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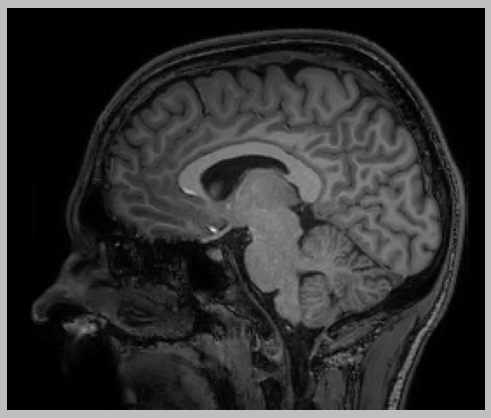
Doctoral Thesis

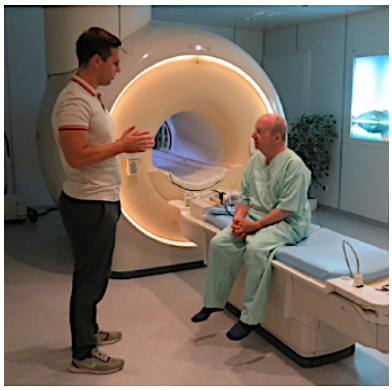
Patrick Manser

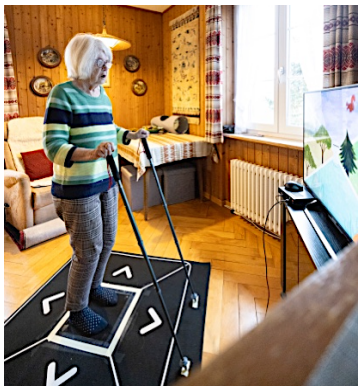
March 2024



Brain-IT

Targeting the **Brain** using **I**nformation **T**echnology for Secondary Prevention of mild Neurocognitive Disorder





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Brain-IT: Targeting the **Brain** using **I**nformation **T**echnology for Secondary Prevention of mild Neurocognitive Disorder

A thesis submitted to attain the degree of

DOCTOR OF SCIENCES

(Dr. sc. ETH Zurich)

presented by:

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2024

“The people who get on in this world are the people who get up and look for the circumstances they want, and if they cannot find them, they make them.“

(George Bernard Shaw)

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Chapter

1

Summary / Zusammenfassung

Abstract of the Doctoral Thesis in English and German

1.1 Summary

Introduction: Effective interventions to mitigate one of the key challenges for aging societies, neurocognitive disorders, are urgently needed. A collaborative international guideline recently recommended physical exercise (PE) for secondary prevention of mild neurocognitive disorder (mNCD). Physical exercises that integrate cognitive exercises and are combined with resonance breathing guided by heart rate variability biofeedback (HRV-BF) target various relevant mechanisms of action to alleviate the pathological state in mNCD. However, this novel intervention approach has not yet been investigated.

Methods: We systematically designed, developed, and evaluated a novel training concept (called 'Brain-IT') specifically for older adults with mNCD that implements this novel intervention approach. The projects' methodology followed the guidelines of the Medical Research Council for the development and evaluation of complex interventions as well as the Multidisciplinary Iterative Design of Exergames (MIDE) - Framework. Primary end users (individuals with mNCD), secondary end users (physiotherapists, occupational therapists, healthcare professionals), exergaming researchers, as well as experts from the exergaming industry were continuously involved to facilitate the acceptance and transfer of the resulting training concept into clinical practice.

Results: In the first phase of the project, we successfully determined a set of design requirements for the 'Brain-IT' training concept in collaboration with 10 experts and 8 individuals with mNCD. This set of design requirements formed the basis for phase 2, where a first prototype of the 'Brain-IT' training concept was co-designed and developed. We iteratively tested and refined this prototype until we achieved an "acceptable" (= feasible, usable, safe, and well accepted) solution. In the final randomized controlled trial (RCT), we observed statistically significant effects with large effect sizes for global cognitive performance, immediate verbal recall, and delayed verbal recall in favor of the intervention group. 55 % of participants showed a clinically relevant improvement in global cognitive functioning in response to training. The remaining (underpowered) statistical analyses revealed no significant effects, but favorable changes in descriptive statistics with small to moderate effects in favor of the intervention group, particularly with regards to quality of life.

Conclusion: Our rigorous methodological approach resulted in a user-centered, personalized, and highly innovative training concept. Notably, we revealed, to the best of our knowledge, as the first research team, that this novel intervention approach of combining exergame training with biofeedback-guided resonance breathing is not only safe, feasible, and highly accepted by individuals with mNCD, but also highly effective in improving cognitive performance. Confirmatory RCTs are warranted to (i) be able to conclude about potential near- and far-transfer effects of the training; (ii) investigate whether the observed improvements in cognitive performance translate to affecting the rates of progression to or onset of dementia; (iii) test the implementation of the training in clinical practice; and (iv) elucidate the underlying biological mechanisms of action.

1.2 Zusammenfassung

Einleitung: Wirksame Massnahmen zur Bekämpfung einer der grössten Herausforderungen für die alternde Gesellschaft, der neurokognitiven Störungen, sind dringend erforderlich. Eine internationale Gemeinschaftsleitlinie empfahl kürzlich körperliches Training zur Sekundärprävention leichter neurokognitiver Störungen (mNCD). Körperliches Training, das kognitives Training integriert und mit einer durch Herzfrequenzvariabilität-Biofeedback (HRV-BF) geleiteten Resonanzatmung kombiniert wird, zielt auf verschiedene relevante Wirkmechanismen ab, um den pathologischen Zustand bei mNCD zu lindern. Dieser neuartige Interventionsansatz ist jedoch noch nicht untersucht worden.

Methoden: Wir haben ein neuartiges Trainingskonzept (genannt 'Brain-IT') speziell für ältere Erwachsene mit mNCD systematisch konzipiert, entwickelt und evaluiert, das diesen neuartigen Interventionsansatz umsetzt. Die Methodik des Projekts folgte den Richtlinien des Medizinischen Forschungsrats für die Entwicklung und Untersuchung komplexer Interventionen sowie dem Multidisziplinären Iterativen Design von Exergames (MIDE) - Rahmenwerk. Primäre Endnutzer (Personen mit mNCD), sekundäre Endnutzer (Physiotherapeuten, Ergotherapeuten, Gesundheitsfachkräfte), Exergaming-Forscher sowie Experten aus der Exergaming-Industrie wurden kontinuierlich einbezogen, um die Akzeptanz und den Transfer des resultierenden Trainingskonzeptes in die klinische Praxis zu begünstigen.

Ergebnisse: In der ersten Phase des Projekts haben wir in Zusammenarbeit mit 10 Experten und 8 Personen mit mNCD erfolgreich eine Reihe von Designanforderungen für das 'Brain-IT'-Trainingskonzept ermittelt. Diese Designanforderungen bildeten die Grundlage für Phase 2, in der ein erster Prototyp des 'Brain-IT'-Trainingskonzepts kollaborativ gestaltet und entwickelt wurde. Wir testeten und optimierten diesen Prototyp iterativ, bis wir eine "akzeptable" (= machbare, nutzbare, sichere und gut akzeptierte) Lösung gefunden hatten. In der abschliessenden randomisierten kontrollierten Studie (RCT) beobachteten wir statistisch signifikante Effekte mit grossen Effektstärken für die globale kognitive Leistungsfähigkeit, das unmittelbare verbale Erinnerungsvermögen und das verzögerte verbale Erinnerungsvermögen zugunsten der Interventionsgruppe. 55 % der Teilnehmer zeigten eine klinisch relevante Verbesserung der globalen kognitiven Leistungsfähigkeit in Reaktion auf das Training. Die verbleibenden (nicht ausreichend aussagekräftigen) statistischen Analysen ergaben keine signifikanten Effekte, aber günstige Veränderungen in der deskriptiven Statistik mit kleinen bis moderaten Effekten zugunsten der Interventionsgruppe, insbesondere im Hinblick auf die Lebensqualität.

Schlussfolgerung: Unser rigoroser methodischer Ansatz führte zu einem nutzerzentrierten, personalisierten und höchst innovativen Trainingskonzept. Insbesondere konnten wir, nach bestem Wissen als erstes Forschungsteam, zeigen, dass dieser neuartige Interventionsansatz, der ein Exergame-Training mit biofeedback-geführter Resonanzatmung kombiniert, nicht nur sicher, machbar und von Personen mit mNCD gut akzeptiert ist, sondern auch hochwirksam zur Verbesserung der kognitiven Leistungsfähigkeit ist. Bestätigende RCTs sind erforderlich, um (i) Rückschlüsse auf potenzielle Nah- und Ferntransfereffekte des Trainings ziehen zu können; (ii) zu untersuchen, ob die beobachteten Verbesserungen der kognitiven Leistungsfähigkeit sich auf die Raten des Fortschreitens oder Auftretens von Demenz auswirken; (iii) die Umsetzung des Trainings in der klinischen Praxis zu testen; und (iv) die zugrunde liegenden biologischen Wirkmechanismen zu ergründen.

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Chapter

2

General Introduction

Background, Rational and Objectives of the Thesis

Neurocognitive disorders represent a key challenge for aging societies. The global prevalence of neurocognitive disorders is projected to increase dramatically, leading to a significant rise in its societal impact and costs. To mitigate this impending escalation, it is imperative to implement sustainable and efficacious measures aimed at averting its progression. [1] Individuals at an early stage of the disease (mild cognitive impairment (MCI) or mild neurocognitive disorder (mNCD) [2-6]) may represent an optimal target population for early pharmacological and non-pharmacological interventions [7]. Current clinical practice guidelines' recommendations for treatment and management of individuals with mNCD/MCI can be classified into four categories: interventions for risk reduction, pharmacologic interventions, non-pharmacologic interventions, and counseling [8]. While pharmacological therapies may become available in the future for older adults with mNCD due to Alzheimer's disease [9], concerns about their safety and affordability [10] make their adoption on a larger scale unlikely in the near future. Moreover, about 10 - 40 % of older adults with mNCD do not have an Alzheimer's disease etiology [5], thus little can be offered to these patients in pharmacological therapeutic terms.

Estimates suggest that potentially modifiable risk factors account for up to half of all cases of dementia worldwide [11, 12]. Consequently, a growing body of research suggests that non-pharmacological interventions and lifestyle changes targeting modifiable risk factors [13] can slow down cognitive decline [14, 15] or even improve cognitive functioning [16-18] and, therefore, hold promise to mitigate the risk for developing dementia [14, 15]. Physical inactivity is linked to various other modifiable risk factors [11]. Consequently, physical training is effective in reducing various cardiovascular risk factors [19] and depressive symptoms [20] across a wide range of populations, including mNCD [21] and was shown to be the predominant non-pharmacological intervention that effectively mitigates cognitive decline in individuals with mNCD [16]. Therefore, physical exercise was recently recommended for secondary prevention of mNCD by a collaborative international guideline [22].

Physical training is proposed to operate through various mechanisms. In mNCD, an abnormal accumulation of proteins in the brain frequently occurs. This process is further exacerbated by excessive oxidative stress, metabolic disorder, and neuroinflammation within the brain leading to neuropathological damage. Physical training has the potential to alleviate this pathological state [23] via the following proposed mechanisms: (1) the enhancement of brain plasticity [23, 24]; (2) the improvement of mitochondrial health, leading to a reduction in oxidative stress and enhanced energy metabolism in the brain [23]; (3) the promotion of cytokine release, subsequently triggering the secretion of neurotrophic factors, reducing immune-inflammatory responses, relieving stress on brain tissue, improving synaptic plasticity, and exerting protective effects on neurons [23, 24]; and (4) the improvement of brain metabolism, manifested in enhanced glucose metabolism, better energy support for brain tissue, reduced insulin resistance, decreased deposition of Tau and Aβ proteins, activation of hippocampal autophagy, and clearance of neurofibrillary tangles; [23, 24]. In addition to the reduction of neuropathological damage, physical training also allows the maintenance or increase of cognitive reserve [12, 24], which empowers individuals to maintain a 'normal' level of functioning, even in the presence of neurodegenerative changes [11, 25, 26]. The mechanisms underlying cognitive reserve may encompass sustained metabolic activity or heightened connectivity within temporal and frontal brain regions [12], while good physical health also contributes to tolerating a higher burden of neuropathology without experiencing cognitive impairment [27].

Where physical frailty can be seen as emerging from dysregulation of multiple interconnected physiological and biological systems that cross a threshold to critical dysfunction, thus severely compromising homeostasis [28], a similar phenomenon can be assumed for cognitive frailty. Several studies have reported the interactions between neuro-immune, immune-metabolic and neuro-metabolic pathways [29], which also bears relevance for individuals with Alzheimer's disease [30, 31]. Consequently, interventions such as motor-cognitive training that have multisystem effects are expected to be more promising to remedy cognitive frailty than interventions targeted at replenishing single systems.

According to the 'guided-plasticity facilitation' framework [32-34], the simultaneous execution of physical and cognitive activities is most beneficial to improve cognitive functioning because it has positive synergistic effects that surpass the mere sum of their individual effects. These additive synergistic effects arise from the "facilitation effects" of physical exercises and the "guidance effects" of cognitive exercises. Physical exercise triggers neurophysiological mechanisms, such as the direct release of brain-derived neurotrophic factor (BDNF), insulin-like growth factor-1 (IGF-1), and vascular endothelial growth factor (VEGF) in the brain, as well as an increase in circulating skeletal muscle-derived biomolecules irisin and cathepsin B. These biomolecules are associated with synaptogenesis, neurogenesis, and angiogenesis. [24, 32-34] The guidance effects provided by cognitive exercises supports these neuroplastic processes, facilitating the survival and integration of new neuronal structures in brain circuits, which is essential for stabilizing the neuroplastic changes induced by motor-cognitive training. [32-34] Theoretically, this works best when the cognitive task(s) are integrated into motor task(s) [34]. This prediction is supported by recent meta-analytic evidence, showing that simultaneous motor-cognitive training was most efficacious for improving cognitive functioning in individuals with mNCD [35].

