Pain Assessment
in Aging and Cognitive Impairment

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Abstract

As dementia progresses, those affected lose their ability to think, speak, and express their inner states verbally. As a result, they are alone with their inner experiences and perceptions. Often, painful conditions go unnoticed by others, and sufferers remain unheard. And although the verbal ability to express pain may be lacking, non-verbal expressions of pain often remain preserved. For instance, an increased nociceptive pain response or facial response to pain is more likely to be observed in individuals with dementia. Additionally, there are specific indicators to measure non-verbal pain responses. Though some indicators, such as facial expressions and observer-based methods, are widely recognized and implemented, the use of autonomic responses to describe pain still lacks empirical robustness.

Thus, this dissertation aimed to describe and evaluate pain assessments that could be implemented in various populations, including individuals with dementia, while considering individual factors such as cognition and aging. Therefore, three empirical studies were conducted. Chapter 1 summarizes the theoretical background, and Chapter 2 describes Study 1, which focused on a practical challenge: How can we efficiently and validly observe what patients cannot say? With the development of a shortened version of the Pain Assessment in Impaired Cognition, an observer-based pain assessment tool was designed that combines clinical relevance with psychometric quality and focuses on facial expressions, body movements, and vocalizations as indicators of pain.

Until now, pain research has primarily been conducted in laboratory settings using standardized pain protocols. In Studies 2 and 3, we applied prior findings to real-world contexts and evaluated pain during motor challenges (box and kettlebell lift), activities of daily living (e.g., movements in bed or walking), and pain stimulation (pressure and heat) in a Living Lab environment.

With Study 2, addressed in Chapter 3, we explored multimodal indicators of pain (facial expressions, autonomic responses, and self-reports) during muscular pre-activation in healthy adults. For this, muscular pre-activation was induced by using an age simulation suit. The results demonstrate the selective sensitivity of specific indicators of pain: facial expressions and heart rate increased with muscle pre-activation, while heart rate variability and self-reports of pain remained surprisingly unaffected. Electrodermal activity increased from round 1 to round

2 only in the group with muscle pre-activation, indicating a delayed electrodermal activity response to muscle pre-activation.

Study 3, described in Chapter 4, extended this approach to older adults with and without cognitive impairment, assessing autonomic responses and self-reports of pain during both pain stimulation and activities of daily living. Surprisingly, cognitive impairment did not influence autonomic responses or self-reports of pain, while age itself proved to be a predictor of both.

Overall, these findings emphasize that integrative pain assessments are particularly useful for accurately describing pain when considering individual factors, which is addressed in Chapter 5. While observer-based assessment tools or facial expressions could be interpreted in isolation, autonomic responses such as heart rate variability and electrodermal activity should be considered as complementary indicators of arousal and not as stand-alone measures of pain, based on the results of this dissertation. Interestingly, even in individuals with mild forms of cognitive impairment, self-reports of pain could be reliably interpreted. These results highlight the importance of selecting context-sensitive pain assessment to reliably capture pain across various populations.

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List of Abbreviations

AD	Alzheimer's disease
ADL	Activity of daily living
ANS	Autonomic nervous system
AU	Facial Action Unit
BAP	Body Action and Posture Coding System
BamLiD	Bamberg Living Lab Dementia
CAN	Central autonomic network
CDA	Continuous decomposition analysis
CI	Cognitive impairment
dACC	Dorsal anterior cingulate cortex
DOMS	Delayed onset muscle soreness
ECG	Electrocardiogram
EDA	Electrodermal activity
EEG	Electroencephalography
ePAT	Electronic Pain Assessment Tool
FACS	Facial Action Coding System
GERT	GERonTologic Simulator Suit
HR	Heart rate
HRV	Heart rate variability
LL	Living Lab
MCI	Mild cognitive impairment
ML	Machine learning
MMSE	Mini-Mental State Examination
NIM	Neurovisceral Integration Model
NRS	Numerical rating scale
PAG	Periaqueductal gray
PAIC	Pain Assessment in Impaired Cognition
PAIC6	Pain Assessment in Impaired Cognition – Short Version (6 items)
PAIC15	Pain Assessment in Impaired Cognition – Full Version (15 items)
PCM	Partial Credit Model
PFC	Prefrontal cortex
RQ	Research question

SCL	Skin conductance level
VAS	Visual analog scale
vmPFC	Ventromedial prefrontal cortex

German Summary

Mit fortschreitender Demenz verlieren Betroffene allmählich ihre Fähigkeit zu sprechen und es fällt ihnen zunehmend schwer, ihre Gedanken und Gefühle verbal auszudrücken (Parisot, 1988). Infolgedessen können schmerzhafte Zustände von anderen unbemerkt bleiben (Achterberg et al., 2021), und Betroffene sind mit ihrem Leid allein. Trotzdem bleiben nonverbale Ausdrucksformen von Schmerzen häufig auch mit Fortschreiten der Erkrankung erhalten, obwohl die Fähigkeit, Schmerzen verbal auszudrücken, fehlen mag. So zeigen Personen mit Demenz beispielsweise eine erhöhte nozizeptive wie auch mimische Reaktion auf Schmerzen (Beach et al., 2017; Kunz et al., 2007; Kunz et al., 2009).

Um schmerzhafte Zustände auch ohne verbale Ausdrucksfähigkeit zu erfassen, stehen daher spezifische Tools zur Verfügung, die verschiedene Indikatoren zur Schmerzbeschreibung heranziehen. In diesem Zusammenhang sind vor allem beobachtungsbasierte Indikatoren (wie Gesichtsausdruck oder Körperbewegung) weithin anerkannt und angewendet (Kunz et al., 2020), allerdings wurden auch autonome Reaktionen als Schmerzmarker vorgeschlagen (Cowen et al., 2015).

Zu den autonomen Reaktionen gehören beispielsweise die Herzfrequenzvariabilität, die Herzfrequenz und die elektrodermale Aktivität. Diese Reaktionen werden autonom gesteuert und spiegeln die Aktivierung des sympathischen und parasympathischen Nervensystems wider (Berntson et al. 1997; Kreibig, 2010), was sie besonders interessant für die Beschreibung von Schmerzen bei Bevölkerungsgruppen mit eingeschränkten sprachlichen Fähigkeiten macht, wie beispielsweise Menschen mit Demenz.

Bisher wurden die verschiedenen Indikatoren zur Schmerzbeschreibung allerdings meist isoliert betrachtet, typischerweise in standardisierten Laborumgebungen. Derzeit gibt es jedoch keinen systematischen Ansatz, der Indikatoren unter ökologisch validen – das heißt alltagsnahen – Bedingungen mit Blick auf relevante individuelle Faktoren wie Alter und Kognition kombiniert. Standardisierte Laborumgebungen sind für Personen mit Demenzerkrankung besonders herausfordernd, da Anforderungen wie Stillsitzen oder

anhaltende Aufmerksamkeit ihre Fähigkeiten übersteigen können. Zudem ist die ökologische Validität unter solchen Bedingungen eingeschränkt.

Um diesen Einschränkungen zu begegnen, wurde Studie 1 auf einer geriatrischen Krankenhausstation sowie in einem Pflegeheim durchgeführt, während die Studien 2 und 3 dieser Dissertation in einer sogenannten Living-Lab-Umgebung stattfanden. Living Labs sind Umgebungen, die reale Alltagsbedingungen für experimentelle Zwecke simulieren und eine aktive Beteiligung der Teilnehmenden im experimentellen Setting ermöglichen. In der Regel sind dabei mehrere Interessengruppen eingebunden, um das Living Lab in einen organisierten und kollaborativen Innovationsprozess zu integrieren (Schuurman, 2015). Living Labs schaffen es damit, standardisierte Forschungsumgebungen mit Alltagsrelevanz zu kombinieren und gleichzeitig ein breites Spektrum an Forschungsfragen zu untersuchen, die von Lebensqualität, Wohlbefinden und Kognition bis hin zu Autonomie, sozialer Integration und sogar Diagnostik reichen können (Figueiredo et al., 2024).

Vor diesem Hintergrund verfolgte die vorliegende Dissertation das Ziel, Schmerzindikatoren in einem realistischen Setting systematisch zu beschreiben und zu bewerten, die bei verschiedenen Bevölkerungsgruppen – einschließlich nonverbaler Personen – eingesetzt werden können. Dabei wurden individuelle Faktoren wie Kognition und Lebensalter berücksichtigt. Entsprechend umfasste diese Dissertation Verhaltensindikatoren (Gesichtsausdruck, Körperbewegung und Vokalisation), autonome Reaktionen (Herzratenvariabilität, Herzrate, elektrodermale Aktivität) und Selbstberichte zum Schmerzerleben in verschiedenen Gruppen – von jungen, kognitiv gesunden Personen bis hin zu Menschen mit schweren kognitiven Einschränkungen.

Kapitel 1 fasst den theoretischen Hintergrund zusammen.

Kapitel 2 stellt Studie 1 (N=309) vor, die sich auf eine praktische Herausforderung konzentrierte: Wie können beobachtungsbasierte Schmerzerfassungsinstrumente so gestaltet werden, dass sie sowohl klinisch praktikabel als auch psychometrisch fundiert sind?

Dafür wurden Verhaltensindikatoren für Schmerzen bei stationär betreuten älteren Erwachsenen ab 65 Jahren mit keinen bis schweren kognitiven Einschränkungen untersucht. Im Gegensatz zu den Studien 2 und 3 basierte Studie 1 auf Daten von Kooperationspartnern in

Berlin und den Niederlanden, die im Rahmen dieser Dissertation weiter aufbereitet und ausgewertet wurden.

Dazu erfassten die Kooperationspartner Beobachterbewertungen mit Hilfe des Pain Assessments in Impaired Cognition (PAIC15; Kunz et al., 2020). Ziel war es, eine verkürzte Version der PAIC15 zu entwickeln: die PAIC6. Dieses verkürzte Tool sollte sich auf die Fremdbeschreibung von Schmerzen durch das Pflegepersonal fokussieren. Die PAIC6 umfasst die Beschreibung des Gesichtsausdrucks, der Körperbewegung und der Vokalisation. Durch die Kürzung konnte eine zeiteffizientere Schmerzbewertung ermöglicht werden, da sich die Anwendungszeit von fünf auf etwa zwei Minuten reduzierte – eine Zeitersparnis von 60 %.

Die Ergebnisse von Studie 1 unterstreichen, dass Verhaltensindikatoren für Schmerzen in psychometrisch fundierten und klinisch nützlichen, beobachterbasierten Tools eingesetzt werden können, die klinische Relevanz mit psychometrischer Qualität verbinden.

Darauf aufbauend und mit dem Ziel, die ökologische Validität bisheriger Erkenntnisse zu erweitern, haben wir in den Studien 2 und 3 alltagsnahe Kontexte genutzt, um Schmerzen bei motorischen Challenges (z. B. Kisten- oder Kettlebellheben), bei Aktivitäten des täglichen Lebens (z. B. Bewegungen im Bett oder Gehen) sowie durch experimentelle Schmerzstimulation (Druck und Hitze) in einer Living-Lab-Umgebung zu erfassen.

In **Kapitel 3** wird Studie 2 (N=43) behandelt, in der wir den Gesichtsausdruck, die autonomen Reaktionen sowie den Selbstbericht zum Schmerzerleben bei jungen, kognitiv gesunden Erwachsenen untersuchten. Mittels eines Alterungsanzugs wurde eine Muskelvoraktivierung induziert, um altersbedingte körperliche Belastungen zu simulieren und so ein Modell für muskuloskelettale Schmerzen zu evaluieren. Ziel war es, zu klären: *Wie reagieren Verhaltens- und autonome Schmerzindikatoren bei experimentellen Schmerzen und motorischen Challenges, und wie wirkt sich die Muskelvoraktivierung auf diese Reaktionen aus?*

Die Ergebnisse von Studie 2 zeigen, dass die Muskelvoraktivierung (d. h. das Tragen des Alterungsanzugs) während motorischer Challenges (Kettlebell- und Kistenheben) zu deutlich höherem selbst berichteten Schmerz und körperlicher Anstrengung führte. Außerdem waren verstärkte schmerzbezogene Gesichtsausdrücke sowie eine erhöhte Herzfrequenz als Reaktion

auf die Schmerzen zu beobachten. Allerdings erwiesen sich nicht alle autonomen Reaktionen als sensitiv für Schmerzen.

Interessanterweise nahmen die selbst berichteten Schmerzen, die elektrodermale Aktivität, die Herzfrequenz und die Herzratenvariabilität im Laufe der sensorischen Challenges (Druck- und Hitzeschmerzen) zu, jedoch unabhängig von der Muskelvoraktivierung. Dies deutet auf eine Summation der Reaktionen im Laufe der Zeit hin, die unabhängig von der Muskelvoraktivierung war.

Insgesamt verdeutlicht Studie 2, dass Selbstbericht, Gesichtsausdruck und Herzfrequenz in der Lage waren, schmerzbezogene Reaktionen zu beschreiben, die durch Muskelvoraktivierung während motorischer Challenges ausgelöst wurden.

Um die Befunde weiter zu prüfen, erweiterte Studie 3 (N=101), den Ansatz auf ältere Erwachsene (65+) mit und ohne kognitive Beeinträchtigung. In **Kapitel 4** wird dazu beschrieben, wie wir autonome Reaktionen sowie Selbstberichte zum Schmerzerleben sowohl während experimenteller Schmerzstimulation als auch während Aktivitäten des täglichen Lebens untersucht haben. Das Ziel von Studie 3 bestand darin, die Rolle von Kognition, Kontextbedingungen und Alter bei der Interpretation dieser Signale zu ermitteln. Dazu stellten wir die folgenden Fragen: *Können autonome Reaktionen als zuverlässige Indikatoren für die Schmerzwahrnehmung bei älteren Erwachsenen mit und ohne kognitive Beeinträchtigungen dienen, und wie beeinflussen individuelle Faktoren (d. h. Alter und Kognition) die Interpretation autonomer Reaktionen als Indikatoren für Schmerzen?*

Die Ergebnisse zeigen, dass nicht die Kognition, sondern das Alter ein signifikanter Prädiktor für autonome Reaktionen sowie selbstberichtete Schmerzen war. Darüber hinaus lösten sowohl Aktivitäten des täglichen Lebens als auch experimentelle Schmerzstimulation eine sympathische Aktivierung hervor, erkennbar an einer erhöhten Herzrate und elektrodermalen Aktivität. Dagegen konnten für die Herzratenvariabilität keine signifikanten Effekte nachgewiesen werden.

Insgesamt deuten die Ergebnisse von Studie 3 darauf hin, dass autonome Reaktionen nur teilweise mit dem Schmerzerleben älterer Erwachsener assoziiert werden konnten: Während Herzrate und elektrodermale Aktivität sich als schmerzsensitiv zeigten, war die Herzratenvariabilität nicht stabil aussagekräftig. Zu berücksichtigen ist zudem, dass keiner der

autonomen Reaktionen spezifisch für Schmerz war, sondern vielmehr allgemeine Erregung widerspiegelte.

Zusammenfassend lässt sich sagen, dass unsere Ergebnisse zeigen, dass sich schmerzbezogene Zustände mithilfe von Verhaltensindikatoren wie Gesichtsausdruck, Körperbewegung und Vokalisation zuverlässig und effektiv beschreiben lassen. Allerdings wurden die autonomen Reaktionen zu Schmerz stark von individuellen Faktoren beeinflusst, insbesondere vom Alter und der Aufgabendauer. Der Selbstbericht von Schmerz war in allen Analysen möglich, in denen verbale Kommunikation möglich war – selbst bei Personen mit leichten kognitiven Beeinträchtigungen. Für das Schmerzassessment im klinischen Setting bedeuten unsere Ergebnisse, dass sich die Schmerzbewertung in erster Linie auf Verhaltensindikatoren stützen sollte, während autonome Reaktionen primär zur Erfassung einer nicht schmerzspezifischen allgemeinen Erregung herangezogen werden können. Die Herausforderung, autonome Reaktionen nur unter Berücksichtigung individueller Faktoren zu interpretieren, bleibt bestehen. Dafür können zukünftige Studien spezifisch untersuchen, wie autonome Reaktionen als Schmerzindikatoren von allgemeiner Erregung abgegrenzt werden können und in welchen Kontexten eine Kombination von multiplen Indikatoren einen Mehrwert bietet.

Chapter 1

General Introduction

1.1 Introduction

In November 1906, German psychiatrist Alois Alzheimer presented a case study of a patient exhibiting short-term memory impairment and unusual behavioral patterns. The patient, Auguste Deter, would become the first documented case of Alzheimer's disease (AD). At the time, life expectancy was around 30 years, so Auguste Deter, at age 51, was considered elderly. The idea of a global aging population was unimaginable at that time.

Fast forward to 2025: The world's population is aging at a rapid rate. In 2020, the number of individuals over 60 reached 1 billion, and this figure is expected to soar to 2.1 billion by 2050, according to the World Health Organization (WHO; 2024). This will be a nearly doubling of the aging population from 12% in 2015 to 22% in 2050, and a major societal shift is expected. Bringing both remarkable opportunities and significant challenges for healthcare systems worldwide.

Among these challenges, an increase in age-related diseases is expected to be accompanied by an increased resource and cost burden for the healthcare system (Moshammer & Schroth, 2024). The WHO and the United Nations (2023) predict major health, social, and economic challenges associated with an aging world population. Among these challenges, dementia is one of the key focuses. Every three seconds, someone worldwide is diagnosed with dementia, according to Alzheimer's Disease International (2024). This corresponds to 55 million individuals in 2019, with a predicted increase to 139 million by 2050 (CanAge, 2022).

Alongside cognitive decline, another issue that can impair the quality of life for the aging population is pain. Especially *chronic pain*, defined as pain that occurs most days or daily over more than three months (Merskey, 1986), is common, with a prevalence of 37.8% among individuals aged 65 and over (LaRowe et al., 2024).

International studies show that prevalence rates range from around 21% to 63% for individuals aged 65 years and over (Huang et al., 2020; Larsson et al., 2017; Liberman et al., 2018), with up to 63% in those over 85 years old (Mallon et al., 2018). Arthritis and chronic back pain are among the most common types of pain in older adults. A systematic review by De Souza et al. (2019) reported a prevalence of low back pain up to 75% in adults aged over 60, while the incidence of arthritis was reported at 47.4% in adults aged 65 years and older (Hootman et al.,

2016). Chronic pain is often accompanied by reduced mobility, an increased risk of depression and mortality (Gureje et al., 1998; Ray et al., 2024; Sheng et al., 2017).

Yet, diagnosing and managing pain in older adults is no simple task. For cognitively healthy individuals, self-report is still considered the standard for pain diagnosis (Kang & Demiris, 2018). Self-report tools include, for example, numerical rating scales (NRS) and visual analog scales (VAS), which are most commonly used to record the intensity on a scale, for instance, from 0 (*no pain*) to 10 (*worst pain imaginable*) (Thong et al., 2018). But what happens in a case like Auguste Deter, when her self-report is compromised due to limitations in communication?

And this is where the problem emerges: when patients' ability to self-report is limited, pain is frequently overlooked (Madariaga et al., 2021). Not only are individuals with Alzheimer's and Parkinson's disease affected by under-recognition of pain (Lawn et al., 2021), but also infants and young children (Von Baeyer, 2009), individuals with severe intellectual disabilities (Defrin & McGuire, 2019), or unconscious patients (D. B. McGuire et al., 2016). Studies show that pain is diagnosed significantly less often in individuals with dementia, leading to undertreatment of symptoms compared to peers (Achterberg et al., 2021; B. E. McGuire et al., 2010). This raises the question: How can we improve pain recognition for those who can no longer talk about their pain?

To address these considerations, this dissertation aims to develop and validate pain assessment approaches by exploring the effectiveness of observer-based, autonomic, and self-report indicators of pain, and how these indicators can be used in a clinically feasible way while considering individual factors that can influence pain experience, such as cognition and age.

1.2 Theoretical Background

1.2.1 Pain and Aging

Understanding and managing pain with age is becoming an increasingly important task due to demographic change. As society ages, chronic pain conditions are becoming more common (Reid et al., 2015). This makes it even more important to find ways to alleviate this healthcare burden for both caregivers and those affected, for example, by developing pain assessment tools that are closely aligned with these needs. The following section will therefore describe the complexity of pain in old age to derive the need for specific assessment strategies.

Aging is a highly individual experience, as is pain in old age. Pain in older adults is often accompanied and influenced by a variety of unique age-related factors that include physiological (e.g., loss of strength and muscle), cognitive (e.g., changes in neural structures), and psychological changes (e.g., depression) (Lin et al., 2022; Van Der Leeuw et al., 2016; Zis et al., 2017). In addition, risk factors such as genetics, gender, and ethnicity further individualize both the experience of pain and the prevalence of pain-related conditions (Keogh et al., 2024; Krupić et al., 2018; Zorina-Lichtenwalter et al., 2016).

While studies suggest that maintaining an active lifestyle and engaging in cultural activities might benefit pain management (LaRowe et al., 2023; Miki et al., 2024), pain remains one of the most prevalent and debilitating health problems among older adults. According to the WHO (2022), musculoskeletal disorders are the biggest contributor to disability worldwide and account for a substantial proportion of the global burden of conditions in people aged 60 and over.

Furthermore, chronic pain is often accompanied by physical, emotional, and social challenges that impair quality of life and increase healthcare needs (WHO, 2024). In contrast to chronic pain, as defined in the previous chapter, *acute pain* is usually associated with a specific cause, such as an injury or surgery, and usually disappears once the underlying cause has healed (International Association for the Study of Pain, n.d.).

Pain conditions come with a variety of physiological and psychological challenges that can lead to serious life impairments for those affected. These include, for instance, social withdrawal due to impaired mobility, depression, sleep disturbances, and increased risk of falls (Cai et al.,

2021; Karos et al., 2018; Mathias et al., 2018). In addition, multimorbidity makes the lives of those affected by pain conditions more difficult.

Multimorbidity is defined as the presence of two or more long-term health conditions (National Institute for Health and Care Excellence, 2016). In individuals with chronic pain, this may involve co-occurring chronic health conditions such as low back pain combined with chronic gastritis, hyperuricemia/gout, cardiac insufficiency, neuropathies, or depression – comorbidities that have been associated with increased pain intensity (Scherer et al., 2016). Hence, the presence of multimorbidity complicates pain management further, as overlapping conditions can mask or worsen pain-related symptoms. In this light, individuals with chronic pain have a higher prevalence of comorbidities and are up to four times more likely to experience multimorbidity compared to matched controls (Foley et al., 2021).

Despite the clinical relevance of pain in aging populations, pain assessment and treatment are often hindered by a combination of factors. Organizationally, high workload demand among nursing staff limits time for individual pain assessments (e.g., Deldar et al., 2018; Kaasalainen et al., 2007). At the patient level, individuals with cognitive impairment (CI) come with specificities in pain expression. Especially in individuals with dementia, the ability to verbal self-report pain may be limited and, in later stages, often disappears altogether (Buffum et al., 2007).

This highlights a dilemma: Although older adults – and especially those with dementia – are at high risk for pain conditions, they are also the group most likely to experience pain underdiagnosis and undertreatment (Achterberg et al., 2020, 2021). This gap in patient-centered pain assessment highlights the need for more user-friendly approaches that consider individual factors and address the needs of those affected.

1.2.2 Pain Communication in Dementia

One major group experiencing difficulty expressing their pain verbally is those affected by dementia. In order to understand the challenges of assessing pain in this population, it is important to consider the nature of dementia and how dementia can impact communication abilities. According to the International Classification of Diseases for Mortality and Morbidity Statistics (ICD-11), *dementia* is characterized by an impairment of two or more cognitive domains (attention, executive functions, language, memory, psychomotor speed, social perception and judgment, visuoperceptual or visuospatial abilities). The observed impairment

is expected to be atypical for a person's age and should therefore lead to a subjective impairment of the affected individual (World Health Organization, 2025).

In dementia, progressive CI is commonly accompanied by a decline in communication abilities, affecting both speech and comprehension (Parisot, 1988). As their ability to verbally express pain declines, the risk of not recognizing pain increases (Achterberg et al., 2021). When the illness progresses, individuals may no longer be able to verbalize their pain experience, making traditional self-report tools, which are considered the "gold standard" in pain assessment (Kang & Demiris, 2018), more difficult to use. In advanced stages or when hospitalized, individuals may not be able to use verbal skills at all to locate or describe their pain, making traditional assessment tools completely unusable.

To understand the discrepancy between earlier assumptions of reduced pain sensitivity and more recent findings of heightened pain responses in individuals with dementia, it is useful to revisit the perspectives that shaped early findings. Earlier findings have suggested that individuals with AD may experience reduced pain intensity. This was based on the assumption that neuropathological changes in limbic brain areas restrict pain processing as a result of the disease (e.g., Scherder et al., 1999).

However, recent findings challenge this assumption, highlighting that pain responses were actually increased in individuals with dementia compared to healthy control participants, as observed via facial expressions (Beach et al., 2017; Kunz et al., 2007), neuronal activation (Cole et al., 2006), or nociceptive responses (Kunz et al., 2009). Hence, these recent findings illustrate that facial expressions can accurately convey internal pain states in individuals with dementia. Interestingly, dementia is frequently associated with increased facial expressivity due to changes in prefrontal areas, specifically a decrease in gray matter volume in the medial orbitofrontal cortex and the anterior cingulate cortex (Bunk et al., 2021). One consequence is a decline in executive function, or a loss of inhibitory control mechanisms, which likely contributes to a reduced ability to inhibit pain. As a result, facial expressions of pain may become more pronounced and more visible to others, suggesting that they can provide valuable diagnostic information for classifying pain, especially when verbal communication is no longer possible.

Therefore, the following sections outline the usefulness of various non-verbal indicators of pain that have been proposed for pain description by research and are currently being tested or used in clinical practice.

1.2.3 Indicators of Pain in Dementia

Facial Expression

One established method for assessing pain non-verbally are facial expressions, which can be coded using the Facial Action Coding System (FACS; Ekman & Friesen, 1978), which enables certified observers to manually code facial expressions, also known as Action Units (AUs). Key AUs associated with pain responses include (Ekman & Friesen, 1978; Kunz et al., 2007):

- AU4 (Brow Lowerer – muscles: *Corrugator supercilii*, *Depressor supercilii*)
- AUs6/7 (Cheek Raiser/Lid Tightener – muscles: *Orbicularis oculi*, *pars orbitalis*/*Orbicularis oculi*, *pars palpebralis*)
- AUs9/10 (Nose Wrinkler/Upper Lip Raiser – muscles: *Levator labii superioris alaeque nasi*, *Levator labii superioris*)
- AUs25/26/27 (Lips Part/Jaw Drop/Mouth Stretch – muscles: *Depressor labii inferioris*, relaxation of *Mentalis*, *Orbicularis oris*/*Masseter*, relaxed *Temporali Raisers* and *Internal pterygoid*/*Pterygoids*, *Digastric*)

Because these expressions can be observed even in the most advanced stages of dementia (Atee et al., 2022), FACS coding offers a valuable non-verbal indicator of pain in individuals with limited verbal abilities.

In practice, FACS coding is performed manually by certified coders, often using software tools such as The Observer XT or Mangold Interact (Mangold International GmbH, n.d.; Noldus Information Technology BV, n.d.). However, this process is very time-consuming, with manual coding requiring about 100 minutes of real time to re-code facial expressions for 1 minute of video material (Cohn et al., 2007), making the implementation of FACS particularly suitable for experimental contexts, while application in clinical practice remains limited.

By contrast, clinical practice often relies on less detailed, more feasible observational pain assessment tools in everyday care. As patients' ability to communicate declines, these tools

enable trained healthcare professionals to observe and assess pain. Several standardized pain assessment tools exist that are specifically designed for use with individuals with dementia.

Prominent examples include the Checklist of Nonverbal Pain Indicators (CNPI; Feldt, 2000), the DOLOPLUS 2 Scale (Lefebvre-Chapiro, 2001), the Pain Assessment in Advanced Dementia scale (PAINAD; Fry & Elliott, 2018), the Mobilization–Observation–Behaviour–Intensity–Dementia (MOBID-2; Husebo et al., 2010), and the PAIC15 (Kunz et al., 2020).

These tools aim to identify pain through observable behavioral descriptors, such as facial expressions, vocalizations, and body movements. The PAIC15 (Kunz et al., 2020) and its shortened version (PAIC6) focus on systematizing potentially painful situations. For example, the PAIC15 includes items such as "Frowning: lowering and drawing the brows together," "Narrowing eyes: narrowed eyes with tension around the eyes," and "Opening mouth: lips parted, jaw dropped" to capture facial expressions of pain.

Despite their widespread clinical use and recognition, observer-based instruments face certain limitations. One such limitation is that observer ratings are subject to individual interpretation. This should be prevented by providing training and regularly analyzing inter-rater reliability to detect rater deviations. In addition, the time demands on clinical staff make application difficult (Burns and McIlfatrick 2015; Knopp-Sihota, Dirk, and Rachor 2019; Minaya-Freire et al. 2020), highlighting the need for time-efficient, user-friendly tools. Given these limitations, there is a growing interest in complementary or alternative approaches that rely less on subjective interpretation and, in the best case, can even be interpreted automatically.

Therefore, advanced technologies designed to enable automated facial analysis are becoming increasingly accessible. For instance, recent projects such as the Pain Face Reader (Otto-Friedrich-Universität Bamberg, n.d.) aim to advance automated facial coding through machine learning (ML), to improve objectivity and efficiency in clinical pain recognition. Similar approaches explore the use of AI-based facial analysis for pain assessment. While tools such as the Electronic Pain Assessment Tool (ePAT; Atee et al., 2017) and PainChek® (Brett & Severn, 2023) are specifically developed for clinical use in individuals with dementia, other software, such as FaceReader (Noldus Information Technology, 2023) and OpenFace (Baltrusaitis et al.,

2016), offer general automated facial coding. These latter tools are increasingly used in research to explore nonverbal expressions of pain.

