provide insights into the brevity of motor control decline and information-processing structures in person with MCI.

Acknowledgement: Special thanks to the European Social Fund (ESF) for funding the project "SENDA".

References: [1] Chen W et al. (2013). Shanghai Arch Psychiatry, 25: 119-120. [2] Makizako H et al. (2013) BMC Neurol, 13: 102. [3] Shin B et al. 2011 J Neurol Science, 305: 121-125 [4] Verghese J et al. 2008 J Am Geriatr Soc, 56: 1244-1251 [5] Deschamps T et al. 2013 Gait & Posture, 39: 628-630 [6] Schieppati M et al. (1994) Electroencephalogr Clin Neurophysiol, 93:286-298. [7] Marner L et al. 2003 J Comp Neurol, 462:144-152 [8] Leandri M et al. (2015). J Alzheimers Dis, 3: 705-707.

Email: andresa.germano@hsw.tu-chemnitz.de
Phone: +49 371 531 38939

Chemnitz University of Technology
Department of Human Locomotion

XXVIII Congress of the International Society of Biomechanics (ISB)
Digital Congress 25-29 Juli 2021

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Curriculum vitae

Personal Information

Name	Daniel Schmidt
Email	daniel.schmidt@hsw.tu-chemnitz.de
Phone	+49(0)371 531 32989
Date of birth, place	January 9th 1985, Goerlitz, Germany
Nationality	German
Current Position	Ph.D. Student and Research Associate
Institution	Chemnitz University of Technology Department of Human Locomotion Motor Control, Cognition, and Neurophysiology Institute of Human Movement Science and Health Faculty of Behavioral and Social Sciences
ORCID iD	https://orcid.org/0000-0001-6730-4621

Education

since 10/2020	Research fellow at the group Motor Control, Cognition, and Neurophysiology (Andresa M.C. Germano, Ph.D.), Chemnitz University of Technology
10/2015 - 092018	PhD-scholarship holder (European Social Fund)
since 04/2013	PhD student at the Department of Human Locomotion (Prof. Thomas Milani), Chemnitz University of Technology
since 10/2012	Research fellow at the Department of Human Locomotion (Prof. Thomas Milani), Chemnitz University of Technology
09/2012	Final degree: "Magister Artium"

10/2005	Enrollment at Chemnitz University of Technology, degree program: Sports Engineering

Internships

11/2010 - 04/2011	Pontificia Universidad Católica del Perú, Peru Facultad de Ciencias e Ingeniería Especialidad Ingeniería Mecánica (Francisco Rumiche, Ph.D.)
10/2009 - 02/2010	University of Calgary, Canada Faculty of Kinesiology Human Performance Laboratory (Darren Stefanyshyn, Ph.D., P.Eng.)

Student Assistant Researcher

10/2008 - 09/2012 (with interruptions)	Chemnitz University of Technology Faculty of Behavioural and Social Sciences Department of Human Locomotion (Prof. Thomas Milani) Data collection, teaching
01/2009 - 06/2009	Chemnitz University of Technology Faculty of Mechanical Engineering Chair of Materials Science (Prof. Lothar Meyer) Execution and analysis of material testing

Scientific Area of Expertise and Interest

- Skin Sensitivity and Influencing Factors
- Sensory Integration
- Human Posture and Balance
- Cognitive Impairment

Lectures and seminars

- Perceptual Phenomena (winter term, lecture)
- Attention and Perception (winter term, seminar)
- Research Fields in Human Movement Science I, II (winter and summer term; seminar, exercise)

- Contributions in the context of round table lectures (current and past)
  - Measurement Methods in Human Movement Science (summer and winter term, lecture and seminar)
  - Measurement Methods in Biomechanics and Motor Function (winter term, lecture)
  - Measurement Methods, Diagnostics, and Assessments (winter term, lecture)
  - Basics of Biomechanics and Human Movement Science (winter term, lecture and exercise)
  - Biomechanics and Sensory Function (winter term, lecture)

Publication Overview

- Full papers: 12 (peer-reviewed)
- Conference contributions: 23

Peer-Reviewed Papers

1 Machado, M.S., Machado, A.S., Guadagnin, E.C., Schmidt, D., Germano, A.M.C., Carpes, F.P. (2021). Effects of increasing temperature in different foot regions on foot sensitivity and postural control in young adults. The Foot, accepted manuscript (YFOOT-D-21-00040R1).