Despite these well-established benefits, the persistently high prevalence of insufficient physical activity among older adults (with mNCD) remains a cause for concern. The majority of older adults (with mNCD) fail to meet the global recommendations on physical activity for health outlined by the World Health Organization [36-38]. In light of this observation, it is imperative to actively recommend and motivate individuals with mNCD or those at risk for cognitive impairment to enhance their levels of physical and cognitive activity. Paradoxically, less than one third of current clinical practice guidelines advocate for physical and/or cognitive activity, only one guideline recommends physical exercise and none specifically endorse physical training or simultaneous motor-cognitive training [8]. Possible barriers for the implementation of simultaneous motor-cognitive training for secondary prevention of MCI/mNCD in clinical practice might include challenges in patient adherence and motivation and/or limited time- and personnel resources as well as standardized protocols. However, successful interventions for secondary prevention of mNCD require that patients adhere to the interventions over the long term.

Technological innovations, such as exergames, provide new avenues for engaging older adults with mNCD in simultaneous motor-cognitive training [39]. Exergaming are *"technology-driven physical activities, such as video game play, that requires participants to be physically active or exercise in order to play the game"* [40]. Exergaming offers improved standardization of training through its ability to provide structured and scalable training options. It offers multisensory feedback to enhance skill acquisition and neuroplasticity by means of repetitive practice in an enriched environment [41] and optimizing resource utilization in intervention implementation, as it is accessible for home-based use

[42]. This, consequently, reduces the amount of time and personnel resources required. Finally, and perhaps most importantly, a key advantage of exergaming over conventional motor-cognitive training is its high acceptance among individuals with mNCD. This high level of acceptance facilitates patient motivation [42] and promotes positive behavioral changes [43], resulting in high rates of adherence to training [42, 44].

Previous systematic reviews and meta-analyses consistently support the positive effects of exergaming on cognitive functioning in individuals with mNCD. However, there is significant variation in exergame-based training approaches [42] and there is room for improvement by developing novel exergames and exergame-based training concepts that ensure implementation of effective training components specifically tailored to requirements and needs of individuals with mNCD [45]. It seems fair to state that purpose-developed exergames and exergame-based training concepts specifically targeting individuals with mNCD will presumably have larger effects in individuals with mNCD.

For older adults with mNCD specifically, it is imperative to also consider that these individuals often have disrupted self-regulatory capacity to flexibly adapt to daily life challenges [46]. This capacity is supported by the central autonomic networks (CAN). According to the Neurovisceral Integration Model, the CAN can be viewed as an integrated component of an internal regulatory system in which the brain controls visceromotor, neuroendocrine, and behavioral responses that are critical for goal-directed behavior, adaptability, and health [47]. To maximize effectiveness of interventions to prevent cognitive impairment, interventions should be designed to also target this network specifically.

This could be achieved by combining exergaming with resonance breathing guided by heart rate variability biofeedback (HRV-BF). HRV-BF training is a behavioral intervention aiming to increase cardiac autonomic control, to enhance homeostatic regulation, and to regulate emotional state [48-50]. An increased cardiac autonomic control is predicted to increase vagal afferent transmission to the forebrain, activate the prefrontal cortex, and improve executive function [48]. In fact, multiple systematic reviews and meta-analyses have indicated that HRV-BF or paced breathing (at resonance frequency) are effective in improving cardiac autonomic control [50, 51], cognitive functioning (in particular executive functions) [52, 53], and emotional regulation [50, 53] (i.e., by decreasing symptoms of depression [50, 53, 54], anxiety [50, 54, 55], and stress [54, 55]) across different age groups and also clinical populations. These effects might be explained by an increase in brain activity in regions relevant for cognitive adaptations [50]. Moreover, there is evidence supporting a causal role of cardiac autonomic control in modulating plasma Alzheimer's disease-related biomarkers [56]. Although HRV-BF has been suggested useful as a complementary treatment [53], its combination with (exergame-based) motor-cognitive training remains to be investigated.

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Chapter

3

Overview of the Thesis

Overview of the Structure and Contents of the Thesis

In this doctorate project, I coordinated - under supervision of Prof. Dr. Eling D. de Bruin and in collaboration with many collaborators and partners acknowledged in chapter 12 - the development of a novel exergame-based training concept specifically for secondary prevention of mNCD. This training concept represents a guideline for applying a combination of exergame-based motor-cognitive training and HRV-guided resonance breathing by standardizing the training characteristics (e.g., training frequency, intensity, duration) as well as the structure and content of training and can be implemented with different hardware and software solutions. The training concept was developed on basis of a structured, iterative, and evidence-based approach based on the MIDE-Framework [57]. This process allowed identification of multiple key requirements for exergame design as well as training characteristics that have formed the basis for determining components of the resulting training concept [45, 58]. A detailed description of the rigorous, structured, iterative, and evidence-based design and development process as well as the first prototype of our resulting 'Brain-IT' training concept were published in the journal 'Frontiers in Aging Neuroscience' [58] and are described in **chapter 4** of this doctoral thesis.

To summarize the methodology of this project, the 'Brain-IT' project was aligned with the recommendations of the MIDE-Framework and structured in three phases: Phase 1 - Contextual Research; Phase 2 - Game Design & Development; and Phase 3 - System Evaluation. In phase 1, a synthesis of evidence was combined with qualitative research by performing focus groups in multidisciplinary teams and semi-structured interviews with older adults with mNCD in order to specify a set of design requirements for the exergame-based training concept. In phase 2, possible concepts for the exergame-based training concept were elaborated by co-design and based on the set of design requirements defined in phase 1. The first prototype of the resulting 'Brain-IT' training concept then entered the iterative cycle of feasibility, usability, safety and acceptance testing and integrating study results for further development based on co-design until an "acceptable" solution was achieved. In this regard, we conducted a pilot randomized controlled study (RCT) including 18 individuals with mNCD. Based on the results of this pilot randomized controlled study, minor modifications were incorporated to further optimize the 'Brain-IT' training concept. Subsequently, in Phase 3, the effectiveness of the addition of the 'Brain-IT' training to usual care was systematically investigated in a RCT.

Phase 1 included two studies/publications. The first was a thorough synthesis of the evidence regarding the effects of cognitive, physical, and combined motor-cognitive training (including exergames) on cognition, brain structure and function, functional physical outcomes, and quality of life in healthy older adults as well as older adults with mNCD. These findings were published within our methodological paper [58] and are part of chapter 4 of this doctoral thesis. The goal of this step was *"to understand the current theoretical and methodological contributions to the technology advancements, research methodologies, design considerations, and intervention evaluations"* [57]. The second step of this phase aimed at determining the *"preferences and needs of the targeted user group from a multi-disciplinary perspective in order to optimize the exergaming experience. In addition to general aspects such as demographics, capability, characteristics, hobbies, and motivators for playing, exergame-specific user models should also include other attributes like the facilitators and barriers to physical activity engagement"* [57]. With this regard, the clinical picture, epidemiology, risk factors, prevention, and therapy options were summarized based on a literature search of the current evidence (see [58] and chapter 4 of this doctoral thesis). In addition, we aimed

to determine the capabilities, treatment preferences, and motivators for the training of older adults with mNCD and the perspectives of individuals on training goals and settings and requirements for exergame and training components in a qualitative study [45]. The qualitative study was published in the journal 'JMIR serious games' [45] and presented in **chapter 5** of this doctoral thesis. This qualitative study included focus groups with 10 experts and health care professionals and individual semistructured in-depth interviews with 8 older adults with mNCD. We concluded that *"the psychosocial consequences of patients' self-perceived cognitive deterioration might be more burdensome than the cognitive changes themselves. Older adults with mNCD prefer integrative forms of training (such as exergaming) and are primarily motivated by enjoyment or fun in exercising and the effectiveness of the training. Putting the synthesized perspectives of training goals, settings, and requirements for exergames and training components into context, our considerations point to opportunities for improvement in research and rehabilitation, either by adapting existing exergames to patients with mNCDs or by developing novel exergames and exergame-based training concepts specifically tailored to meet patient requirements and needs."* [45] Finally, this first phase of the project also included determining the therapeutic needs with the aim to: (1) *"specify the users' fitness goals, training settings, and outcome measures"* [57]; and (2) *"determine the core components of the training plan (e.g., type of exercise, target outcomes, based on FITT-VP: Frequency, Intensity, Type, Time, Volume, and Progression model)"* [57]. To specify the patients' training goals and -settings and to support the determination of the most suitable exergame intervention components, we relied on the integration of the outcomes of (a) a comprehensive literature synthesis regarding moderating effects of training interventions on training efficacy (see [58] and chapter 4 of this doctoral thesis), and (b) the qualitative study including semi-structured interviews with older adults with mNCD and focus groups with healthcare professionals (see [45] and chapter 5 of this doctoral thesis). This phase also included considerations about technology scoping and a sustainability strategy, both reported in [45] and chapter 4 of this doctoral thesis. Finally, we integrated all the acquired knowledge of this phase to determine a set of design requirements for a training concept (see [45] and chapter 4 of this doctoral thesis).

This set of design requirements built the basis for phase 2 of the project, where we aimed to develop a fully functional prototype supported by multidisciplinary teamwork including the exergaming industry, game designers, clinical experts, researchers, and, of course, the end user [57]. Our reflections on these game design considerations and our proposed solutions are summarized in [45] and chapter 5 of this doctoral thesis. As we were confronted with evidence that one the one hand a very well-working progression algorithm and progression rules to ensure that the patients are optimally challenged and avoid causing frustration and/or refusal of playing games due to under or over demanding training, but on the other hand the existing progression algorithm were reported not to work properly in patients with mNCD [45] and the optimal marker(s) to monitor internal training load remains to be discovered [59], we conducted an additional study aiming to investigate the reliability and validity of promising new parameter(s) for monitoring internal training load. This study has been submitted to the journal 'BMC Sports Science, Medicine and Rehabilitation' in June 2023 and is still under review. The results of this study helped working out the first prototype of our training concept, but did not play a key role in the project. Therefore, it was considered a side project and not included in this doctoral thesis. Subsequently, we developed a first version of the training concept (called 'Brain-IT', published as supplementary file 3 of [58] and conducted a pilot randomized controlled feasibility study to evaluate feasibility, system usability, and acceptance of the 'Brain-IT'

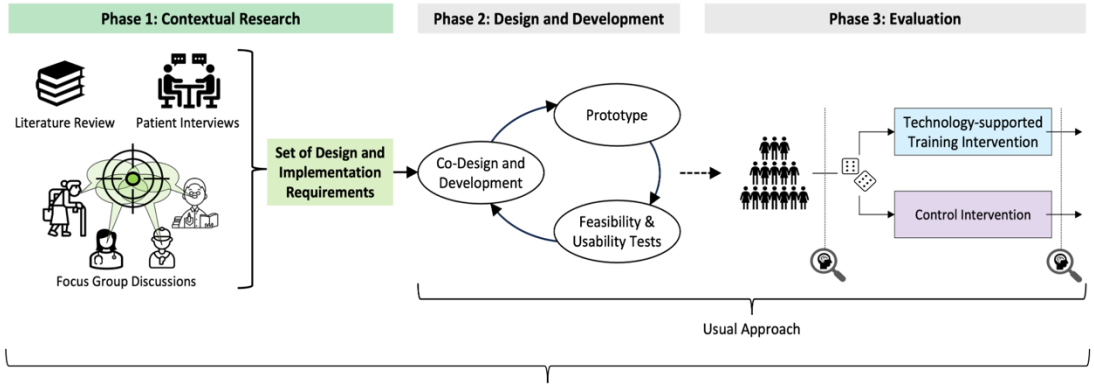
training for older adults with mNCD. This pilot RCT was published in the journal 'Frontiers in Aging Neuroscience' [60] and is presented in **chapter 6** of this doctoral thesis. We concluded that feasibility and usability of the 'Brain-IT' training implemented with the 'Senso Flex' are acceptable. To optimize feasibility, either improvements or alternative solutions are required in the hardware and software of the exergame used to implement the 'Brain-IT' training. The 'Brain-IT' training itself was well accepted by older adults with mNCD. Based on the findings of this study, minor modifications were incorporated to further optimize the 'Brain-IT' training concept, making it applicable for the systematic evaluation of effectiveness in samples of older adults with mNCD.

In Phase 3, we systematically investigated the effectiveness of the addition of the 'Brain-IT' training to usual care compared to usual care alone. The study protocol was published in the journal 'JMIR Research Protocols' [61] and is presented in **chapter 7** of this doctoral thesis. As primary outcome, global cognitive functioning is assessed. As secondary outcomes, the effects of the 'Brain-IT' training on (a) domain-specific cognitive functioning (i.e., learning and memory, complex attention, executive function, and visuospatial skills), (b) brain structure and function, (c) spatiotemporal parameters of gait, (d) instrumental activities of daily living (IADL), and (e) psychosocial factors (i.e., QoL [quality of life], and levels of depression, anxiety, and stress), and (f) cardiac vagal modulation (i.e., resting vagally-mediated heart rate variability [vm-HRV]) in older adults with mNCD as compared with usual care were explored. The main results of this study were submitted to the journal 'Alzheimer's & Dementia' in February 2024 (manuscript under review) and are presented in **chapter 8** of this doctoral thesis. The results of this study provide robust evidence that 'Brain-IT' training is effective for enhancing global cognitive performance, immediate verbal recall, and delayed verbal recall. More specifically, we found significant effects with large effects sizes in favor of the intervention group for global cognitive functioning ($F(1, 36) = 8.32$, $p = 0.007$, partial η^2 (η^2_p) with 90 % confidence interval [$CI_{90\ \%}$] = 0.197 [0.034, 0.371]) as well as immediate ([$F(1, 34) = 5.83$, $p = 0.022$, η^2_p [$CI_{90\ \%}$] = 0.154 [0.013, 0.332]) and delayed ([$F(1, 34) = 8.18$, $p = 0.007$, η^2_p [$CI_{90\ \%}$] = 0.204 [0.034, 0.382]) verbal recall. A post-hoc power analysis with G*Power (version 3.1.9.6) [453] revealed a statistical power of 0.832 for the analysis on the primary outcome. 55 % of participants in the intervention group and 23 % of participants in the control group were responders, showing a clinically relevant improvement in global cognitive performance. The remaining (underpowered) statistical analyses revealed no significant effects, but favorable changes in descriptive statistics with small to moderate effects in favor of the intervention group, especially with regards to quality of life. Details on the methods for analyzing the magnetic resonance imaging scans (secondary objective (b)) are dependent on the above-mentioned findings, because we aimed to explore possible underlying neural changes of the training in relation to adaptations in cognitive performance. Therefore, these results will be reported separately in focused manuscripts. These analyses are ongoing and are done by the doctoral candidate in collaboration with experts for magnetic resonance imaging, however, were outside the scope of this doctoral thesis.