However, automated systems designed to detect facial expressions of pain also have certain limitations. While applicability via mobile applications is significantly facilitated, automatic coding shows only moderate matches with manually coded faces, especially with older people. For example, FaceReader7 reached a sensitivity of around 36% in detecting pain-relevant facial expressions (Lautenbacher et al., 2022). This lack of agreement could be due to the fact that AU detection algorithms are usually trained with the faces of young individuals, which may reduce performance when applied to aged individuals (Lautenbacher et al., 2022). In addition, automated facial recognition systems often lack validation in clinical settings, which are characterized by disruptive influences such as poor lighting, masks, and the face being obscured by nursing activities or patients. In contrast, corresponding algorithms are frequently trained under highly standardized conditions with high-resolution cameras, suitable angles, and lighting (see Asgarian et al., 2019), which is rarely achieved in nursing settings. These factors underscore the importance of further training and testing existing algorithms under real-world conditions.

Taken together, facial expressivity in response to pain often remains relatively intact or is even heightened in individuals with dementia. It can be interpreted for pain description via manual coding (FACS), automatic coding (algorithms), or observer-based tools. This dissertation includes facial expressions assessed via an observer-based tool as well as via FACS coding to describe pain assessment approaches evaluated across different populations and settings. Before outlining how these assessment methods were collected, the following sections will first describe additional behavioral indicators of pain that can be considered in assessments.

Body Movement

Body movement is an important behavioral descriptor of pain and is commonly included in observer-based pain assessment tools, particularly for individuals with CI. Well-known instruments are, for example, PAINAD, MOBID-2, and the PAIC15 operationalized behavior-descriptive items (Fry & Elliott, 2018; Husebo et al., 2010; Kunz et al., 2020). In individuals with CI, commonly reported movement-related indicators of pain include restlessness (agitation), rubbing, guarding, and rigidity, particularly in response to pain-provoking activities such as transfers, walking, or personal care procedures (Strand et al., 2019). In this dissertation, movement-related pain behaviors were assessed exclusively by using observer-based tools (i.e.,

the PAIC). Specifically, the PAIC15 includes items such as "Rubbing: tugging or massaging affected area" and "Freezing: stiffening, avoiding movement, holding breath," which are frequently observed in both clinical and experimental studies and serve as a valuable indicator for the presence of pain in individuals with limited cognitive ability (Kunz et al., 2020).

Due to reduced executive functioning, individuals with dementia may experience movement-related pain behaviors more frequently and with greater intensity. As Kunz et al. (2015) demonstrated, executive functioning is the strongest predictor of pain responsiveness. By definition, *executive functions* include higher-order cognitive processes such as attention regulation, behavioral inhibition, and decision-making (Diamond, 2013). This means that when executive functioning is impaired, as it is in individuals with dementia, they may be less able to inhibit or modulate pain-related movements, such as turning toward the source of the pain.

In addition to observer-based tools, several quantitative approaches have been suggested to enable body movement-based pain description. One such method is actigraphy, which measures human activity and rest cycles and was originally developed to be used in sleep research (Littner et al., 2003). Guu et al. (2024) showed high practicability and reliability of wrist-worn actigraphy devices in monitoring agitation states in patients with late-stage AD, suggesting their potential utility in the assessment of pain. In addition, they demonstrated that patients wore the actigraphy watch with high levels of compliance. Similarly, a review by Torres-Guzman et al. (2024) highlights the utility of actigraphy data to describe movement-based patterns associated with chronic pain, such as higher pain intensity associated with lower physical activity.

Although, to our knowledge, actigraphy data has not yet been systematically used for pain prediction in dementia, correlations between activity patterns measured by actigraphy and behavioral symptoms such as agitation have been well established (e.g., Knuff et al., 2019). Nevertheless, it should be noted that actigraphy is only capable of capturing certain movement and sleep patterns, as also emphasized by Torres-Guzman et al. (2024). However, it does not provide information about the underlying cause of these patterns, or specify whether they are pain-related, nor does it allow for an interpretation of pain intensity.

In addition to wearable technologies, body movements can be described manually by using standardized coding systems. For example, the Body Action and Posture Coding System (BAP; Dael et al., 2012) allows the description of body movements on an anatomical (direction and orientation) and functional (communicative and self-regulatory functions) level. Specifically, the BAP allows the categorization of postural and movement features such as tension, rigidity,

hand movements towards the pain, and guarding, which have been linked to the experience of pain (Viseux et al., 2022; Walsh et al., 2014). However, while the BAP has been successfully used to analyze non-verbal pain behavior in other contexts (e.g., Walsh et al., 2014), to our knowledge, there are no systematic descriptions of pain in individuals with CI or dementia using the BAP.

Furthermore, home systems are available that enable behavior monitoring that can potentially be utilized for pain description. For example, smart floor technologies have been described to characterize movements in individuals with dementia. Systems like the intelligent sensor floor (Smart Floor), which is used in the Bamberg Living Lab Dementia (BamLiD; University of Bamberg, n.d.), or the SensFloor® (Monge et al., 2023), utilize embedded capacitive sensors to monitor movement and detect changes in gait parameters such as speed, step length, and gait symmetry. Nevertheless, the use of these systems to describe pain remains limited, as systems only describe general movement patterns, without directly linking them to pain.

Overall, body movements are commonly used in observer-based pain assessment scales, particularly in dementia care. However, a standardized, fine-grained interpretation of pain-related movement patterns – for example, using frameworks like the BAP – is still lacking. More advanced methods for analyzing body movement, such as smart floor technologies, are currently only accessible within research settings and are able to describe general movement patterns. There is a pressing need to build a bridge between clinical applications and scientific tools. One way to achieve this is by developing user-friendly mobile applications that can detect pain-related body movements, as has already been done in the field of facial action analysis (e.g., Brett & Severn, 2023). However, until standardized coding systems and sensor technologies are validated, observer-based assessment tools are the best approach for describing body movements associated with pain, as they were used in this dissertation.

Vocal Expression

Vocalization is considered a core domain in many observer-based pain assessment instruments (e.g., PAIC15, PAINAD; Fry & Elliott, 2018; Kunz et al., 2020). These tools typically focus on explicit pain-related expressions (e.g., “ouch”, “aua”), moaning, groaning, or crying.

Experimentally, vocal expressions of pain can be analyzed using software such as ProsodyPro (Xu, 2013), which helps to describe prosodic features (intonation and speech melody). For example, Misiewicz et al. (2018) showed that the emotional voice is altered in individuals with

dementia, especially the voice prosody. While these parameters have shown potential in differentiating pain from non-pain vocalizations in healthy populations (e.g., Lautenbacher et al., 2017), their application in individuals with dementia remains largely exploratory. To date, no validated reference framework exists that systematically links prosodic features to pain states in individuals with CI. Hence, current research, including the BamLiD project (Universität Bamberg, n.d.), aims to investigate whether vocal parameters can serve as indicators of pain in individuals with limited verbal communication abilities.

Overall, although prosodic features seem promising for describing pain, observer assessment of vocalizations remains the clinically proven method for using vocalization as an indicator of pain. Therefore, this dissertation exclusively used an observer-based description to assess vocalizations as indicators of pain.

Autonomic Indicators

In addition to behavioral descriptors of pain, the use of autonomic nervous system (ANS) responses to describe pain has been proposed (Cowen et al., 2015). ANS parameters include, for example, heart rate variability (HRV), heart rate (HR), and electrodermal activity (EDA). These markers are driven autonomously and reflect sympathetic and parasympathetic activation (Berntson et al. 1997; Kreibig, 2010), which makes them particularly interesting for describing pain in populations with limited verbal abilities, such as individuals with dementia.

ANS activation during pain has been extensively studied in healthy adults, and to a lesser extent, in clinical populations. Particularly, meta-analyses indicate reduced parasympathetic activation during pain stimulation in healthy adults, as reflected by decreased HRV (e.g., Forte et al., 2022; Koenig et al., 2014). This means that HRV was able to predict the experimentally induced pain stimulation in these findings. Furthermore, Forte et al. (2022) found an association between subjective pain reports and ANS activity, suggesting that self-report and autonomic responses of pain align in healthy adults.

However, findings remain less consistent in individuals with dementia. For example, Rainero et al. (2000) demonstrated that, although stronger pain stimuli elicited similar autonomic responses (heart rate and systolic blood pressure) in individuals with Alzheimer's disease (AD) as in healthy controls, individuals with AD showed weaker responses to mild pain stimuli. These findings highlight that the interpretability of ANS responses in individuals with AD might be limited. In particular, AD signals in this population appear to be less sensitive to pain

stimuli. For the interpretation of such stimuli, this could mean that ANS signals could lead to an underestimation of pain in individuals with AD.

Notably, to date, very few studies have directly investigated HRV responses to pain stimulation in individuals with dementia. This research gap is most likely due to altered autonomic responsiveness in individuals with dementia, which makes interpreting autonomic responses as indicators of pain particularly challenging. In fact, several studies highlight that individuals with dementia commonly suffer from parasympathetic dysregulation. A meta-analysis by Cheng et al. (2022), for example, found that individuals with dementia had significantly lower resting HRV values than healthy controls. Similarly, in a recent review article, Arakaki et al. (2023) state that impaired heart-brain communication plays a role in neurocognitive diseases such as dementia, whereby abnormal changes of HRV (i.e., decreased vagal functioning) can indicate dysregulation. For this dissertation, it was therefore particularly relevant to include individuals with CI and to further investigate their autonomic response to pain.

Furthermore, many studies investigating cognition and pain, especially in the context of acute pain, have been conducted in standardized laboratory settings (see Khera & Rangasamy, 2021). However, little is known about how autonomic responses affect acute pain experienced during everyday activities. Interestingly, a promising starting point in this field of research is wearable technologies for physiological monitoring (e.g., smart watches), which offer perspectives for pain assessment in daily care. Yet, despite providing a theoretical framework for implementing indicators of pain in wearable technologies, clinical implementation is still in its early stages. A recent pilot study by Snene et al. (2024), with N=10, evaluated the feasibility of an AI-supported wearable sensor to detect pain in older individuals using physiological signals such as EDA, skin temperature, and mobility. The results indicate that these signals show potential for pain detection, although further research is required to validate their clinical applicability in larger samples.

In recent years, there has been growing interest in collecting large data sets to create a foundation for developing ML models for pain classification. A well-known dataset is, for example, the BioVid Heat Pain Database conducted by Walter et al. (2013). This database contains various datasets, including skin conductance level (SCL), electrocardiogram (ECG), electromyogram (EMG), and electroencephalography (EEG) data, as well as facial expression videos from 90 healthy participants during heat pain stimulation.

Based on this dataset, Pouromran et al. (2021) developed several ML models to predict pain intensity by extracting features from EDA, ECG, and EMG signals. Of these, EDA features were most promising for estimating pain intensity. Another example for ML-based classification of pain is the PainMeter project (Albahdal et al., 2024), which tested an ML model using EDA, ECG, and EMG data and achieved a pain classification accuracy of up to 87%.

Overall, the current findings highlight the potential and limitations of interpreting autonomic responses as indicators of pain, especially since these are highly dependent on individual factors such as cognitive functioning. While HRV, EDA, and ECG data have shown potential as indicators of pain in healthy adults, their application to individuals with CI and dementia remains limited.

Given these findings, it becomes clear that interpreting pain responses, particularly autonomic responses to pain, in individuals with CI requires a deeper understanding of the individual factors that influence the interpretability of pain markers. The following section will therefore further explore the theoretical basis for using autonomic responses for assessing pain in this population.

1.2.4 Theoretical Basis for Using Autonomic Responses in Pain Assessment

In individuals with CI or dementia, interpreting non-verbal responses – particularly autonomic signals – is complex because autonomic change may reflect not only nociceptive processes but also individual factors (e.g., age, cognition) or emotional processes.

In this context, the *Neurovisceral Integration Model* (NIM) by Thayer and Lane (2000, 2009) describes a theoretical framework that helps to interpret autonomic responses in the context of pain. According to the model, there is an interconnection between autonomic, affective, and cognitive systems via a shared neural network known as the *central autonomic network* (CAN; Benarroch, 1993). Key structures of the CAN include the dorsal anterior cingulate cortex (dACC), the periaqueductal gray (PAG), and the insula (Benarroch, 1993), all of which are involved in autonomic regulation and pain processing (Hohenschurz-Schmidt et al., 2020). Based on these shared neuronal structures, Hohenschurz-Schmidt et al. (2020) proposed a bidirectional interaction between pain processing and the ANS, as they observed a correlation between low-frequency HRV and the functional connectivity of the dACC and PAG during

pain stimulation. Based on these considerations, the NIM may be useful for guiding the interpretation of autonomic responses as indicators of pain, especially in individuals with CI.

Thus, the model is frequently used to explain the connection between HRV and emotional and cognitive flexibility, as higher HRV values are associated with stronger top-down control and more emotional and cognitive flexibility (Thayer et al., 2012). Related research emphasizes the role of executive functions (higher-order cognitive processes) in pain modulation. For example, in individuals with chronic pain, preserved executive functioning could be linked to better coping mechanisms, as indicated in pain interference and life control (Berginström et al., 2024). In addition, Kunz et al. (2015) demonstrated that among various cognitive domains, executive functioning best predicted pain responsiveness, even after controlling for general cognitive performance, suggesting that intact executive functioning can be associated with higher pain coping ability. Accordingly, cognitive processes should be considered when interpreting autonomic responses in the context of pain, particularly to ensure the application of these assessment methods in populations with CI.

Interestingly, HRV is the referenced indicator in this framework due to its strong association with parasympathetic (vagal) arousal. Yet, other autonomic responses, such as HR and EDA, are also modulated by prefrontal and limbic brain regions, including the insula, medial prefrontal cortex (PFC), and anterior cingulate cortex (Critchley, 2002; Oppenheimer et al., 1992). However, HRV has been consistently associated with top-down cognitive control due to its vagal activation pathway (Thayer et al., 2012). In contrast, HR and EDA cannot be attributed to vagal control (Martini et al., 2003; Visnovcova et al., 2013). On this theoretical basis, the assessment of HRV in pain contexts may provide valuable insights into the pain regulation capacity.

Particularly, findings may be especially relevant for individuals with mild levels of cognitive decline. During these, communication abilities may not yet be affected, while prefrontal processes could already be altered (Wu et al., 2024), potentially resulting in autonomic dysregulation. Specifically, autonomic dysregulation could occur earlier than verbal limitations, meaning changes in HRV or EDA might not only reflect pain responses but also alterations in cognition. This highlights that cognition should be considered as an important individual factor when interpreting autonomic responses to pain, especially in individuals with

CI of mild severity. Accordingly, this dissertation investigated how with mild levels of CI may influence the interpretability of autonomic responses to pain.

Now, before describing the methodological framework of this dissertation, the following section will explore how age-related factors can further modulate the interpretability of indicators of pain.

1.2.5 The Impact of Age on Indicators of Pain

In addition to cognition, age might influence the interpretation of non-verbal indicators of pain further. Hence, research has shown that both human raters and automatic facial recognition systems tend to interpret neutral expressions in older faces more slowly and less accurately than in younger faces (Freudenberg et al., 2015). Freudenberg et al. (2015), therefore, conclude that facial wrinkles can bias our interpretation of facial perception in older adults. Similarly, findings by Hess et al. (2012) indicate that wrinkles in older adults can reduce "signal clarity" as the same underlying emotion in older adults is described less specifically than in younger adults by human raters.

Although age-related physiological changes such as wrinkles might affect facial perception in general, empirical findings rarely indicate age-related effects on pain. For instance, Kunz et al. (2008) found that young and elderly participants did not differ in their frequency of facial responses during noxious mechanical and electrical stimulations. Similarly, Atee et al. (2017) observed that facial expressions of pain in individuals with dementia did not vary with age. Both findings suggest that despite age-related changes in facial appearance, pain-related facial expressions may remain reliably interpretable even in higher ages.

Therefore, for this dissertation, we decided to focus primarily on assessing age-related changes in autonomic responses to pain. Autonomic responses such as HRV and EDA, in particular, demonstrate a clearly reduced reactivity with higher age (Uchino et al., 2010). This makes their interpretation in older age challenging, as it becomes difficult to distinguish whether autonomic responses are due to age-related autonomic changes or actual pain experience.

Taken together, this dissertation examines how individual factors, namely age and cognition, influence the interpretability of autonomic responses to pain. The following section outlines the methodological framework that forms the foundation for the studies in this dissertation.

1.2.5 Integrating Multiple Indicators of Pain

Following the general concept of *multimodal diagnostics*, which refers to the structured combination of multiple data sources and assessment methods to increase diagnostic validity (Baumann & Stieglitz, 2008), this dissertation describes *multimodal pain assessment* as the structured combination of different sources of information and measurement methods to evaluate pain.

Over the past decade, the concept of multimodal pain assessment has gained increasing attention. In this context, the *Multimodal Assessment Model of Pain* (MAP; Wideman et al., 2019) was proposed as a theoretical framework that highlights the necessity of multidimensional pain assessment through qualitative (e.g., words and behaviors) and quantitative (e.g., self- and non-self-reported) measurements.

Although the model has not yet been described in the context of CI or dementia, the same principle is used in various clinical applications to describe pain in these conditions; for example, through the combination of diverse qualitative and quantitative indicators of pain (e.g., facial expressions, vocalizations, and body movements) (Kunz et al., 2007; Strand et al., 2019).

While the MAP emphasizes that self-reports of pain should be the main factor in pain assessment in healthy adults, an equivalent approach for individuals with limited verbal ability could be to combine qualitative, observer-based descriptions with quantitative indicators (e.g., autonomic responses).

Therefore, as part of this dissertation, self-reported pain was collected in Studies 2 and 3, which involved participants with preserved verbal abilities. Here, self-reports of pain were combined with behavioral and autonomic data. By contrast, Study 1 relied solely on observer-based descriptions of pain, since verbal ability could be limited due to CI.

To build on these theoretical considerations and ensure terminological clarity and conceptual consistency, this dissertation defines three key domains of pain assessment:

- *Behavioral indicators* include observable non-verbal expressions of pain. These cover facial expressions, vocalizations, and body movements, which are assessed through systems such as observer-based tools (e.g., PAIC15) or structured coding systems (e.g., FACS coding, BAP coding).
- *Autonomic responses* refer to physiological signals reflecting the activity of the ANS. For this dissertation, we conducted HRV, HR, and EDA responses.
- *Self-reports of pain* involve a subjective description of pain experience by those affected. In this dissertation, these include standardized questions, such as "Choose a number from 0 to 10 that best describes your pain" (see Rodriguez, 2001).

In addition, *individual factors* – such as cognition and age – were considered essential for interpreting autonomic responses to pain. While not a main domain of pain assessment, individual factors provide a crucial background for the interpretation of pain responses.

A pain assessment approach that incorporates these domains is especially relevant in populations with dementia, when diagnostics are difficult, for example, due to limited verbal ability and multimorbidity, which can mask possible underlying mechanisms (Buffum et al., 2007; Horgas et al., 2023).

Although no comprehensive guide to multimodal pain assessment in individuals with CI exists to date, the American Geriatrics Society (AGS; Connelly, 1998) provides a recommendation for assessing pain in this population. Specifically, pain assessments should include the six behavioral domains of pain: namely, facial expressions, vocalizations, body movements, changes in interpersonal interactions, changes in activity patterns or routines, and changes in mental status.

These domains have formed the basis for numerous observer-based tools, including the PAIC15, DoloPlus2, and MOBID-2 (Husebo et al., 2010; Kunz et al., 2020; Lefebvre-Chapiro, 2001), as well as semi-automated systems such as ePAT (Atee et al., 2017).

Building on this foundation, this dissertation focuses on three main *behavioral indicators* of pain: facial expression, vocalization, and body movement. These three domains were selected due to their high relevance in existing clinical tools, their diagnostic value in research with CI, and their observational feasibility (see Kunz et al., 2020).

Other behavioral domains, such as interpersonal interactions, were not considered further because they are more difficult to standardize for immediate pain assessment and typically require patient records.

In sum, this dissertation combines behavioral indicators, autonomic responses, and self-reports to describe pain, which allows for a systematic description of pain while further considering individual factors (cognition and age). The following section describes how this theoretical indicator framework was applied to a setting close to everyday life to increase the practical application of the findings.

1.2.6 Ecological Validity and Living Lab Approach

Pain research has frequently been conducted in standardized laboratory settings. In these settings, pain is typically induced via standardized stimulation protocols, such as thermal or pressure stimuli. For individuals with CI, especially those with dementia, these forms of presentation impose demands, such as sitting still and paying sustained attention for an extended period, that often exceed their abilities. Additionally, ecological validity is limited under such conditions.

To address these limitations, Studies 2 and 3 of this dissertation were conducted in a Living Lab environment. *Living Labs* (LLs) are defined as environments that resemble real-life conditions for experimental use and include the active involvement of participants, commonly involving multiple stakeholders in an organized and collaborative innovation process (Schuurman, 2015). Hence, LLs aim to combine standardized research settings with conditions of everyday life, while exploring a broad spectrum of research questions, ranging from quality of life, well-being, and cognition to autonomy, social integration, and even diagnostics (Figueiredo et al., 2024).

In this context, this dissertation used an LL environment to examine behavioral and autonomic responses to pain during motor challenges (e.g., lifting a box or a kettlebell) and activities of daily living (ADLs; e.g., moving around in bed or walking). As multi-sensor environments, LLs are designed to capture natural behavior, which makes them particularly valuable for research in populations with CI who may become overwhelmed more quickly in classic laboratory environments.

The furnishings and layout of LLs vary greatly – from environments that include several living areas – such as bedrooms, bathrooms, dressing rooms, living rooms, and kitchens – to more purpose-specific rooms.

A recent review identified 15 LL concepts aimed at exploring aiding solutions for individuals with dementia or CI, most of them in Europe (Figueiredo et al., 2024). For example, the Bremen Ambient Assisted Living Lab (Universität Bremen, n.d.) in Germany or the LUSAGE Gerontechnology lab (Pino et al., 2013) in France are equipped as multi-room environments to test assistive technologies under real-life conditions.

In contexts where physical LLs are not available, alternatives include hospital-like care environments or the use of virtual reality to simulate realistic settings that can be adapted flexibly and cost-effectively (Figueiredo et al., 2024).

The BamLiD (University of Bamberg, n.d.) is one such environment in which Studies 2 and 3 of this dissertation were conducted. The BamLiD provides a sensor-equipped room that allows continuous recording of behavioral and autonomic data during, for example, motor challenges (e.g., box and kettlebell lift) or ADLs (e.g., movements in bed or walking). It integrates data sources such as video recordings (for motion analysis and facial expressions), ECG (e.g., HRV and EDA), and motion tracking (smart floor and actigraphy).

By combining controlled stimulation protocols with real-world tasks, research in LL environments is able to capture a more nuanced and realistic representation of pain experiences. This supports the assumption that the home-like environment promotes more natural behavior and reduces the reactivity typically observed in artificial laboratory settings (Verloo et al., 2021). This combination of ecological relevance and methodological control allowed for a more accurate understanding of pain behavior, especially in the context of older adults with and without CI.

Taken together, LL approaches can increase the ecological validity of study outcomes while assessing pain in a highly standardized, technological environment. Integrating the recording of pain responses into these environments enabled more comprehensive observation of behaviors for this dissertation. The goal was to use these observations to inform the development of adaptable pain assessment strategies for real-world environments.

Considering this, Table 1 provides an overview of the assessment domains, study settings, and sample characteristics incorporated in this dissertation. The following section describes the overall aim of this dissertation.

Table 1

Overview of assessment domains, study settings, and sample characteristics

Study	Behavioral Responses	Autonomic Responses	Self-report Responses	Setting	Cognitive Group	Age *M* (*SD*)	Female %
Study 1 (*N*=309)	Pain Assessment in Impaired Cognition (PAIC15)	–	–	Geriatric ward and nursing home	Healthy and CI	Sample 1: 87.10 (7.89) Sample 2: 85.33 (7.50)	Sample 1: 86% Sample 2: 62%
Study 2 (*N*=43)	FACS coded Facial Expressions	HRV HR EDA	NRS pain and exertion ratings	Living lab	Healthy	24.41 (3.20)	49%
Study 3 (*N*=101)	–	HRV HR EDA	NRS pain and exertion ratings	Living lab	Healthy and CI	78.70 (6.40)	53%

Note. CI = Cognitive impairment. NRS = Numerical rating scale. PAIC15 = Pain Assessment in Impaired Cognition (Kunz et al., 2020). HRV = Heart rate variability. HR = Heart rate. EDA = Electrodermal activity.

Study 1 was conducted in a geriatric ward and a nursing home. It involved pain assessments based on observations, which were collected by partners in these settings. Studies 2 and 3 were conducted in a multi-sensor Living Lab environment. CI in Study 3 was defined based on CERAD total score (Consortium to Establish a Registry for Alzheimer's Disease) and MMSE performance (MMSE; Chandler et al., 2005; Folstein et al., 1975), differentiating between subgroups with and without CI.

1.3 Aims of this Dissertation

The current state of research, as described in the previous sections, has mostly assessed behavioral indicators, autonomic responses, and self-reports of pain separately, typically in a standardized laboratory setting. However, there is currently no systematic approach that combines these indicators of pain while accounting for relevant individual factors, such as age and cognition.

This research gap is particularly important for evaluating pain when verbal expression is limited. Current methodological approaches underscore the necessity of advancing pain assessment methods. Multimodal assessment methods, which integrate behavioral, autonomic, and self-report responses, are a promising way to capture pain responses beyond verbal self-report.

Therefore, this dissertation aims to improve the assessment of pain by evaluating the usefulness of behavioral indicators, autonomic responses, and self-reported pain in relation to individual factors such as age and cognition, in ecologically valid settings. The following main question is derived from this aim:

- How can pain be assessed in an ecologically valid and clinically feasible way using behavioral, autonomic, and self-report indicators across different age and cognitive ability levels?

To address this main question, three studies were conducted:

Study 1 (*N*=309) focused on behavioral indicators of pain in older adults (65+) with none to severe CI, recruited from a geriatric ward and a nursing home. Unlike Studies 2 and 3, Study 1 was based on data from cooperation partners in Berlin and the Netherlands, whereby the data were further processed for evaluation and interpretation as part of this dissertation. Therefore, cooperation partners collected observer ratings of facial expressions, body movements, and vocalizations using the PAIC15 in a geriatric ward and a nursing home. Study 1 aimed to develop and validate the PAIC6, a short-form observer assessment of pain designed to improve clinical feasibility, all while preserving psychometric quality.

Study 2 (*N*=43) focused on assessing behavioral indicators of pain (assessed via FACS coding), autonomic responses (HRV, HR, and EDA), and self-reports of pain in young healthy adults.

The study examined the influence of muscle pre-activation (induced with an aging suit) on pain responses.

Study 3 (*N*=101) investigated autonomic responses (HRV, HR, and EDA) and self-reports of pain in an older population (65+), including individuals with and without CI. The study was conducted with the aim of investigating the predictive value of cognitive status, phase (rest vs. activity), and age on autonomic and self-reported responses to pain.

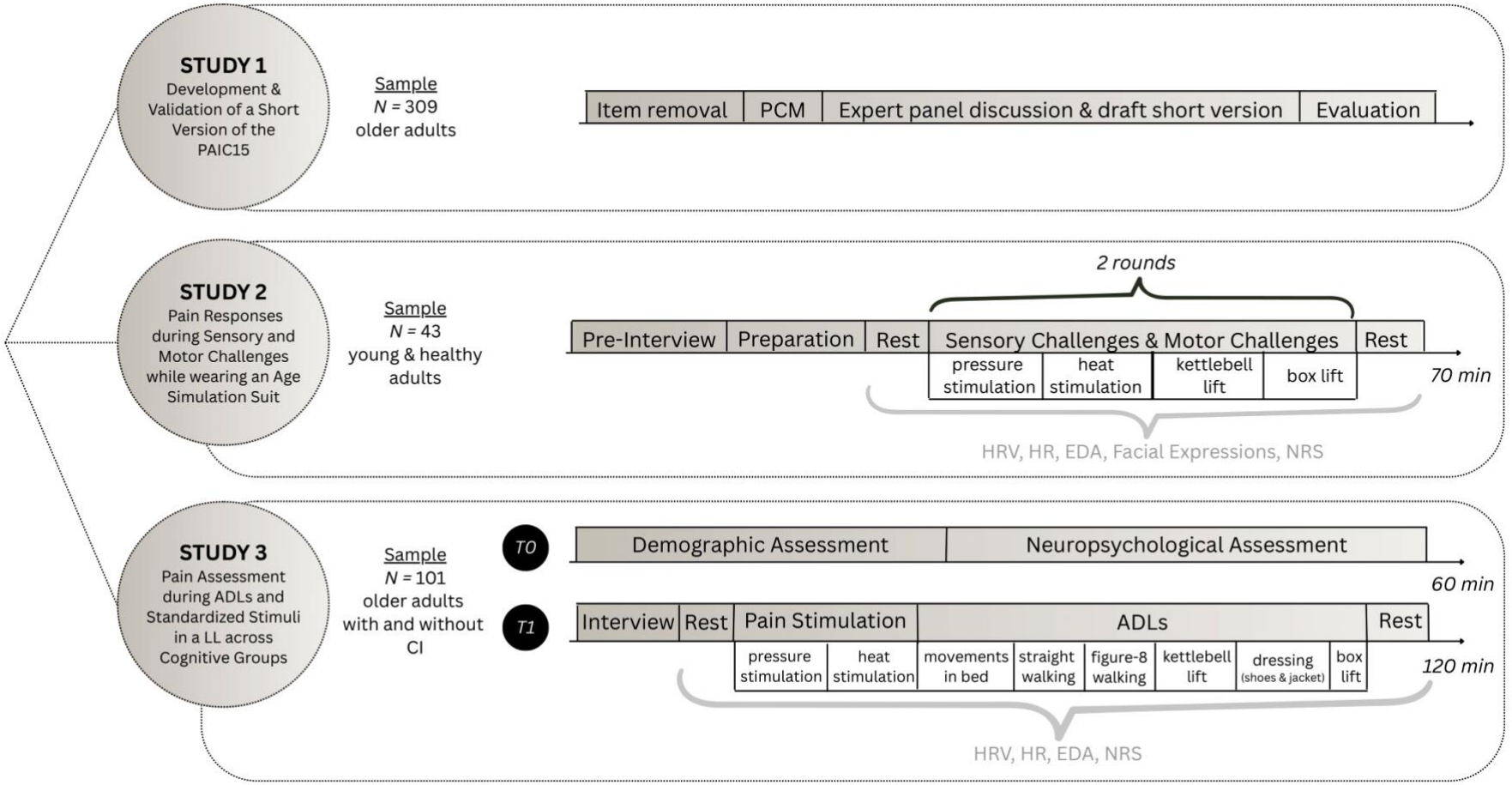
While Study 1 was conducted in a geriatric ward and a nursing home, Studies 2 and 3 were conducted in an LL environment. Specifically, the studies conducted for this dissertation aim to answer these three further research questions:

- How can observer-based pain assessment tools be optimized with clinical usability in mind? (*Study 1*)
- How do behavioral and autonomic indicators of pain respond during experimental pain and motor challenges, and how does muscle pre-activation (induced by an age simulation suit) affect these responses? (*Study 2*)
- Can autonomic responses serve as reliable indicators of pain perception in older adults with and without CI, and how do individual factors (i.e., age and cognitive status) affect the interpretation of autonomic responses as indicators of pain? (*Study 3*)

Figure 1 on the following page illustrates the study procedures for the three studies that were conducted for this dissertation. Following, the subsequent chapter presents the design, methodology, and results of these studies, beginning with Study 1 – “Development and Validation of a Short Version (PAIC6) of the Pain Assessment in Impaired Cognition Scale.”