2 Schmidt, D., Carpes, F.P., Milani, T.L., Germano, A.M.C. (2021). Different visual manipulations have similar effects on quasi-static and dynamic balance responses of young and older people. PeerJ 9:e11221. Link

3 Schmidt, D., Schlee, G., Milani, T.L., Germano, A.M.C. (2020). Thermal sensitivity mapping - warmth and cold detection thresholds of the human torso. Journal of Thermal Biology, 90, 102718. Link

4 Schmidt, D., Schlee, G., Germano, A.M.C., & Milani, T.L. (2020). Larger contactor area increases low-frequency vibratory sensitivity in hairy skin. PEERJ, 8, Article e8479. Link

5 Müller, K., Fröhlich, S., Germano, A.M.C., Kondruganta, J., Agoitia Hurtado, M.F., Rudisch, J., Schmidt, D., Hirtz, G., Stollmann, P., & Voelcker-Rehage, C. (2020). Sensor-based systems for early detection of dementia (SENDA): a study protocol for a prospective cohort sequential study. BMC Neurology, 20, 84. Link

6 Schmidt, D., Germano, A.M.C., & Milani, T.L. (2019). Subjective sensitivity data: Considerations to treat heteroscedasticity. Cogent Medicine, 6, Article 1673086. Link

7 Germano, A.M.C., Heß, T., Schmidt, T., & Milani, T.L. (2018) Effects of plantar hypothermia on quasi-static balance: Two different hypothermic procedures. Gait and Posture. Link

8 Schmidt, D., Germano, A.M.C., & Milani, T.L. (2018). Effects of water immersion on sensitivity and plantar skin properties. Neuroscience Letters, 686, 41-46. Link

9 Schmidt, D., Germano, A.M.C., & Milani, T.L. (2017). Effects of active and passive warming of the foot sole on vibration perception thresholds. Clinical Neurophysiology Practice, 2, 38–43. Link

10 Germano, A.M.C., Schmidt, D., & Milani, T.L. (2016). Effects of hypothermically reduced plantar skin inputs on anticipatory and compensatory balance responses. BMC Neurosci, 17(41), 1-14. Link

11 Germano, A.M.C., Schmidt, D.,Schlee, G., Milani, T.L. (2016). Plantar sensory vibration thresholds are not influenced by body position. Cogent Medicine, 3(1), 1-6. Link

12 Schmidt, D., Germano, A.M.C., Milani, T.L. (2015). Aspects of dynamic balance responses: Inter- and intra-day reliability. PLoS ONE, 10(9), Article e0136551. Link

Conference Contributions

1 Machado, M.S., Machado, A.S., Guadagnin, E.C., Schmidt, D., Germano, A.M.C., Carpes, F.P. (2021). O impacto de diferentes formas de aquecimentos da pele sobre a sensibilidade cutânea plantar em adultos jovens [Poster]. XIX Congresso Brasileiro de Biomecânica - Ambiente virtual. Setembro 13-17, 2021.

2 Machado, M.S., Machado, A.S., Guadagnin, E.C., Schmidt, D., Germano, A.M.C., Carpes, F.P. (2021). Efeitos de aquecimento dos pés sobre o controle postural em idosos [Poster]. XIX Congresso Brasileiro de Biomecânica - Ambiente virtual. Setembro 13-17, 2021.

3 Germano, A.M.C., Schmidt, D., & Milani, T.L. (2021) Eye-foot coordination in normal aging and mild cognitive impairment (MCI) [Oral presentation]. i-FAB 2021 - International Foot & Ankle Biomechanics Meeting April 11 to 14, 2021 - Virtual Meeting, Sao Paulo, Brazil. ISBN: 978-65-00-20826-9.

4 Schmidt, D., Germano, A.M.C., & Milani, T.L. (2021) Longitudinal aspects of foot sensitivity in normal aging and mild cognitive impairment (MCI) [Poster]. i-FAB 2021 - International Foot & Ankle Biomechanics Meeting April 11 to 14, 2021 - Virtual Meeting, Sao Paulo, Brazil. ISBN: 978-65-00-20826-9.