Chapter 9 provides a general discussion of the thesis and future prospects. **Chapter** 10 provides supplementary files related to chapter 8. **Chapter 11** contains the bibliography of the thesis. In **chapter 12**, I acknowledge the most important partners and collaborators who have directly or indirectly contributed to the success of this thesis. **Chapter** 13 contains my curriculum vitae.

Chapter

4



Our Approach

with continuous active involvement of:

Primary End Users
↳ Older Adults with mNCD

Secondary End Users
↳ Physiotherapists
↳ Occupational Therapists
↳ Healthcare Professionals

Other Exergaming Researchers
↳ experienced with other technologies

Exergaming Industry
↳ Experts
↳ Representatives

Paper 1:

Making the Best Out of IT: Design and Development of Exergames for Older Adults With Mild Neurocognitive Disorder - A Methodological Paper

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4.1 Abstract

Background: Utilizing information technology (IT) systems, for example in form of computerized cognitive screening or exergame-based (also called active videogames) training, has gained growing interest for supporting healthy aging and to detect, prevent and treat neurocognitive disorders (NCD). To ameliorate the effectiveness of exergaming, the neurobiological mechanisms as well as the most effective components for exergame-based training remain to be established. At the same time, it is important to account for the end-users' capabilities, preferences, and therapeutic needs during the design and development process to foster the usability and acceptance of the resulting program in clinical practice. This will positively influence adherence to the resulting exergame-based training program, which, in turn, favors more distinct training-related neurobiological effects.

Objectives and Methods: This methodological paper describes the design and development process of novel exergame-based training concepts guided by a recently proposed methodological framework: The 'Multidisciplinary Iterative Design of Exergames (MIDE): A Framework for Supporting the Design, Development, and Evaluation of Exergames for Health' [57].

Case Study: A step-by-step application of the MIDE-framework as a specific guidance in an ongoing project aiming to design, develop, and evaluate an exergame-based training concept with the aim to halt and/or reduce cognitive decline and improve quality of life in older adults with mild neurocognitive disorder (mNCD) is illustrated.

Discussion and Conclusion: The development of novel exergame-based training concepts is greatly facilitated when it is based on a theoretical framework (e.g., the MIDE-framework). Applying this framework resulted in a structured, iterative, and evidence-based approach that led to the identification of multiple key requirements for the exergame design as well as the training components that otherwise may have been overlooked or neglected. This is expected to foster the usability and acceptance of the resulting exergame intervention in "real life" settings. Therefore, it is strongly recommended to implement a theoretical framework (e.g., the MIDE-framework) for future research projects in line with well-known checklists to improve completeness of reporting and replicability when serious games for motor-cognitive rehabilitation purposes are to be developed.

4.2 Introduction

4.2.1 Background

Utilizing information technology (IT) systems, for example in form of computerized cognitive screening or exergame-based (also called active videogames) training, has gained growing interest for supporting healthy aging and to detect, prevent and treat neurocognitive disorders [62, 63]. *"An exergame is a videogame that promotes (either via using or requiring) players' physical movements (exertion) that is generally more than sedentary and includes strength, balance, and flexibility activities"* [64]. Specifically designed and/or implemented games within these training settings are also called 'serious games'; games developed with a purpose beyond play [65, 66]. Using exergames for therapeutical interventions complements traditional exercises by using virtual reality, feedback principles and gamification to increase patient motivation and engagement [67]. This offers *"the unique opportunity for patients to interact in an enriched environment, providing structured, scalable training opportunities augmented by multi-sensory feedback to enhance skill learning and neuroplasticity through repeated practice"* [41]. Recent meta-analytic reviews have synthesized that exergame-based training interventions significantly improved various health-related outcomes, including cognitive performance [62, 68] and functional physical outcomes (i.e., balance, mobility, exercise capacity) [68, 69] in healthy older adults (HOA) as well as in populations with conditions associated with NCD. Furthermore, exergame-based interventions are greatly accepted in individuals with mNCD and increase training adherence and engagement through facilitating training motivation and satisfaction [42].

Exergames are a form of simultaneous motor-cognitive training with incorporated cognitive task demands [34]. According to the 'guided-plasticity facilitation' framework [32-34], acute physical exercise is assumed to enhance brain metabolism and promote neuroplastic processes, whereas these changes in brain plasticity are guided by cognitive stimulation [32, 33, 70]. These cognitive and physical exercise demands may exert synergistic effects on brain structural and functional adaptations as well as on cognition, indicating an advantage for combined training against isolated training of either physical or cognitive functions [70, 71]. Indeed, meta-analytic results have recently synthesized simultaneous motor-cognitive training to be the most effective type of training for improving cognitive functioning in HOA [35, 72] and older adults with mNCD [35, 73, 74]. This is also evidenced by slightly superior effects of exergames on cognitive functioning when compared to physically or cognitively active control interventions [62, 68, 75]. However, there are often substantial between-study heterogeneities and inconsistent reporting of interventions, which makes it difficult to draw reliable conclusions about the effectiveness of simultaneous motor-cognitive [70, 71, 76-78] or exergame-based [42, 62, 68, 79-81] training interventions. Further investigations are needed *"to establish the neurobiological mechanisms and effective components of exergames for cognition, and apply this understanding in the development of evidence-based exergame interventions"* [62] in older adults with NCDs [42, 44, 62, 71, 78, 80-83].

Besides establishing the most effective components [i.e., qualitative (e.g., type and content of training) and quantitative (e.g., frequency, intensity/complexity, session duration, intervention dose and adaptation over time) exercise and training variables] of exergames for cognition, it is crucial to also account for the users' perspective when designing and developing novel exergames or training concepts. A recent meta-analysis of training intervention studies in older adults with NCDs has shown

that *"improvements in cognitive function were greater in samples that reported greater adherence to the exercise training interventions"* [84]. Therefore, *"maximizing the effectiveness of interventions to increase and maintain exercise behavior will necessitate an understanding of the dynamic nature of the behavior-change process"* [85]. In short, adherence to training interventions is key to obtain and preserve health benefits [85].

"Adherence can be intended as 'maintaining an exercise regimen for a prolonged period following the initial adoption phase'" [86, 87] and is usually calculated as *"the proportion between the number of sessions attended and the number of sessions offered, reported in percentage"* [86]. Adherence rates are generally high in exergame-based intervention studies including HOA [69, 88] and older adults with NCDs [42, 44]. However, factors and strategies that mediate adherence of exergame-based interventions remain to be established, like indicated by two systematic reviews. Howes et al. (2017) aimed to explore the properties of exergame-based training interventions associated with improved adherence and showed that *"detail of interventions and game design were generally poorly described in terms of promoting adherence, with research in this area still at the stage of testing intervention efficacy, rather than methods of encouraging long-term adherence"* [68]. Stanmore et al. (2017) stated that the *"variance in participant adherence to the different interventions could not be accounted for in our analyses (as adherence/engagement variables were insufficiently reported across the eligible studies)"* [62].

From physical training studies, it is known that various factors contribute to the individual's decision to adhere to a training program in older adults. These factors include a range of program characteristics as well as person-level factors (e.g., demographic factors, health status, physical- and cognitive abilities, psychosocial factors) [89], but also the attitude toward the value and importance of training, the perceived behavioral control/self-efficacy, the perceived social support, as well as the perceived benefits/barriers and motivation/satisfaction of continued activity [90]. *"Because adherence (or lack thereof) is so crucial to obtain study outcomes, effective strategies and adequate resources should be deployed to address this issue"* [86]. A recent narrative review synthesized a wide range of support strategies to promote adherence to physical training in older adults with NCD and reported that training interventions *"should be individually tailored, include a learning or adaptation period, provide sufficient information and use phone calls, pedometers, exercise logs and/or reminders as well as supervision and planning to support adherence to the intervention"* [91].

When considering the design of computer-based cognitive training programs, the characteristics, needs, and experiences of the target population should be taken into account. A recent systematic review of Diaz Baquero et al. (2021) synthesized, that most often, an end-user centered methodological design is adopted [92]. Ideally, this process fulfills *"the international standards proposed by ISO9241-210 [93] for the development of programs: (1) understanding and specifying the context of use (type, characteristics and tasks of users, and physical or social environment), (2) specifying the user requirements, (3) producing design solutions, and (4) evaluating the design"* [92]. However, it was shown that only half of the studies took the standard 'specification of user requirements' into account [92]. Diaz Baquero et al. (2021) concluded that *"it is therefore strongly recommended that future studies use an interactive and participatory design, including end users from the beginning of the pre-prototype development, carrying out evaluations in order to identify user requirements and, in turn, including them in the final development of the prototype"* [92].

Additionally, their finding indicates *"the need to apply this methodology in a more standardized way"* [92].

Recently, a novel methodological framework was introduced that deems to be suitable to optimally support the process of developing exergames for health in older adults: the 'Multidisciplinary Iterative Design of Exergames (MIDE): A Framework for Supporting the Design, Development, and Evaluation of Exergames for Health' [57]. The MIDE-Framework aims to provide comprehensive, integrative, and specific guidance in the design, development, and evaluation of exergames for older adults on basis of an integrated and multifaceted approach. The novelty of the MIDE-Framework is, that is does not only focus on game elements or game development considerations, but also provides a systematic process to guide other relevant stages, such as contextual research and system evaluation. [57]

4.2.2 Objectives

The aim of this methodological paper is to describe the design and development process of a novel exergame-based training concept for older adults with mNCD guided by the MIDE-Framework.

4.3 Methods

A step-by-step application of the MIDE-framework in an ongoing project aiming to design, develop, and evaluate an exergame-based training concept to halt and/or reduce cognitive decline and improve quality of life in older adults with mNCD is illustrated in a case study.

4.4 Case Study

4.4.1 Overview

The ongoing project is called 'Brain-IT' and started in August 2020. In this project, it is aimed to (a) determine the most suitable components for an exergame-based training in older adults with mNCD; (b) explore novel strategies for a real-time adaptive exergame system to individually tailor exergame demands according to the users' physical and/or cognitive capabilities; (c) incorporate the acquired knowledge into an exergame-based training concept with the aim to halt and/or reduce cognitive decline and improve quality of life and finally; (d) to evaluate the effectiveness of the resulting training intervention in older adults with mNCD.

According to the MIDE-Framework the project was structured in three phases: Phase 1 - Contextual Research; Phase 2 - Game Design and Development; and Phase 3 - System Evaluation. In phase 1, a synthesis of evidence was combined with qualitative research by performing focus groups in multidisciplinary teams and semi-structured interviews with older adults with mNCD in order to specify a set of design requirements for the exergame-based training concept. In phase 2, possible concepts for the exergame-based training concept were elaborated based on the set of design requirements defined in phase 1. The resulting training concept is currently being tested on its feasibility, usability, and acceptance (Phase 2 - Game Design and Development, Step 4 - Pilot-testing of the Exergame-based Training Concept; see Table 4-1.

Table 4-1: Overview over the three phases of the overall project

Overall Aim	Specific Goal	Methods / Studies	Section
Phase 1 - Contextual research (July 2020 - January 2021)			
Specify design requirements of the exergame-based training concept to be followed in the design and development phase.	Step 1: Synthesis of Current Knowledge	Literature Review	*"Step 1: Literature Review"*
	Step 2: User Modeling	Literature Review, Qualitative Study	*"Step 2: User Modeling"*
	Step 3: Determination of Therapeutic Needs	Literature Review, Qualitative Study	*"Step 3: Therapeutic Needs"*
	Step 4: Technology Scoping	Collaboration with Dividat AG	*"Step 4: Technology Scoping"*
	Step 5: Sustainability Strategy	Collaboration with Dividat AG	*"Step 5: Sustainability Strategy"*
Phase 2 - Game Design and Development (February 2021 - March 2022)			
Development of a fully functional prototype of the exergames and the exergame-based training concept supported by multidisciplinary teamwork including the exergaming industry, game designers, clinical experts, researchers, and the end user.	Step 1: Game Design	Literature Review, Qualitative Study	*"Step 1: Game Design"*
	Step 2: Development and Validation of Adaptation Loop	Systematic Review, Validation Study	*"Step 2: Development and Validation of Adaptation Loop"*
	Step 3: Development of the Exergame-based Training Concept		*"Step 3: Development of Exergame-based Training Concept"*
	Step 4: Pilot-testing of the Exergame-based Training Concept	Pilot Randomized Controlled Study	*"Step 4: Playtesting of Exergame-based Training Concept"*
	Step 5: Modification of Exergame- & Intervention Components		*"Step 5: Modification of Exergame-based Training Concept"*
Phase 3 - System Evaluation (Start: April 2022)			
Evaluate of the effectiveness of the resulting exergame-based training concept.	To systematically evaluate the effectiveness and user acceptance of the resulting exergame-based training concept with respect to global cognition as primary outcome and domain-specific cognitive functioning, brain structure and function (measured by magnetic resonance imaging), cardiac vagal modulation (heart rate variability and its associations to neurobiological and cognitive changes), gait and psychosocial factors (e.g., quality of life, motivation, depression, anxiety, stress) will be investigated.	Randomized Controlled Trial	*"Phase 3: Svstem Evaluation"*

In this project, the exergame training system Dividat Senso (Dividat AG, Schindellegi, Switzerland; CE certification) and its home-based version Dividat Senso Flex are used. In both cases, the system contains a pressure-sensitive platform (1.13 m × 1.13 m; strain gauges measuring at 50 Hz) thereby detecting participants' position and timing of movements. The stepping platform is divided into five areas: (1) center (home position), (2) front, (3) right, (4) back, and (5) left. Weight-shifting and stepping movements to the four directions enable the interaction and control of the virtual exergame scenarios that are displayed on a screen right in front of the participant. Visual, auditory and

somatosensory (vibrating platform) feedback is provided in real-time in order to enrich the game experience.