Figure 1

Schematic representation of the study procedure



Note. PAIC15 = Pain Assessment in Impaired Cognition (Kunz et al., 2020). PCM = Partial Credit Model. CI = Cognitive impairment. ADLs = Activities of daily living. HR = Heart rate. HRV = Heart rate variability. EDA = Electrodermal activity. NRS = Numerical rating scale. LL = Living Lab. T0 = time point 0 (first measurement). T1 = time point 1 (second measurement). Study 1 describes the development of a shortened version of the PAIC15. Study 2 involved experimental sensory and motor challenges with healthy young adults. Study 3 focused on older adults with and without CI during standardized pain stimulation and naturalistic ADLs. Data for Study 1 were collected in a geriatric ward and a nursing home. Studies 2 and 3 were conducted in a sensor-equipped Living Lab environment.

Chapter 2

Development and Validation of a Short Version (PAIC6) of the Pain Assessment in Impaired Cognition Scale

Study 1 – This study has been published:

Schreiber, V., Kunz, M., Achterberg, W., Van der Steen, J. T., Lobbezoo, F., Langner, B. & Lautenbacher, S. (2025). Development and Validation of a Short Version (PAIC6) of the Pain Assessment in Impaired Cognition Scale. *European Journal Of Pain*, *29*(3), e4795. https://doi.org/10.1002/ejp.4795

(Except the reference list, which is included in the full list of references at the end of this dissertation.)

Abstract

Background: Observer pain scales are commonly used to assess pain in individuals with impaired cognition. However, nursing staff have highlighted that extremely tight time schedules and increasing workload demands prevent regular use. With the development of a short version of the Pain Assessment in Impaired Cognition (PAIC15), we aimed to reduce implementation barriers in everyday clinical practice.

Methods: We developed a new 6-item short version (PAIC6) in a first sample (N=59) and validated its psychometric properties in a second sample (N=250) of older individuals with cognitive impairments. The item reduction and evaluation involved four steps. First, we used Sample 1 to exclude items based on item quality statistics (e.g., difficulty, reliability). Second, the Partial Credit Model (PCM) was utilized for further reduction using again Sample 1. Third, an expert panel evaluated the preceding steps and suggested a draft short version with six items (PAIC6). Fourth, psychometric properties of the short version were evaluated in the independent Sample 2. Thereafter, the final short version was approved.

Results: The new PAIC6 showed a high correlation with the total scale PAIC15 (r=0.870), good reliability (Cronbach's α=0.684), and high convergent construct validity, as observed by a high correlation with the established Pain Assessment in Advanced Dementia (r=0.602).

Conclusions: Overall, we developed a valid, reliable, and clinically valuable PAIC6 that allows a more time-efficient pain assessment, by reducing the assessment time from 5min to approximately 2min (60% time saving). Significance: Observer pain scales are commonly used to assess pain in individuals with impaired cognition. However, nursing staff have highlighted that extremely tight time schedules and increasing workload demands prevent regular use. To address this, we developed PAIC6, a short version of the Pain Assessment in Impaired Cognition 15 (PAIC15). PAIC6 includes six items and takes 2min for completion after training, realising a 60%-time reduction compared to the original scale while keeping the psychometric quality high.

Keywords: dementia | impaired cognition | PAIC15 | pain assessment | short scale

2.1 Introduction

Observer assessment is the commonly used method for diagnosing and assessing pain in individuals with impaired cognition when self-report starts to fail (Achterberg et al. 2013, 2020; Herr, Zwakhalen, and Swafford 2017). However, despite their clinical effectiveness in these persons (Chow et al. 2016; Hadjistavropoulos et al. 2014), time constrains are often highlighted by nurses as major barrier for implementation of observational pain assessment tools into daily routine (Burns and McIlfatrick 2015; Knopp-Sihota, Dirk, and Rachor 2019; Minaya-Freire et al. 2020). The various observational pain assessment tools differ regarding the necessary observation time, that is, how long a patient should be observed, and the scoring time, that is, how long it takes to fill in the scores. Most tools take between 1 and 8min for observation and 2–5min for scoring (Felton et al. 2021; McGuire et al. 2016). These time differences are partly due to differences in item complexity, observation difficulty, rating systems (see, Chow et al. 2016; Lints-Martindale et al. 2012) and most importantly due to the number of items included. The observer scale 'Pain Assessment in Impaired Cognition 15' (PAIC15; Kunz et al. 2020) designed by a European initiative as an internationally agreed-upon meta-tool consists of 15 items found to be best possible amongst 12 established observer scales (Corbett et al. 2014). Therefore, its clinical applicability and handiness would also benefit from a scale shortening. Given that the PAIC15 scale was developed with a pragmatic focus (easy handling, simple items, clear content coverage) (Kunz et al. 2020), reducing the number of items could be dared without losing psychometric quality. In the present form, approximately 5min are required for observation and scoring the PAIC15. Consequently, with a reduction to 5–10 items, we anticipated a time reduction from 5 to 2–3min. Successful shortening should still allow for covering all three key domains of pain assessment, namely "facial expression", "body movements", and "vocalisation" as recommended (Husebo et al. 2012; Lints-Martindale et al. 2012; AGS: The Management of Chronic Pain in Older Persons 1998). Further, we aimed to reach a minimum item reduction of 50% in order to achieve noticeable timesaving. We employed a four-step approach for scale shortening and evaluation. Step 1 involved computing classical item statistics for each item as a pre-selection of psychometric favourable items. In Step 2 we implemented the Partial Credit Model (PCM), only using the remaining items from Step 1. The PCM allows for identifying and removing items with low discriminative power, which are items that cannot effectively differentiate the latent variable (pain intensity) (Tennant and Conaghan 2007). In Step 3 we formed an expert panel with a multi-professional background to evaluate the statistical item selection in Steps 1 and 2, mainly in terms of

comprehensibility, user-friendliness, and applicability of the remaining items in everyday care. In Step 4, we evaluated the draft short version in a second independent large sample to validate the psychometric quality of the draft short version and to end with a final short version.

2.2 Methods

The complete development of a short version out of PAIC 15 consisted of two parts: (1) analyses for item reduction were conducted to form a draft short version using the data of Sample 1, and (2) this draft short version was evaluated using the data of the independent Sample 2, to come up with a final short version.

2.2.1 Participants

Sample 1 (*N*=59 with 51 females; age: *M*=87.10; *SD*=7.89; range=66–102) was recruited from a geriatric ward of a hospital and a nursing home in Berlin: Malteser-hospital Berlin Charlottenburg and the nursing home Malta, respectively. Sample size was based on a posteriori power analysis (GPower) based on the Partial Credit Model and using the noncentral chisquared distribution while expecting large effect sizes, given that all items of the PAIC15 have already undergone critical item selection. This part of the study was initiated as a cooperative project between the Berlin institutions and the University of Bamberg. Data collection took place from April to August 2020 in Berlin. Most participants were tested in the morning. Participants received their usual medication before the observer assessment of pain. To determine the cognitive status as well as functional disability of the participants, the Global Deterioration Scale (GDS; Reisberg et al. 1982) and Barthel Index BI (Mahoney and Barthel 1965) were assessed, but outside of the pain assessment session. The GDS was used to assess the severity of dementia, while the BI assessed the ability to perform activities of daily living. Participant provided written informed consent prior to their participation. The study protocol was approved by the ethics committee at the Otto-Friedrich University of Bamberg, as the study was conducted as a collaborative project between the hospital and nursing home in Berlin and the University of Bamberg. Sample 2 consisted of 250 participants (156 females; age: *M*=85.33; *SD*=7.50; range=65–108). Participants were recruited in the Netherlands from several nursing homes' locked wards with 24/7 oversight. In these departments, most individuals have a clinical diagnosis of dementia. The GDS was used to assess the severity of dementia. Excluded were participants with a life expectancy shorter than 1 week. In Sample 2, a family member or legal representative in most of the cases, especially in those with severe dementia, provided written

informed consent. In some cases, this was done together with the participant, if possible, while in other cases, the family member or representative provided consent on behalf of the participant alone. A more detailed description of the data collection process can be found elsewhere (van der Steen, Waal, and Achterberg 2021). This study protocol was approved by the Medical Ethics Review Committee of the Leiden University Medical Center.

2.2.2 Material and Protocol

Protocol

Sample 1. Two nurses conducted the observational pain assessment; applying the PAIC 15 first followed by another observational pain scale, namely the DoloPlus2 (Lefebvre-Chapiro 2001) with a maximum total duration of 15 min per observation. The DoloPlus2 was the scale that had already been implemented for some time and that the nurses were familiar with from its regular use in everyday care. Although the nurses did not have much experience with the PAIC15, the e-training (https://paic15.com/en/e-training-en/) made it possible to train the nurses quickly and reliably to keep the assessment quality consistently high for both scales1. Each participant was observed during rest (e.g., sitting in a chair while watching TV), and during mobilisation (e.g., transfer in bed and getting up, walking, and getting dressed in the morning). Given that pain is more likely to occur during mobilisation, we focused on the PAIC15 scores assessed during this condition for further analyses. Both nurses were simultaneously present and filled in the PAIC15 independently. The Rasch Partial Credit Model (PCM) favours scoring of a single person as a starting point because the model claims that responses are ordinal and reflect individual performance or ability. The combination of two raters can violate this assumption, as the computation of mean values generates artificial values. We ultimately chose to use Rater A's ratings. Upon reviewing the ratings, it became clear that Rater A provided more differential and graded assessments compared to Rater B. To further illustrate this, we first compared internal consistency and inter-item correlations for both raters. The internal consistency was particularly high for Rater B (Cronbach's α=0.932), which is often interpreted as redundancy or lower discriminatory ability of the items (Taber 2018). In contrast, Rater A showed well-balanced ratings, with satisfactory internal consistency (Cronbach's α=0.871), indicating a more differential and graded scoring of the items. When comparing the inter-item correlations, Rater B showed especially high inter-item correlations (mean Rater A = 0.38 and mean Rater B = 0.47, difference between raters: $t(163) = -3.58$, $p < 0.001$), indicating a stronger overlap and a lower differentiation ability of the ratings by Rater B. Thus,

Rater B showed less differential and graded assessment, potentially missing finer behaviour distinctions.

Global Deterioration Scale (GDS; Reisberg et al. 1982). The GDS is used to assess cognitive functioning in patients with primary degenerative dementia. It divides dementia into seven severity levels from without cognitive decline (stage 1) to very severe cognitive decline (stage 7). The GDS has good test–retest reliability (Gottlieb, Gur, and Gur 1988) and a high external validity (Mavioglu et al. 2006; Moreno 2003; Reisberg et al. 1982). The GDS was assessed outside of the pain assessment session as part of a general cognitive assessment in everyday clinical care. In Sample 1 the GDS was filled out in German and in Sample 2 in Dutch.

Barthel Index (BI; Mahoney and Barthel 1965). The BI assesses functional impairments of geriatric populations to estimate their care needs in everyday life. It consists of 10 activities of daily living (ADL) that are scored with two points (0 or 5; e.g. bathing), three points (0, 5 or 10; e.g. toilet use) or four points (0, 5, 10 or 15; e.g. transfers). The final total score can reach a maximum of 100. The BI shows good reliability: Cronbach's α=0.94 (dos Santos Barros et al. 2022). The Barthel index (sum score) was only assessed in Sample 1, conducted in German, prior to the pain assessment session.

Sample 2. The observational pain assessments were conducted by physicians or trained staff members and started with the assessment of Pain Assessment in Advanced Dementia (PAINAD), followed by the evaluation by the PAIC15. The physicians could hand over the assessment to staff members if an introduction to the observations was given beforehand. In this sample, observational pain assessment was only conducted during resting conditions, given that the severe cognitive and functional limitations in this sample did not allow for mobilisation of all patients and pain became sufficiently detectable already in this resting condition.

Observational Pain Assessment

Pain Assessment in Impaired Cognition (PAIC15; Kunz et al. 2020). (Assessed in Sample 1 and 2). The PAIC15 is a 15-item observer scale administered by trained healthcare professionals to assess pain in patients with impaired cognition. It consists of three sub-scales: facial expression, body movements, and vocalisation. The items (e.g., facial expression: “Frowning—lowering and drawing brows together”; body movements: “Freezing—stiffening, avoiding movement, holding breath” and vocalisation: “Shouting—using a loud voice to express words”) are recorded on a 4-point scale. The raters were trained by successfully

completing the 30-min PAIC 15 e-training (https://paic15.com/en/e-training-en/). In the training, items are explained by video examples, and PAIC15 scoring is practiced by training videos, including expert feedback. The PAIC15 shows very high inter-rater reliability for all three scales (Cohen's kappa for facial expression: 0.91, vocalisation: 0.93, and body movement: 0.92; Kappesser et al. 2020). The PAIC15 has been translated into 11 languages. In Sample 1, the PAIC15 was used in German; in Sample 2, in Dutch.

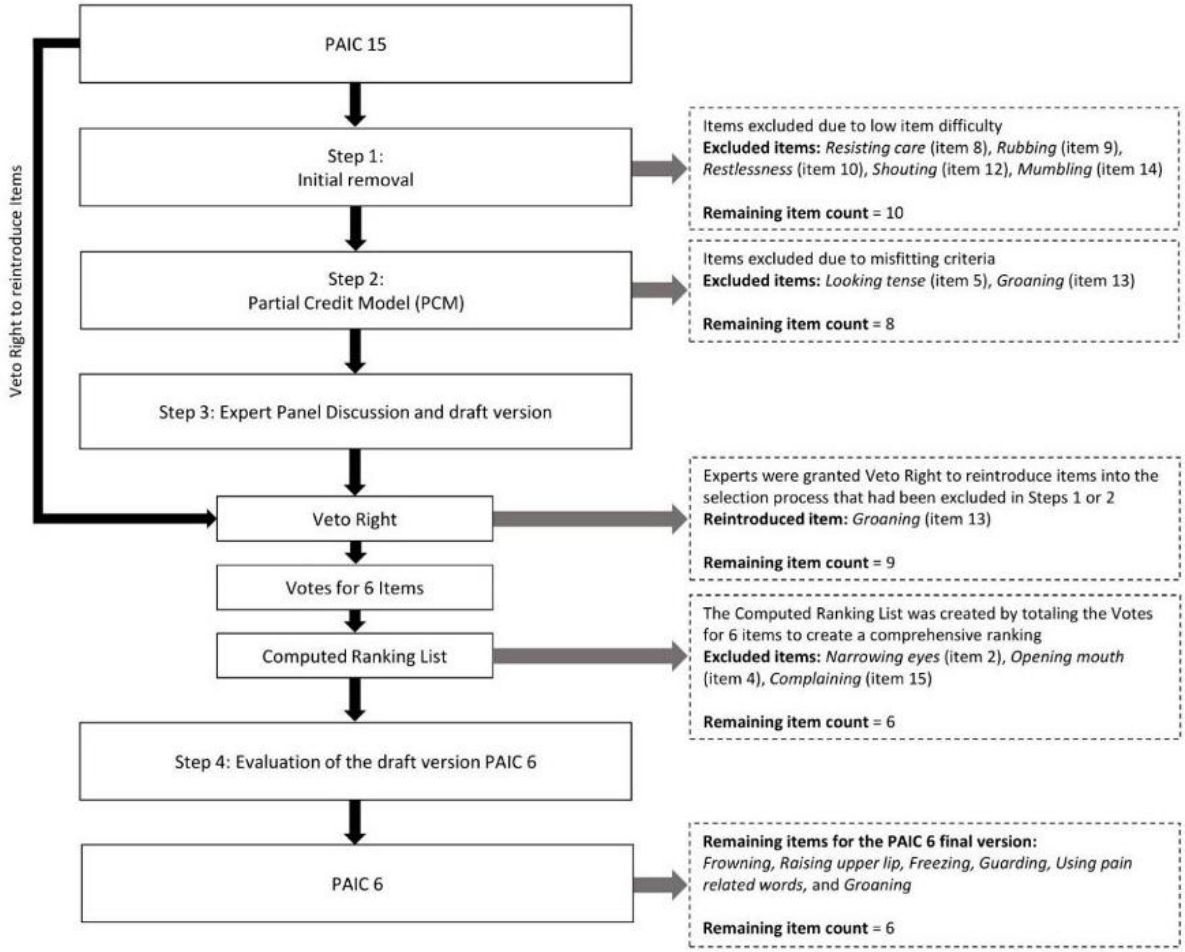
Pain Assessment in Advanced Dementia (PAINAD; Warden, Hurley, and Volicer 2003). (Assessed in Sample 2). The PAINAD is a well-established observer pain behaviour assessment and consists of five categories of potential pain behaviour: breathing, negative vocalisation, facial expression, body language, and controllability; rated in three categories from 0 (*normal*) to 2 (*very noticeable*). The PAINAD is recommended for pain assessment in individuals with dementia, as it covers the first three AGS domains ("facial expression," "body movements," and "vocalisation"), has high validity, especially in terms of agreement with self-reported pain, and strong test-rest reliability (Herr, Zwakhalen, and Swafford 2017; Lints-Martindale et al. 2012). The PAINAD overall demonstrates good reliability: Cronbach's α=0.80 (Fry and Elliott 2018). The total score can reach from 0 to 10. The PAINAD was applied in Sample 2 in Dutch and used to calculate the convergent construct validity (correlation of the new PAIC short version with an established pain indicator also assessed by the PAINAD).

2.2.3 Data Analysis

The data were analysed using descriptive and inferential statistics to evaluate the current item pool and to identify items eligible for a short version. Statistical analyses were performed using R version 4.2.2 (2022-10-31 ucrt) in RStudio version 2022.07.2+576, open-sourced under an AGLP v3 licence. PCM analysis was performed using the eRm R package (Mair, Hatzinger, and Maier 2021; Mair and Hatzinger 2007). The significance criterion alpha for all tests was 0.05. For Sample 1, the PAIC15 during mobilisation was used, as this dataset had an optimal distribution of item scores for scale shortening. In Sample 2, the participants were more severely impaired, allowing only for assessment of the PAIC15 at rest. Already in the rest condition, pain reached levels, which were sufficient to observe and score non-verbal pain responses in sample 2. The item reduction to a draft short version and the evaluation of this draft short version to finalise the short scale took place in four steps (see also Figure 2).

Figure 2

Overview of the steps used to develop the short version PAIC6 out of PAIC15



Note. In Step 1 we used item statistics (psychometric analyses) to exclude items. In Step 2 we applied the Partial Credit Model (PCM) reduction approach for the remaining items. In Step 3 an Expert Panel had the task of reviewing the item selection. In Step 4 we evaluated the draft short version further. In the end, six items remained for the PAIC6 final version.

2.2.4 Step 1: Initial Removal

We started in Step 1 as a pre-selection of psychometric favourable items with an examination of the original 15 items of PAIC15 using several established tests highlighting items with psychometric high quality. Thus, this step was based on item statistics that are described as useful criteria for item reduction (Goetz et al. 2013): item difficulty, item correlation with the total score, scale reliability when an item is excluded, and missing values. Item difficulty is measured from 0 to 1, where high values indicate that an item was frequently scored ("easy") whereas low values indicate infrequent scoring ("difficult"; Sim and Rasiah 2006). Based on

the PAIC15 development approach (Kunz et al. 2020), items with difficulties 0.90 were considered too easy or too difficult and were therefore excluded.

Item representativeness for the total PAIC15 score was evaluated by the correlation of every item score with the total score (item-total correlation). The established criterion for excluding items was $r<0.4$ (Erhart et al. 2010). Next, we considered how the reliability of the total scale changed when individual items were excluded. Cronbach's α was used, with values ≥ 0.70 being considered an indication of good internal consistency (Bland and Altman 1997; DeVellis and Thorpe 2022). We excluded items that lowered the scale's reliability. Items with more than 50% missing values were excluded, as in this case difficulties in observing the associated behaviour and in completing the evaluation can be assumed. The criteria were considered one after the other, excluding all items that met at least one of these exclusion criteria.

2.2.5 Step 2: Partial Credit Model

The Partial Credit Model (PCM; Masters 1982) was used as an additional finer filtering process following the preselection of items in Step 1. As a generalisation of the dichotomous Rasch model, the PCM offers an interpretation-free exclusion method based on fixed criteria for purely statistical scale reduction, a method successfully implemented in previous studies (see Cantó-Cerdán et al. 2021; Hamilton et al. 2021; van Nispen tot Pannerden et al. 2009). The PCM allows consideration of underlying measurement constructs as it provides an estimate of latent variables by establishing a model across all individuals based on the given item responses. The latent variable was in our case the intensity of pain experience. The model thus makes it possible to identify items with too low discriminative power (Tennant and Conaghan 2007). The exclusion of items by the PCM had one restriction, namely that each of the three key domains of pain behaviours (“facial expression,” “body movements,” and “vocalisation”) was still represented with at least two items. To interpret the PCM model fit, we analysed commonly used PCM statistics (Pesudovs et al. 2007; Smith, McCarthy, and Anderson 2000; Tennant and Conaghan 2007). The item that was excluded first met the most misfit criteria during iteration:

1. Item-trait interaction: The chi-square statistic evaluates the fit between the expected and observed item structure, with a non-significant p-value ($\alpha>0.05$) indicating a satisfactory model fit (Hamilton et al. 2021).
2. Item infit and outfit mean square error term (MSQ): We calculated the MSQ for an item to determine whether an item corresponds to the linear function. Infit and outfit mean

squares between 0.70 and 1.30 indicate a good model fit (Pesudovs et al. 2007). While values below 0.70 indicate possible item redundancy, values above 1.30 indicate a deviation from the measurement construct of the overall scale (Pesudovs et al. 2007).

3. Standardised infit static: Items with a highly negative standardised infit static (less than −2) were excluded since item redundancy must be assumed in this case (Beaton, Wright, and Katz 2005).
4. Separation index: The separation index was calculated, which serves as a reliability descriptor. Acceptable values, indicating good reliability, are >0.80 for person separation reliability and >0.90 for item separation reliability (Cantó-Cerdán et al. 2021). Further details on the calculation and interpretation basis can be found in Mair and Hatzinger (2007).

2.2.6 Step 3: Expert Panel Discussion and Draft Short Version

An expert panel was formed to select the best possible items in terms of comprehensibility, user-friendliness, and applicability (see Figure 2) based on the statistical pre-selection in step 1 and 2. Six experts from a multi-professional background all dealing with care, management, or research in aged individuals or persons with dementia participated: physician (n=1), dentist (n=1), geriatric nurses (n=2), and psychologists (n=2). The experts were given a veto right to indicate whether an item excluded during step 1 and 2 was indispensable. In this case, a consensus discussion was started until general agreement and a possible re-introduction of the item. Thereafter, we asked the experts to vote for those six items amongst the remaining items after step 1 and 2 they wanted to be included in a shortened PAIC. That the experts should vote for six items was based on our aim that the PAIC short version should comprise not more than six items to achieve considerable time reduction. We summed up the votes for each item and computed a ranking list. The six items ranking highest were selected for the draft short PAIC version.

2.2.7 Step 4: Evaluation of the Draft Short Version

For the evaluation of the draft short version, we used an independent Sample 2 as methodological guidelines recommend (Goetz et al. 2013; Hinkin 1998; Smith, McCarthy, and Anderson 2000). We computed the correlation of the draft short version with the PAIC15 (scale-total correlation) and the internal consistency using Cronbach's α. To examine convergent construct validity, we calculated the correlation of the draft short version with the Pain Assessment in Advanced Dementia scale (PAINAD; Warden, Hurley, and Volicer 2003).

2.3 Results

Descriptive characteristics of both samples are displayed in Table 2. Both samples are comparable with regard to age. However, the degree of cognitive impairment (GDS) was more pronounced in the Dutch Sample 2 than in the German Sample 1. Functional impairments amongst participants were assessed only in Sample 1 using the Barthel Index. Most participants reached moderate to severe dependency scores. PAIC15 scores were comparable between samples. Given that a PAIC score of ≥3 has been suggested to indicate pain (van der Steen, Waal, and Achterberg 2021), average PAIC15 scores indicated the presence of pain in both samples.

Table 2

Descriptive characteristics of Sample 1 and Sample 2

	Sample 1		Sample 2	
N	59		250	
Age in years (mean (SD))	87.10	(7.89)	85.33	(7.50)
Sex (females/ males)	51/8		156/94	
Cognitive decline, GDS (*N* (%))[a]				
None (level 1)	14	(8)	0	(0)
Very mild (level 2)	17	(10)	1	(0)
Mild (level 3)	9	(5)	4	(2)
Moderate (level 4)	9	(5)	22	(9)
Moderate severe (level 5)	7	(4)	67	(27)
Severe (level 6)	3	(2)	117	(47)
Very severe (level 7)	0	(0)	39	(16)
Functional dependency, BI (*N* (%))[b]				
Non–mild (BI: 91–100)	5	(8)	-	
Moderate– severe (BI: 21–90)	51	(86)	-	
Total dependency (BI: 0–20)	3	(5)	-	
PAIC15 (mean (SD))[c]	4.85	(4.78)	4.53	(5.00)

[a] GDS (Global Deterioration Scale).

[b] BI (Barthel Index).

[c] PAIC15 (Pain Assessment in Impaired Cognition Scale). – indicates that BI was not observed in Sample 2.

2.3.1 Step 1: Initial Removal

Table 3 shows the results of the item analysis which served as first selection to find psychometric favourable items. We excluded five items due to an item difficulty below 0.10: Resisting care (item 8), Rubbing (item 9), Restlessness (item 10), Shouting (item 12), and Mumbling (item 14); that is, these items were scored very infrequently. All remaining 10 items showed acceptable item-total correlations between 0.45 and 0.76. No item was excluded when considering the reliability when the item was dropped, that is, no item would have increased the overall scale reliability (Cronbach's α) by its exclusion. Only Mumbling (item 14) had missing values, although these are negligible at 1.69%. Thus, after Step 1 10 items remained (see Figure 2): All five items of the facial expression scale remained, as well as Freezing (item

6) and Guarding 7 (item 7) of the body movements scale and Using pain-related words (item 11), Groaning (item 13), and Complaining (item 15) of the vocalisation scale. The internal consistency of the remaining 10 items was high (Cronbach's α=0.888).

Table 3

Item Analysis of all 15 items of the Pain Assessment in Impaired Cognition (PAIC 15) scale (Sample 1)

PAIC items		Missings	Mean	SD	Item difficulty[a]	Item-total correlation[b]	α if deleted[c]
Facial Expression							
1	Frowning	0.00%	0.51	0.68	0.25	0.73	0.85
2	Narrowing eyes	0.00%	0.46	0.73	0.23	0.68	0.86
3	Raising upper lip	0.00%	0.32	0.51	0.16	0.64	0.86
4	Opening mouth	0.00%	0.93	0.64	0.47	0.58	0.86
5	Looking tense	0.00%	0.78	0.79	0.39	0.76	0.85
Body Movements							
6	Freezing	0.00%	0.44	0.60	0.22	0.74	0.85
7	Guarding	0.00%	0.44	0.68	0.22	0.70	0.86
8	Resisting care	0.00%	0.00	0.00	-	-	0.88
9	Rubbing	0.00%	0.02	0.13	0.02	0.46	0.87
10	Restlessness	0.00%	0.02	0.13	0.02	0.46	0.87
Vocalisation							
11	Using pain-related words	0.00%	0.32	0.65	0.16	0.74	0.85
12	Shouting	0.00%	0.00	0.00	-	-	0.88
13	Groaning	0.00%	0.32	0.65	0.11	0.45	0.87
14	Mumbling	1.69%	0.09	0.28	0.09	0.39	0.87
15	Complaining	0.00%	0.20	0.48	0.10	0.76	0.85

Note. Sample 1 was used. Total scale Cronbach's α=0.871.

[a] Refers to the probability of an item being rated high or low.