5 Schmidt, D., Schlee, G., Germano, A.M.C., & Milani, T.L. (2019, July 31-August 4). Thermal sensitivity mapping - Warmth and cold detection thresholds of the torso [Poster]. XXVII Congress of the International Society of Biomechanics (ISB2019), Calgary, Alberta, Canada.

6 Germano, A.M.C., Schmidt, D., & Milani, T.L. (2019, July 31-August 4). Cutaneous sensitivity in normal aging and mild cognitive impairment (MCI) [Poster]. XXVII Congress of the International Society of Biomechanics (ISB2019), Calgary, Alberta, Canada.

7 Schmidt, D., Germano, A.M.C., & Milani, T.L. (2018, August 14-17). Subjective sensitivity data: Considerations to treat heteroscedasticity [Poster]. 20th Biennal Meeting of the Canadian Society for Biomechanics (CSB), Halifax, Nova Scotia, Canada.

8 Germano, A.M.C., Schmidt, D., & Milani, T.L. (2018, August 14-17). Plantar temperatures and foot sensitivity: Effects of 30 minutes of walking on a treadmill with and without special insoles [Poster]. 20th Biennial Meeting of the Canadian Society for Biomechanics (CSB), Halifax, Nova Scotia, Canada.

9 Schmidt, D., Germano, A.M.C., Drechsel, T., & Milani, T.L. (2017, 8.-11. August). Effects of water immersion on plantar skin properties and sensitivity [Poster]. 41st Annual Meeting of the American Society of Biomechanics (ASB), Boulder, CO, USA.

10 Germano, A. M. C., Schmidt, D., Zippenfennig, C., & Milani, T. L. (2017, 8.-11. August). Age-related differences in postural control: Effects of different visual manipulations on dynamic balance responses [Poster]. 41st Annual Meeting of the American Society of Biomechanics (ASB), Boulder, CO, USA.

11 Drechsel, T., Schmidt, D., & Milani, T.L. (2017, 8.-11. August). Influence of short-term visual deprivation and reduced auditory capability on quasi-static balance performance in healthy adults [Poster]. 41st Annual Meeting of the American Society of Biomechanics (ASB), Boulder, CO, USA.

12 Wynands, B., Zippenfennig, C., Germano, A. M. C., Schmidt, D., Drechsel, T. J., & Milani, T. L. (2017, 8.-11. August). Correlation between plantar vibration sensitivity and COP-parameters during dynamic balance [Poster]. 41st Annual Meeting of the American Society of Biomechanics (ASB), Boulder, CO, USA.

13 Zippenfennig, C., Schmidt, D., Germano, A.M.C., & Milani, T. L. (2017, 2.-5. July). Effects of electrical stimulation on dynamic balance [Poster]. 23th Congress of the European Society of Biomechanics (ESB), Sevilla, Spain.

14 Schmidt, D., Germano, A. M. C., & Milani, T. L. (2016, 2.-5. August). Effects of textured insoles on plantar temperatures and vibration perception [Poster]. 40th Annual Meeting of the American Society of Biomechanics, Raleigh, NC, USA.

15 Schmidt, D., Germano, A. M. C., & Milani, T. L. (2016, 19.-22. July). Effects of plantar temperature and mechanical stimulation on vibration perception thresholds [Poster]. 19th Biennial Meeting of the Canadian Society for Biomechanics 2016, Hamilton, ON, USA.

16 Germano, A. M. C., Schmidt, D., & Milani, T. L. (2016). Effects of magnetic insoles on balance and plantar temperatures [Poster]. 19th Biennial Meeting of the Canadian Society for Biomechanics Hamilton, ON, USA.

17 Germano, A. M. C., Schmidt, D., & Milani, T. L. (2016, 2.-5. August). Effects of peripheral acute fatigue on balance and reflex responses [Oral presentation]. 40th Annual Meeting of the American Society of Biomechanics, Raleigh, NC, USA.

18 Germano, A.M.C., Schmidt, D., & Milani, T.L. (2014, 6.-11. July). Effects of a six-week slackline training on dynamic balance [Poster]. 7th World Congress of Biomechanics, Boston, USA.