4.4.2 Phase 1: Contextual Research

The overall goal of phase 1 is to specify a *"set of design requirements that includes design considerations, accessibility recommendations, user modeling elements, and technological reflections to be followed in the design and development phase"* [57]. Therefore, the project started by a thorough literature review and synthesis of evidence of the current knowledge regarding the effects of cognitive, physical, and combined motor-cognitive training (including exergames) on cognition, brain structure and function, functional physical outcomes, and psychosocial factors in HOAs as well as older adults with NCD. Building on that, a user modeling and determination of therapeutic needs was performed. By combining an evidence-based approach with theoretical and practical workshops in multidisciplinary teams including older adults with mNCD, healthcare professionals, and experts of the exergaming industry, possible concepts for the exergame-based training were elaborated. Finally, the hardware and software requirements to allow the integration of these concepts into exergames suitable for clinical use were determined.

Step 1: Literature Review

The project started with synthesizing recent systematic reviews and meta-analyses regarding the effects of cognitive, physical, and combined motor-cognitive training (including exergames) on cognitive functioning, brain structure and function, functional physical outcomes, and psychosocial outcomes (e.g., depressive symptoms, quality of life) in HOAs as well as older adults with NCD. The goal of this step was *"to understand the current theoretical and methodological contributions to the technology advancements, research methodologies, design considerations, and intervention evaluations"*[57].

Cognitive Training

Recent systematic reviews and meta-analyses have synthesized a large body of evidence that cognitive training interventions are effective at improving global cognitive abilities in HOA [70, 94-98]. For specific cognitive outcomes the findings have been inconsistent. More specifically, recent meta-analyses have synthesized conflicting evidence regarding cognitive training on complex attention (i.e., improvement[70, 94, 96, 97, 99] vs. no effect [100-102]), executive function (i.e., improvement [99] vs. mixed results (improvements in cognitive inhibition, but no effect on cognitive shifting [100]) vs. no effect [94, 96, 97, 101]), learning and memory (i.e., improvement [96, 97, 99] vs. no effect [94, 100-102]), visuo-spatial skills (i.e., improvement [97] vs. no effect [99, 101-103]), and working memory (i.e., improvement [70, 97, 99, 103] vs. no effect [94, 101]). Although transfer-effects are still debated [104, 105], and three meta-analyses have shown smaller improvements in non-trained compared to trained outcomes [95, 103, 106], these effects were still significant in two of these meta-analyses [95, 106].

In older adults with mNCD or dementia the evidence for the effects of cognitive training remains conflicting. Based on meta-analytic synthesis of evidence, improvements in learning and memory [107-111] and working memory [107-111] have been shown, whereas the evidence for cognitive training remains inconsistent for complex attention (i.e., improvement [108, 109] vs. no effect [107, 110]), executive function (i.e., improvement [109, 110] vs. no effect [107, 108, 111]), global cognition

(i.e., improvement [95, 107-112] vs. no effect [113]), verbal fluency (i.e., improvement [108, 110] vs. mixed effects (improvement in verbal category fluency but not in verbal letter fluency [109]) vs. no effect [107]), or psychosocial factors like anxiety or depression (i.e., improvement [108, 112, 114] vs. no effect [107, 109, 113]), while cognitive training seems to exert no significant effect on visuo-spatial skills [108], functional physical performance or activities of daily living [107-109, 112], and quality of life [107, 109]. Reviewed neuroimaging studies have indicated a training induced *"increase in brain activation (particularly in frontoparietal regions) and either an increase or maintenance in connectivity"* [115]. This is consistent with another systematic review, that has found *"no effects […] on hippocampal volumes post-training, but cortical thickening and increased grey matter volumes"* [116], suggesting that the brain remains highly plastic in older adults with NCD [115, 117]. An overview of the synthesized meta-analytic results is provided in Supplementary Table S1 in Supplementary File 1.

Physical Training

Recent systematic reviews and meta-analyses have shown that physical training interventions improve global cognitive abilities in HOA [70, 98, 118-121]. Regarding specific cognitive outcomes, physical training (including aerobic, resistance, and multicomponent training) was shown to significantly improve complex attention [70, 76, 98, 119, 121], executive functions [70, 72, 98, 119-121], learning and memory [119, 120], visuo-spatial skills [98], and working memory [98, 119], although these effects didn't always reach statistical significance and depend on exercise and training variables [119, 120, 122]. Additionally, physical training interventions were shown to reduce fall rates [123] and exert a positive effect on cardiac autonomic control [124] and hippocampal volumes [125] in HOA.

Systematic reviews and meta-analyses for the effects of physical training on cognition in older adults with mNCD or dementia are less consistent and suggest improvements in executive functioning [72, 73, 120, 126] and visuo-spatial skills [126], whereas no significant changes in complex attention [73, 122, 127], and mixed findings for global cognition (i.e., improvement [73, 75, 84, 118-121, 126-130] vs. no effect [113, 122, 131]), language (i.e., improvement [126] vs. no effect [73, 122, 127]), learning and memory (i.e., improvement [126] vs. mixed effects (i.e., improvement in delayed recall and no effect on immediate recall [73]) vs. no effect [120-122, 127]), and working memory (i.e., improvement [127] vs. no effect [73, 121, 122]) were synthesized. Additionally, meta-analytic results have synthesized significant improvements in activities of daily living [128, 131, 132], balance [132], behavioral problems [127], endurance [132], gait (i.e., step length and walking speed) [132], and mobility [132]. Furthermore, positive effects on depressive symptoms [131] and inconsistent findings on fall rate (improvement [123] vs. no effect [132]) were found. Nonetheless, the preventative effect of physical training seems to be limited, as analyzed by the meta-analysis of de Souto Barreto et al. (2018) that has found no significant effect on cognitive decline and risk of onset of mild or major NCD [133].

Moreover, several systematic reviews have indicated positive effects of physical training on brain structure and function. The systematic reviews of Firth et al. (2018), Joubert and Chainay (2018), Haeger et al. (2019), Herold et al. (2019b), Marinus et al. (2019), and Stillman et al. (2020) have indicated positive effects of physical training on structural (i.e., overall gray and white matter volume, hippocampal volume) and functional (i.e., functional connectivity, cerebral blood flow, task-related

oxygenation, concentration of neurochemicals) changes in the brain of HOA [70, 83, 125, 134-136]. There are already meta-analytic results that corroborate some of these effects by showing that aerobic training slows down the decline in hippocampal volume [125] and strength training or combined training increase peripheral BDNF concentration [134] that might be related to changes in cognitive abilities [70]. For older adults with mNCD or dementia, only a small number of studies examining the interrelation of structural and functional brain changes with changes in cognitive performance is available [83, 117, 135, 136]. Aerobic training seems to exert a protective effect on structures vulnerable to neurodegenerative processes including *"frontal, temporal and parietal regions, such as the hippocampal/parahippocampal region, precuneus, anterior cingulate and prefrontal cortex"* [83, 135]. Resistance training was additionally shown to ameliorate resting state functional connectivity (i.e., "*among the posterior cingulate cortex, the left inferior temporal lobe, and the anterior cingulate cortex and between the hippocampus and the right middle frontal lobe"*) [136]. An overview of the synthesized meta-analytic results is provided in Supplementary Table S2 in Supplementary File 1.

Motor-Cognitive Training

When considering specific training types, aerobic and multicomponent physical training were shown to be beneficial training types [84, 120, 127, 128], while cognitively engaging training appears to have the strongest effect on cognition [35, 62, 68, 70-76, 81, 100, 137-139]. These findings are consistent with the 'guided-plasticity facilitation' framework [32-34]: Acute physical exercise is assumed to enhance brain metabolism and promote neuroplastic processes, whereas these changes in brain plasticity are guided by cognitive stimulation [32, 33, 70]. Importantly, the systematic reviews of Joubert and Chainay (2018) and Lauenroth et al. (2016) have suggested that cognitive and physical training demands may exert synergistic effects on brain structural and functional adaptations as well as on cognition, indicating an advantage for combined training [70, 71]. Therefore, one might assume, that combined motor-cognitive training is more effective compared to isolated physical or cognitive training.

Multiple meta-analyses in HOA have synthesized evidence for significant improvements in executive functions [68, 72, 100] and working memory [100] in response to sequential or simultaneous motor-cognitive training while the evidence for global cognition (i.e., improvement [35, 62, 72, 119, 138] vs. no effect [74]) and learning and memory (i.e., mixed findings (improvement in updating memory but no effect on delayed memory [100])) remains conflicting, and no significant effects were synthesized for complex attention [100, 101], and verbal fluency [62]. Additionally, improvements in balance [68, 69] and functional exercise capacity [68] have been synthesized while the evidence for mobility remains conflicting (i.e., improvement [35, 69] vs. no effect [68]) and no significant effects have been synthesized for activities of daily living [140]. When considering meta-analytic results for exergaming specifically, significantly larger improvements in complex attention [62], executive functions [62, 68], global cognition [62], visuospatial processing [62], and also functional physical outcomes (i.e., balance, mobility) [68], and fear of falling [68], but not activities of daily living [140] or functional exercise capacity [68] have been synthesized compared to physically or cognitively active control interventions.

For older adults with mNCD or dementia, significant improvements in complex attention [141], global cognition [35, 62, 73-75, 138, 141], learning and memory [73, 141], and visuo-spatial skills [141] have

been meta-analytically synthesized, whereas there is conflicting evidence for executive functioning (i.e., improvement [73] vs. no effect [141]) and language [138], and no effects have been synthesized for working memory [141]. Additionally, improvements in physical outcomes (e.g., mobility, balance) [35] and psychosocial factors (i.e., neuropsychiatric symptoms, depression, quality of life) [35] have been synthesized. For exergames specifically, significantly larger increases in global cognitive function have been synthesized when compared to physically and cognitively active control interventions [62]. Moreover, exergame-based training interventions are greatly accepted in individuals with mNCD and increase training adherence and engagement through facilitating training motivation and satisfaction [42].

Therefore, especially exergaming seems to be a promising type of simultaneous motor-cognitive training for improving cognition in cognitively impaired individuals, although the optimal training components (e.g., type of exergame, training intensity and duration) remain to be established [35, 42, 44, 62, 81, 137]. The positive effects of simultaneous motor-cognitive training on cognition may be explained by neurophysiological changes of the brain, including changes in hemodynamics, electrophysiology, or neurotrophic factors [70, 71, 77, 78, 83, 137]. The Systematic Review of Muiños and Ballesteros (2021) concluded that motor-cognitive training (more specifically: dancing) *"can be effective for inducing neuroplasticity and that the duration of the intervention and the intensity of the dancing exercise might be important to induce brain changes and cognitive improvements"* [142]. For exergames specifically, Stojan and Voelcker-Rehage (2019) concluded in their systematic review, that *"neurophysiological changes with regard to exergaming (within exergamers or by group x time effects) were present in all corresponding studies (either on hemodynamics, electrophysiology, or neurotrophic factors) indicating brain plastic adaptations in response to exergaming"* [137]. Nonetheless, the evidence of structural and functional changes in the brain in response to motor-cognitive training in mNCDs is limited to single studies with inconsistent outcomes [78, 83, 117]. Further investigations are needed *"to establish the neurobiological mechanisms and effective components of exergames for cognition, and apply this understanding in the development of evidence-based exergame interventions"* [62] in older adults with NCDs [42, 44, 62, 71, 78, 80-83]. An overview of the synthesized meta-analytic results is provided in Supplementary Table S3 in Supplementary File 1.

Step 2: User Modeling

The second step of the project is aimed at determining the *"preferences and needs of the targeted user group from a multi-disciplinary perspective in order to optimize the exergaming experience. In addition to general aspects such as demographics, capability, characteristics, hobbies, and motivators for playing, exergame-specific user models should also include other attributes like the facilitators and barriers to physical activity engagement"* [57]. With this regard, the clinical picture, epidemiology, risk factors, prevention, and therapy options were summarized based on a literature search of the current evidence. The capabilities, treatment experience- and preferences as well as motivators for training of older adults with mNCD were determined based on a synthesis of evidence in combination with the results of a qualitative study. Our qualitative study included: (1) focus groups with experts/healthcare professionals; and (2) individual semi-structured interviews with older adults with mNCD. With this regard, 5 - 10 experts/healthcare professionals with a variety in age, gender, educational level and experience in therapy of older adults with mNCD and 5 - 10 older adults with mNCD with variations in age, education, training habits and technology use were purposively

recruited. The focus groups and individual semi-structured interviews were both organized as semi-structured interviews along an interview guide and were conducted between November 2020 and January 2021 [45].