[b] Item-total correlation corrected for item overlap and scale reliability.

[c] Cronbach's α if an item is deleted. — indicates item score >1 was not observed, therefore item difficulty and item-total correlation could not be calculated. Excluded items are highlighted in grey.

2.3.2 Step 2: Partial Credit Model

The Partial Credit Model (PCM; Masters 1982) was used as an additional finer filtering process following the preselection of items in Step 1. Table 4 shows the fit statistics for three iterations of the PCM that we calculated. It is important to note that further iterations would computationally have been possible. However, we set the predefined criteria to stop with further iterations when each of the three key domains of pain behaviours ("facial expression," "body movements," and "vocalisation") was no longer represented by at least two items. We excluded one misfitting item after each iteration. The initial 10 items had outfit mean square values between 0.44 and 1.84 and infit mean square values between 0.61 and 1.51, where infit and outfit mean squares between 0.70 and 1.30 indicate a good model fit. Z-standardised values ranged for infit mean square between −2.36 and 1.67, where highly negative standardised infit static (>−2) indicates item redundancy (Beaton, Wright, and Katz 2005). First, after iteration 1, Looking Tense (item 5) was excluded because it met most misfitting criteria (outfit and infit MSQ 1.30). Third, after iteration 3, Complaining (item 15) exhibited a lower-than-desired MSQ (outfit=0.39 and infit=0.62), which indicates the possibility of item redundancy (Linacre 2002). In addition, Freezing (item 6) and using pain related words (item 11) showed a slightly lower-than desired outfit MSQ (item 6 outfit MSQ=0.65 and item 11 outfit MSQ=0.56). Considering that item redundancy can never be completely avoided, we opted to keep item 15 as well as items 6 and 11 to meet our criterion of representing the three AGS-recommended pain assessment domains ("facial expression," "body movements," and "vocalisation") with at least two corresponding items. The calculation of PCM was thus completed. The item selection after Step 2 reduced the item pool by two items and left eight items over (see Figure 2): Frowning (item 1), Narrowing eyes (item 2), Raising upper lip (item 3), and Opening mouth (item 4) of the facial expression scale, as well as Freezing (item 6) and Guarding (item 7) of the body movements scale, and using pain-related words (item 11) and Complaining (item 15) of the vocalisation scale. The internal consistency of the remaining eight items was high (Cronbach's α=0.868.

Table 4

Partial Credit Model (PCM): Iterations 1 to 3 (Sample 1)

PAIC items		Chisq	DF	p	outfit MSQ	infit MSQ	outfit Z	infit Z
Iteration 1								
Facial expression								
1	Frowning	50.50	50	.454	0.99	0.89	0.06	-0.48
2	Narrowing eyes	40.53	50	.828	0.79	0.96	-0.38	-0.09
3	Raising upper lip	37.14	50	.911	0.73	0.83	-0.75	-0.80
4	Opening mouth	52.99	50	.360	1.04	1.01	0.26	0.12
5	Looking tense	27.02	50	.997	0.53	0.61	-2.43	-2.36
Body movements								
6	Freezing	35.93	50	.933	0.70	0.81	-1.13	-0.98
7	Guarding	45.48	50	.655	0.89	1.05	-0.19	0.32
Vocalisation								
11	Using pain related words	30.76	50	.985	0.60	1.06	-0.50	0.29
13	Groaning	93.65	50	< .001	1.84	1.51	1.46	1.67
15	Complaining	22.49	50	1.000	0.44	0.70	-0.80	-1.03
Iteration 2								
Facial Expression								
1	Frowning	51.78	50	.404	1.01	0.90	0.14	-0.43
2	Narrowing eyes	42.71	50	.758	0.84	0.99	-0.30	0.05
3	Raising upper lip	38.04	50	.892	0.75	0.85	-0.78	-0.71
4	Opening mouth	44.37	50	.698	0.87	0.87	-0.64	-0.71
Body movements								
6	Freezing	33.48	50	.965	0.66	0.77	-1.49	-1.21
7	Guarding	41.18	50	.808	0.81	0.96	-0.51	-0.09
Vocalisation								
11	Using pain related words	24.29	50	.999	0.48	0.91	-0.89	-0.25
13	Groaning	77.43	50	.008	1.52	1.46	1.09	1.53
15	Complaining	19.14	50	1.000	0.38	0.65	-1.13	-1.27
Iteration 3								
Facial Expression								
1	Frowning	50.19	49	.426	1.00	0.91	0.10	-0.41
2	Narrowing eyes	47.22	49	.545	0.94	1.07	-0.00	0.38
3	Raising upper lip	40.47	49	.802	0.81	0.93	-0.55	-0.29
4	Opening mouth	49.62	49	.448	0.99	0.96	0.04	-0.13
Body movements								
6	Freezing	32.42	49	.967	0.65	0.76	-1.56	-1.25
7	Guarding	38.55	49	.858	0.77	0.95	-0.63	-0.16
Vocalisation								
11	Using pain related words	27.82	49	.994	0.56	0.94	-0.69	-0.12
15	Complaining	19.37	49	1.000	0.39	0.62	-1.10	-1.38

Note. Sample 1 was used. Items with a significant chi-square *p*-value were excluded. Items with an infit or outfit MSQ outside the range of 0.70–1.30 were excluded. Items with a highly negative standardised infit static (z-value

>−2) were excluded. Iteration 3: Item 15 was retained despite misfitting criteria to meet our criterion of representing three of the pain assessment domains recommended by the American Geriatrics Society: "facial expression," "body movements," and "vocalisation," each with at least two corresponding items. The separation index for the remaining eight items after the PCM was high (person separation reliability >0.99 and item separation reliability >0.99), indicating high reliability. Excluded items are highlighted in grey.

2.3.3 Step 3: Expert Panel Discussion and Draft Short Version

The expert panel had the task of reviewing the selection process and the remaining items. The experts could veto and reintroduce items, which were already excluded in Step 1 or Step 2 (see Figure 2). The experts reintroduced the item Groaning (item 13) which had been excluded in Step 2 due to misfitting criteria in the PCM that indicated a deviation from the measurement construct of the overall scale and item redundancy. The experts justified their decision by stating that Groaning is an essential component of pain response in the context of cognitive impairment. With the reintroduction of Groaning (item 13), nine items remained: Frowning (item 1), Narrowing eyes (item 2), Raising upper lip (item 3), Opening mouth (item 4), Freezing (item 6), Guarding (item 7), Using pain-related words (item 11), Groaning (item 13) and Complaining (item 15). Now, each expert was asked to vote for six items out of the nine that they deemed indispensable for a shortened version. All six experts unanimously voted for including Freezing (item 6) and using pain-related words (item 11) in the short version (100% expert voting). Frowning (item 1) received five expert votes (83% expert voting) while Raising upper lip (item 3), Guarding (item 7), and Groaning (item 13) each received four expert votes (66% expert voting). Opening mouth (item 4) received two expert votes (33% expert voting). Narrowing eyes (item 2) received one expert vote (17% expert voting). Finally, Complaining (item 15) did not receive any expert votes (0% expert voting). Finally, we totaled the expert votes for each item to create a ranking list and find the six highest ranked items: Using pain-related words (item 11) and Freezing (item 6) (6 votes), Frowning (item 1) (5 votes), Raising upper lip (item 3), Guarding (item 7) and Groaning (item 13) (all 4 votes). With selection of these six items for the draft short version, our criteria of including all three key domains of pain assessment ("facial expression," "body movements," and "vocalisation") and reducing the item number by at least 50% were met. An overview of the item selection is also given in Table 4.

2.3.4 Step 4: Evaluation of the Draft Short Version

The draft version of PAIC6 was evaluated using an independent sample (Sample 2). Sample 2 included a wide range of dementia severities, was unique because of its high number and was—as a multi-center study—representative for senior home residents in the Netherlands. However,

we would have run into major problems if the reliability and other psychometric properties of the PAIC6 deteriorated in Sample 2 along with the severity of the disease. To put this concern to test, we divided Sample 2 into two data sets—2.i with GDS scores less than 6 (early-stage dementia; n=94) and 2.ii with GDS scores greater and equal to 6 (advanced dementia; n=156), likely including non-verbal individuals. For both sub-samples, we were able to demonstrate a high internal consistency (Cronbach's α: 2.i=0.72 and 2.i=0.82). These reliability values are comparable to Sample 1 with a Cronbach's α=0.87. In summary, these data suggests that both subsamples show a similar, very good, internal consistency—indicating the independence of the scale quality in this aspect from the level of dementia deterioration. The mean PAIC6 score of Sample 2 was 1.14 (SD=1.80; range=0–13). The correlation of the draft short version PAIC6 with the PAIC15 total score was high (r(248)=0.830, p<0.001). As a measure of convergent construct validity, we found a high correlation between the draft short version PAIC6 and PAINAD (r(248)=0.602, p<0.001), which is only slightly lower than the correlation between PAIC15 and PAINAD (r(248)=0.763, p<0.001). Only item 13 had missing data of 10%. A large proportion of the items were rated with 0; ranging from 61% (item 1) to 94% (item 7). The draft short version PAIC6 has good reliability (Cronbach's α=0.684). After this final evaluation of the draft short version of PAIC6, we decided to maintain this version. Our final PAIC6 can be found in Figure 3 and includes the following items: *Frowning* and *Raising upper lip* of the facial expression scale, *Freezing* and *Guarding* of the body movements scale as well as *using pain related words* and *Groaning* of the vocalisation scale. This results in a final PAIC6 with a maximum total score of 18, where higher values indicate a higher level of pain.

2.3.5 PAIC6 Cut-Off Values

We aimed to establish a cut-off score for the PAIC6 as has been done for the PAIC15 to indicate when pain is like present. For the PAIC15 a total score of ≥4 has been suggested to indicate "possible pain", while a total score of ≥5 has been suggested to indicate "pain" (van der Steen, Waal, and Achterberg 2021). Accordingly, we tried to establish a cut-off score for the PAIC6. For Sample 2, we observed that 51% of participants were classified as experiencing pain for a PAIC6 total scores>1, aligning with meta-analyses that report pain frequencies of 46%–56% amongst individuals with dementia (Tan et al. 2015; van Kooten et al. 2016). Therefore, we suggest that a PAIC6 total score ≥1 indicate "possible pain", while a total score of ≥2 indicate "pain."

Figure 3

Form for the newly developed PAIC6, using the same layout as for the long version PAIC15 to help former users to quickly become familiar with the new scale

Pain Assessment in Impaired Cognition (PAIC6)

Item	Meaning of items	Not at all	Slight degree	Moderate degree	Great degree	Not scorable
FACIAL EXPRESSION						
Frowning	lowering and drawing brows together	**0**	**1**	**2**	**3**	x
Raising upper lip	upper lip raised, nose may be wrinkled	**0**	**1**	**2**	**3**	x
BODY MOVEMENTS						
Freezing	stiffening, avoiding movement, holding breath	**0**	**1**	**2**	**3**	x
Guarding	protecting affected area, holding body part, avoiding touch, moving away	**0**	**1**	**2**	**3**	x
VOCALIZATION						
Using pain-related words	using pain words, like "ouch", "ow", or "that hurts"	**0**	**1**	**2**	**3**	x
Groaning	making a deep, inarticulate sound	**0**	**1**	**2**	**3**	x
SUM=						

PAIC 6

Pain Assessment in Impaired Cognition

2.5 Discussion

Implementing psychometrically excellent observational pain assessment tools into nursing practice in senior homes is invaluable, given that pain assessment based on self-report becomes more invalid when cognitive impairment accompanies increasing age (Achterberg et al. 2020; Chow et al. 2016; Lukas et al. 2013). However, enormous time pressure and immense workload

of nursing staff, often make observational pain assessments challenging. Shortening available observational pain assessment tools by a few minutes might be critical for more successful implementation. With this study, we aimed to create a short version of the PAIC15 that decreases application time while maintaining its psychometric quality. With our 6- item short version of the PAIC15 (called PAIC6), we achieved a total assessment time reduction from five to approximately 2 min (60% time saving). Furthermore, two major quality criteria were met: (i) the PAIC6 still covers the three main non-verbal domains of pain recommended by the American Geriatric Society (AGS: The Management of Chronic Pain in Older Persons 1998) with two items for "facial expression," "body movements," and "vocalisation" and (ii) item count was reduced by at least half. Maintaining the psychometric quality of the long version is particularly important when creating a short scale. The PAIC15 was initially created not to be the shortest scale possible but rather to ensure extensive coverage of the essential pain dimensions. For that purpose, the best items out of 12 established observational pain scales were selected to create a meta-tool (Corbett et al. 2014; Kunz et al. 2020). Only after this meta-tool had been developed, it was possible to reduce the item count further, creating the short version PAIC6. A high correlation between PAIC15 and PAIC6 total scores was observed, thus, suggesting high agreement between the long and short versions. Moreover, the PAIC6 demonstrated high convergent construct validity as observed by a high correlation with the PAINAD. PAINAD is considered a standard for observational pain assessment in individuals with dementia (Herr, Zwakhalen, and Swafford 2017; Lints-Martindale et al. 2012), with high validity and reliability and significant importance in clinical application (Warden, Hurley, and Volicer 2003). Thus, the high agreement between PAIC6 and PAINAD speaks for a high validity of the PAIC6. We placed a special focus on increasing time efficiency when creating a comprehensive pain screening tool that is applicable for routine use in daily clinical practice. There have been similar attempts to develop a short scale like ours. Van Nispen tot Pannerden et al. (2009) already demonstrated that by shortening the Pain Assessment Checklist for Seniors with Limited Ability to Communicate (PACSLAC) from 60 to 31 items, it was possible to reduce the scoring time by half. Moreover, attempts have been made to shorten the DoloPlus-2; resulting in the Doloshort (Pautex et al. 2007) and the ALGOPLUS (Ratl et al. 2011). Although the Doloshort shows promising psychometric properties (Pautex et al. 2007, 2009), it lacks the inclusion of items referring to the facial expression. The ALGOPLUS (Ratl et al. 2011) was developed specifically as an acute pain assessment tool and is therefore, not applicable to all care situations. Furthermore, neither Doloshort nor ALGOPLUS have yet been included in major guidelines for the assessment of pain in older people, such as the German

(Sirsch et al. 2012) or the UK (Schofield 2018) National Guidelines. Thus, several research groups have attempted to shorten observational scales to assess pain in dementia although the already existing scales are not outstandingly long. Doloplus-2 (Lefebvre-Chapiro 2001), Mahoney Pain Scale (MPS; Mahoney and Peters 2008), Mobilisation-ObservationBehaviour-Intensity-Dementia-2 (MOBID-2; Husebo et al. 2010), and PAINAD, include between 3 and 10 items and usually take 1–5min to complete (Herr, Zwakhalen, and Swafford 2017). The PAIC with 15 items requires about 5min to complete: consisting of 3min of observation time and 2min of scoring time. We assumed that the PAIC items are homogenous and do not differ in their item complexity (i.e., item length), observation difficulty (e.g., motor gestures might be easier to observe than facial expressions), and rating system (e.g., binary ratings or categorical ratings). For note, most PAIC6 items describe respondent (reflex-like) behaviour, which is unlikely to vary substantially over time. Therefore, no item of the PAIC15 should be an outlier in application time. With this assumption, we anticipate a maximum time reduction from 5min (300 s) with 15 items to 1.7min (100 s) with five items; and consequently, a time reduction of approximately 2min (120 s). This accumulation of attempts to develop time efficient observational tools raises the question whether these attempts really meet the needs of the end-users, namely the nursing staff. We would argue "yes", given that prior studies underline that time constraints or "time required for application" are common barriers that hinder nurses to use observational pain assessment tools (Burns and McIlfatrick 2015; Knopp-Sihota, Dirk, and Rachor 2019; Minaya-Freire et al. 2020). One of the present authors (BL), a nurse and nurse supervisor, confirms that caregivers often refrain from using pain assessment scales and prioritise their intuitive expertise, due to a lack of. One difficulty might be that miniaturised tools—even if of best psychometric quality as we tried to develop—may raise scepticism and might be viewed as too concise to be good. Zwakhalen et al. (2006) pointed out this type of scepticism, which must be considered in the phase of implementation. For sure, there are other implementation barriers such as poor workplace conditions (Achterberg et al. 2020), and uncertainty regarding usage (Jonsdottir and Gunnarsson 2021) and interpretation of the scales (Jonsdottir and Gunnarsson 2021; Zwakhalen et al., 2018). However, the lack of time seems to be amongst these most pressing ones. For the present development of the PAIC6, it was unavoidable that participants first filled in PAIC15, from which the six items of the PAIC6 were extracted. Follow-up studies should also directly compare the new complete PAIC6 with the complete PAIC15. Future studies should also validate the PAIC6 for other situational contexts, besides the nursing home context, such as different hospital settings and hospice care. The varying clinical situations encompass variations in patients' mobility, dementia severity, and

patient's ability to communicate and interact. Furthermore, investigating the PAIC6 in different subgroups with other forms of cognitive impairment, like individuals with intellectual disabilities, Huntington's disease Korsakoff's syndrome or Parkinson's disease, is conceivable. Previous studies using the PAIC15 have already shown good applicability in some of these subgroups (Defrin et al. 2021; Kunz et al. 2020; Oudman et al. 2023). For persons, who are already using observational pain assessment tools, other than the PAIC6, the question may arise why they should change the diagnostic instrument. The PAIC15, and its short version PAIC6, offer several advantages: The PAIC15 was developed as a meta-tool that integrates the best items from multiple well-established pain assessment tools, by an international team and is translated into 11 languages. It also offers comprehensive e-training modules for practicing its use efficiently (https://paic15.com/). All advantages of the PAIC15 also apply to the PAIC6. However, despite these advantages, it is of course better to use any of the established observational scales for pain assessment in dementia instead of using none.

2.5.1 Limitations

There are limitations to be mentioned. The Dutch study (Sample 2) assessed the PAIC6 items during rest condition compared to the German study (Sample 1), which used observations during mobilisation. We did that for the following reason. Sample 1 participants were non-frail and required mobilisation to recognisably display pain, while the frail individuals in Sample 2 showed sufficient pain behaviours already at rest. Inspection of the data showed that the two samples neither differed regarding the number of missing data nor regarding the distribution of the items scores. Observational scale developments have often started with non-frail and only slightly cognitively impaired persons because the comparison with the subjective report of pain is of interest. Furthermore, participants were predominantly female. This uneven sex distribution can mainly be attributed to the high prevalence of women living in senior residences. It requires additional studies with a higher percentage of men, exploring the impact of sex on the psychometric qualities and applicability of the PAIC6. Additionally, the studies differed in their construct validation methods: DoloPlus2 was used for Study 1, while PAINAD was used for study 2. However, both tools are widely recommended (McLennan et al. 2024), and as a benefit, we were able to obtain independent information about the construct validity, which corroborated each other.

2.5.2 Conclusion

We developed a valid, reliable, and clinically valuable short form of the PAIC15, namely the PAIC6, which requires only 2min for completion after training, realising a 60%-time reduction compared to the original PAIC15 scale. Thus, this shortened version of a worldwide available observer scale for assessing pain in persons with cognitive impairments considers the significant workload demands in the daily nursing practice, offering timesaving benefits while keeping the psychometric quality high. Future studies should explore the application of PAIC6 in various subgroups (e.g., patients with developmental disabilities, Parkinson's disease) and in other contexts (e.g., hospital settings with post-operative acute care or outpatient care).

Chapter 3

The Effect of Muscle Pre-Activation and Resultant Motor Fatigue on Musculoskeletal Pain

Study 2 – Unpublished manuscript.

3.1 Introduction

Musculoskeletal pain is quite frequent and belongs to the most prevalent types of pain (Cimmino et al., 2011). For most patients with musculoskeletal pain, the pain can affect widespread body areas and occur in multiple anatomical sites. When studying which factors moderate musculoskeletal pain and might be accessible for pain treatment, some researchers have used experimental models to induce musculoskeletal pain (Graven-Nielsen, 2022). Such experimental models have the advantage that the pain stimulus can be specified and standardized, and that frequent comorbidities of musculoskeletal pain (e.g., age, gender, depression, deficient conditioned pain modulation) can be studied in a controlled fashion. The most prominent experimental model used to induce clinically relevant musculoskeletal pain is exercise-induced pain, or delayed onset muscle soreness (DOMS; MacIntyre et al., 1995). DOMS often peaks after 24 to 48 hours after intensive or unfamiliar exercise, and is characterized by soreness, swelling, stiffness, strength loss, and mild to moderate musculoskeletal pain (Lau et al., 2015; Nie et al., 2006). Using DOMS protocols, various factors have been identified that moderate musculoskeletal pain (e.g., pain catastrophizing, depression, sex; Bishop et al., 2011; Dannecker et al., 2003; Niederstrasser et al., 2014).

However, most of the experimental protocols of exercise-induced musculoskeletal pain have focused on regional forms of motor activity, mainly muscle-specific exercises such as presses, pulls, or holds in isometric training (e.g., Koltyn et al., 2014; Naugle et al., 2014; Vaegter et al., 2015, 2017). There have been a few attempts to use DOMS to investigate more widespread pain by protocols with multi-site stimulation (e.g., Niederstrasser et al., 2014). However, they still target specific muscles, resulting in localized soreness at multiple sites after several hours. Protocols that allow musculoskeletal pain to be induced by a more generalized muscle load across the body within minutes are mostly lacking so far. To experimentally produce such widespread and generalized muscle load, we used part of an age simulation suit. These simulation suits allow for a simulation of widespread motor limitations associated with aging, such as mobility limitations, loss of muscle strength, and muscle fatigue (e.g., Bowden et al., 2021; W. L.-S. Cheng et al., 2020; Lavallière et al., 2017). Thus, in contrast to previous studies that primarily targeted single muscle groups to investigate the effect of sustained muscle activation on pain through isometric exercises (Koltyn et al., 2014; Naugle et al., 2014; Vaegter et al., 2015) or cycling (Vaegter et al., 2017), the age simulation suit activates many muscle groups simultaneously (Moll, 2020). Accordingly, we used the musculoskeletal-burdensome

components of the GERonTologic Simulator (GERT; Moll, 2020) to experimentally pre-activate muscles all over the body before the actual pain tests.

To investigate whether and how this sustained muscle pre-activation might impact the pain response system, we chose two different types of pain-inducing challenges: (i) motor challenges and (ii) sensory challenges. First, participants were asked to complete two motor challenges (lifting weights from a shelf and lifting a box, leading to an additional muscle load) that might induce pain related to muscle activation (musculoskeletal pain). Second, pain not related to muscle activation, because experimentally induced by pressure and heat, was tested in two sensory pain challenges. Motor and sensory challenges were repeated once, resulting in round 1 and round 2, to further follow the effect of sustained muscle pre-activation and resultant motor fatigue on pain. Besides self-report ratings of pain, we also assessed facial expressions of pain as a more reflexive and, by that, objective pain response. Moreover, heart rate (HR), heart rate variability (HRV), and electrodermal activity (EDA) were assessed as autonomic pain responses. Exertion ratings were assessed as indicators of physical strain and motor fatigue (manipulation check).

In summary, we aimed to investigate how a sustained muscular pre-activation (wearing an age simulation suit) might impact pain responses during additional motor and sensory pain challenges. To this aim, we used a randomized control design, with half of the participants wearing components of a musculoskeletal-burdensome age-simulation suit (GERT) (experimental group) while completing the two rounds of motor and sensory pain challenges. The control group completed the same challenges without wearing these GERT components.

3.2 Method

This study is an unpublished manuscript that was created for dissertation purposes. This research was funded by the Deutsche Forschungsgemeinschaft (DFG, KU2294/11) and the Bayerisches Staatsministerium für Gesundheit, Pflege und Prävention.

3.2.1 Participants

We recruited 43 young participants via flyers and emails distributed at the University of Bamberg. Participants were randomly assigned to the experimental and the control group based on sex and appointment time (morning or afternoon). Thus, 22 participants were assigned to the experimental group and 21 participants to the control group. Although the two groups

differed significantly in terms of age, the difference was less than 2 years and is therefore not of clinical relevance, as can be seen in Table 5. Furthermore, Table 5 shows that the experimental and control groups did not differ in terms of self-reported frequency of physical activity and activity level.

Table 5

Study 2: Sample characteristics

	Experimental group[a] (n=22)	**Control group** (n=21)	Group differences
Female/Male	10/12	11/10	X^2 (p=.882)
Regular exercise[b] (yes/no)	18/4	18/3	X^2 (p=1)
Activity level[c] (more/as active/less)	4/14/4	6/14/1	X^2 (p=.337)
	M (SD)	M (SD)	
Age	24.41 (3.20)	22.52 (2.16)	t-test (p=.029)

Note.

[a] musculoskeletal-burdensome age-simulating suit

[b] Do you exercise regularly?

[c] Compared to others your age, do you consider yourself more active, about as active, or less active?

Exclusion criteria were acute COVID-19 symptoms, acute and chronic pain conditions, other physical and mental illnesses, and the habitual use of psychotropic drugs and analgesics. Participants were instructed not to consume CNS-active drugs or alcohol 24 hours before testing. No caffeinated beverages or nicotine were to be consumed two hours prior to testing. Participants received either 40 euros or course credit for their participation. Participants provided written informed consent before participation. The study protocol was approved by the ethics committee of the University of Bamberg.

3.2.2 Procedures and Materials

All tests were conducted between 9:00 a.m. and 6:00 p.m. Light (simulated daylight; 5500 Kelvin) and temperature were kept constant (21°C). The testing included a pre-survey (demographic data and questionnaires; 5 minutes), a preparation phase (attaching the electrodes for the physiological responses; 5 minutes), followed by a brief rest period (10 minutes), the

two sensory challenges (experimental pressure pain and heat pain; 10 minutes) and the two motor challenges (lifting tasks A and B; 10 minutes). Next, the motor (10 minutes) and the sensory challenges (10 minutes) were performed a second time, followed by a second brief rest period (10 minutes) and a short debriefing and post-survey (5 minutes). In total, the entire testing lasted between 60 and 70 minutes.

3.2.3 Muscle Pre-Activation (Experimental Group)

Wearing the GERonTologic Simulator (GERT) suit by Moll (2020) was used to trigger sustained muscle pre-activation in a widespread fashion all over the body in the experimental group (see Figure 4). The GERT consists of 11 components that create musculoskeletal strain. These included a neck brace, elbow, and knee bandages to restrict the range of motion and mobility, as well as a weight vest (10 kg), wrist weight cuffs (1.5 kg), and ankle weight cuffs (2.3 kg) to increase the physical effort required for movement, thereby inducing sustained muscular activation and resultant muscle fatigue. Additionally, special gloves were used to decrease grasping ability.

3.2.4 Sensory Challenges

Pressure pain

We applied pressure stimuli using a pressure algometer (Algometer Type II, SOMEDIC Electronics, Hörby, Sweden) with a probe area of 1 cm^2 following a protocol of Bunk et al. (2020). Four different pressure intensities were applied with ascending intensity levels (50, 200, 400, and 500 kPa) to the left and right shoulder (above the trapezius muscle, midway between the neck and shoulder line) and the left and right inner forearm (midway between the wrist and elbow flexion). This resulted in a total of 16 pressure stimuli (4 intensities × 2 body sides × 2 stimulation sites). In each area, we increased pressure steadily for two seconds until the desired intensity was reached, at which point it was kept constant for five seconds.

Heat pain

Participants stood at a kitchen counter and were asked to immerse their right hand approximately 2 cm above the wrist into a water-filled sink with a thermostatically (Sous-Vide Cooker SV 100 Professional from Steba) controlled temperature of 46.5 °C (Granot et al., 2008;

Jurth, Rehberg, & Dincklage, 2014; Lautenbacher et al., 2002) for 3 seconds. The immersion was repeated three times before a 10-second pause for a total of nine immersions (3–3–3).

3.2.5 Motor Challenges

Lift Task A

Participants stood in front of a shelf and were instructed to lift two kettlebells of 2 kg with outstretched arms from the middle board (86 cm) to shoulder height as well as to the top edge of the shelf (160 cm) and hold this position for 5 seconds before placing the kettlebells back on the middle board (adapted from Thibault et al., 2008). Next, participants placed the kettlebell on the bottom board (9 cm), and, after a pause of 5 seconds, they lifted the weight onto the middle board again. The same challenges were performed twice, once at 27.5 and once at 59.5 cm, standing away from the shelf.

Lift Task B

Based on a protocol by Lussanet (2012), participants were asked to lift a box (40 x 30 x 22 cm) with both hands weighted with sandbags (8 kg) from the floor on his/her right, remain upright for 1 second, and placed the box back on the floor on his/her left side and stand up straight again. The box was then lifted from the left side and had to be placed on the right side. Altogether, 10 trunk rotation movements were performed.

Both lifting tasks were set up to further increase the muscle load for a short time to add strain to the pre-activated muscles in the experimental group or to test singular effects of muscle activation in the control group.

Figure 4

Example of a participant wearing the GERonTologic Simulator suit for sustained muscle pre-activation

Note. The lift task A added further muscle load for a short time (experimental group; shown on the left side); on the right side, a participant was shown without the GERonTologic Simulator during the same lift task A.

3.2.6 Assessment of Multiple Pain Responses

Self-report of pain

After each stimulus (pressure pain) or after completing each task (heat pain, lift tasks A and B), participants were asked to report their maximum pain experienced on an 11-point Numerical rating scale (NRS) ranging from 0 (*no pain)* to 10 (*worst pain imaginable*). For further analyses, pain ratings were averaged (i) across both sensory challenges as well as (ii) across both motor challenges, separately for round 1 and round 2.