19 Schmidt, D., Germano, A.M.C., & Milani, T.L. (2014, 6.-11. July). Learning effects and intra-day reliability of balance using the Pusturomed® device [Poster]. 7th World Congress of Biomechanics, Boston, USA.

20 Heß, T., Schmidt, D., & Germano, A. M. C. (2013, 15.-17. Mai). Der Vergleich der Muskelaktivität des Achillessehnenreflexes zwischen den Geschlechtern und die Korrelation mit der Körpergröße [Poster]. 8. Jahrestagung der Deutschen Gesellschaft für Biomechanik, Neu-Ulm, Deutschland.

21 Germano, A.M.C., Heß, T., Schmidt, D., Schlee, G., & Milani, T.L. (2013, 04.-09. August). Influence of induced plantar hypothermia on the Achilles Tendon Stretch Reflex [Oral presentation]. XXIV Congress of the International Society of Biomechanics, Natal, Brazil.

22 Germano, A.M.C., Schmidt, D., Heß, T., Schlee, G., & Milani, T.L. (2013, 04.-09. August). Effects of induced plantar hypothermia on dynamic balance [Oral

presentation]. XXIV Congress of the International Society of Biomechanics, Natal, Brazil.

23 Schmidt, D., Heß, T., & Germano, A.M.C. (2013). Der Einfluss plantarer Hypothermie auf COP Parameter unter dynamischen Gleichgewichtsbedingungen [Oral presentation]. Tagung der dvs-Sektion Biomechanik, Chemnitz, Deutschland.

Computer Skills

- Microsoft Office (Word, Excel, Powerpoint) and R

Language Experiences

- German (native language)
- English (good)
- Spanish (intermediate)
- Portuguese (beginner level)

Other Relevant Information

- Supervision of more than 30 academic theses (Bachelor and Master level)
- Reviewer activity for the "International Journal of Environmental Research and Public Health". OA journal, 2020 impact factor: 3.390.
- Departmental Erasmus+ Coordinator
- Contact person for international contacts within the Master program "Human Movement Science" at the Chemnitz University of Technology
- Contributions during the application process of third-party funds, e.g.:
    - "SenseCare" (High-tech sensor technology for demographic challenges in Saxony), 2016-2019, ~1.4 Mio €
    - "SENDA" (Sensor-based systems for early detection of dementia), 2017-2020, ~1.1 Mio €
    - DAAD exchange projects with Brazil (two projects: 2020-2021, 2022-2024, ~32.000 € each project) and Canada (2022-2023, ~28.000 €)

Statement

I, Daniel Schmidt, born in Goerlitz on January 9, 1985, hereby declare that I wrote this doctoral thesis by my own hand, only used the sources and materials referred to, and that each citation is made explicit. Therefore, I agree that an electronic verification regarding possible plagiarism can be performed on the present thesis. Moreover, I declare that I neither use/used the present doctoral thesis in this or any other form as a thesis, nor have I submitted this work as a dissertation to another faculty. Finally, I declare that this doctoral thesis is a cumulative thesis, which is a compilation of five published manuscripts. The present doctoral thesis was supervised by Prof. Dr. Thomas L. Milani.

Daniel Schmidt

Erklärung

Ich, Daniel Schmidt, geboren in Görlitz am 09. Januar 1985, erkläre hiermit, dass ich diese Doktorarbeit selbstständig verfasst habe, dass sämtliche Quellen und Zitate vollständig sind sowie, dass ich keine anderen als die angegebenen Hilfsmittel genutzt habe. Daher bin ich einverstanden, dass eine elektronische Überprüfung meiner Dissertation auf etwaige Plagiate erfolgen kann. Außerdem erkläre ich, dass ich diese Doktorarbeit weder in dieser noch in einer anderen Form als Dissertationsverfahren weder in der Vergangenheit oder gleichzeitig bei einer anderen Stelle (z.B. andere Fakultät) beantragt habe. Schließlich erkläre ich, dass diese Dissertation eine kumulative Doktorarbeit ist, die eine Zusammenstellung von fünf veröffentlichten Manuskripten darstellt. Die vorliegende Dissertation wurde von Herrn Prof. Dr. Thomas L. Milani betreut.

Daniel Schmidt