Clinical Picture

The clinical picture of mNCD represents an intermediate stage of cognitive impairment between the normal aging process and dementia [2, 5-7, 143-145]. It is diagnosed on basis of: *"(A.) Evidence of modest cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual motor, or social cognition) based on: (1) Concern of the individual, a knowledgeable informant, or the clinician that there has been a mild decline in cognitive function; and (2) A modest impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment. (B.) The cognitive deficits do not interfere with capacity for independence in everyday activities (i.e., complex instrumental activities of daily living such as paying bills or managing medications are preserved, but greater effort, compensatory strategies, or accommodation may be required). (C.) The cognitive deficits do not occur exclusively in the context of delirium. (D.) The cognitive deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia)"* [5]. Older adults with mNCD can also be referred to as individuals with mild cognitive impairment (MCI). *"The main difference between MCI and mild NCD is that the research work that led to the construct of MCI took place in the context of geriatric populations (even though age was not part of the definition of MCI), whereas mNCD encompasses acquired cognitive disorders of all age groups"* [146]. Older adults with mNCD can be classified into four subtypes, according to the presence or absence of memory impairment (i.e., amnestic or non-amnestic MCI) and whether multiple cognitive domains are affected (single domain or multiple domains MCI) [7, 147, 148]. Deteriorations in episodic memory and executive function represent the most prevalent cognitive impairments [149]. The objective cognitive decline is associated with structural changes in the brain, including declines in gray matter volume and alterations in the connectivity of the temporal, parietal, and frontal lobes, the amygdala, fusiform gyrus, as well as the cingulate, parietal and occipital lobes and the insula [7, 149, 150]. Especially the structural changes in the hippocampus predict the conversion of MCI to dementia [151, 152].

Epidemiology

The global prevalence of mNCD increases with age, is more than twice as high than for dementia, and ranges between 3 and 54 % depending on the clinical classification [2, 7, 153-156]. The global incidence of MCI is estimated to increase from 2 % at age 75 - 79 increasing up to 7 % [7, 157]. In the general population, approximately 4.9 % of individuals diagnosed with MCI convert to dementia every year, whereas the adjusted annual conversion rate in clinical MCI populations is 9.6 % [158]. Fortunately, between 14 % (clinical populations) and 31 % (community-based cohort) revert to normal cognitive functioning for their age [159, 160]. Nonetheless, a recent meta-analysis reported a pooled progression rate of 34 %, more than twice as high as the pooled reversion rate of 15 % [154]. This dichotomy between conversion to dementia and reversion to normal cognition suggests the presence of modifiable risk factors contributing to this cognitive decline [145, 159].

Risk Factors, Prevention and Treatment Options

Age is considered to be the strongest risk factor for developing mNCD ([7, 145, 153, 154, 161]. Other risk factors include the male sex [154, 162, 163], the presence of the apolipoprotein E allele [164], a family history of cognitive impairment [165], the presence of vascular risk factors (i.e., metabolic syndrome, hypertension, hyperlipidemia, coronary heart disease, diabetes mellitus, or stroke) [166-168], or a physically or cognitively sedentary lifestyle [169, 170]. Hence, changes in lifestyle that increase physical activity and/or reduce vascular risk factors are powerful protectors for brain atrophy and cognitive decline [171-179]. When considering therapy options for incident MCI, physical and cognitive training were even shown to outperform pharmacological therapies [113]. Indeed, *"there is currently no effective pharmacological intervention for MCI"* [159]. The evidence for pharmacological treatment options (e.g., cholinesterase inhibitors, antihypertensive-, anti-inflammatory or lipid-lowering medication, or hormone therapies) and nutritional supplements is largely insufficient and does not support its use for improving cognitive performance, slowing down cognitive decline or reducing the risk for developing dementia [129, 180-184]. Consequently, it was suggested to focus on multi-domain treatment strategies including physical training and cognitive stimulation [145, 159]. In fact, *"a burgeoning body of evidence suggests that targeting modifiable risk factors in midlife may hold promise for mitigating or even preventing Alzheimer's disease and related dementias in later life"* [14, 185-188]. As already stated in section *"Motor-Cognitive Training"*, especially exergaming seems to be an effective mode of simultaneous motor-cognitive training for improving cognitive functioning in older adults with mNCD.

Capabilities

According to the definition of mNCD, capacity for independence in everyday activities is preserved, despite modest (i.e., for mild NCD, performance typically lies in the 1-2 standard deviation range; between the 3rd and 16th percentiles) deteriorations in cognitive functioning [5]. When considering the results of our qualitative study, the most often described impairments referred to cognitive functioning including impairments in executive function, complex attention, learning and memory, visuo-spatial skills, language, and social cognition from the experts' viewpoint. These cognitive changes were also described to affect psychosocial factors, mainly by causing psychological distress and feelings of insecurity, leading patients trying to hide their impairments. In line with the experts' viewpoint, cognitive deteriorations were frequently described to mainly affect learning and memory, complex attention, and executive function, while no serious restrictions in physical capabilities, mobility, and ADLs were mentioned by the patients themselves. However, from patient's perspective, the consequences of their cognitive decline on psychosocial factors were most prominent, mainly by causing psychological distress, feelings of insecurity, and depression [45].

Treatment Preferences

The findings of our qualitative study suggested that - according to the experience of the experts/healthcare professionals - solely cognitive forms of training (e.g., computerized cognitive training) or physical training (e.g., resistance training) were often experienced as boring in the long run by older adults with mNCD. More integrative forms of training including gamified tasks close to everyday life, multimodal animation, and acoustic feedback were reported to be preferred by patients. From a patient's perspective, computerized cognitive training was reported to be perceived as

challenging, fun, and enjoyable. Although being perceived as useful, patients reported to be insecure about the effectiveness of computerized cognitive training [45].

The previous experience in the use of exergames (i.e., Dividat Senso) with patients with mNCD was described as good by the experts in our qualitative study. The simple and clear design structures of the games were reported to be highly appreciated by patients and to promote good comprehensibility of the tasks [45]. This is also consistent with the literature, showing that exergame-based training interventions are greatly accepted in individuals with mNCD and increase training adherence and engagement through facilitating training motivation and satisfaction [42]. Accordingly, adherence to exergame-based training interventions is typically high in older adults with NCD [42, 44]. Nonetheless, various minor usability issues were reported in our qualitative study that need to be considered when developing a training concept specifically for older adults with mNCD. These usability problems include some minor issues in the interaction with the exergame training system Dividat Senso (e.g., unintendingly walk off the middle-plate without noticing the feedback on the screen), but were mainly related to capabilities of older adults with mNCD. Patients were often described to be cognitively overloaded when trying out new exergames or when in unexpected situations or experiencing technical errors. Additionally, some games were reported to start at an already (too) challenging level for older adults with mNCD and progress too fast while there is a limited range of games and/or adaptability of task demands at the lower end of difficulty levels. This was mentioned to mainly be apparent for the cognitive task demands (e.g., game speed, task complexity) while the physical exercise intensity is often low and could be increased. Overwhelming task demands were described to cause frustration and/or refusal of playing games, although the feedback mechanisms to indicate errors work rather subtle. On the other hand, exergames that are perceived as being too easy lead to boredom. Therefore, the findings of the qualitative study illustrated that applying an optimal challenge is central to promote the use of exergames in patients with mNCD over the long-term [45].

Motivators for Treatment

The ‘Self-determination Theory’ [189] has demonstrated considerable efficacy in explaining exercise motivation and behavior [190]. It accounts for the quality of different levels of motivational regulation in physical activity settings and is considered useful to gain a better understanding and promoting training motivation, enjoyment, and adherence [191-194]. More autonomous forms of motivation refer to engagement in a task based on intrinsic motivators (e.g., enjoyment, personal importance). This is considered advantageous and linked with positive behavioral changes (e.g., in exercise) [43]. The ‘Self-determination Theory’ [189] is in line with multiple empirical observations that predicted favorable exercise and training behavior with more autonomous forms of motivational regulation in healthy adults ([194-197], HOA [194, 198-200], and also in clinical populations like stroke patients [201], patients with cardiovascular disease [202], or patients with NCD [203]. For example, in a large cohort of regular exercisers, more autonomous forms of motivation (i.e., identified and integrated regulation) predicted training frequency, intensity, and duration [195]. Depending on the population, different factors determine how more autonomous motivation can be promoted. A small case-control study with a balance exergaming platform evaluated that *“older adults were more intrinsically motivated by the joy of playing and extrinsically motivated by the perceived health effects (physical and cognitive), with less regard for the in-game rewards”* [204]. For patients with NCDs specifically, a new theoretical model, the ‘PHYT in dementia’ [205], was recently introduced. It includes both

individual-level and environment-level constructs with the aim to *"inform effective interventions to promote physical activity"* [205] in patient with NCDs. It proposes that self-efficacy including embarrassment (e.g., supervision of activity had a negative impact on engagement in the intervention), personal concerns (e.g., fear of falling) and routine (e.g., flexible integration of physical activity intervention into daily life regarding place and time of performance), as well as appropriate challenge are considered additional key elements for promoting physical activity behavioral changes [205]. To account for these factors, especially for the preference that *"the routine can be performed at home and at different times during the day"* [205], a detailed awareness of participants motivators is required, since self-determined motivation may be a central aspect for the adherence in home-based training programs [202].

This is consistent with the findings of our qualitative study, showing that the most frequently described motivators can be classified as intrinsically regulated motivators that are directly related to the exergames. It was described that excitement, enjoyment or fun is perceived as a central motivator for performing exergames that is maintained by the inclusive character of exergames that is supported by specific game characteristics. More specifically, mainly game tasks or -designs close to everyday life or with a personal relation/memory including music/sound effects, animal/plants, landscapes, or colors were reported to promote intrinsic motivation. Additionally, patients were described to be intrinsically motivated by gamification and the feeling of being optimally challenged. However, when task demands get too high or too low patients' have been observed to promptly lose their willingness to perform the exergames [45].

Step 3: Therapeutic Needs

In step 3, it was aimed to: (1) *"specify the users' fitness goals, training settings, and outcome measures"* [57]; and (2) *"determine the core components of the training plan (e.g., type of exercise, target outcomes, based on FITT-VP: Frequency, Intensity, Type, Time, Volume, and Progression model)"* [57]. To specify the patients' training goals and -settings and to support the determination of the most suitable exergame intervention components, we relied on the integration of the outcomes of (a) a comprehensive literature synthesis regarding moderating effects of training interventions on training efficacy, and (b) the qualitative study including semi-structured interviews with older adults with mNCD and focus groups with healthcare professionals (as described above).

Training Goals and Outcomes

According to the findings of our qualitative study, mainly cognitive functioning should be targeted in the training intervention in experts' viewpoint, while also addressing ADLs and mobility, physical capabilities, and accounting for psychosocial factors. When asking experts about the training goals of patients, improving ADLs and mobility were stated most frequently besides cognition and physical functioning. Additionally, psychosocial factors were reported that include socializing or just having fun. This is consistent with patients' viewpoint that most frequently reported quality of life and independence as primary training goals [45].

When comparing these perspectives with the literature, similar results have been synthesized. An online survey in 2018 evaluated the *"outcome and treatment preferences of patients and caregivers who had completed a multicomponent behavioral intervention for mild cognitive impairment (MCI)"* [206]. The most important outcome priority for MCI patients was quality of life, followed by self-

efficacy, depression, basic Activities of Daily Living (ADL), memory-based ADL, anxiety and memory performance [206]. A better self-efficacy is expected to improve perceived quality of life [207].

Core Components of the Training Plan

To get a better understanding of previous investigations and the dose-response relationships of different qualitative (i.e., type and content of training) and quantitative (i.e., frequency, intensity/complexity, session duration, intervention dose and adaptation over time) exercise and training variables, recent meta-analytic results were synthesized (Supplementary Table S4 in Supplementary File 1) and summarized (Table 4-2) and complemented with additional evidence if required to make an informed decision. These findings were then used to guide the formulation of requirements for an optimal intervention design in line with the findings of the qualitative study, to ensure that the resulting intervention design is also considered feasible based on experts' and patients' viewpoint.

Qualitative Training Components:

Based on the synthesized (Supplementary Table S4 in Supplementary File 1) and summarized (Table 4-2) evidence on moderating effects of different training interventions, combined (preferably simultaneous) motor-cognitive training can be considered the most effective type of training for improving cognition in HOA [35, 72] and older adults with mNCD [35, 73]. One approach to apply simultaneous motor-cognitive training is exergaming. The currently available evidence suggests slightly superior effects of exergame training on cognitive abilities when compared to physically or cognitively active control interventions [62, 68]. Moreover, exergame-based training interventions are greatly accepted in individuals with mNCD and increase training adherence and engagement through facilitating training motivation and satisfaction [42]. Therefore, using exergames is the most promising approach for the training intervention.

The specific mode of motor-cognitive exergame training may be motor-cognitive training with incorporated cognitive tasks [34]. The content of the exergames should mainly focus on working memory and memory training as part of a multi-domain training program [95, 109, 110]. Furthermore, the exergames should integrate specific tasks demanding cognitive flexibility that engage multiple cognitive domains (e.g., related to spatial memory) at the same time [34, 208]. Preferably, the specific components of the exergame interventions are tailored to the individual, based on objective assessments of individual capabilities such as cognitive abilities, physical fitness, motor abilities, as well as demographic characteristics (e.g., age, gender, health status, and the socioemotional status including motivation, mood, or stress) [34]. Furthermore, the preferred postural modality in which exercise is performed should be in a vertical body loading position [209]. Exercise performed in standing position that requires a changing base of support to play the games better meets the specifics for training postural control [210] and puts a higher demand on spatial processing demands [211] next to enhancing both processing speed and attentional selectivity [212]. Such effects of improved balance and executive functions are not observed for exercise performed pedaling a bicycle in a seated position [213, 214] possibly due to a lack of a dynamic influence on visual working memory performance [211]. In this context an ecologically more valid motor-cognitive training type that allows for controllable activities and to incorporate complexity, novelty, and diversity in the training design, can be enabled by virtual reality-based video gaming [215].