Facial expression of pain

Twelve cameras recorded the entire experiment. A frontal camera view of the face was used to analyze facial expressions using the Facial Action Coding System (FACS; Ekman & Friesen, 1978). The FACS allows the motion analysis of facial muscles and distinguishes between 44 different Action Units (AUs). Two certified FACS coders evaluated the frequency and intensity (5-point scale) of 44 AUs in an offline analysis. Interrater reliability (using the Ekman–Friesen formula; Ekman & Friesen, 1978) between the coders was high at 0.76. We used the program Observer Video-pro (Noldus Information Technology, Wageningen, The Netherlands) for FACS coding. Given the enormous time it takes to FACS code the data (one minute of video material takes approximately up to two hours to process; Ekman & Friesen, 1978), we only

coded segments within each sensory and motor challenge. More precisely, time segments of 3 seconds of heat pain (time of hand immersion) and Lift B task (approximate time for each trunk rotation movement), and 5 seconds of pressure pain (plateau of target intensity) and Lift A task (duration of lifting the kettlebell) were selected for FACS coding. Frequency and intensity values of each AU were multiplied, and AUs indicative of pain (Kunz et al., 2019), namely AU4 (corrugator muscle), AU6/7 (orbicularis oculi muscle), AU9/10 (levator muscle), and AU25/26/27 (orbicularis oris muscle) were combined (averaging) to form one pain-indicative facial expression composite variable as done in previous studies (Kunz et al., 2023). For further analyses, pain-indicative facial expressions were averaged (i) across both sensory as well as (ii) across both motor challenges; separately for rounds 1 and 2.

Autonomic Responses

We assessed the electrocardiogram (ECG) and electrodermal activity (EDA) using the wireless NeXus-10 MKII biosignal system (MindMedia, Herten, The Netherlands; sampling rate: 256 Hz) during all challenges.

ECG

Self-adhesive ECG electrodes were placed according to Lead II setup on the right and left clavicle and on the left lower costal arch (according to the device manual). Mean heart rate (HR; in bpm) and heart rate variability (as root mean square of successive differences, RMSSD; in ms) were analyzed using Kubios HRV Premium (version 4.0.2) software (Tarvainen, Niskanen, Lipponen, Ranta-Aho, et al., 2014). Before data analysis, we visually inspected the ECG data for anomalies and artifacts and applied low-threshold artifact correction (0.35 seconds; Baumgartner et al., 2019).

EDA

Electrodermal activity (EDA, in µS) was measured using finger electrodes (index and middle finger). The skin conductance level (SCL) was recorded within a range of 2–20 µS, with specific attention to its change (1–3 µS). The data were analyzed using continuous decomposition analysis (CDA) via the Ledalab toolbox for MATLAB. For this study, the mean tonic activity (CDA Tonic) was used as the primary variable for analysis. If the skin conductance values are above 20 µS, the values indicate excessive noise or artifacts (BIOPAC Systems, Inc., n.d.), most likely due to measurement errors, and were therefore excluded. For

that reason, three participants were excluded from the EDA analysis, leaving us with 21 participants in the experimental group and 19 participants in the control group.

For each sensory and motor task, the 30 seconds preceding the task completion were chosen as time segments for ECG and EDA analyses. Baseline values were calculated from the final 8th min of both 10-min resting periods (mean values). We then computed delta values (task values – baseline values) for each task. For further analyses, delta values were averaged across both sensory and both motor challenges, separately for round 1 and round 2.

Manipulation check (Self-report of physical exertion)

An 11-point numerical ratings scale (NRS) was used, where participants were asked to rate the maximum physical exertion during each motor task performed (0 = *no exertion*, 10 = *maximum imaginable exertion*). Given that the sensory challenges did not require noteworthy motor activity, we did not assess exertion after pressure and heat stimulation. For further analyses, the exertion ratings were averaged across both motor challenges; separately for rounds 1 and 2.

3.2.7 Statistical Analysis

Manipulation check

Repeated measurement ANOVAs (within-subject factor round 1 and round 2) were conducted to compare the effect of the muscular pre-activation by wearing the GERT on self-report of exertion between the experimental and control group (between-subject factor GERT) during the motor challenges.

3.2.8 Impact of Muscle Pre-Activation and Resultant Motor Fatigue on Pain

To investigate whether pain responses differed between experimental (muscle pre-activation due to wearing the GERT) and control groups, repeated measure ANOVAs with the between-subject factor GERT and the within-subject factor round (round 1 and round 2) were conducted. The outcome variables were pain ratings, pain-indicative facial expressions, EDA, HR, and HRV (measured as root mean square of successive differences; RMSSD) separately for (i) the motor challenges and (ii) the sensory challenges.

Analyses of variances were performed using the ez R package (Lawrence, 2016). For F Tests, we used Greenhouse-Geisser correction for the degrees of freedom in case of violation of sphericity (Abdi, 2010) and reported generalized eta-squared (η^2G) as effect sizes (Bakeman,

2005). If significant group differences were found, we conducted post-hoc t-tests using the emmeans R package, where p-values were adjusted using the Tukey method (Lenth, 2023) and reported Cohen's *d* as effect size (Cohen, 1988). The significance criterion alpha for all tests was α<.05.

3.3 Results

3.3.1 Manipulation Check

With regard to self-report of physical exertion, the ANOVA revealed a significant effect for GERT (F(1, 41)=16.74, p<.001, η^2G=.28), with higher self-reported exertion ratings for the experimental group (M=5.72, SD=2.20) compared to the control group (M=3.27, SD=2.08). This main effect shows that our manipulation of muscle pre-activation and resulting motor fatigue seems to have been subjectively successful. There was no significant effect for round (F(1, 41)=3.20, p=.081, η^2G<.01) and no significant GERT × round interaction effect (F(1, 41)=0.74, p=.393, η^2G<.01).

3.3.2 Impact of Muscle Pre-Activation and Resultant Motor Fatigue on Pain

Self-report of pain – motor challenges

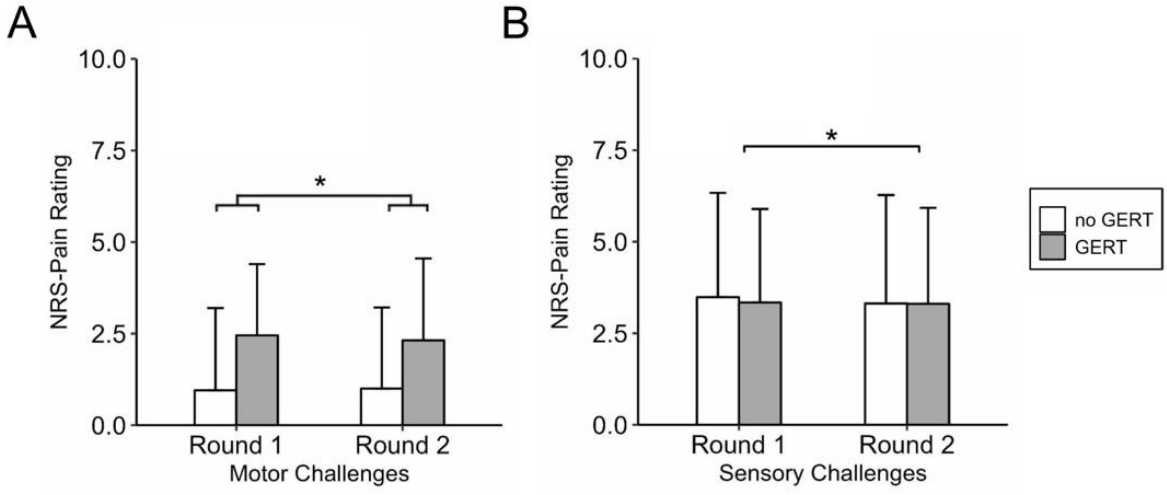
The ANOVA yielded a significant main effect for GERT (F(1, 41)=4.89, p=.033, η^2G=.10), but no significant main effect for round (F(1, 41)=0.07, p=.793, η^2G<.01) and no significant GERT × round interaction effect (F(1, 41)=0.30, p=.586, η^2G<.01). Higher pain ratings were observed for the experimental group (GERT; see Figure 5A). This was true during motor challenges, when the participants had to rate the painfulness of the additional muscle load due to lifting weights.

Self-report of pain – sensory challenges

During sensory challenges, the ANOVA yielded a significant main effect for round (F(1, 41)=4.25, p=.046, η^2G<.01), with slightly lower NRS-pain ratings for round 2 compared to round 1 (see Figure 5B). The main effect for GERT (F(1, 41)=0.04, p=.844, η^2G<.01) and the GERT × round interaction effect (F(1, 41)=1.77, p=.191, η^2G<.01) were not significant. Thus, the muscular pre-activation did not influence the painfulness of the sensory pain tests.

Figure 5

Mean and standard deviation of NRS-pain ratings during motor challenges and sensory challenges



Note. The mean and standard deviation of NRS-pain ratings during motor challenges (A) and sensory challenges (B), shown separately for experimental (GERonTologic Simulator; GERT) and control (no GERT) groups and separately for the two rounds. NRS = Numerical rating scale (0 = *no pain*, 10 = *worst pain imaginable*). *p<.05.

Facial expression of pain – motor challenges

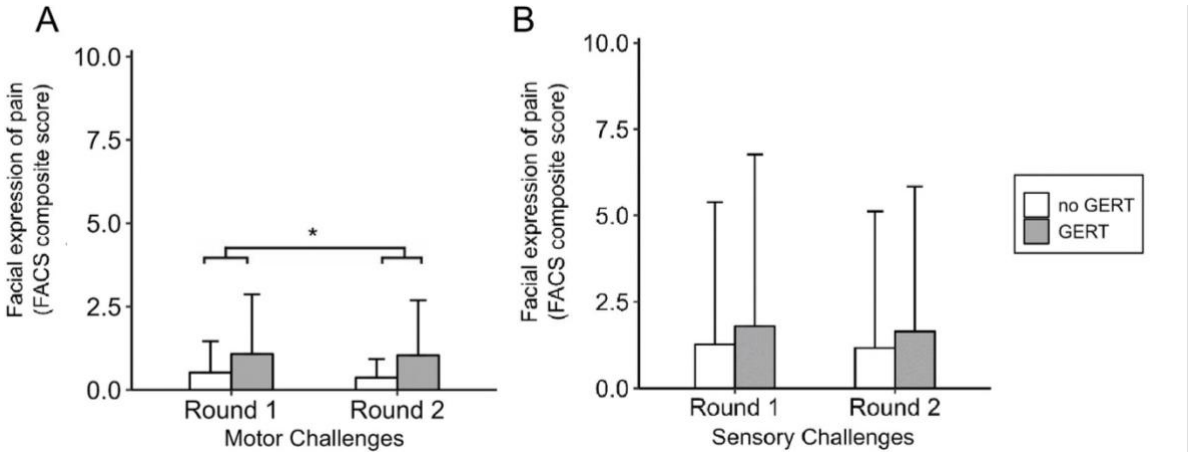
During motor challenges (weightlifting), the ANOVA revealed a significant main effect for GERT (F(1, 41)=4.63, p=.037, η^2G=.10). We observed an increase in facial expressions of pain in the experimental group (GERT) compared to the control group (see Figure 6A). No significant main effect was observed for round (F(1, 41)=1.56, p=.219, η^2G<.01), nor was there a significant GERT × round interaction effect (F(1, 41)=0.54, p=.466, η^2G<.01). This means that weightlifting led to stronger facial expressions of pain only in those participants with pre-activated muscles.

Facial expression of pain – sensory challenges

During sensory challenges, we observed no significant difference in facial expression of pain between groups (F(1, 41)=0.40, p=.530, η^2G=.01), between rounds (F(1, 41)=0.55, p=.462, η^2G<.01) or GERT × round interaction effect (F(1, 41)=0.02, p=.885, η^2G<.01), as shown in Figure 6B.

Figure 6

Mean and standard deviation of facial expression of pain during motor challenges and during sensory challenges



Note. The mean and standard deviation of facial expressions of pain during motor challenges (A) and sensory challenges (B), shown separately for experimental (GERonTologic Simulator; GERT) and control (no GERT) groups and separately for the two rounds. FACS = Facial Action Coding System. *p<.05.

Electrodermal activity (EDA) – motor challenges

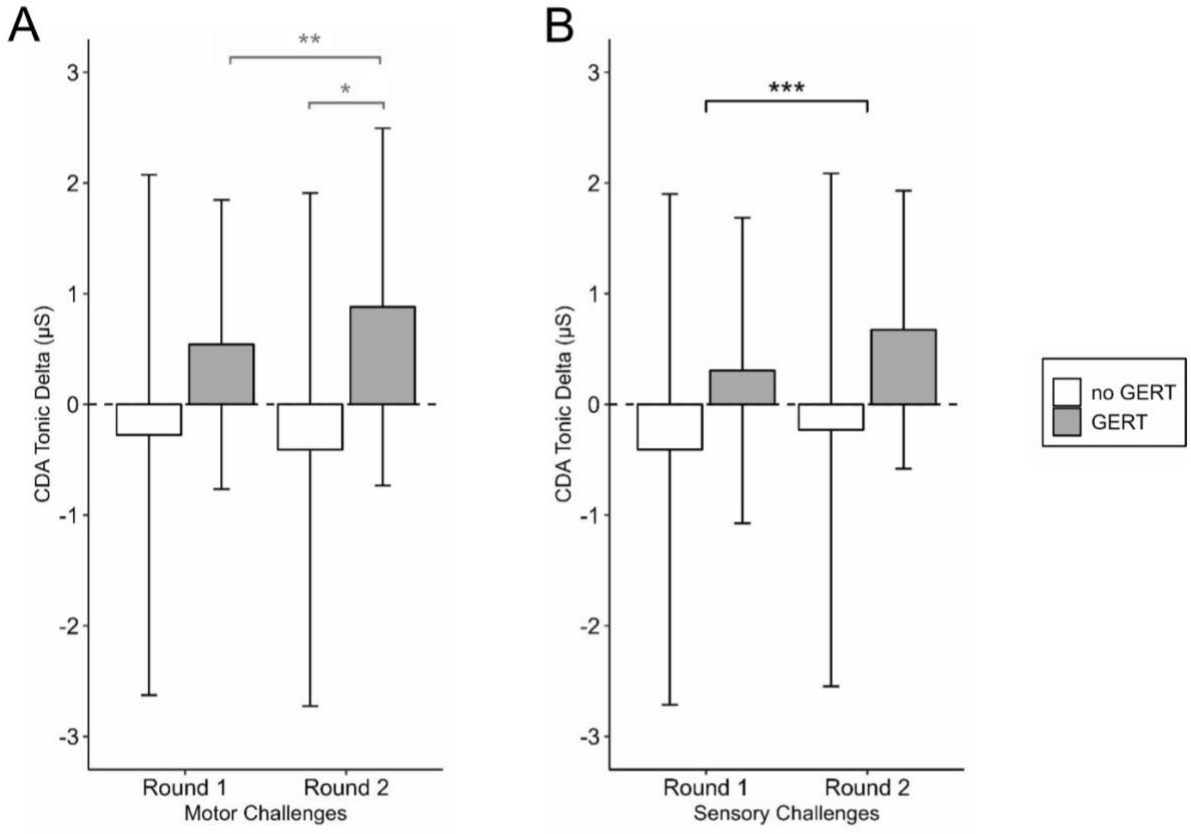
Regarding the tonic EDA during motor challenges, we found a significant GERT × round interaction effect (F(1, 38)=9.55, p<.01, η^2G<.01). Post hoc tests showed a significant difference for round 1 vs. round 2 for the experimental group (GERT; t(38)=-3.23, p=.003, d=-0.52), but not for the control group (t(37)=1.20, p=.239, d=0.19). A significant difference was observed between experimental and control group within round 2 (t(38)=-2.03, p<.05, d=-0.64) but not in round 1 (t(38)=-1.36 p=.182, d=-0.43), as can be seen in Figure 7A. We found no significant main effects for GERT (F(1, 38)=2.95, p=.094, η^2G=.07) or round (F(1, 38)=1.84, p=.184, η^2G<.01). Thus, skin conductance increases due to weightlifting became increasingly prominent in the GERT group with pre-activated muscles, the longer the test session lasted.

Electrodermal activity (EDA) – sensory challenges

For the sensory challenges, the ANOVA comparing electrodermal activity (EDA) responses yielded a significant main effect for round (F(1, 38)=22.13, p<.001, η^2G=.01) but no significant main effect for GERT (F(1, 38)=1.95, p=.171, η^2G=.05). No significant GERT × round interaction effect was found (F(1, 38)=2.74, p=.106, η^2G<.01). As can be seen in Figure 7B, EDA increased across rounds. The EDA increases due to sensory pain stimulation were not influenced by the pre-activation of the muscles and became stronger during the session.

Figure 7

Mean and standard deviation of tonic electrodermal activity during motor challenges and during sensory challenges



Note. The mean and standard deviation of tonic electrodermal activity (EDA) were analyzed using continuous decomposition analysis (CDA) during motor (A) and sensory (B) challenges, shown separately for experimental (GERonTologic Simulator; GERT) and control (no GERT) groups and separately for the two rounds. ***p<.001, **p<.01, *p<.05.

HR/HRV – motor challenges

Regarding HR responses during motor challenges, the ANOVA yielded a significant main effect for both GERT (F(1, 41)=5.29, p=.027, η^2G=.11) and round (F(1, 41)=23.63, p<.001, η^2G=.03), but no significant GERT × round interaction effect (F(1, 41)=0.19, p=.662, η^2G<.01). As can be seen in Figure 8A, the experimental group (GERT) showed increased HR responses compared to the control group. Moreover, HR slightly increased across rounds. Regarding the HRV (measured as RMSSD) during motor challenges, we found no significant main effect of round (F(1, 41)=3.76, p=.060, η^2G=.01) or GERT (F(1, 41)=1.25, p=.270, η^2G=.03) and no significant GERT × round interaction effect (F(1, 41)=0.06, p=.804, η^2G<.01), as can be seen

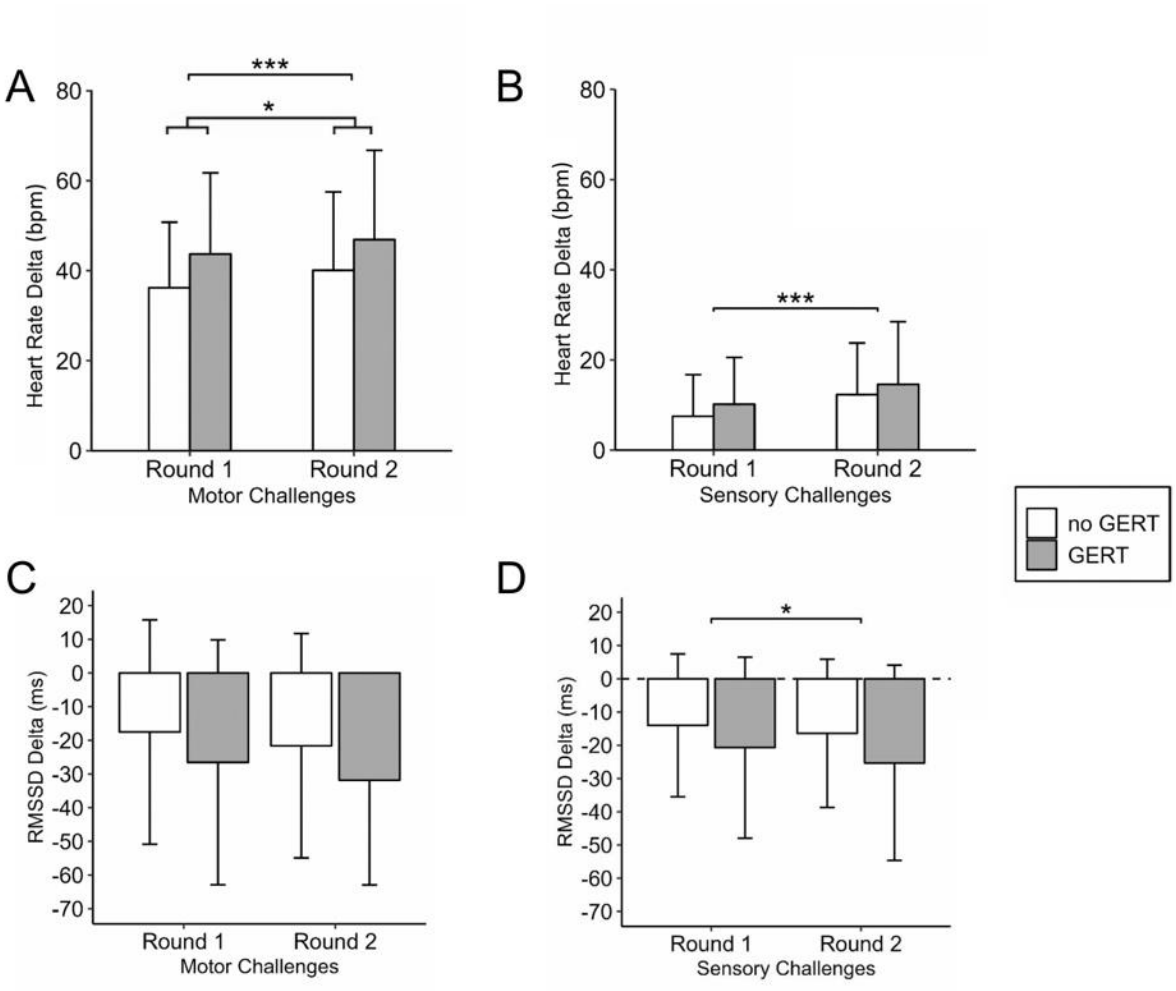
in Figure 8C. Pre-activation of the muscles led to stronger HR increases due to an additional muscle load (weight lifting).

HR/HRV – sensory challenges

Regarding heart rate responses during sensory challenges, the ANOVA yielded a significant main effect for "round" ($F(1, 41)=29.83$, $p<.001$, $\eta^2G=.13$) but not for GERT ($F(1, 41)=2.30$, $p=.137$, $\eta^2G=.04$). No significant GERT × round interaction effect was found ($F(1, 41)=006$, $p=.811$, $\eta^2G<.01$). Figure 8B shows the increase in HR from round 1 to round 2. For the HRV (measured as RMSSD), the ANOVA during sensory challenges revealed a significant main effect for round ($F(1, 41)=4.54$, $p=.039$, $\eta^2G=.01$). The second main effect for GERT was not significant ($F(1, 41)=1.45$, $p=.235$, $\eta^2G=.03$). Neither was the GERT × round interaction effect ($F(1, 41)=0.45$, $p=.505$, $\eta^2G<.01$). From round 1 to round 2 there is a decrease in HRV, as can be seen in Figure 8D.

Figure 8

Mean and standard deviation of heart rate and heart rate variability during motor challenges and during sensory challenges



Note. The mean and standard deviation of heart rate during motor challenges (A) and sensory challenges (B), and heart rate variability (measured as root mean square of successive differences, RMSSD) during motor challenges (C) and sensory challenges (D), shown separately for experimental (GERonTologic Simulator; GERT) and control group (no GERT) across the two rounds. ***p<.001, *p<.05.

In sum, wearing the GERT and pre-activating muscles in a widespread fashion (experimental group) led to a higher self-reported exertion during further motor challenges, e.g., weightlifting, compared to the control group (manipulation check). Moreover, the muscle pre-activation increased the effectiveness of the weightlifting task as a method to elicit pain and physiological responses, which produced increases in self-reported pain, facial expression of pain, as well as in EDA and HR. In contrast, no group differences were found during sensory challenges

(painful heat and pressure stimulation). Here, only time effects (round 1 vs. round 2) were evident.

3.4 Discussion

In the present study, we investigated the impact of widespread muscle pre-activation and resulting motor fatigue induced by a suit (GERonTologic Simulator, GERT), with loads of weights at the limbs and movement barriers at certain joints, on the pain system. We tested its effects in everyday motor challenges (lifting weights) and sensory challenges (hot water immersion, noxious pressure), which are supposed to produce pain. We assumed that participants would only feel pain and become sympathetically aroused during additional experimental muscle loads (e.g., weightlifting) if their muscles were pre-activated and fatigued, whereas pain responses during the sensory challenges would remain unaffected by the muscle pre-activation.

Our findings show that motor challenges led to an increase in pain ratings when the participants wore the GERT suit. The same pattern of results occurred for the facial expression of pain. Interestingly, the HR and EDA responses were only increased during the motor challenges in the experimental group and not during the sensory challenges. Only HRV was not affected by muscle pre-activation. Thus, pre-activating muscles for only a couple of minutes may trigger motor fatigue, which results in musculoskeletal pain when further muscle power is required. This pain reaction was accompanied by sympathetic arousal. However, the state described does not constitute a general hyperalgesia because non-motor related pain stimuli (sensory challenges) were processed unaltered in the experimental group.

It may appear almost trivial that pre-activated muscles, starting to develop motor fatigue, produce pain when further muscle power is required. The corroboration of this observation by non-verbal and non-subjective behavioral indicators of pain, like the facial expression of pain, makes the finding, however, more informative. Because, unlike self-reports, facial expressions, for example, are to a greater extent spontaneous and are less subject to voluntary modulation (Prkachin, 1992), which makes the finding more robust than if only self-reports had been used.

Moreover, the ANS exhibited elevated reactions, including the sympathetic-mediated HR and EDA responses, in addition to motor-related experimental pain in the experimental group. This is similar to the findings of Greco et al. (2019), who could predict muscle fatigue using phasic and tonic EDA responses. Thus, we were able to develop an experimental musculoskeletal pain

model that comprised a widespread pre-activation of muscles and additional acute muscle loads, which led to subjective, behavioral, and autonomic pain reactions.

Previous studies primarily focused on more regional forms of muscle activity, mainly specific exercises of certain muscle groups (e.g., Koltyn et al., 2014; Naugle et al., 2014; Vaegter et al., 2015, 2017). DOMS is one frequently used example for this kind of experimentally induced regional pain, which is felt in certain muscles after unaccustomed or strenuous exercise, with a delay of 24 to 72 hours after the exercise (e.g., Hotfiel et al., 2018; Lewis et al., 2012). Whereas most DOMS focused on localized eccentric loading of specific muscle groups, particularly in sports and training contexts (e.g., Hotfiel et al., 2018; Lewis et al., 2012), we focused on a much broader activation of many muscles that may more accurately reflect the complex physical demands encountered in everyday activities and might help to model widespread musculoskeletal pain. Thus, wearing the GERT suit, which has weight loads on the limbs and movement barriers on strategic joints, for just a few minutes may prepare the body for the sensation of "aching" when additional muscle strength is required. Furthermore, our findings highlight that the GERT suit can be used in environments that closely resemble everyday life, and this framework allows for studying how daily activities may induce pain even in pain-free individuals.

In addition to demonstrating the feasibility of using the GERT suit in real-life environments, we also tested the specificity of our experimental model for musculoskeletal pain in two ways, namely by (i) focusing on the pain specificity of the outcome and (ii) by applying two types of challenges (sensory vs. motor challenges). (i) In contrast to autonomic responses (EDA, HR) that show limited pain specificity and subjective pain ratings that might be biased, facial responses allow for an unbiased and pain-specific assessment of pain. It has been shown that pain is accompanied by a specific set of facial AUs (Kunz et al., 2019; Prkachin, 1992b) that help to differentiate pain from other negative affective states (e.g., disgust, anger; Kunz et al., 2013; Simon et al., 2008). If the generalized pre-activation of muscles with weights and the resulting motor fatigue lead specifically to pain and not just to nonspecific discomfort due to exhaustion when paired with additional muscle loads, this should be evident in the activation of these pain-specific AUs. This is what happened in the present study.

Those AUs, which have been shown to differentiate pain from other negative and aversive experiences (Kunz et al., 2013; Simon et al., 2008), became dominant in the individuals wearing the GERT during the motor challenges. (ii) We did not assume that wearing the GERT leads to a generalized hyperalgesia, which should become obvious with all kinds of noxious stimuli. In

contrast, we assumed an increased pain sensitivity specific to the musculoskeletal system, which can be demonstrated only by additional muscle loads (motor challenges). This is what we found in the present study. Thus, our experimental pain model makes individuals susceptible to musculoskeletal pain, but not to general discomfort or hyperalgesia.

Having established the technical setup and methodological protocol for studying acute widespread musculoskeletal pain, which affects subjective experience, facial reactions, and the sympathetic branch of the ANS, enables the investigation of pharmacological and non-pharmacological pain interventions, for example. Furthermore, this approach enables the study and comparison of individuals with clinical musculoskeletal pain and pain-free individuals in terms of their ability to withstand pain evoked by everyday motor activities.

3.4.1 Limitations

There are two main limitations of this study that need to be addressed. First, we did not consider individual fitness in our analysis. This may be a starting point for future studies, as a higher fitness level may favor the probability of less pain, as prior studies have shown (Johnson et al., 2012; Ohlman et al., 2018; Schmitt et al., 2020; Tesarz et al., 2012). Second, our study missed direct indicators for muscle fatigue, such as surface electromyography, that is commonly used to detect muscle fatigue (Merletti & Farina, 2016).

3.4.2 Conclusion

Pre-activating muscles in a widespread fashion by wearing weights on the limbs and limiting motions by mechanical barriers at strategic limbs prepares even a pain-free person to feel pain when performing everyday motor tasks, whereas control conditions with noxious sensory but non-motor related challenges did not induce pain responses. The effect of both muscle pre-activation, resulting in motor fatigue and further acute increases in muscle power, not only induces subjective pain responses but also elicits pain-specific facial responses. Furthermore, motor task-related heart rate and tonic EDA increases also occurred in the experimental group. Thus, we were able to establish an experimental model for acute widespread musculoskeletal pain, especially suitable for use in natural environments.

Chapter 4

Autonomic Responses to Activities of Daily Living and Pain Stimuli in Individuals With and Without Cognitive Impairment

Study 3 – Unpublished manuscript.

Demographic change is accompanied by an increase in the prevalence of cognitive impairment (CI). In the US alone, an estimated 6.9 million people aged 65 and older will be living with Alzheimer's dementia in 2024, with a most common diagnosis (33.4%) among those aged 85 years and older (Better, 2023). Importantly, CI does not only include dementia, but also milder forms are described that do not yet meet the criteria for clinical diagnosis, such as mild cognitive impairment (MCI; Albert et al., 2011; Idowu et al., 2024; Petersen et al., 1999). MCI is characterized by a decline in cognitive abilities such as memory, executive functions, and attention (Petersen et al., 1999) and is often called a "symptomatic predementia phase of Alzheimer's disease" (Albert et al., 2011, p. 271) with a relative preservation of activities of daily living (ADLs; Bradfield, 2023).

CI has been described in relation to multiple neurobiological factors such as synaptic processes or genetic expressions (Berchtold et al., 2014; Mufson et al., 2012). However, research also suggests that CI is linked to changes in the ANS function (Forte et al., 2019; Nicolini et al., 2022), typically assessed using indicators such as heart rate (HR), heart rate variability (HRV), or electrodermal activity (EDA). HRV is referred to as the variation in the time intervals (ms) between successive heartbeats (R-R intervals; Malik et al., 1996), and lower HRV typically indicates increased sympathetic activation (Berntson et al., 1997), while HR generally reflects autonomic activity (Malik et al., 1996), with increased HR being associated with sympathetic activation (White & Raven, 2014). EDA, in addition, captures sympathetic activation by measuring the electrical conductivity of the skin, which varies depending on the sweat level (Benedek & Kaernbach, 2010).

Importantly, lower HRV is typically associated with poorer performance in cognitive domains such as executive functions, inhibitory control, or cognitive flexibility (Forte & Casagrande, 2025; Magnon et al., 2022; Ottaviani et al., 2019). These findings highlight that autonomic functioning may be highly dependent on cognitive functioning. In this context, the Neurovisceral Integration Model (NIM) by Thayer and Lane (2000, 2009) serves as a theoretical framework that might explain how autonomic reactivity and cognitive functioning are linked, suggesting a direct link between appropriate peripheral (autonomic) regulation and cognitive and emotional processes. From this perspective, the NIM emphasizes the importance of autonomic responses in populations with CI, as changes in cognition may affect the interpretability of these responses. This becomes especially relevant when autonomic responses

are interpreted as indicators of pain, where, for example, EDA has been proposed as a potential non-verbal indicator of pain in previous studies (Pouromran et al., 2021).

In addition to autonomic processes, pain perception can also change due to cognitive decline. Research in cognitively healthy adults commonly illustrates that experimentally induced pain stimuli increased sympathetic nervous system activity and reduced parasympathetic activation, as reflected by decreased HRV (Forte et al., 2022; Koenig et al., 2014). These findings suggest that autonomic responses – such as HRV, HR, and EDA – may serve as non-verbal indicators of pain, particularly when self-report may be limited due to CI.

However, findings in individuals with dementia are inconsistent. Here, autonomic responses to pain appear to be altered, with some research suggesting attenuated autonomic responses (HR and systolic blood pressure) to low-intensity pain stimuli in patients with Alzheimer's disease compared to healthy controls, while responses to higher-intensity stimuli were comparable (Rainero et al., 2000). Others found that HRV was significantly reduced in individuals with dementia and MCI (Cheng et al., 2022). Overall, these findings suggest altered autonomic responses to pain in individuals with dementia; however, these results are heterogeneous and difficult to transfer to real-life contexts. Particularly, it is still unclear whether mild cognitive changes already affect autonomic responses to pain. To address this, we combined autonomic and self-report responses in individuals with and without CI of mild severity, not only using standardized laboratory protocols (pressure and heat pain), but also incorporating ADLs.

ADLs, such as actions to maintain hygiene, eating, or mobility (Klimczuk, 2016), are necessary for independent living in old age. They typically involve an interplay of cognitive, emotional, and physiological processes (Wollesen et al., 2023), which makes them a useful paradigm to describe everyday functionality with ecological validity. By measuring autonomic responses and subjective pain ratings during ADLs, we aimed to provide an ecologically valid understanding of autonomic processes while considering cognition.

Therefore, participants were classified into two cognitive status groups: individuals without CI (no CI) and individuals with CI (CI) (details in the Method section). The classification criteria used were based on a combined score of the CERAD (Consortium to Establish a Registry for Alzheimer's Disease) total score (Chandler et al., 2005) and the Mini-Mental State Examination

(MMSE; Folstein et al., 1975), which is inspired by the concept of MCI but is not equivalent to the clinical diagnosis (Bradfield, 2023).

Based on existing findings and theoretical models, the current study explored these four main research questions:

Research question 1 (RQ1):

> Does cognitive status (no CI vs. CI) predict baseline autonomic function (HRV, HR, and EDA)?

Research question 2 (RQ2):

> Do cognitive status and phase (baseline rest vs. ADLs) predict autonomic responses during ADLs?

Research question 3 (RQ3):

> Do cognitive status and phase (baseline rest vs. pain stimulation) predict autonomic responses to standardized pain stimuli (pressure and heat)?

Research question 4 (RQ4):

> Does cognitive status predict self-reported ratings of pain and physical exertion during ADLs, and self-reported pain during pain stimulation?

In summary, we aimed to investigate how autonomic responses and self-report ratings differ between older adults with and without CI. We examined autonomic responses at baseline, during ADLs, and during experimentally induced pain to better understand the relationship between cognitive status and autonomic functioning. Each dependent variable – autonomic responses (HRV, HR, EDA) and self-report measures (pain and physical exertion) – was analyzed in separate regression models. The predictors were cognitive status and phase. As age significantly differed between cognitive status groups, we included age as a covariate in the models. The study was conducted in the modern Bamberg Living Lab Dementia (BamLiD),

which was designed as a realistic living environment to enable research close to everyday life in a controlled setting.

4.2 Method

This study is an unpublished manuscript that was created for dissertation purposes. This research was funded by the Deutsche Forschungsgemeinschaft (DFG, Ku2294/11), the Bayerisches Staatsministerium für Gesundheit, Pflege und Prävention (reference number: G42d-G8300-2017/365), and by the Oberfrankenstiftung (reference number: FP00482) assigned to Miriam Kunz and Stefan Lautenbacher.

4.2.1 Participants (Table 6)

One hundred and one participants were aged between 65 and 93 years (M=78.7 years, SD=6.4) and included 53 females (53%). Participants were recruited through leaflets placed in letterboxes, pharmacies, and local shops, and through a newspaper advertisement. We randomly assigned participants to appointment times (morning or afternoon).

Participants were categorized into two groups: those without CI (no CI) and those with CI (CI). This categorization was based on a combined criterion including the CERAD total score (Consortium to Establish a Registry for Alzheimer's Disease) and the Mini-Mental State Examination (MMSE; Chandler et al., 2005; Folstein et al., 1975). The CERAD total score (TS-I score with a maximum of 100) was calculated following the procedure described by Chandler et al. (2005) and combines performance across multiple cognitive subtests. Participants were assigned to the CI group if either (a) the TS-I score was ≤ 77, (b) the TS-I score was between 78–85 and the MMSE ≤ 26, or (c) the MMSE was ≤ 26 despite a TS-I score above 85. All others were considered as without CI. This classification was used to assign participants to the two cognitive status groups (no CI vs. CI) in all subsequent analyses.

Of 101 participants, 58 (57%) had no cognitive impairment, while 43 (43%) showed signs of CI. Table 6 shows the sample characteristics. We found a significant age difference between groups, with individuals with CI being older on average than those without CI (t(98.91)=5.41, p<.001, d=1.04). Therefore, age was included as a covariate in the following analyses. There were no significant group differences in sex distribution (χ^2(1)=0.69, p=.405, V=0.10), self-reported frequency of physical activity (χ^2(2)=0.10, p=.949, V=0.03), or activity level (χ^2(1)=0.72, p=.395, V=0.11).

Table 6

Study 3: Descriptive characteristics of the participants

	Individuals without CI (n=58)		**Individuals with CI** (n=43)	
Sex (F/M)	33/25		20/23	
Regular exercise (yes/no)	18/39		18/25	
Activity level (more/as active/less)	30/24/3		23/17/2	
	M (*SD*)	Range	*M* (*SD*)	Range
Age (years)	76.19 (6.43)	65–91	82.14 (4.61)	75–93
BMI (kg/m^2)	25.41 (3.69)	19–34	25.44 (3.57)	19–33
MMSE	28.95 (0.94)	27–30	26.65 (2.66)	17–30
CERAD total score	86.40 (5.01)	77–95	69.67 (9.34)	44–88

Note. CI = Cognitive impairment. BMI = Body mass index. MMSE = Mini-Mental Status Examination. CERAD total score = Consortium to Establish a Registry for Alzheimer's Disease total score by Chandler et al. (2005). Regular exercise refers to the question, "Do you exercise regularly?" Activity level refers to the question, "Compared to others your age, do you consider yourself more active, about as active, or less active?"

Exclusion criteria were regular use of analgesics or regular use of sleeping pills in the past three months, neurological diseases in the past (e.g., stroke or brain aneurysm), color blindness, and other visual, severe physical illness, mental illness, and obesity (defined as body mass index [BMI, kg/m2]≥35). Participants were instructed not to take any CNS-active drugs or alcohol for 24 hours before testing. The use of nicotine or caffeine was also prohibited for two hours before the test. Participants were paid 70 euros for their participation, and (if necessary) their travel costs were covered. The ethics committee of the University of Bamberg approved the study protocol.

4.2.2 Procedures and Materials

Participants were invited to two sessions, 2–14 days apart. The data were collected between 9 am and 4 pm in the Living Lab environment of the Bamberg Living Lab Dementia (BamLiD; University of Bamberg, n.d.) with simulated daylight (5500 Kelvin) and a constant temperature of 21 degrees Celsius. The first session (T0) included demographic data (5 minutes), pain interview (10 minutes), neuropsychological test battery (35 minutes), and health questions (10 minutes). The neuropsychological test battery included the CERAD-Plus (Satzger et al., 2001), the Farbe-Wort-Interferenztest (FWIT; Bäumler, 1985), and the Screeningverfahren für Exekutivfunktionen (SEF; Lubitz & Niedeggen, 2018). Health-related questionnaires comprised the Pain Catastrophizing Scale (PCS; Sullivan et al., 1995), the Geriatric Depression Scale (GDS; Yesavage et al., 1982), and the Short Form-36 Health Survey (SF-36; Ware & Sherbourne, 1992). The second session (T1) consisted of a pre-survey (questionnaires, 5 minutes), followed by the application of the ECG system, a rest period at baseline (10 minutes), the two pain stimulations (pressure and heat pain; 10 minutes) and six ADLs (movements in bed, walking (straight and 8), kettlebell lifting, putting on shoes and jacket, and box lifting; 60 minutes). Finally, there was another short rest period (10 minutes) and a post-survey with a debriefing session (5 minutes). The total duration was approximately 60 minutes for T0 and 120 minutes for T1.

4.2.3 ADLs (Figure 9)

The study included six motor ADLs, which are essential for self-care and can be particularly easily associated with movement-induced pain. These were selected in such a way that they can

trigger both mild to moderate pain due to biomechanical strain, as well as emotional responses associated with anger or joy due to failures and successes.

Bed

We instructed the participants to lie down on the bed and perform a series of exercises. With palms facing upwards, we asked them to alternately open and close their hands. Then, they stretched their arm overhead one at a time, bent each foot at the ankle, bent and straightened each knee, and stretched each leg straight up in the air. Next, participants turned to their right and left sides and sat up with their legs extended. Finally, they sat on the edge of the bed and stood up. These exercises have been standardized for recording mobilization effects, according to Husebo et al. (2014).

Walk

We asked participants to walk along a six-meter straight line twice (Walk straight). After that, we instructed them to walk a figure-eight pattern (Walk 8) marked on the floor clockwise and counterclockwise – a total of six times (see Belluscio et al., 2020).

Kettlebell Lift

For the kettlebell lift, we asked participants to stand 27.5 cm in front of the shelf. Their task was to lift two 1 kg kettlebells (adapted from Thibault et al., 2008) with outstretched arms from the middle shelf (86 cm) to shoulder height and hold this position for 5 seconds. After that, their task was to lift both kettlebells to the top edge of the shelf (160 cm) and hold this position for 5 seconds. Between lifts, we asked participants to place the kettlebells on the middle shelf and pause for 5 seconds. We then asked them to place the kettlebells on the bottom shelf (9 cm) and wait another 5 seconds before lifting them back to the middle shelf. The task was repeated with the participants standing at a distance of 59.5 cm from the shelf. Before this exercise, we carried out a trial run with the participants to allow them to practice the movement and ask questions in advance.

Shoes

Participants were seated in a height-adjusted chair so that their feet were firmly on the floor. In this position, we asked them to put on and take off their shoes. Shoes and jackets were provided by us for standardization. We instructed them to put on the shoe by pulling their foot toward them using both hands, without crossing their legs. They started with the right shoe. After this,

the left shoe followed. The shoes were removed in the same manner, by pulling the foot toward them.

Jacket

Participants were given a jacket. They were instructed to put the jacket on by first reaching into the sleeve with their dominant arm and then grabbing the other sleeve. While putting on the jacket, the participants stood upright. Once the jacket was put on, it is closed with a zipper.

Box Lift

For the box lift, participants were instructed to lift a box filled with weighted sandbags (40 x 30 x 22 cm; maximum 4 kg). The box had two side handles and was positioned on their right side. They were asked to bend towards the box using the map trunk rotation movement (see De Lussanet et al., 2012), lift the box with both hands, stay straight for 1 second, and then place the box on their left side. For the next turn, participants lifted the box from left to right. This movement was repeated 8 times. During the movement, the feet had to be placed firmly on the floor without shifting. To practice the movement in advance, we conducted a trial run where participants had the opportunity to ask questions and select an acceptable weight (0, 2, or 4 kg).

4.2.4 Pain Stimulation

Pressure pain

Sixteen individual pressure stimuli were induced with the pressure algometer (Algometer Type II, SOMEDIC Electronics, Hörby, Sweden) with a probe area of 1 cm^2. We followed a protocol by Bunk et al. (2020), where four pressure intensities in an ascending sequence with (50, 200, 400 and 500 kPa) were applied to the right and left shoulder (above the trapezius muscle, midway between the neck and shoulder line) and the left and right inner forearm (midway between the wrist and elbow flexion). This results in 4 intensities × 2 sides of the body × 2 stimulation points.

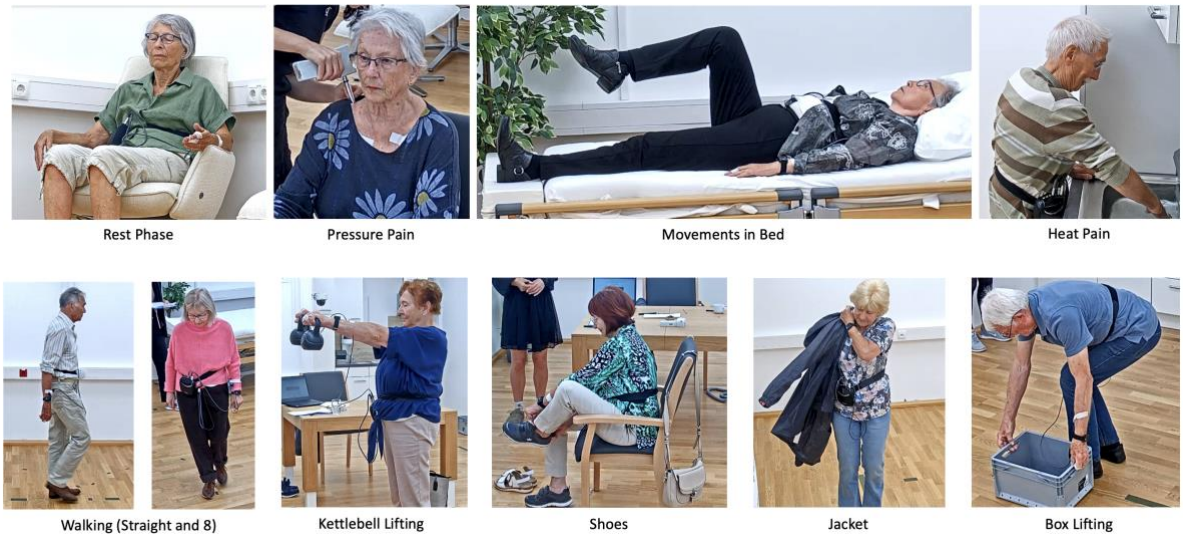
Heat pain

A water basin was heated to 46.5 °C (Granot et al., 2008; Jurth et al., 2014; Lautenbacher et al., 2002) using a thermostatically controlled sous-vide cooker (SV 100 Professional by Steba). The participants had the task of dipping their right hand three times into the water basin

(approximately 2 cm deep). This procedure was repeated three times before a 10-second break, for a total of nine dips (3–3–3).

Figure 9

Examples of participants engaged in activities of daily living



Note. This figure shows the progression of participants through the experimental protocol. The protocol included a baseline rest phase, various activities of daily living (ADLs), including movements in bed, walking (straight and 8), kettlebell lifting, putting on shoes and jacket, and box lifting. Also, two pain stimulation protocols that included pressure and heat pain.

4.2.5 Assessment of Pain and Physical Exertion

Self-report of pain and physical exertion

Participants reported the maximum pain they experienced after each pressure pain stimulus and after each ADL on an 11-point numerical rating scale (NRS) from *no pain* = 0 to *worst pain imaginable* = 10. Besides, an 11-point NRS was used to rate the maximum physical exertion during each ADL performed (0 = *no exertion*, 10 = *maximum imaginable exertion*). Since pain stimulation did not require physical exertion, we only recorded the exertion rating after the ADLs, but not after pressure and heat stimulation.

Autonomic Responses

The NeXus-10 MKII biosignal system (MindMedia, Herten, The Netherlands; sampling rate: 256 Hz) was used to assess electrocardiogram (ECG) and EDA. We placed self-adhesive ECG

electrodes according to Lead II setup on the right and left clavicle and on the left lower costal arch. EDA was measured using finger electrodes (index and middle finger). The biosignal system was attached to the participants at the beginning of T1 and wirelessly worn during all exercises.

For the analyses of HRV, HR, and EDA, time segments of 30 seconds were formed for each pain stimulation and each ADL by using 30 seconds preceding the task completion. In addition, the baseline rest period at the beginning was shortened to 8 minutes by cutting off 2 seconds at the beginning to ensure the exclusion of measurement artefacts. The initial rest period served as the baseline rest condition in the following analyses. For further analyses, HRV, HR, and EDA values were averaged across both pain stimulations and ADLs.

ECG

For the evaluation of ECG, we used Kubios HRV Premium (version 4.0.2) software (Tarvainen, Niskanen, Lipponen, Ranta-aho, et al., 2014) to visually inspect and process heart rate variability (as the root mean square of successive differences, RMSSD [ms]) and HR (bpm). An artifact correction of 0.35 seconds, recommended by Baumgartner et al. (2019), was used to process anomalies and artifacts.

Missing values were filled using group-specific nearest neighbor interpolation as recommended for HRV data (Benchekroun et al., 2023). It was noted that a maximum of 50% missing values may be present, as the nearest neighbor interpolation gives the most realistic results (Benchekroun et al., 2023).

Specifically, RMSSD values above 200 ms were again visually inspected for potential motion artefacts in Kubios HRV Premium (Tarvainen, Niskanen, Lipponen, Ranta-aho, et al., 2014). The literature suggests that such high values may indicate measurement errors (Rocha et al., 2024). Intervals with RMSSD values above 250 ms were generally excluded as they were considered implausible.

After the exclusion of high RMSSD values as well as intervals with measurement artifacts, the total proportion of missing RMSSD values was 1.89% in the total sample, and 13 participants were affected by artefacts, with a maximum of 36.36% per person. The missing values were replaced by interpolation, using nearest neighbor interpolation (NNI) with the R function na.locf() from the R package zoo (Zeileis & Grothendieck, 2005). The dplyr package in R was used for group-specific processing (Wickham et al., 2023).

For HR values, the total proportion of missing values was 0.90% (with 8 participants affected by artefacts), with a maximum of 18.18% per person. We again used NNI for interpolation.

EDA

EDA was recorded as skin conductance level within a physiological range of 2–16 µS. The Ledalab toolbox for MATLAB was used to visually inspect the raw data and to process it using continuous decomposition analysis (CDA). We applied a downsampling to 16 Hz. The resulting CDA tonic activity was used for further analyses.

During visual inspection, we identified seven individuals with artifacts in the EDA track, all occurring during the 8-minute baseline assessment at the start of the session. For EDA data reconstruction, multiple interpolation methods are available (Pattyn et al., 2023), most commonly using the area before and after the artifact as the data basis for the reconstruction.

In the present study, however, there were signal interruptions of up to 10 minutes, with values of over 250 µS (n=8). Due to the long duration of the signal interruptions, we decided against interpolation to ensure the accuracy of the data.

Additionally, following the guidelines of Braithwaite et al. (2013), participants with EDA values exceeding 16 µS were excluded as they were assumed to reflect measurement artifacts, and one participant was removed accordingly. Finally, for EDA analyses, 92 participants were included. Fifty-two (57%) participants had no CI, while 40 (43%) showed signs of CI.

4.2.6 Statistical Analysis

For analyses, self-report pain ratings were averaged (i) across both pain stimuli and (ii) across ADLs. Physical exertion ratings were averaged across ADLs.

To test research questions RQ1–RQ3, separate linear models were calculated for each parameter: HRV, HR, and EDA. The lm function from the R package stats (version 3.6.2; R Core Team, 2019) was used.

To investigate potential differences between cognitive status groups in baseline autonomic function (RQ1), cognitive status was used as a predictor and age as a covariate. To test for differences in autonomic reactivity between baseline rest and ADLs (RQ2), we used cognitive status (no CI vs. CI) and phase (baseline rest vs. ADLs) as predictors and age as a covariate. To assess differences in autonomic responses to pain stimuli, we used cognitive status and phase

(baseline rest vs. pain stimulation) as predictors and age as a covariate. To examine differences in self-report ratings (RQ4), we calculated linear models separately for pain and physical exertion ratings, with cognitive status as a predictor and age as a covariate.

To account for the collinearity of the variables, we calculated the variance inflation factor (VIF) using linear regression analysis, with a threshold of VIF<5 indicating acceptable levels of multicollinearity (Menard, 2002). For t-tests, Cohen's *d* is reported as an estimate of effect size (Cohen, 1988). The chi-squared test was used to compare categorical variables with Cramér's V as an effect size (Cramér, 1991). For linear regression analyses, the unstandardized regression coefficient (*b*) is reported (Kutner et al., 2005). The alpha level of significance for all tests was α<.05.

R version 4.4.2 (2024-10-31 ucrt) was used for all calculations. An a priori power analysis using G*Power (version 3.1.9.7; Faul et al., 2007), based on previous studies with similar dependent variables (Eggenberger et al., 2020), indicated a required sample size of *N*=80 to achieve 80% power at α=.05 in a multiple linear regression model with four predictors**.** The final sample size of *N*=101 exceeded this requirement.

4.3 Results

4.3.1 Descriptive Measures

The mean values and standard deviations of the dependent variables (HRV, HR, and EDA) and self-reported pain and physical exertion are presented in Table 7.

Table 7

Autonomic responses and self-reported pain and physical exertion ratings in the phases of rest at baseline, activities of daily living, and pain stimulation for individuals without cognitive impairment and individuals with cognitive impairment

		Individuals without CI (n=58)*		**Individuals with CI** (n=43)*	
		M (*SD*)	Range	*M* (*SD*)	Range
Phase	Variable				
Rest	HRV (ms)	43.37 (43.90)	4.65–237.17	54.69 (42.71)	3.95–159.07
	HR (bpm)	67.61 (12.42)	38.62–109.93	69.57 (11.63)	52.28–123.48
	EDA (µS)	0.92 (0.51)	0.39–2.48	0.87 (0.38)	0.37–2.13
ADLs	HRV (ms)	43.17 (27.32)	5.84–168.11	70.09 (53.61)	10.07–203.90
	HR (bpm)	84.08 (13.29)	61.80–123.79	81.99 (9.67)	63.46–116.52
	EDA (µS)	1.66 (0.85)	0.43–4.84	1.61 (0.95)	0.59–4.75
Pain stimulation	HRV (ms)	38.41 (33.10)	4.27–170.36	61.24 (59.80)	3.93–213.47
	HR (bpm)	71.76 (12.11)	48.63–109.22	71.67 (9.74)	47.96–90.67
	EDA (µS)	1.58 (0.87)	0.44–4.13	1.49 (0.86)	0.40–3.99
Self-report measures					
Pain (ADLs)	NRS (0–10)	1.66 (1.14)	0.00–5.00	2.15 (1.63)	0.00–6.80
Physical Exertion (ADLs)	NRS (0–10)	2.09 (1.27)	0.14–5.29	2.34 (1.65)	0.14–6.29
Pain (Pain stimulation)	NRS (0–10)	3.91 (1.67)	0.89–7.67	3.72 (1.78)	0.00–7.33

Note. Range is indicated for each variable within each group. CI = Cognitive impairment. HRV = Heart rate variability (as root mean square of successive differences, RMSSD [ms]). HR = Heart rate (bpm). EDA = Electrodermal activity (tonic level, µS). ADLs = Activities of daily living. * Only 92 participants (total) had complete EDA data (no CI: n = 52; CI: n = 40). Pain and physical exertion ratings were measured using the numerical rating scale (NRS) and ranged from 0 to 10, with higher scores indicating greater physical exertion or pain.

4.3.2 Baseline Autonomic Function (RQ1; Figure 10)

Linear regression analyses were conducted to determine whether cognitive status (no CI vs. CI) predicts baseline HRV, HR, and EDA. Age was included as a covariate in the models.

Baseline heart rate variability (HRV)

There was no significant effect of cognitive status or age on baseline HRV ($F(2, 98)=2.67$, $p=.074$, *adjusted* $R^2=.032$). Specifically, Cognitive status did not significantly predict baseline HRV ($b=2.82$, $SE=9.71$, $t(98)=0.29$, $p=.772$), though age showed a non-significant negative trend ($b=1.43$, $SE=0.75$, $t(98)=1.90$, $p=.060$), indicating that older age may be associated with higher baseline HRV (Figure 10A).

Baseline heart rate (HR)

The overall model for baseline HR was not statistically significant ($F(2, 98)=1.80$, $p=.171$, *adjusted* $R^2=.016$). Neither cognitive status nor age significantly predicted baseline HR (cognitive status: $b=4.10$, $SE=2.71$, $t(98)=1.51$, $p=.134$; age: $b=-0.36$, $SE=0.21$, $t(98)=-1.71$, $p=.090$). Thus, neither predictor (cognitive status nor age) was associated with altered HR during baseline rest (Figure 10B).

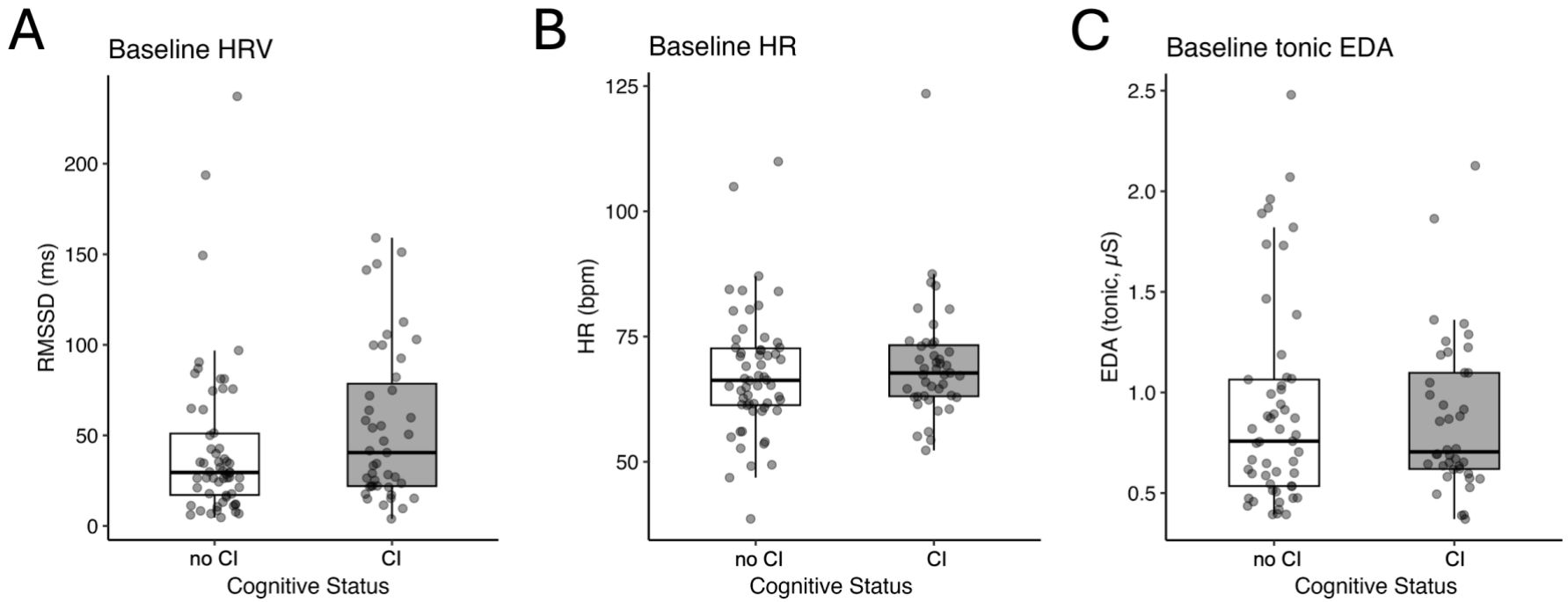
Baseline electrodermal activity (EDA)

EDA at baseline was not significantly predicted by the model ($F(2, 90)=0.15$, $p=.863$, *adjusted* $R^2=-.019$). Neither cognitive status ($b=-0.06$, $SE=0.11$, $t(90)=1.51$, $p=.134$) nor age ($b<0.01$, $SE<0.01$, $t(90)=0.14$, $p=.893$) significantly predicted tonic EDA at baseline. These results suggest that there were no baseline differences in tonic EDA between cognitive status and age groups (Figure 10C).