Quantitative Training Components:

The analysis of moderating variables of training parameters influencing the effectiveness of the interventions (Tables 2, Supplementary Table S4 in Supplementary File 1) revealed several preferences. Based on meta-analytical results from motor-cognitive training in older adults with mNCD, a moderate physical training intensity [73] and a moderate training volume (60 - 120 min/week) [74] have been shown to be the most effective to improve cognitive functioning. When complementing findings for motor-cognitive training in HOAs, higher trainings frequencies (≥ 3x/week [72], ≥ 5x/week [119]), higher challenging motor tasks [123], shorter session durations [100], and either longer (≥12 weeks) [62] or shorter (≤ 12 weeks) [35, 72, 73] intervention durations have been shown to improve effectiveness of motor-cognitive training interventions. However, these conclusions are opposed by other meta-analyses [72, 73, 100]. In older adults with mNCD, higher training frequencies have been shown to improve effectiveness of physical- (i.e., ≥ 4x/week) [120] and cognitive training (i.e., > 3x/week) [109], while shorter session durations (i.e., ≤ 30 min) [120] of physical exercise and longer intervention durations of cognitive training interventions (i.e., ≥ 3 months) [109] have been shown to exert more pronounced training effects. When considering the cognitive demands (e.g., task complexity) of the training intervention, no difference between simple and complex cognitive games have been found for cognitive training interventions in HOA [96] and the optimal cognitive load for motor-cognitive training remains unknown. There is also no evidence regarding the optimal progression, variation, or specificity of motor-cognitive training interventions. When considering findings for solely cognitive training, multi-domain training [95, 109, 110] including memory [95, 110] and working memory specific training [95] has been shown to be the most effective for improving cognition in HOA and older adults with mNCD, while the use of fewer games (≤ 6 games) [96] tends to be beneficial for HOA.

Taken together, the meta-analytically synthesized evidence suggests that an exergame-based motor-cognitive training intervention with a high training frequency (i.e., ≥5x/week), shorter session durations (i.e., ≤ 30 min), longer intervention durations (i.e., ≥ 12 weeks) and a moderate training volume (60 - 120 min/week) predicts the largest effects on cognition. The physical part of the training should focus on aerobic activities at moderate intensities performed in a vertical body position with body loading, whereas the cognitive challenges should include multicomponent demands including working memory and memory-specific training. The optimal level of cognitive demand remains to be established. Likewise, the adaptation of the intervention over time (i.e., variability, progression, periodization) remains to be determined, but preferably, both are adapted to the individuals' abilities.

Table 4-2: Moderating effects on effectiveness evaluated on basis of meta-analyses or meta-regressions
Abbreviations: HOA = healthy older adults, NR = not reported, mNCD = mild neurocognitive disorder

Training Parameter		Cognitive Training		Physical Training		Motor-Cognitive Training		Preferred Choice for Brain-IT
		no effect	(near) sign. moderating effect	no effect	(near) sign. moderating effect	no effect	(near) sign. moderating effect	
Frequency	mNCD	[109]	• higher (> 3x/week)[109]	[128]	• higher (≥ 4x/week)[120]	NR	NR	high frequency (≥ 5x/week)
	HOA	NR	• lower (≤ 2x/week[95], ≤ 3x/week)[97]	NR	• higher (≥ 2x/week[120], ≥ 3x/week[72], ≥ 5x/week)[119] • lower (≤ 3x/week)[130]	[100]	• higher (≥ 3x/week[72], ≥ 5x/week)[119]	
Intensity / Complexity	mNCD	NR	NR	[72, 120]	• moderate intensity[73] • moderate-high intensity[127]	[72]	• moderate physical exercise intensity[73]	physical load: moderate intensity motor complexity: high challenge cognitive load: unknown
	HOA	[96]	NR	[120]	• moderate to vigorous[119] • high challenge (motor)[123]	NR	• high challenge (motor)[123]	
Type (of training)	mNCD	[109, 112, 114]	• computer-based[112] • individual training[110]	[127]	• aerobic training[84, 128] • multicomponent[120, 128]	[74]	• simultaneous training[35] • combined training[73]	individually applied simultaneous motor-cognitive training
	HOA	NR	• video-game based training[96, 97]	[120]	• multicomponent[119]	NR	• simultaneous training[35, 72] • exergaming[100]	
Time (exercise duration)	mNCD	NR	NR	NR	• shorter (≤ 30 min)[120]	NR	NR	≤ 30 min
	HOA	[97]	• shorter (≤ 30 min)[95]	[72, 120] [124]	• shorter (≤ 30 min)[130] • longer (≥ 45 min)[119]	[72, 100]	• shorter[100]	
Duration (of the intervention)	mNCD	[109]	• longer (≥ 3 months)[109]	[74, 120]	NR	[74]	NR	≥ 12 weeks
	HOA	[99]	• shorter (≤ 6 weeks)[96]	[120]	• shorter (≤ 12 weeks)[72, 119] • longer (> 16 weeks)[130]	[73]	• longer (≥ 12 weeks)[62] • shorter (≤ 12 weeks)[35, 72, 73]	
Volume (i.e., total intervention / exercise time)	mNCD	[110, 111]	NR	[127]	• higher (≥ 24 h[127]) • moderate (60 - 120 min/week)[74] • lower[73] (≤ 2h/week)[130]	NR	• moderate (60 - 120 min/week)[74]	moderate (60 - 120 min/week)
	HOA	[97]	• higher (≥ 20h, ≥ 20 sessions)[95]	[124]	• higher (≥ 3 h/week[123])	[100]	• higher volume (≥ 120 min/week)[68]	

Progression & Periodization	mNCD	NR	NR	NR	NR	NR	NR	unclear
	HOA	NR	NR	NR	NR	NR	NR	
Variability / Variation	mNCD	NR	NR	NR	NR	NR	NR	unclear
	HOA	NR	• fewer games (≤ 6 games) tend to be beneficial[96]	NR	NR	NR	NR	
Specificity	mNCD	[109, 111]	multi-domain training[109, 110] including memory[110] -specific training	NR	NR	NR	NR	focus on working memory and memory training as part of a multi-domain training
	HOA	NR	multi-domain training[95, 110] including working memory[95] and memory[95, 110] -specific training	NR	NR	NR	NR	

Herold et al. (2019) proposed an adapted exercise prescription that could be used for monitoring the cognitive task demands as well as the adaptation of the intervention over time. This adapted exercise prescription suggests that the exercise parameters are operationalized and adapted to the individual by tailoring external training loads (e.g., by manipulating exercise intensity) using specific markers of the internal training load to provide comparable inter-individual exercise doses [59]. The internal training load can be described as acute individual response [i.e., biomechanical, physiological, and/or psychological response(s)] to training components (e.g., external training load) and other influencing factors (e.g., climatic conditions, equipment, ground condition) [216]. This adapted exercise prescription approach is believed allowing further insights into dose-response relationships and to result in more distinct training effects [59, 137]. Fortunately, exergames are well suited for such individualized training concepts. In fact, individual real-time adaptivity of task demands according to monitored parameters such as performance, measures of brain activity, or internal training load is considered a key advantage of serious video games (such as exergames) [80, 217, 218], *"games that do not have entertainment, enjoyment or fun as their primary purpose"* [219]. Therefore, developing an exergame-system in line with this adapted exercise prescription could be a key advantage for monitoring the cognitive task demands as well as the adaptation of the intervention over time. Additionally, variability of exergames can easily be applied for example by offering multiple exergames for the training of a specific neurocognitive function. Based on these findings, different evidence-based concepts and ideas for the design of the remaining exergame parameters (i.e., complexity, progression and periodization, and variability/variation) were synthesized (see Table 4-3 for an overview and Supplementary File 2 for a description of the suggested concepts):

Diamond and Ling (2016) hypothesized that games that combine physical activity with motor skill task learning through provision of complexity, novelty, and variety within the training context will be most effective for executive functions improvement [220]. Regarding the monitoring of neurocognitive demands (i.e., game complexity), and in line with the adapted exercise prescription proposed by Herold et al. (2019) [59], using a biocybernetic adaptation loop (BIOLOOP) based on monitoring internal training load would most certainly be the optimal approach. In short, a *"biocybernetic loop is a modulation technique from the physiological computing field, which utilizes body signals in real-time to alter the system in order to assist users"* [221-224]. *"This model of closed-loop control detects deviations from an optimal state of brain activity and uses these variations to cue changes at the human-computer interface in order to "pull" the psychological state of the user in a desired direction"* [225]. Optimally, it would work on basis of specific markers of internal training load to adapt the external training demands [59]. However, the optimal marker(s) for internal training load remain to be determined [59]. Alternatively, this adaptation loop could also be based on performance metrics of the exergame (e.g., speed, accuracy, reaction time), like described in the concept of the performance adaptation loop (PERF-LOOP). For the physical exercise intensity, the concept of monitoring target intensity (TARGETINT) is often used. In this concept, intensity is displayed in real-time by monitoring parameters of internal/external training load (e.g., heart rate). Participants have to change their behavior (e.g., increase stepping frequency) in order to reach the target intensity [84, 120]. Optimally, these concepts would be applied concurrently, to ensure the optimal (i.e., moderate) predefined level of physical exercise intensity while adapting the neurocognitive demands (i.e., game complexity) to the individuals' capabilities. This concept will be called BIOTARGETLOOP and will be introduced in more detail in section *"Step 2: Development and Validation of Adaptation Loop"*.

Regarding training progression, the concept of performance plateau (PLAT), in combination with dips and leaps may be used [226]. These are behavioral markers that relate to motor skill acquisition and can be analyzed with a focus on micro dynamics of individual performance curves [226]. In this concept, chosen games will be played and performance plateaus, dips and leaps are identified. The occurrence of the performance plateau (after several training sessions) will for example mark the introduction of a new (slightly more difficult) exergame. Future long-term brain training studies using long-term video game training interventions seems ideal for capturing detailed longitudinal data [226], from which big data can be harvested and analyzed from gaming records.

Regarding the variability of exergames, the concept of MYCHOICE seems to be promising. It describes a self-determined choice of games within groups of games for neurocognitive domains. More specifically, in this concept, exergames will be grouped into the trained neurocognitive domains (e.g., learning and memory, executive function, complex attention, visuo-spatial skills) and each participant gets to choose which game within these groups he wants to play.

Table 4-3: Possible ideas/concepts for training monitoring and related evidence

Training Parameter	Type of Exercise			Preferred Choice for Brain-IT
	Cognitive exercises	Physical exercises	Motor-Cognitive exercises	
Complexity	• BIOLOOP (= Biocybernetic adaptation loop) • PERF-LOOP (= Performance adaptation loop)	• TARGETINT (=Monitoring of target intensity)	• BIOLOOP (= Biocybernetic adaptation loop) • PERF-LOOP (= Performance adaptation loop)	• BIOTARGETLOOP
Progression & Periodization	• PLAT (= Performance Plateau)	• ADAPT (= Adaptation of intensity according to training progress) • HRV-GUIDE (= HRV guided exercise prescription)	• PLAT (= Performance Plateau)	• PLAT
Variability / Variation	• MYCHOICE (= Self-determined choice of games within groups of games for cognitive domains)		• MYCHOICE (= Self-determined choice of games within groups of games for cognitive domains)	• MYCHOICE

Integration of Chosen Training Parameters Into Requirements for a Training Concept

Based on the synthesized evidence an exergame-based motor-cognitive training intervention with a high training frequency (i.e., ≥5x/week), short session durations (i.e., ≤30 min), and a moderate training volume (60 - 120 min/week) applied over a duration of at least 12 weeks predicts the largest effects on cognition. The physical part of the training should focus on aerobic activities at moderate intensities, whereas the cognitive challenges should include multicomponent demands including skill-learning elements, working memory, and memory-specific training. The optimal level of cognitive demands as well as the adaptation of the intervention over time (i.e., variability, progression, periodization) may be monitored and adapted by the exergame device integrating the concepts of BIOTARGETLOOP, PLAT, and MYCHOICE.

The findings of our qualitative study suggested the use of exergames as a form of coupled motor-cognitive training that should be prescribed domain-specific depending on a patients' cognitive

abilities. The recommended training frequency ranged between two to five or more training sessions per week, largely dependent on training location and motivation. Training at home was reported to be preferred, since it represents a known environment which makes patients feel more secure and to enable a higher training frequency. However, multiple factors need to be considered to make a home-based training intervention feasible, like the improvement of game instructions, accessibility of a handrail or similar for mobility support, avoidance of technical problems, and the integration of a guided familiarization period or support of a carer to make the transfer to home-based exergaming easier. The recommended session durations should range between a minimum of 15 - 20 min up to a maximum of 30 min with the aim to reach a moderate training volume of approximately 150 min/week. Shorter sessions and a higher training frequency were reported to be preferable to reach this training volume mainly due to attentional exhaustion. The physical exercise intensity should be maintained at a light to moderate level, while the focus should be on game complexity that should be challenging but feasible. Individualization of the exergame-based training concept should mainly account for two aspects: (1) task type (i.e., choice of exergames to individually focus on neurocognitive functioning), and (2) task demands (i.e., adapt the game demands according to the individual capabilities to maintain a challenging but feasible cognitive training load). The task demands can be varied on multiple levels, for example: (1) stability support (use of handrail with both hands, one hand, or no support), (2) stepping direction, (3) game choice and tasks included, (4) game duration, or (5) game speed. To maintain the training program in the long-term (preferably > 12 weeks), motivation is a key factor and should be facilitated by the playful character of the exergames as well as a variation in the choice of games [45]

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Table 4-4: Overview of preferred training parameters and final decision for Brain-IT

Exercise and Training Parameters	Preferences based on:			Requirements for Training Intervention Concept
	Meta-Analytic Results	Additional Evidence	Qualitative Study	
Frequency	high frequency (≥ 5x/week)		high frequency (≥ 5x/week), but only if home-based training is possible	high frequency (≥ 5x/week)
Intensity / Complexity	physical load: moderate intensity motor complexity: high challenge cognitive load: unknown	real-time closed-loop adaptation of exergame demands to internal training load (BIOTARGETLOOP)	physical load: moderate intensity cognitive load: challenging but feasible	real-time closed-loop adaptation of exergame demands to internal training load (BIOTARGETLOOP)
Type (of training)	individually applied simultaneous motor-cognitive training		exergaming	exergame-based simultaneous incorporated motor-cognitive training
Time (exercise duration)	≤ 30 min		< 30 min	≤ 30 min
Duration (of intervention)	≥ 12 weeks		long-term	≥ 12 weeks
Volume	moderate (60 - 120 min/week)		moderate (60 - 120 min/week) to high	moderate (60 - 120 min/week)
Progression & Periodization	unclear	adaptation based on performance plateau according to predefined taxonomy	unclear	adaptation based on performance plateau according to predefined taxonomy
Variability / Variation	unclear	self-determined choice	use a certain routine with slight variations over time	self-determined choice
Specificity	focus on working memory and memory training as part of a multi-domain training	multi-domain training including working memory, memory + flexibility tasks	focus on cognitive deficits	individualized (deficit-oriented) focus in a multi-domain training including working memory, memory training

Based on the MIDE framework-based considerations so far, requirements for the optimal training components based on the findings of the qualitative study as well as the synthesized evidence were summarized (Table 4-4). As can be seen in Table 4-4, most of the optimal evidence-based training parameters are in line with the recommendations of experts and the preferences of patients as indicated by the results of the qualitative study. Based on the integration of these findings, the following components for a theoretically optimal training intervention concept were determined: The training should consist of an individually adapted multi-domain exergame-based simultaneous motor-cognitive training with incorporated cognitive tasks adopted with a deficit-oriented focus. A high training frequency (i.e., ≥ 5x/week), short session durations (i.e., ≤ 30 min), and a moderate training volume (60-120 min/week) should be applied over a duration of at least 12 weeks. The exergame demands should be individually adapted to maintain a moderate physical exercise intensity and a challenging but feasible neurocognitive demand.