Overall, we found no evidence that individuals' cognitive status (no CI vs. CI) was associated with differences in baseline autonomic functioning in HRV, HR, or EDA for RQ1.

Figure 10

HRV, HR, and EDA during the 8-minute rest period at baseline by cognitive status



Note. This figure shows the distribution of heart rate variability (HRV, as root mean square of successive differences, RMSSD, ms, panel A), heart rate (HR, bpm, panel B) and electrodermal activity (EDA, tonic level, µS, panel C) during the baseline rest period for individuals without cognitive impairment (no CI) individuals and individuals with cognitive impairment (CI).

4.3.3 Autonomic Responses during ADLs (RQ2; Figure 11)

We used linear regression analyses to see how well cognitive status (no CI vs. CI) and phase (baseline rest vs. ADL) predict HRV, HR, and EDA. We included age as a covariate in the models.

HRV during ADLs

The overall model for HRV during ADLs was statistically significant ($F(4, 197)=5.62$, $p<.001$, *adjusted* $R^2=.084$), indicating that the predictors explained approximately 8.4% of the variance. Age was a significant predictor of HRV ($b=1.58$, $SE=0.51$, $t(197)=3.13$, $p=.002$), indicating that with each year increase in age, HRV increased by 1.58 ms. No significant effects were found for cognitive status ($b=-1.91$, $SE=8.75$, $t(197)=-0.22$, $p=.827$), phase ($b=13.75$, $SE=8.80$, $t(197)=1.56$, $p=.120$), or the cognitive status × phase interaction ($b=-14.53$, $SE=11.61$, $t(197)=-1.25$, $p=.212$). These results suggest that only age was significantly associated with HRV during ADLs, while cognitive status or phase showed no significant effects (Figure 11A).

HR during ADLs

HR during ADLs was significantly predicted by the model ($F(4, 197)=20.54$, $p<.001$, *adjusted* $R^2=.28$), indicating that the predictors explained approximately 28% of the variance. Phase had a significant effect on HR ($b=12.67$, $SE=2.58$, $t(197)=4.91$, $p<.001$), with HR increasing by 12.67 bpm during ADLs compared to baseline. No significant effects were found for cognitive status ($b=-3.17$, $SE=2.56$, $t(197)=-1.24$, $p=0.218$), age ($b=-0.20$, $SE=0.15$, $t(197)=-1.37$, $p=.174$) or their interaction ($b=3.97$, $SE=3.40$, $t(197)=1.17$, $p=.245$). The results indicate that HR was significantly elevated during ADLs, suggesting ADLs led to physiological activation, while HR did not differ by cognitive status or age (Figure 11B).

EDA during ADLs

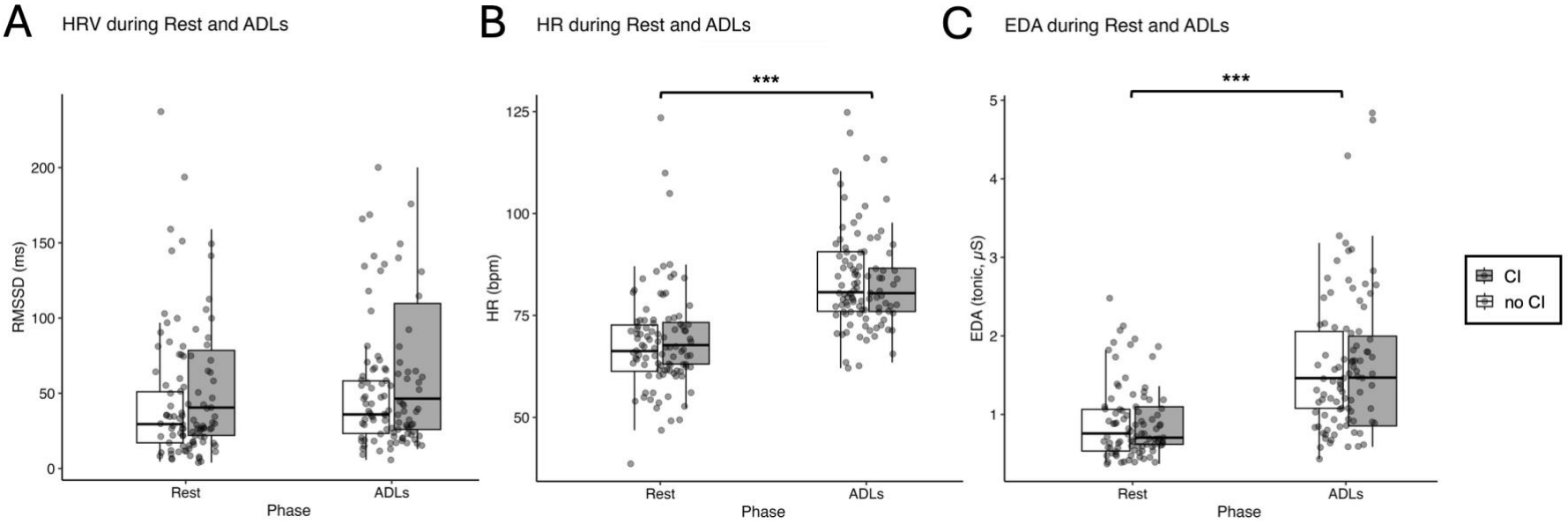
The model significantly predicted EDA during ADLs ($F(4, 181)=13.48$, $p<.001$, *adjusted* $R^2=.23$), indicating that approximately 23% of the variance in EDA was explained by the predictors. Phase significantly predicted EDA ($b=0.75$, $SE=0.14$, $t(181)=5.42$, $p<.001$), indicating that EDA increased by 0.75 µS during the ADLs compared to the baseline phase. There were no significant effects of cognitive status ($b=-0.13$, $SE=0.16$, $t(181)=-0.83$, $p=.408$), age ($b=0.01$, $SE=0.01$, $t(181)=1.55$, $p=.122$), or their interaction ($b=-0.01$, $SE=0.21$, $t(181)=-0.03$, $p=.980$). The findings show that EDA was significantly elevated during ADLs,

while cognitive status and age were not associated with EDA differences during ADLs (Figure 11C).

Overall, for RQ2, we found that phase (baseline rest vs. ADLs) significantly predicted HR and EDA, but not HRV. Cognitive status was not a significant predictor of any autonomic response. However, age significantly predicted HRV but did not affect HR or EDA.

Figure 11

HRV, HR, and EDA during the 8-minute rest period at baseline and activities of daily living by cognitive status



Note. This figure shows the distribution of heart rate variability (HRV; as root mean square of successive differences, RMSSD, ms, panel A), heart rate (HR, bpm, panel B) and electrodermal activity (EDA, tonic level, µS, panel C) during the baseline rest period and during activities of daily living (ADLs) for individuals without cognitive impairment (no CI) and individuals with cognitive impairment (CI). $^{***}p<.001$.

4.3.4 Autonomic Responses during Pain Stimulation (RQ3; Figure 12)

Linear regression analyses were performed to investigate whether autonomic responses (HRV, HR, EDA) differ between cognitive status (no CI vs. CI) and phase (baseline rest vs. pain stimulation). Additionally, age was included as a covariate.

HRV during Pain stimulation

HR during pain stimulation showed a significant association with the predictors in the model ($F(4, 197)=4.75$, $p<.01$, *adjusted* $R^2=.069$), indicating that the predictors explained approximately 6.9% of the variance. Age was a significant predictor ($b=1.77$, $SE= 0.54$, $t(197)=3.26$, $p=.001$), indicating that for each year increase in age, HRV increased by 1.77 ms. No significant effects were found for cognitive status ($b=-0.77$, $SE=9.40$, $t(197)=-0.08$, $p=.935$), phase ($b=6.56$, $SE=9.46$, $t(197)=0.69$, $p=.489$), or their interaction ($b=-11.51$, $SE=12.48$, $t(197)=-0.92$, $p=.357$). The results indicate that only age significantly influenced HRV during pain (Figure 12A).

HR during Pain stimulation

The model significantly predicted HR during pain stimulation ($F(4, 197)=2.45$, $p=.047$, *adjusted* $R^2=.028$), suggesting that the predictors explained approximately 2.8% of the variance. Age was the only significant predictor ($b=-0.32$, $SE=0.14$, $t(197)=-2.23$, $p=.027$), indicating that with each year of age, the HR decreased by 0.32 beats per minute. No significant effects were found for phase ($b=2.11$, $SE=2.49$, $t(197)=0.85$, $p=0.40$), cognitive status ($b=-3.86$, SE=2.47, $t(197)=-1.56$, $p=0.12$), or the phase × cognitive status interaction ($b=2.04$, $SE=3.28$, $t(197)=0.62$, $p=0.53$). The results suggest that HRV during pain stimulation was significantly associated with age, but not with phase or cognitive status (Figure 12B).

EDA during Pain stimulation

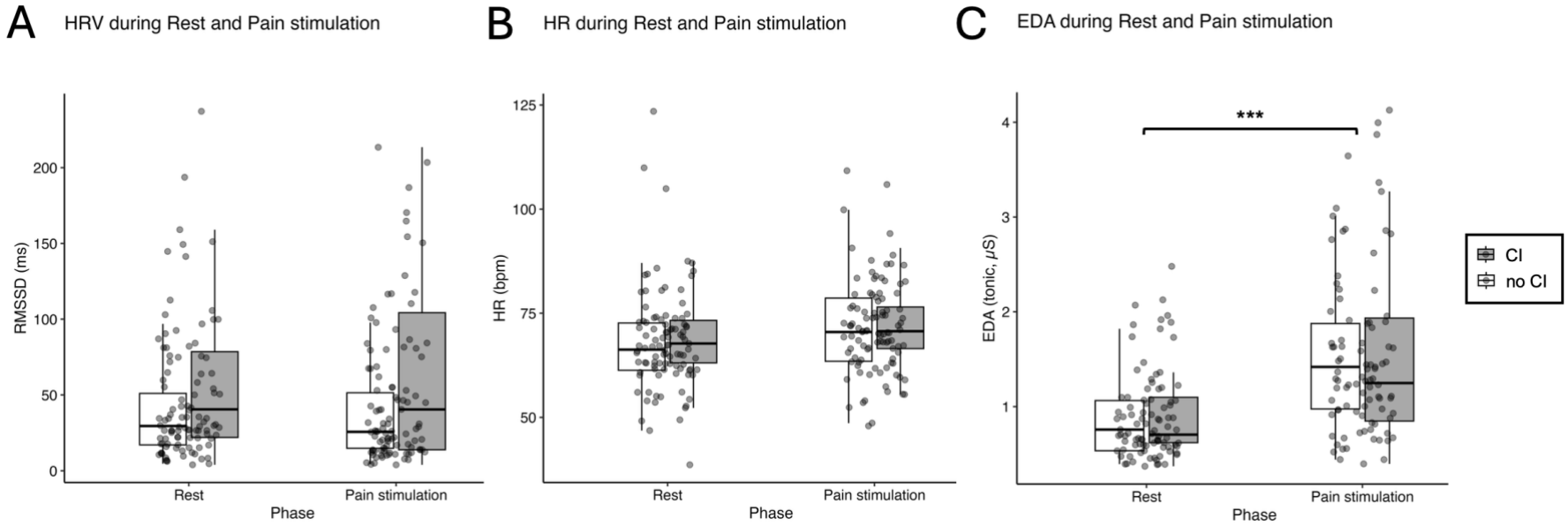
The model for tonic EDA during pain stimulation was statistically significant ($F(4, 181)=10.23$, $p<.001$, *adjusted* $R^2=.166$), indicating that the predictors explained approximately 16.6% of the variance. Phase was a significant predictor ($b=0.66$, $SE=0.14$, $t(181)=4.90$, $p<.001$), with EDA increasing by 0.66 µS during the pain phase compared to rest at baseline. No significant effects were found for cognitive status ($b=-0.09$, $SE=0.15$, $t(181)=-0.56$, $p=.576$), age ($b=0.01$, $SE=0.01$, $t(181)=0.71$, $p=.482$), or the phase × cognitive status interaction ($b=-0.04$, $SE=0.21$,

$t(181)=-0.19$, $p=.848$). The results indicate that tonic EDA increased significantly from baseline to pain stimulation, while cognitive status and age were not associated with EDA (Figure 12C).

To summarize, for RQ3, we found that phase (baseline rest vs. pain stimulation) significantly predicted EDA, but not HRV or HR. Contrary, cognitive status (no CI vs. CI) was not a significant predictor for any autonomic response. Age, however, significantly predicted HRV and HR, but not EDA.

Figure 12

HRV, HR, and EDA during the 8-minute rest period at baseline and pain stimulation by cognitive status



Note. This figure shows the distribution of heart rate variability (HRV; as root mean square of successive differences, RMSSD, ms, panel A), heart rate (HR, bpm, panel B) and electrodermal activity (EDA, tonic level, µS, panel C) during baseline rest and during pain stimulation for individuals without cognitive impairment (no CI) and individuals with cognitive impairment (CI). $^{***}p<.001$.

4.3.5 Self-reported Pain and Physical Exertion (RQ4; Figure 13)

We explored whether self-reported ratings of pain and physical exertion would differ based on cognitive status (no CI vs. CI). Therefore, we used linear regression analyses with cognitive status as a predictor and age as a covariate.

Pain ratings during ADLs

The overall model for pain ratings during ADLs was statistically significant ($F(2, 98)=3.53$, $p=.033$, adjusted $R^2=.048$), indicating that the predictors explained 4.8% of. Cognitive status was not a significant predictor ($b=-0.21$, $SE=0.31$, $t(98)=-0.70$, $p=.488$), while age showed a non-significant trend ($b=0.05$, $SE=0.02$, $t(98)=1.96$, $p=.053$). These findings suggest that while age may be a marginal predictor of self-reported pain during ADLs, cognitive status, in our analysis, was not (Figure 13A).

Pain ratings during Pain stimulation

The model significantly predicted pain ratings during pain stimulation ($F(2,98)=3.50$, $p=.034$, *adjusted* $R^2=.048$), indicating that the predictors explained 4.8% of the variance. Age was a significant predictor ($b=0.08$, $SE=0.03$, $t(98)=2.58$, $p=.011$), with pain ratings increasing by 0.08 units for each additional year of age. Cognitive status was not a significant predictor ($b=-0.64$, $SE=0.38$, $t(98)=-1.70$, $p=.093$). These results highlight that self-reported pain ratings during pain stimulation increased with age, while cognitive status showed no significant effect (Figure 13B).

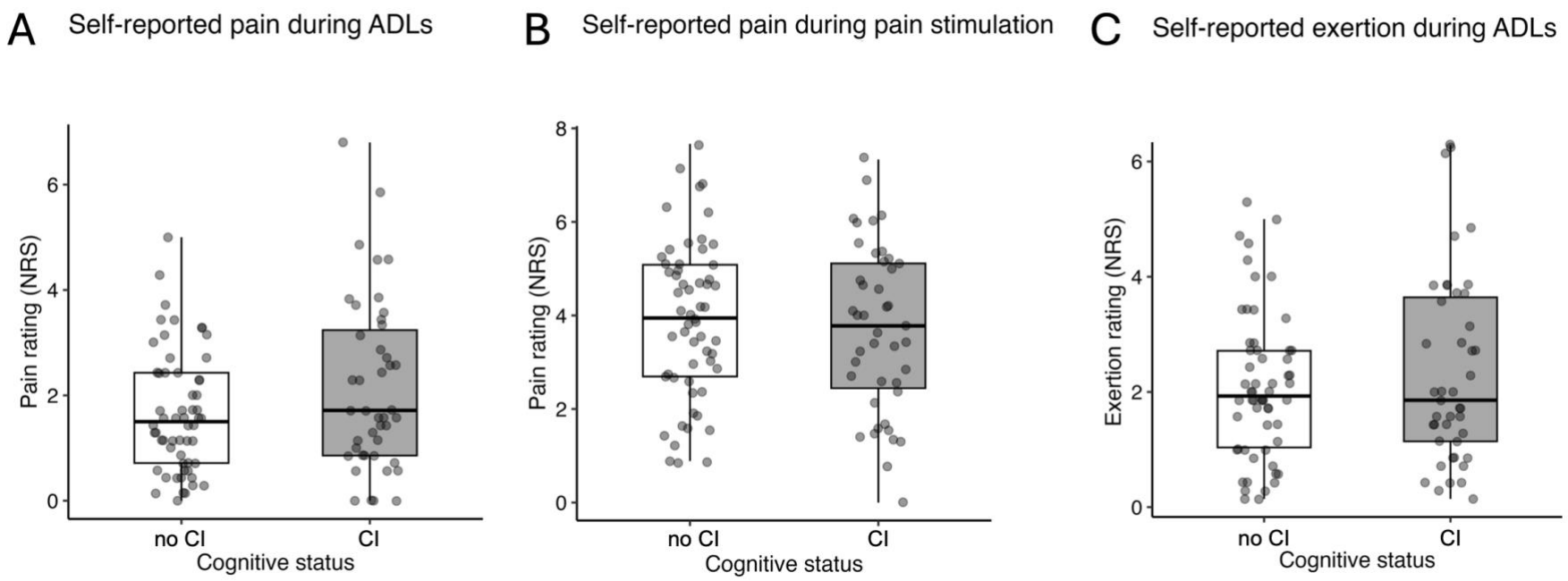
Physical Exertion ratings during ADLs

Physical exertion ratings during ADLs were significantly predicted by the model ($F(2, 98)=3.16$, $p=.047$, *adjusted* $R^2=.041$), indicating that 4.1% of the variance was explained by the predictors. Age was a significant predictor ($b=0.06$, $SE=0.02$, $t(98)=2.35$, $p=.021$), with physical exertion ratings increasing by 0.06 units for each additional year of age. However, no significant effect was found for cognitive status ($b=0.09$, $SE=0.32$, $t(98)=0.29$, $p=.771$). These findings suggest that older participants reported higher physical exertion ratings during ADLs than younger participants, while cognitive status was not associated with physical exertion ratings (Figure 13C).

Taken together, for RQ4, we found that cognitive status was not a significant predictor for self-report ratings in any of the models. However, age was a significant predictor of self-reported pain ratings during pain stimulation and physical exertion ratings during ADLs.

Figure 13

Self-reported pain and physical exertion during activities of daily living and pain stimulation by cognitive status



Note. This figure shows self-reported pain during activities of daily living (ADLs; panel A) and pain stimulation (panel B), and self-reported physical exertion during ADLs (panel C) for individuals without cognitive impairment (no CI) and individuals with cognitive impairment (CI).

4.4 Discussion

This study aimed to investigate the differences in autonomic responses and self-report ratings between older adults with and without CI. The focus was to aid the ecologically valid understanding of responses to pain by measuring them during daily activities and standardized pain stimulation.

With RQ1, we examined whether cognitive status could predict baseline autonomic function (HRV, HR, and EDA). Surprisingly, cognitive status was not a significant predictor of autonomic functioning during baseline. Prior studies, however, suggested that participants with higher resting vagal tone could be expected to perform better on cognitive tasks (Forte & Casagrande, 2025; Forte et al., 2019; Magnon et al., 2022). One possible explanation for the lack of significance in the present study is methodological. While we used a categorial comparison of cognitive status (no CI vs. CI), others examined continuous correlations between HRV and cognitive performance (e.g., Forte & Casagrande, 2025; Forte et al., 2019). Such categorial comparison may be less sensitive to detecting nuanced relationships. Nevertheless, our categorial distinction was chosen deliberately as prior research suggested that this method is suitable for capturing mild cognitive changes (Polcher et al., 2022). Future research may benefit from a continuous measurement approach to detect nuanced associations with greater specificity.

Next, with RQ2, we examined whether cognitive status (no CI vs. CI) and phase (baseline rest vs. ADL) were associated with autonomic dysregulation. HR and EDA increased during ADLs compared to baseline. This aligns with prior research, as HR and EDA are recognized as indicators for mild physiological activation during everyday activities (Kreibig, 2010; Steptoe et al., 2000), as well as for increased stress, emotional, or cognitive demand (Schubert et al., 2009; Society for Psychophysiological Research, 2012). Interestingly, cognitive status did not predict HRV, HR, or EDA during ADLs, indicating that CI was not associated with greater autonomic dysregulation.

For RQ3, we investigated whether cognitive status (no CI vs. CI) and phase (rest vs. pain stimulation) were predictors of autonomic functioning. Contrary to previous findings, which had described a significant decrease in HRV during pain (Forte et al., 2022; Koenig et al., 2014), phase was not a significant predictor of HRV and HR. However, EDA increased from baseline

to pain stimulation, indicating that pain stimulation may evoke sympathetic activation. Additionally, cognitive status did not predict HRV, HR, or EDA during pain stimulation, indicating that we observed no autonomic dysregulation based on cognition.

Based on the NIM (Thayer & Lane, 2000, 2009), which links well-functioning prefrontal control structures to autonomic flexibility, we expected that individuals with CI might show signs of autonomic dysregulation. However, one possible explanation for this lack of significance is that individuals with mild levels of CI may not exhibit impaired prefrontal control accordingly – as assumed by the NIM. For individuals with mild levels of CI, prefrontal control may still be largely intact, or compensatory mechanisms could be masking the actual decline. Supporting this, a recent study by Wu et al. (2024) highlights that individuals with MCI may exhibit changes in functional connectivity within the PFC, potentially reflecting compensatory mechanisms or neural reorganization. These compensatory processes may mask subtle differences in autonomic functioning, particularly in individuals with mild forms of CI, as investigated in the present study. Future studies should therefore explore the relationship between autonomic reactivity and PFC activity in more depth, especially in individuals with CI of mild severity.

Beyond cognitive status, we also examined the effects of age on autonomic functioning during ADLs and pain stimulation, as age was included as a covariate in all models. In the ADL models, older participants showed higher HRV, indicating increased parasympathetic activity with older age. This is partly in contrast to previous findings, which report a decrease in HRV (measured as RMSSD) with older age (Tegegne et al., 2020; Umetani et al., 1998). However, other studies show that RMSSD can also be unchanged with age, steadily decreasing from childhood until around 60, followed by a stabilization or an increase in variability in older adults (Reardon & Malik, 1996). Notably, age was not a significant predictor for HR or EDA in the ADL models, which may indicate that HRV is more age-sensitive than HR or EDA. In the pain stimulation models, age significantly influenced HRV and HR, suggesting that older participants exhibited higher HRV (measured as RMSSD) and lower HR values. These findings suggest a heightened parasympathetic activation with older age. One possible explanation is that pain thresholds increase with age. For example, González-Roldán et al. (2020) found that older adults exhibited compensatory adaptation in the sensory areas of the brain (e.g., decreased connectivity) compared to younger adults, which was linked to an increase in pain thresholds.

Across RQ1–RQ3, the results suggest that autonomic reactivity did not differ significantly between individuals with and without mild levels of CI. Moreover, autonomic responses in this study did not provide a reliable basis to distinguish between pain and other arousal states, and their diagnostic value for identifying pain could not be demonstrated. Notably, only age was a significant predictor of autonomic functioning, suggesting that individual factors could play a role in interpreting autonomic responses. Future studies should therefore investigate individual factors influencing autonomic responses to pain – such as the severity of CI – further.

For RQ4, we explored whether cognitive status (no CI vs. CI) could predict self-reported pain and physical exertion ratings. Across all models, cognitive status was not a significant predictor of self-reported pain or physical exertion, highlighting that self-report ratings of pain and physical exertion did not differ between individuals with and without mild levels of CI. One possible explanation for the absence of group differences in our findings is that the association between CI and self-reported pain may depend on specific cognitive domains, as suggested by Madariaga et al. (2021). In their study, poorer memory performance predicted lower pain scores, whereas poorer executive function predicted higher pain scores. Such contrasting patterns may cancel each other out when comparing groups by general cognitive performance. In addition, prior research reported lower levels of self-reported pain in individuals with severe CI (Dubé et al., 2018; Monroe et al., 2012), but not in individuals with CI of mild severity (Madariaga et al., 2021). For RQ4, our findings suggest that self-reported pain and physical exertion are not affected by global cognitive performance, at least in individuals with CI of mild severity.

Contrary to cognitive status, age was a significant predictor of pain ratings during pain stimulation and physical exertion ratings during ADLs. Here, older participants reported higher pain and physical exertion. This finding may reflect an age-related decline in physical fitness (Grässler et al., 2021), which could explain higher physical exertion ratings in our study. Additionally, these findings could be due to physiological changes with aging, although assessing those remains an area for future research.

4.4.1 Limitations

There are certain limitations to name. First, we used a 30-second task and 8-minute baseline rest intervals, which may have restricted the accuracy of ANS responses, as research indicated that especially long-term (24h) recordings can provide a more complete understanding of circadian factors in CI (e.g., Tranah et al., 2011). Second, cognitive status groups were

classified based on global cognitive performance scores, which were then implemented as categorical cutoffs. This approach may have limited the representation of continuous variations in cognition in the present study. Third, this study only included individuals aged 65 and over. However, results indicate that age itself appears to be a key factor influencing autonomic responses. Therefore, future research should explore how autonomic responses vary among different age groups, including young participants, in the presence of pain.

4.4.2 Conclusion

This study explored differences in autonomic responses and self-report ratings between older adults with and without CI. Across the tested models, cognitive status showed no significant association with autonomic responses (HRV, HR, EDA) or self-reports (pain, physical exertion). These findings suggest that, in individuals with CI of mild severity, autonomic responses and self-reports to pain may be preserved despite changes in global cognitive performance.

In contrast, ADLs and pain stimulation were associated with increased sympathetic activity, and age was a predictor of both autonomic and self-report responses. Interestingly, while autonomic markers indicated increased parasympathetic activity with older age, self-reports showed increased pain and physical exertion ratings, suggesting nuanced age-related changes in pain responses. Future research should investigate specific cognitive domains (e.g., memory or executive functioning) at different stages of CI and across various age groups, to better understand the interaction of cognition, ageing, and autonomic responses to pain.

Chapter 5

Concluding Discussion

5.1 Summary of Key Findings

This dissertation aimed to describe and evaluate indicators of pain that could be used with various populations, including non-verbal individuals, while considering individual factors such as cognition and aging. Therefore, this dissertation included behavioral indicators (i.e., facial expressions), autonomic responses (i.e., HRV, HR, EDA), and self-reports of pain. The following section outlines the key findings from the three studies. First, we asked:

> *How can observer-based pain assessment tools be optimized with clinical usability in mind?*

In Study 1, we developed a short version of the PAIC15 (called the PAIC6) to increase the applicability of observer assessment in individuals with moderate to severe CI. This allowed us to address barriers in clinical use, such as time constraints. We demonstrated that the PAIC6 is both psychometrically and clinically valuable, reducing the number of items from 15 to 6, while retaining three pain assessment domains: facial expressions, body movements, and vocalizations (according to the AGS Panel on Persistent Pain in Older Persons, 2002). These findings highlight the fact that behavioral indicators of pain can be implemented in psychometrically sound and clinically useful observer-based assessments. Second, we explored:

> *How do behavioral and autonomic indicators of pain respond during experimental pain and motor challenges, and how does muscle pre-activation (induced by an age simulation suit) affect these responses?*

In Study 2, we tested a model of musculoskeletal pain using the GERT aging suit to simulate age-related physical strain. The study design combined facial expressions, autonomic responses, and self-reports of pain. Results indicate that muscle pre-activation (i.e., wearing the aging suit) led to significantly higher self-reported pain and physical exertion, enhanced facial expression, and heightened HR during motor challenges (i.e., kettlebell and box lift), while HRV and EDA did not reach significance. Interestingly, self-reported pain, EDA, HR, and HRV increased over time during sensory challenges (i.e., pressure and heat pain), but there were no group differences between participants with and without muscle pre-activation. This suggests a summation of responses over time that was independent of muscle pre-activation. These

findings emphasize that self-reporting, facial expressions, and HR were able to describe pain-related responses induced by muscle pre-activation during motor challenges. Third, we asked:

> *Can autonomic responses serve as reliable indicators of pain perception in older adults with and without CI?*

With Study 3, we explored whether cognitive status (no CI vs. CI), phase (rest vs. ADL/pain), or age could predict autonomic (HRV, HR, EDA) and subjective responses (pain and physical exertion) during baseline condition, ADLs, and standardized pain stimulation. Surprisingly, cognitive status could not predict autonomic functioning or self-reported pain and physical exertion. Instead, age emerged as a predictor for autonomic responses and self-report ratings, suggesting that age may influence both autonomic and subjective pain experience. Additionally, phase (rest vs. ADL/pain) influenced autonomic responses (EDA and HR), but not HRV, indicating that both ADLs and pain stimuli may evoke sympathetic activation. However, again, the sensitivity of HRV as an indicator of pain could not be demonstrated. These findings suggest that autonomic responses are sensitive to ADLs but have limited specificity for pain detection, especially in older adults, as age emerged as a modulating individual factor.

In sum, across studies, behavioral indicators, such as facial expressions, vocalizations, and body movements, reliably and effectively described pain-related states, even among older adults with CI of mild severity. However, both autonomic and self-report pain responses were strongly influenced by individual factors, particularly age and task phase. EDA and HR indicated arousal when they increased during active phases, while HRV was primarily associated with age.

For effective pain assessment, this suggests assessments should rely primarily on behavioral indicators, while autonomic responses can be used to primarily capture non-pain-specific general arousal. Self-reports were feasible in all analyses where verbal communication was possible, also in individuals with CI of mild severity. Before concrete recommendations for multimodal assessments are given, individual factors that influence indicators of pain should be considered in the following section.