To be able to apply a theoretically optimal training intervention concept, the following exergaming technology requirements are to be considered (see *"Step 4: Technology Scoping"*). In this phase of the project, we determined the hardware and software requirements for developing and deploying the exergames [57].

Step 4: Technology Scoping

A previous study showed good results in people with major neurocognitive disorders using a Dividat Senso platform [209]. We will use this device and can thus use some of the existing exergames by adapting these to the determined requirements for our future studies. As described in section *"Treatment Preferences"* and *"Motivators for Treatment"*, the use of exergames (i.e., Dividat Senso) was positive, especially because of the simple and clear design structures of the games that were highly appreciated by patients and that were comprehensible for the training tasks. An additional motivation for the use of exergames are the feelings of excitement, enjoyment or fun that is maintained by the inclusive character of exergames as previously reported [227]. Therefore, only minor modifications of the exergame device and game scenarios are required. These required modifications were synthesized in our qualitative study and mainly covered adjustments in game complexity at the start of the game (i.e., widening the opportunities to adjust task difficulty downwards) and several minor game-specific adaptations. Finally, the technological requirements to meet the requirements of training parameters for the project are summarized in Table 4-5. As can be seen, the usability of the home-based version (Dividat Senso Flex) needs to be tested, and additional studies as well as the expertise of the development team of Dividat AG will be required to integrate novel game designs or -elements (i.e., development, validation and integration of novel/adjusted adaptation loop, identification of performance plateau).

Table 4-5: Hardware and software requirements of the Dividat Senso for 'Brain-IT'

Training Parameter	Requirements for Intervention concept	Technological requirements	
		Requirements met?	necessary advancements:
Frequency	high frequency (≥ 5x/week)	partially	• Usability of the Dividat Senso Flex
Intensity / Complexity	real-time closed-loop adaptation of exergame demands to internal training load (BIOTARGETLOOP)	no	• Development & Validation of Adaptation Loop • Integration of Adaptation Loop into Software
Type (of training)	exergame-based simultaneous incorporated motor-cognitive training	yes	
Time (exercise duration)	< 30 min	yes	
Duration (of intervention)	12 weeks	yes	
Volume	moderate (60 - 120 min/week)	yes	
Progression & Periodization	adaptation based on performance plateau according to predefined taxonomy	partially	• Identification of Performance Plateau by Software
Variability / Variation	self-determined choice	yes	
Specificity	individualized focus in a multi-domain training including working memory, memory + flexibility tasks	partially	• Development of new Games (i.e., Episodic Memory, Working Memory)

Step 5: Sustainability Strategy

The goal of this step was to *"consider strategies to be distributed/maintained outside of the research period so that they are available more widely and for longer-term by end-users and healthcare institutions"* [57].

The exergame training system we intend to use (Dividat Senso) is CE-marked as a medical device and available at more than 150 places (i.e., mainly senior residences, rehabilitation clinics and physiotherapies) in Switzerland. Additionally, a home-based telerehabilitation version (Dividat Senso Flex) is currently developed and expected to be accessible soon. Therefore, availability of the training system is ensured and is expected to be further improved (by accessibility of the Dividat Senso Flex) in the near future.

4.4.3 Phase 2: Game Design and Development

The overall goal of phase 2 was to develop a fully functional prototype supported by multidisciplinary teamwork including the exergaming industry, game designers, clinical experts, researchers, and, of course, the end user [57]. First, the required adaptations [game design (see section *"Step 1: Game Design"*), development and validation of the adaptation loop (see section *"Step 2: Development and Validation of Adaptation Loop"*)] were addressed before proposing the novel exergame-based training concept (see section *"Step 3: Development of Exergame-based Training Concept"*). In a next phase, this exergame-based training concept is currently being tested on its feasibility, usability, and acceptance (see section *"Step 4: Playtesting of Exergame-based Training Concept"*). Based on the finding of the evaluation of feasibility, usability and acceptance, the training concept will then be modified (see section *"Step 5: Modification of Exergame-based Training Concept"*) and will finally enter Phase 3 (see section *"Phase 3: System Evaluation"*) for the final evaluation of effectiveness.

Step 1: Game Design

The MIDE framework requires several considerations regarding the game design. In this section we will reflect on these considerations and propose our solutions. Our goals in the first step of game design were *"to better understand the goal of the exergames and related training programs"* [57], and *"to establish a mutual exergame design expectation"* [57].

For the existing games, several game-specific adaptations were reported to be required. They mainly included adaptations in monitoring task demands as well as the game designs [45]. These changes were implemented upon request by the development team of Dividat AG. In addition to these game-specific adaptations, multiple novel game designs or -elements were suggested and discussed by the focus groups in our qualitative study to optimally address patients' needs. In general, it was recognized that there is a need for new games specifically targeting the neurocognitive functions of (motor) learning and memory as well as executive functions (i.e., working memory, cognitive inhibition) in general [45].

When designing novel exergames for older adults with mNCD, specific criteria were reported to be central in our qualitative study. In general, the games should use simple graphics and ensure good contrast. A good level of comfort with and good usability of the exergames need to be ensured by using easily comprehensible and clearly designed tasks with a certain closeness to everyday life. Multimodal animations including multisensory feedback should additionally be integrated focusing on positive reinforcement mechanisms to motivate patients during exergaming. Additionally, it is important that the main task is in the center of the screen and that only elements that are related to the game task are included. Moreover, too confronting performance feedback and unexpectedly appearing items or technical problems should be avoided [45].

Based on these findings and criteria for the game designs, multiple games were designed and submitted to Dividat AG for future training interventions. The suggested new games included a total of nine game suggestions in the neurocognitive domain of (motor) learning and memory, four game suggestions in the neurocognitive domain of executive functioning, and one game suggestion in the neurocognitive domain of visuo-spatial skills. Additionally, a new game mode was designed and submitted to Dividat AG that is based on HRV biofeedback and cardiac coherence training with the aim to be used as a behavioral intervention in order to improve the dynamic balance of the autonomic

nervous system (ANS) and to regulate emotional state [49]. Of all these suggestions, four games in the neurocognitive domain of learning and memory as well as the new game mode for cardiac coherence training were implemented by Dividat AG to be used in our project. The specific game design and tasks are illustrated and explained in Supplementary File 3 in detail.

Step 2: Development and Validation of Adaptation Loop

As discussed in section *"Quantitative Training Components"*, instant adaptability is considered a key advantage of exergames, while the concept of BIOTARGETLOOP based on marker(s) of internal training load would be the optimal to ensure the optimal (i.e., moderate) predefined level of physical exercise intensity while adapting the neurocognitive demands (i.e., game complexity) to the individuals' capabilities. This concept will now be introduced in more detail.

It is known that during motor-cognitive training (e.g., exergaming), the external task demands are mainly dependent on neurocognitive task demands and the physical exercise intensity [228]. Comprehensive guidelines and checklists are available that provide classifications of exercise intensities and -doses for numerous parameters (e.g., percentage of individual maximal heart rate) [59, 229-232]. According to the American College of Sports Medicine, relative aerobic exercise intensities ranging between 40 and 59 % heart rate reserve (HRR), 64 and 76 % of maximal heart rate (HR_{max}), or 45 and 67 % of maximal oxygen uptake ($VO_{2,\,max}$) are considered moderate [233]. Therefore, objective monitoring of the relative physical exercise intensity is readily applicable, although these methods are not without limitations. All these methods are based on prescribing exercise intensity relative to maximal anchors, which have been reported to result in an indistinct and heterogeneous homeostatic perturbation [234]. Nonetheless, *"studies involving only moderate exercise intensity (e.g., 60 % VO_{2max}) might reasonably choose % VO_{2max}, % HR_{max}, % VO_{2R}, or % HRR over threshold-based relative exercise intensity prescription"* [235]. For the neurocognitive demand - that serves as the driving mechanisms for task-specific neuroplasticity [228] - the optimal internal training load remains to be established. Using specific markers to quantify the neurocognitive demand would be advantageous, since an adequate dose acts as an essential factor for triggering neurobiological processes [59]. To be able to differentiate between the physical- and neurocognitive demands during exergaming, a theoretical model was proposed (Figure 4-1). In this model, the total individual internal training load is subdivided into a fixed component (i.e., physical exercise intensity) and a variable component (i.e., game demand). The fixed component comprises the relative exercise intensity that is independent of the game demands. It will be individually determined, set to a moderate level (i.e., 40 - 59 % HRR), and held constant over the course of the exergaming intervention. On top of this fixed physical exercise intensity, a variable amount of external training load will be presented that is regulated on basis of the game demands (e.g., game type, task complexity, predictability of required tasks). Since the physical exercise intensity is kept constant, changes in the overall internal training load can mainly be attributed to these game demands and, accordingly, the internal training load can be adjusted on basis of these game characteristics. This allows an individualized adaptation of the external training load according to the internal training load and will serve as a basis for the evaluation of the progression algorithm.

Optimally, such an algorithm would work on basis of specific markers of internal training load to adapt the external training demands [59]. Currently, the exergame training system Dividat Senso offers the concept of a PERF-LOOP (performance adaptation loop; as discussed in section *"Quantitative Training Components"*). The progression algorithm is based on performance indicators such as reaction times or point rate. However, the underlying progression algorithm was not yet formally validated or experimentally investigated. Additionally, the optimal marker(s) for internal training load remains to be discovered [59]. Therefore, we have conducted and are currently writing the manuscript of an experimental study with the aim to explore novel strategies for a real-time adaptive exergame system to individually tailor exergame demands according to the users' physical and/or cognitive capabilities. More precisely, based on our findings in a recently published systematic review, the reactivity of vagally mediated heart rate variability (HRV) is evaluated as a promising monitoring parameter for internal training load that is easily measurable [236]. Based on the findings of this study [237], the monitoring strategy for the final training concept was set and possible future advances for monitoring and adapting the external training load characteristics to ensure optimal internal training load were explored. However, these possible future advances remain explorative due to the constraints in time and resources within this project and may be further investigated at a later timepoint.

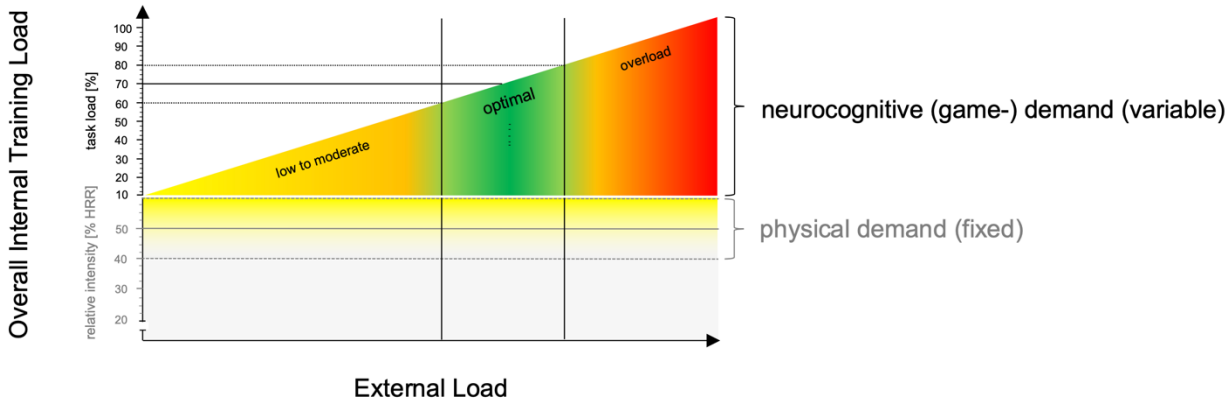

Figure 4-1: Methodological framework for the contribution of physical- and neurocognitive- (i.e., game-) demands during exergaming

Step 3: Development of Exergame-Based Training Concept

Based on the MIDE framework-based considerations so far, we developed an exergame-based training concept that will be described in the following sections together with a provision of the development rationale. To increase the probability that the resulting training concept will be deemed feasible in future clinical practice, we used our considerations to guide the decision process of the theoretically optimal intervention design. The final training concept was developed on basis of the requirements for the optimal training components summarized in Table 4-4 that were defined based on the findings of the qualitative study as well as the synthesized evidence. Based on the integration of these findings, the following components of the training concept were determined, that were planned and will be reported using the Consensus on Exercise Reporting Template (CERT) [238] [for more detail, consider Supplementary File 3 which contains our complete exergame-based concept with sufficient details about the exergame components as well as the exercise and training

characteristics (i.e., including all predefined levels of task demands as well as the detailed progression rules) to allow full replication].

Overview

The final training concept consists of an individually adapted multi-domain exergame-based simultaneous motor-cognitive training with incorporated cognitive tasks that will be adopted with a deficit-oriented focus on the neurocognitive domains of (1) learning and memory, (2) executive functioning, (3) complex attention, and (4) visuo-spatial skills. According to the training concept, each participant is instructed to train at least 5x/week for 21 min per session resulting in a weekly training volume of ≥105 min. All training sessions are planned to take place at participant's homes using the exergame training system Dividat Senso Flex.