5.2 Individual Factors Influencing Autonomic Responses to Pain

Autonomic responses can potentially be useful to describe pain in non-verbal populations. However, without self-report, the risk of misinterpretation increases since autonomic responses are especially prone to being influenced by individual factors, such as age and cognition.

Although facial expressions are widely used and well-researched as indicators of pain, research on autonomic responses as indicators of pain is still in its early stages, particularly when describing how individual factors influence these signals.

This dissertation, therefore, specifically investigated the effect of individual factors on autonomic responses. Notably, our study design included individuals with CI of mild severity who were all able to self-report pain, enabling us to compare autonomic and self-report responses to pain.

In this section, the interaction between autonomic responses and individual factors should be discussed, while also considering self-report measures to aid the interpretation of autonomic responses in the context of pain. To this end, we asked the following question:

> *How do individual factors (i.e., age and cognitive status) affect the interpretation of autonomic responses as indicators of pain?*

Previous studies indicate that cognitive changes are associated with alterations in autonomic regulation (Forte et al., 2019). For example, HRV, an indicator of parasympathetic activity (Berntson et al., 1997), has been linked to cognitive performance. Specifically, research has found that reduced HRV is consistently associated with poorer cognitive performance and executive function in healthy adults (Arakaki et al., 2023; Forte et al., 2019). Similarly, a meta-analysis by Cheng et al. (2022) found significantly reduced HRV in individuals with dementia and MCI.

In contrast, the results of Study 3 indicated that cognitive status was not a significant predictor of autonomic responses (HRV, HR, or EDA). These findings suggest a certain stability of autonomic responses relative to mild severity of CI. This lack of significance was surprising, as the NIM (Thayer & Lane, 2000, 2009) suggests a tight link between prefrontal functioning and autonomic flexibility as reflected in HRV. Thus, in our Study 3, we did not find a significant association between autonomic reactivity and cognitive functioning in individuals with mild severity of CI, contrary to what the model suggests.

However, the lack of significance may reflect the presence of mild severity of CI in the sample used, as previous research has mostly measured HRV in individuals with dementia or MCI (see Cheng et al., 2022) or associated prefrontal functioning directly with autonomic dysregulation. The latter aspect could not be assessed in our setting, as this would have required the use of imaging methods. Instead, we classified cognitive status groups based on cognitive screening

cut-offs, which are less specific and therefore may not reflect clinically relevant diagnostic criteria.

It is still too early to interpret these results clinically, as several studies have demonstrated contrary results to our findings. For example, studies have shown that EDA can serve as a valid indicator of pain in ML models (Pouromran et al., 2021; Susam et al., 2018). However, the results of Study 3 suggest that autonomic responses (HRV, HR, and EDA) could not be interpreted as being specific to pain.

Another individual factor, age, was a significant predictor of autonomic responses (i.e., HRV and HR) in our findings. Older adults showed higher HRV and lower HR during tasks, suggesting heightened parasympathetic activity. These patterns may reflect potential compensatory mechanisms in autonomic regulation, which could affect the ability to detect dysregulation in individuals with CI of mild severity. These processes were interpreted by Wu et al. (2024) as compensatory mechanisms, which could preserve cognitive performance in mild levels of CI. Although Wu et al. (2024) did not consider autonomic functioning in their study, it is conceivable that similar compensatory mechanisms may support autonomic balance in mild levels of CI. Nevertheless, future studies using brain imaging and autonomic responses are necessary to conclusively interpret the role of compensatory mechanisms in autonomic responses to pain with older age.

Interestingly, although this autonomic response pattern reflects increased parasympathetic activity with older age, older adults self-reported higher physical exertion and pain, suggesting that the increased ANS regulation was not perceived subjectively. Such a discrepancy indicates that the interpretation of autonomic responses in the context of pain remains complicated. This pattern is broadly consistent with previous studies predicting an increase in HRV with age (Umetani et al., 1998). Nevertheless, these findings suggest that age should be taken into account when interpreting autonomic responses to pain.

Overall, these findings highlight the challenge of interpreting autonomic responses without considering individual factors. It is important to note that age can influence pain-related signals, especially in autonomic responses, as we could demonstrate. Therefore, future research should consider individual factors further when interpreting autonomic responses to pain.

A comprehensive synthesis of all findings will be provided in the subsequent section to address the question of how behavioral, autonomic, and self-reported responses can be used in a pain assessment across various populations, considering verbal abilities, cognition, and aging.

5.3 Combining Clinically Feasible Indicators of Pain Across Populations

As part of the main research question, this dissertation aimed to examine how pain can be assessed across age and cognition, which indicators are suitable in which population, and how these indicators can be combined in an ecologically valid, i.e., practical, way for pain assessment. For the practical combination of several indicators, the concept of a multimodal pain assessment was used, which is based on the idea that a combination of different sources of information and measurement methods can lead to an increase in diagnostic validity (Herr et al., 2006; McAuliffe et al., 2009).

Therefore, a combination of behavioral, autonomic, and self-report responses of pain may compensate for the weaknesses of individual methods, whereby the combination should also make sense in terms of clinical applicability.

In this dissertation, various indicators of pain were examined both individually and in combination. Based on the findings, recommendations will be offered for applying specific indicators of pain in different populations, depending on cognition and age. To guide the process, we asked:

> *How can pain be assessed in an ecologically valid and clinically feasible way using behavioral, autonomic, and self-reported indicators across different age and cognitive ability levels?*

For populations with intact communication ability, self-report remains the standard for a time-efficient assessment of pain (Kang & Demiris, 2018). Multimodal assessment methods are useful for this population only under certain conditions, such as in research when it is especially important to increase the validity of one single assessment by combining it with another

method. In this context, self-reports of pain can be usefully combined with facial expressions, for example.

Self-reports offer the advantage that they are particularly straightforward to assess, while facial expressions provide a more spontaneous expression of pain. Both combine well, as we were able to demonstrate in Study 2.

However, it is important to note that even facial expressions cannot be considered completely objective indicators of pain either, particularly in healthy individuals, as facial expressivity is highly dependent on frontostriatal activity, which allows individuals to downregulate their facial expressions during pain perception (Kunz et al., 2011).

Additionally, social display rules play a particular role in the expressivity of pain, as it has been shown that individuals show more facial expressions of pain in the presence of a familiar partner than in the presence of a neutral person (Karmann et al., 2014). The combination of facial expressions with self-reports of pain can be, therefore, particularly useful as one can give individuals the opportunity to express their pain verbally.

However, beyond the advantages of combining both methods, it is important to consider their practicality in clinical practice. In contrast to self-report assessments, the analysis of facial expressions of pain is often more complex, but can also be simplified by recent technological developments, such as the PainChek® app (Brett & Severn, 2023), which combines standardized questionnaires with the recording of video-based automatic facial expression analysis, thus enabling a time-effective method of analysis.

Next, for individuals with CI of mild severity whose verbal communication ability is largely intact, self-reports of pain can be used effectively to describe pain conditions, as we were able to demonstrate in Study 3. Additionally, as with individuals without CI, combining self-reports with facial expressions can increase the validity of each method depending on the setting. For example, this combination can increase validity in research contexts.

It needs to be considered that cognitive decline can affect the ability to self-report pain, which can make a combination of self-report and other measurements, such as observer-based tools or facial expressions, useful as additional indicators for pain recognition. In this context, Pautex and Lautenbacher (2017) and Hadjistavropoulos et al. (2014) emphasize that self-report of pain can be valid in mild to moderate stages of dementia, by asking questions at a slow pace and reminding the person of the instructions. It is recommended that self-reports of pain can be used

if the person can answer simple questions consistently and appropriately (Herr et al., 2011). However, before deciding which assessment to use, it is crucial that the individual care provider assesses whether self-reports can still be used effectively.

Further, in a non-verbal population such as those with a dementia diagnosis, the International Association for the Study of Pain (Kunz & Lautenbacher, 2021) recommends the use of observer-based tools such as the PACSLAC, PAIC, MOBID-2, and DoloPlus2 to assess pain (Fuchs-Lacelle & Hadjistavropoulos, 2004; Husebo et al., 2014; Kunz et al., 2020; Lefebvre-Chapiro, 2001). These tools integrate various behavioral aspects of pain and, with the development of PAIC6 as part of this dissertation, we were able to enhance the clinical applicability of observer-based pain assessment further.

Additionally, the use of automated pain recognition systems is feasible for individuals with dementia and can already be recommended for practice; by using tools such as ePAT (Atee et al., 2017) or PainChek® (Brett & Severn, 2023), which have been specifically developed for clinical use in individuals with dementia. For example, ePAT is a mobile application that uses video material of facial expressions alongside questions about five areas of pain-related behavior: voice, movement, behavior, activity, and body (Atee et al., 2017). Its clinical applicability has been evaluated in use with aged care residents with moderate to severe dementia, demonstrating strong agreement with a classic observer-based method, namely the Abbey Pain Scale (Atee et al., 2017). These results underscore the high clinical applicability of multimodal assessment methods for pain identification using mobile applications.

Finally, autonomic responses can be useful as general indicators of arousal, particularly when working with individuals with mild to moderate CI. However, as we demonstrated in Study 3, their interpretability as pain responses is limited by individual factors such as age and by the fact that autonomic responses to pain can only be interpreted as general arousal states.

Overall, self-reports to assess pain remain the standard for pain assessment in individuals with intact communication ability. However, in contexts that require a higher level of assessment validity, such as for research purposes, self-reports can be combined with facial expressions, as demonstrated in Study 2.

Notably, facial expressions of pain can be interpreted regardless of verbal ability. For individuals with limited or no-verbal communication, observer-based tools – such as the PAIC6 or automated solutions like ePAT (Atee et al., 2017) – are recommended. However, further

clinical studies are needed to test the practicality of such tools in everyday care and to consider feedback from nursing staff. By contrast, autonomic responses could not be interpreted as specific to pain, as demonstrated in Study 3. Therefore, they may be more effective in providing information about general arousal states than about pain.

Table 8 summarizes the results of this section and provides recommendations for pain assessment methods in different populations with various communication abilities.

Table 8

Recommendations for pain assessment methods in different populations and various communication abilities

Population *Age*	Communication Ability	Self-report (NRS)	Observer-Based Behavioral Tools (PAIC15, PAIC6)	Facial Expressions (FACS coded, automated)	Autonomic Responses (HR, EDA)
No CI, *younger adults*	Verbal	**Recommended**	Valid	Valid	Reflects general arousal, not pain-specific
No CI, *older adults*	Verbal	**Recommended**	Valid	Valid	Influenced by individual factors (i.e., age)
Mild levels of CI, *younger adults*	Mostly verbal	**Recommended** if verbal ability intact	Valid	Valid	Reflects general arousal, not pain-specific
Mild levels of CI, *older adults*	Mostly verbal	**Recommended** if verbal ability intact	Valid	Valid	Influenced by individual factors (i.e., age)
Severe CI *younger and older adults*	Non-verbal	Not applicable	**Recommended**	Valid	Influenced by individual factors (i.e., age and cognition)

Note. NRS = Numerical rating scale. CI = Cognitive impairment. PAIC = Pain Assessment in Impaired Cognition (Kunz et al., 2020). FACS = Facial Action Coding System. HR = Heart rate. EDA = Electrodermal activity.

Green fields indicate that the method is recommended for the respective population or communication ability. Yellow fields indicate that the method is possible but optional, or with limitations. Red fields indicate that the method is not applicable and not recommended.

The terms *younger* and *older adults* were used in line with findings in the literature on autonomic responses, which report autonomic changes in individuals over the age of 60 (Reardon & Malik, 1996), whom we refer to here as *older adults*.

5.4 Strengths, Limitations, and Future Directions

The dissertation outlines several approaches to advancing pain assessment in research and clinical settings, with a particular focus on different age and cognitive ability groups. Beyond the empirical findings, the results contribute to novel methodological possibilities due to the study design.

A central innovation of the method used in Studies 2 and 3 is the incorporation of motor challenges and ADLs in an ecologically valid LL setting. Although ADLs are specific stressors relevant to everyday life, they have not yet been considered in this way in pain research.

By contrast, prior research has largely relied on classic laboratory experiments and pain protocols such as the induction of pressure pain to evaluate non-verbal pain markers such as facial expressions (see Kunz et al., 2021). This standardized description of pain markers is useful for identifying pain-related signals under controlled conditions, but their ecological validity may be limited when it comes to pain assessment in real-world contexts. Therefore, the following section highlights the key methodological strengths of the applied method as part of this dissertation and reflects on its limitations to derive implications for future research.

5.4.1 Strengths

A particular strength of this dissertation is the application of pain stimulation in a practical context. This is achieved by using motor challenges and ADLs alongside standardized stimulation protocols (e.g., pressure, heat) in Studies 2 and 3. Thus, our setting allowed for a comparison of ecologically valid pain induction methods and standardized pain stimulation protocols, which was often lacking in prior research.

Another methodological strength is the combination of established and exploratory assessments of pain across various settings. Study 1 employed an observer-based pain assessment in a geriatric ward and a nursing home, while Studies 2 and 3 incorporated the assessment of facial expressions, autonomic responses, and self-reports of pain within a multi-sensor LL environment. This combination of methods provides for a novel perspective that combines various pain-describing variables and enables promising data streams for developing automated pain recognition systems.

Taken together, this dissertation builds a bridge between standardized laboratory conditions and ecologically valid real-world settings, which are particularly important for the interpretability of results for clinical application. That said, the following section will explore the applicability of LL settings for pain research further and offer insights into their potential future use.

5.4.2 Perspectives on Pain Research in Living Labs

In order to validate the applicability of classic laboratory study results, it is essential to transfer pain research into contexts relevant to the everyday lives of older adults. While classic laboratory experiments are widely used in pain research (see Kunz et al., 2021), studies conducted under real-world conditions are also becoming increasingly common; for example, those using wristbands to detect pain (e.g., Hirayama et al., 2025).

However, both laboratory experiments and studies conducted under real-world conditions face limitations. While laboratory experiments often suffer from a lack of alignment with real pain conditions – using standardized pain protocols rather than specific diagnoses such as lower back pain – studies conducted in real-world settings often face challenges in achieving the same level of standardization, for example, due to environmental factors such as temperature or ambient noise.

To address these challenges, LLs offer a balanced approach that combines the strengths of both methods by enabling the evaluation of everyday activities using standardized procedures.

Building on this, the present dissertation used pain assessments in an LL environment to record multiple indicators of pain simultaneously – such as facial expressions, autonomic responses, and self-reports – whereby this approach enabled combined analyses of indicators within one sample for methodological stabilization.

Extending ecological validity further, Studies 2 and 3 incorporated the use of motor challenges and ADLs to trigger pain, which is a fairly new concept. These tasks, such as lifting weights or walking, were selected to closely resemble common everyday challenges to accurately reflect the daily lives of older adults.

Considering this, we examined the effectiveness of these tasks to induce pain. Therefore, in Study 2, we found that wearing an age simulation suit to induce motor fatigue led to significantly higher levels of self-reported pain, highlighting the potential of using motor challenges in combination with muscle fatigue to induce pain. In contrast, in Study 3, we found

no significant main effects in the ADL models, with pain ratings of older adults not differing significantly by age or cognitive status, suggesting that neither age nor cognitive status influenced self-reported pain during ADLs.

Interestingly, when comparing autonomic responses between ADLs and rest, we observed that in older adults, autonomic responses (i.e., HR and EDA) increased during ADLs, indicating heightened general arousal in response to the ADLs. Similarly, an increase in HR was observed when participants wore the age simulation suit compared to the control group. However, EDA did not differ significantly between the age simulation and no age simulation groups.

For the application of such tasks in pain research, our findings suggest that motor challenges and ADLs can function as ecologically valid stressors that elicit physiological and – in some cases – subjective pain responses. Additionally, these findings establish a unique connection between laboratory settings and real-world contexts by emphasizing alternative methods of pain induction, such as the use of ADLs instead of pain stimulation protocols.

The described motor challenges and ADLs can potentially be adopted in future research to ensure methodological standardization when implementing real-world challenges in pain research.

Beyond its methodological strength, the LL approach has the potential to generate benchmark data to train ML models or digital pain assessment systems. In this regard, the combination of different data streams, such as facial expressions and autonomous reactions, is particularly interesting for building and improving pain assessment systems. These systems could be a promising starting point for clinical pain assessment by enabling continuous pain monitoring, especially in non-verbal individuals.

Before concluding the discussion on the applicability of LL and ADLs in pain research, some open questions about these approaches should be discussed. A key question is whether LL approaches should only serve to enable pain research in a realistic context, or whether such technologies can or should also be implemented in clinical practice. Therefore, further research is required to determine whether more accessible solutions – such as mobile devices with apps, wearable sensors, or smartwatches – are sufficient for generating valid data streams or if clinics require the full technological scope of an LL environment to assess high-quality sensor data.

Another concern is the extent to which findings on an ADL-based pain induction can be translated into clinical practice. While it is conceivable, for example, that specific ADLs could

be performed as part of a standardized pain assessment, a challenge in practical implementation could be that not all individuals are physically able to perform such tasks, especially older adults with physical limitations. These considerations highlight that ADLs appear to be of limited use in individuals with severe physical limitations and that their clinical usefulness needs to be evaluated in more detail in future studies.

Taken together, the findings of this dissertation highlight the potential of the LL environment for pain research. The methodological approach demonstrated that an environment close to everyday life helps align experimental research with the real lives of older adults, enabling ecologically valid pain assessment conditions. The combination of multiple data streams in the LL sensor environment offers promising avenues for technological development, such as automated pain detection systems. However, it remains to be answered how LL technologies and ADLs can be implemented in clinical practice to improve current pain assessment approaches.

5.4.3 Limitations and Future Directions

While the three studies conducted as part of this dissertation offer valuable insights into the applicability of pain assessments across various populations, certain limitations should be acknowledged and serve as directions for future research.

First, while Study 1 involved older adults with none to severe CI recruited from both a geriatric ward and a nursing home and focused on observer-based pain assessments, Studies 2 and 3 were limited to individuals without CI or with CI of only mild severity. The latter studies examined facial and autonomic responses to pain in individuals with intact communication ability. As a result, the relationship between cognition and facial expression or autonomic responses to pain could only be explored in a sample without CI. Although facial expressions of pain have been largely studied in individuals with severe CI (Lautenbacher & Kunz, 2017), the transferability of such results to real-world settings has been rare. In particular, the applicability of prior findings and methods – such as FACS coding – has rarely been investigated during movements, such as ADLs. Thus, the open question remains: How well would facial expressions or autonomic responses serve as indicators of pain during activities of daily living in individuals with more advanced cognitive decline?

Second, specific cognitive domains may influence pain processing and expression. While this dissertation did not find an effect of mild levels of CI on autonomic responses, previous research

suggests that declines in specific domains (e.g., inhibition or working memory) can lead to a modulation of autonomic responses in individuals without dementia (Forte et al., 2019; Forte & Casagrande, 2025). Future studies should therefore specifically assess cognitive domains while also including populations with more severe CI, such as those with advanced stages of dementia.

Third, the evaluation of non-verbal pain assessment methods should not be limited to individuals with dementia. Instead, future research should adapt these approaches for use in other clinical conditions. For example, pain assessments via facial expressions or autonomic responses could be implemented with individuals experiencing Parkinson's disease, intellectual disabilities, or post-stroke conditions, as their verbal ability can be equally declined. It is also important to note that neither the ADL-induced pain nor the standardized pain stimulation methods used in this dissertation represented chronic pain conditions, such as lower back pain, postoperative pain, or arthritis, which are often associated with different physiological mechanisms (i.e., inflammation or nerve damage), which makes the applicability of our findings in this context limited. Future research should therefore investigate whether similar behavioral and autonomic pain assessment systems can be implemented with other types of clinically relevant pain conditions.

Fourth, it should be noted that, while useful, the assessment of pain responses in an LL likely cannot capture the complexity of clinical applications of the assessments used. To address this issue, it is particularly important to transfer the concepts described in this dissertation to actual care settings; for instance, by using a long-term ambulatory monitoring of autonomic responses during everyday activities (e.g., 24-hour ECG monitoring) or through wearable devices such as EDA sensors (see Snene et al., 2024). In addition, LL sensors generate extensive data streams from various sources, such as video and audio recordings, actigraphy, and smart floor data. However, not all data streams could be included in our work. In this dissertation, where we faced time constraints in manually evaluating facial expressions in older adults, finding a solution for the continued use of the data appears especially crucial, for example, using ML models and automated pain detection systems to further interpret multiple data streams.

Fifth, making data accessible through open access could be a possible solution for time-effectively reusing multi-sensor data streams. Thus, several existing examples, such as the BioVid Heat Pain Database or the PainMonit dataset (Gouverneur et al., 2024; Walter et al., 2013), demonstrate how open-access data frames can be used for advancing automated or ML-

based pain assessment methods and therefore contribute to time efficiency and transparency in the research context.

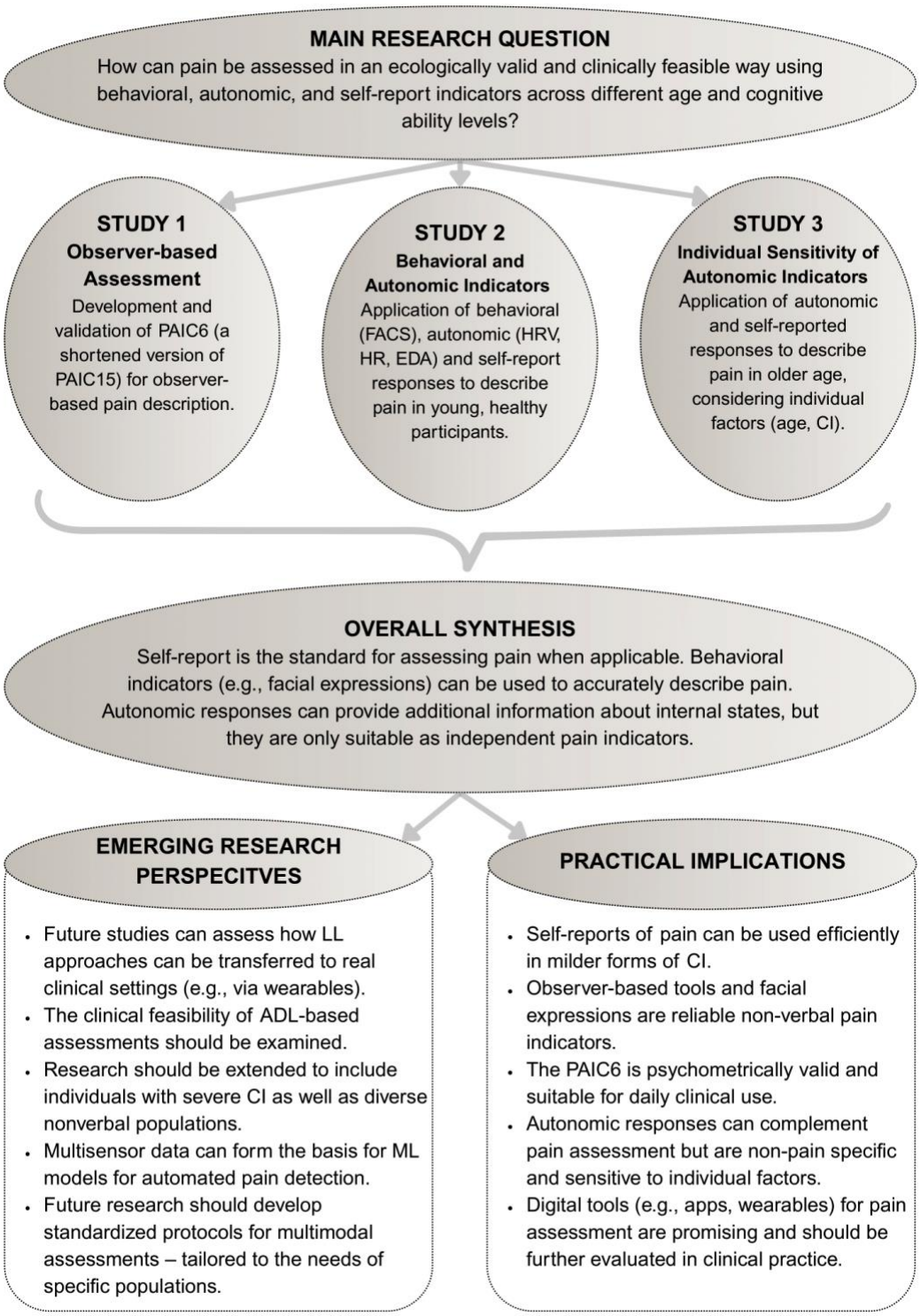
Sixth, the interpretation of autonomic responses remains challenging as they can not only be influenced by individual factors such as age and cognition, but also by contextual factors. For instance, HR and EDA may be affected by stress, medication, and comorbidities such as chronic pain (e.g., Saleem et al., 2023; Schubert et al., 2009; Yeater et al., 2021). At this point, it seems essential to explore the influence of individual and contextual factors on autonomic responses further before interpreting them as indicators of pain, which should be an angle for future research. A promising starting point for this kind of research could be latent class analyses, which allow for the identification of unobserved (latent) subgroups within the data that may share similar autonomic response patterns during pain. An example of how latent class modeling can be used in this context is illustrated by Zhao et al. (2024), who demonstrated the applicability of ML and latent class modeling to further classify chronic pain.

Taken together, these considerations underscore the importance of extending the findings of this dissertation to other populations in future studies. For example, this could include individuals with more severe CI, Parkinson's disease, or stroke. This is especially true for assessing pain using autonomic responses, as research in this area is still in its early stages. Furthermore, the ability of autonomic indicators to describe pain is limited by individual and contextual factors until further studies shed more light on the correlations. Additionally, open-source data sets offer the possibility of using data for automated and ML-based analyses in a time-efficient manner. Findings from the LL, such as the finding from Study 3 that there are no differences in autonomic responses between individuals without CI and individuals with CI of mild severity, should be replicated in clinical settings. Similarly, it would be useful to extend the findings of this dissertation to chronic pain conditions, as we only considered experimentally induced pain as part of this dissertation.

To provide an overview of the conceptual framework, findings, and implications of this dissertation, Figure 14 is presented on the following page.

Figure 14

Conceptual framework, findings and implications of this dissertation



Note. This figure illustrates the conceptual framework for how the various indicators of pain were brought together in this dissertation. It provides an overview of the findings, presents avenues for future research and the practical implications of these findings.

PAIC6 = Pain Assessment in Impaired Cognition, short version. PAIC15 = Pain Assessment in Impaired Cognition, full version (Kunz et al., 2020). CI = Cognitive impairment. LL = Living Lab. ADL = Activity of Daily Living. HR = Heart rate. HRV = Heart rate variability. EDA = Electrodermal activity. FACS = Facial Action Coding System.

5.5 Conclusion

This dissertation aimed to answer the main research question of how pain can be assessed in an ecologically valid and clinically feasible way. To this end, three studies were conducted that used different indicators of pain, including observer-based tools, facial expressions, autonomic responses, and self-reports of pain, conducted across different age and cognitive ability levels.

The key contribution of this dissertation lies in its integration of diverse methodological approaches, ranging from standardized pain induction protocols (i.e., pressure and heat pain) to more ecologically valid methods, such as the use of ADLs for pain induction. This approach enabled a specific focus on individual and contextual factors that influence pain assessments across various populations.

While our findings indicate that observer-based pain assessments and facial expressions of pain are currently the most reliable form of pain description – especially when working with non-verbal individuals – autonomic responses, especially HR and EDA, present an interesting new avenue in pain description.

However, our findings indicated that autonomic responses to pain were highly dependent on individual factors, such as age, and could only be interpreted as general physiological activation, not as specific to pain. Future research should therefore aim to disentangle the influences of individual factors (e.g., age and cognition) and contextual factors (e.g., medication) on autonomic responses, particularly focusing on non-verbal or cognitively impaired individuals.

Furthermore, this dissertation included a methodological innovation, as we were able to use an LL environment to conduct pain research. Hence, by conducting two of three studies in the BamLiD – a multi-sensor LL environment – we were able to show that such settings enable a standardized assessment of indicators, while methodologically bridging the gap between laboratory standard and clinical practice.

In particular, we were able to show that ADLs (e.g., kettlebell lifts) can trigger subjective and autonomic activation, especially when combined with muscle pre-activation (age simulation suit). However, the feasibility of LL technologies and ADL-based pain assessments in clinical practice still needs to be tested in future studies.

Furthermore, data collected in multi-sensor LL environments shows great promise for future research as their big data frameworks can be used to develop data-driven models (e.g., ML models) for pain detection. For this purpose, sharing data in open-access databases could be useful to enable efficient and transparent further use, for example, to improve ML models for pain recognition.

For the clinical applicability of multimodal, technology-based assessments, automated tools such as ePAT or PainChek® (Atee et al., 2017; Brett & Severn, 2023) seem to be particularly useful, as they enable time-efficient pain assessment in non-verbal individuals and have been specifically tested for people with dementia. In this context, the standardized use of specific ADLs to provoke everyday-relevant pain could be useful but requires physical fitness for the successful performance of ADLs.

Overall, although others described the successful implementation of autonomic responses as indicators of pain in ML models (Susam et al., 2018), based on our findings, it remains unclear whether autonomic responses can be considered specific indicators of pain. Additionally, future research should clarify whether LL-based approaches or simplified wearable alternatives (e.g., wristbands and smart watches) can be realistically translated into clinical routines. Future research should also explore the acceptance of technological tools and wearable pain devices by users, particularly among vulnerable populations such as individuals with dementia.

Ultimately, this dissertation provides a basis for the informed selection of pain assessment methods for diverse populations, using various indicators of pain to establish a highly individual-focused, context-sensitive pain assessment system tailored to the needs of individuals and caregivers.

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