The training concept is structured in three phases. It starts with a familiarization period of two weeks. During this phase, most of the training sessions (i.e., 4 out of 5 sessions) are supervised. After this initial guided familiarization period, supervision of training sessions is gradually reduced to 1x/week during a four-week transition phase. This transition phase aims to lead participants to being able to train independently while being remotely monitored. In this transition phase, the amount of supervision of training sessions is individually determined within a predefined range (see Figure 4-2) in accordance with the capabilities and preferences of the participants. From the 7th week until completion of the training intervention, semi-autonomous training with one supervised training session per week is prescribed for each participant.

Structure of Each Exergame Session

Throughout the training intervention period, all sessions will be prescribed following the same basic structure: Each session consists of three blocks with three phases per block (see Figure 4-2).

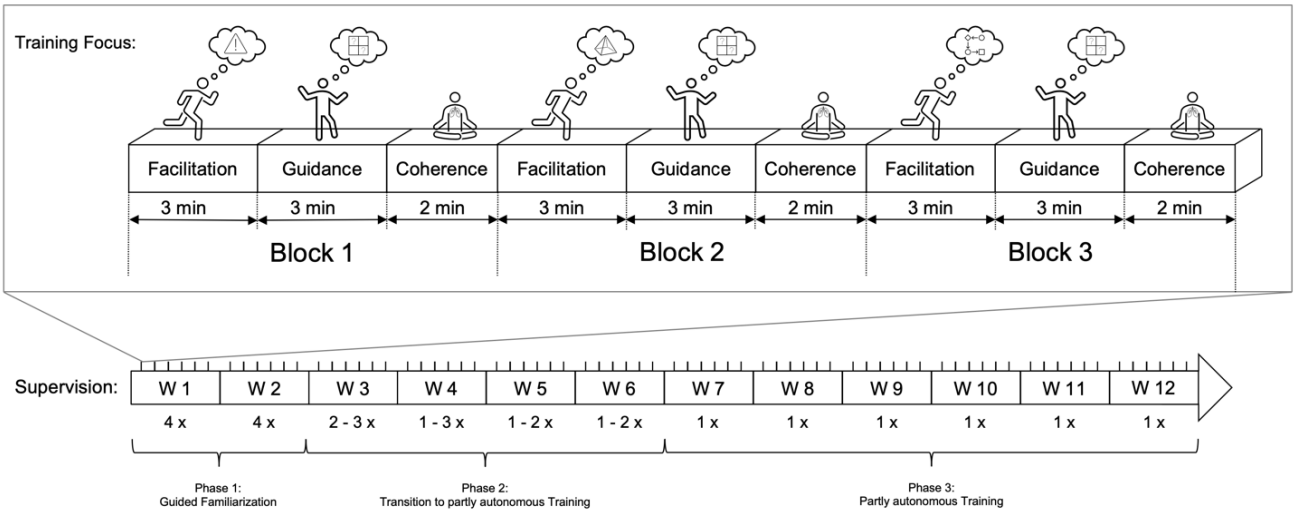

Figure 4-2: Overview of the exergame-based intervention concept and the basic structure of each exergame session (here as an example for a patient with amnestic-single domain mild neurocognitive disorder with a training focus on learning and memory in week 1).

Phase 1 - Facilitation aims to apply a moderate physical exercise intensity in the context of challenging but feasible cognitive and motoric demands mainly intending to *"trigger neurophysiological mechanisms, which promote neuroplasticity"* [34, 239] while additionally using *"cognitive stimulation […] to "guide" these neuroplastic processes"* [34, 239, 240]. This phase includes games focusing on neurocognitive domains that are least impaired. The external task demand is individually adapted to ensure an appropriate internal training load. More specifically, the internal training load is subdivided into a fixed component (i.e., physical exercise intensity) and a variable component (i.e., neurocognitive (game-) demand). An additional stepping task is used to set the level of physical exercise intensity. It includes walking on the spot at a predefined stepping frequency that is needed to reach a moderate level of physical exercise intensity (i.e., ranging between 40 and 59 % HRR [233]). The stepping frequency will be individually determined for each participant (see section *"Phase 1 - Facilitation"*). A battery figure add-on is visible in the center of the screen that provides real-time visual feedback whether the predefined stepping frequency is reached. More specifically, if the predefined minimal required stepping frequency is reached or exceeded, the battery stays at equilibrium or fills. If the battery level is above 80 % (indicated by a line), the battery stays green. If the participants' stepping frequency falls below the predefined minimal required stepping frequency, the battery level decreases, and the battery turns orange (40 - 80 %) or red (below 40 %) indicating that the stepping frequency should be increased. On top of this fixed physical exercise intensity, a variable amount of neurocognitive (game-) demands (e.g., game type, task complexity, predictability of required tasks) is applied. Since the physical exercise intensity is kept constant, changes in the overall internal training load can mainly be attributed to these neurocognitive and motoric (game-) demands and, accordingly, the internal training load can be adjusted on basis of these game characteristics according to predefined progression rules (see section *"Progression Rules for Monitoring Internal Training Load and Adapting External Training Loads"*).

Phase 2 - Guidance aims to make use of the triggered neurophysiological mechanisms from phase 1 to specifically guide neuroplastic processes of the mainly impaired neurocognitive domain. Therefore, games focusing on the mainly impaired neurocognitive domain for the individual participant (e.g., amnestic single domain → learning and memory) are used. These games solely focus on cognitive and motoric demands, but not on physical exercise intensity. The cognitive-motoric demands of the exergame are individually adapted to ensure an appropriate total internal training load according to predefined progression rules (see section *"Progression Rules for Monitoring Internal Training Load and Adapting External Training Loads"*).

Phase 3 - Coherence aims to implement a structured approach as a surrogate for the breaks between games. Patients with mNCD often exhibit depressive symptoms and anxiety, which are in turn important indicators for progression to dementia [241, 242]. To account for these psychological factors, resonance breathing guided by heart rate variability biofeedback (HRVB) will be used. HRVB training is a behavioral intervention aiming to increase cardiac autonomic control, to enhance homeostatic regulation, and to regulate emotional state [48, 49]. It consists of a regular breathing practice at a specific frequency that is individually determined that produces high amplitude of HRV. Usually, this resonance breathing frequency is around 6 breaths/min [243]. An increased HRV is predicted to increase vagal afferent transmission to the forebrain, activate the prefrontal cortex, and improve executive function [48]. In fact, multiple systematic reviews and meta-analyses have indicated that HRVB training or paced breathing (at resonance frequency) is effective in decreasing

depressive symptoms and anxiety in healthy adults and also clinical populations. Additionally, improved sleep quality, quality of life, HRV and brain activity in regions relevant for cognitive adaptations have been reported [50, 53, 55]. The evidence for older adults (i.e., ≥ 60 years) or patients with cognitive impairments is sparse, but decreases in depression, anxiety, and increases in attentional performance (no sign. difference in executive functioning) have already been reported, suggesting that older adults may benefit from HRVBT much like the younger populations [244]. Additionally, *"after initial training some people still achieve better results by following a heart monitor, while others do just as well doing paced breathing at their resonance frequency, once this frequency has been determined by biofeedback, following the second hand on a clock or counting seconds silently"* [53]. Therefore, for the sake of simplicity, we will make use of this transfer to resonance breathing. Before starting the training intervention, the resonance frequency is determined according to the protocol of Lehrer et al. (2013) (i.e., visit 1 of their protocol) [245]. During the training intervention, coherence breathing includes paced breathing for 2 min following the rhythm of the individually predetermined resonance frequency visualized on the screen of the exergame device (i.e., a sun is displayed within a landscape. When the sun gets bigger, the patients breath in. When the sun gets smaller, the patients breath out).

Progression Rules for Monitoring Internal Training Load and Adapting External Training Loads

Phase 1 - Facilitation. As described above, the internal training load will be subdivided into the physical exercise intensity of the stepping task and the neurocognitive and motoric (game-) demands of the games in phase 1. The stepping frequency of the stepping tasks will be predetermined for each participant with the aim to reach a moderate level of physical exercise intensity (i.e., ranging between 40 and 59 % HRR [233]). To avoid overload, the participants will be introduced stepwise; first, all the stepping frequency will be determined while the level of neurocognitive demand is held at level 1. Afterward, the total level of internal training load will be monitored and adapted.

Phase 1a - Determination of minimal stepping frequency:

All participants will start with a stepping frequency of 100 steps/min and at Level 1 of neurocognitive demands in the first training session. The target physical exercise intensity is determined based on the target heart rate (HR) that is calculated using the Karvonen method with a target intensity of 40 % HRR: $HR_{target} = (HR_{max} - HR_{rest}) \cdot 0.40 + HR_{rest}$ [246, 247]. For this calculation the age-predicted maximal heart rate: $HR_{max} = 208 - 0.7 \cdot age$ and HR_{rest} measured at the pre-measurements will be used. The stepping frequency will then be increased by 5 steps/min at each training session, until the minimal level of physical exercise intensity is reached, but to a maximal level of 140 steps/min. The evaluated stepping frequency will then be considered as a fixed component of the overall external training load. In all subsequent training sessions, this fixed physical exercise intensity will be kept constant and the focus shifts to monitoring and adapting the total internal training load.

Phase 1b - Monitoring and adaptation of total internal training load:

Since the physical exercise intensity in phase 2 is kept constant, changes in the overall internal training load can mainly be attributed to the variable level of neurocognitive demand. The level of neurocognitive demand will be standardized according to predefined game levels. Phase 2 will be continued with game level 1, until a plateau in performance is reached. Unfortunately, reading out a plateau of performance by the software of the exergame training system is not (yet) implemented.

Therefore, a plateau in performance will be read out visually guided by the following predefined criteria: (1) a performance increase of less than or equal to 5 % compared to the previous exergame session while (2) there was an increase in performance from session to session over at least the previous three training sessions. Each time a plateau in performance is reached, the game level will be increased by one level or a new (slightly more difficult) exergame will be introduced.

Phase 2 - Guidance. In phase 2, the mainly impaired neurocognitive domain will be trained. Therefore, the focus of monitoring and adapting the task demands will solely focus on neurocognitive demands (i.e., motor- and cognitive demands that are linked because both change as a function of game complexity). The level of neurocognitive demand will be standardized according to predefined game levels. All participants will start with level 1. Each time a plateau in performance is reached, the game level will be increased by one level or a new (slightly more difficult) exergame will be introduced.

The Concept of MYCHOICE to Ensure Sufficient Variability

The concept of MYCHOICE describes a self-determined choice of exergames within groups of games for cognitive domains so that the preferences of each participant can be taken into account while the time spent at training each neurocognitive domain is still standardized within participants with the same training focus (i.e., predetermined according to the deficit-oriented focus on the neurocognitive domains). The advantage of this concept is that it promotes self-efficacy, which might have a positive influence on training motivation [205]. According to the 'Optimizing Performance through Intrinsic Motivation and Attention for Learning (OPTIMAL)' theory of motor learning [248], this is expected to enhance performance expectancies which - accompanied with these autonomy-supportive conditions - *"contribute to efficient goal-action coupling by preparing the motor system for task execution"* ([248]. This is further proposed *"to facilitate the development of functional connectivity across brain regions, and structural neural connections more locally, that support effective and efficient motor performance and learning"* [248, 249]. With this regard, the exergames were grouped into mainly trained neurocognitive domains of learning and memory, executive function, complex attention, visuo-spatial skills (see Supplementary Table S1 in Supplementary File 3) and each participant gets to choose which game within these groups he/she prefers to play.

Step 4: Playtesting of Exergame-Based Training Concept

Goal: *"Through multiple playtesting and informal feedback sessions, specific game preferences and game elements will be modified based on the feedback from older adults and healthcare professionals during their one-on-one interactions with the prototype"* [57].

The resulting training concept is currently being tested on its feasibility, usability, and acceptance. With this regard, a two-arm, parallel-group, single-blinded (i.e., outcome evaluator of pre- and post-measurements blinded to group allocation) pilot randomized controlled trial (RCT) with an allocation ration of 2:1 (i.e., intervention:control) including 17 - 25 older adults with mNCD is conducted. In this study, the active control group proceeds with usual care as provided by the (memory) clinics where the patients are recruited. The intervention group performs a 12-week training intervention according to the newly developed exergame-based training concept in addition to usual care. The primary outcomes include feasibility (i.e., recruitment, adherence, compliance, attrition), usability (i.e., system usability), and acceptance (i.e., enjoyment, training motivation and perceived usefulness) of the

resulting exergame-based training concept for older adults with mNCD. As a secondary objective, preliminary effects of the intervention on cognition, brain resting-state functional connectivity, gait, cardiac autonomic regulation, and psychosocial factors (i.e., quality of life, and levels of depression, anxiety, and stress) are explored. This will allow to synthesize data for a sample size calculation on basis of a formal power calculation for a future RCT. The study was registered at clinicaltrials.gov (NCT04996654) and will be reported according to the *"The Consolidated Standards of Reporting Trials (CONSORT) 2010 statement: extension to randomized pilot and feasibility trials"* [60, 250].

Step 5: Modification of Exergame-Based Training Concept

The MIDE framework also requires a system evaluation in phase 3. Based on the results of our pilot RCT [60], the intervention concept will be modified for its final evaluation on effectiveness with expected contributions from end users, clinicians, researchers, and data analysts.

4.4.4 Phase 3: System Evaluation

Goal: To systematically evaluate the exergame system *"to ensure the exergames meet their intended goals"* [57] regarding therapeutic outcomes, user experience, and technology performance [57].

In the final phase, we will aim to evaluate the effectiveness of the newly developed exergame-based training intervention in older adults with mNCD with respect to cognition, brain structure and function and quality of life. We will strive to recruit n (depending on an a priori sample size calculation) participants that will be randomly assigned to either the intervention group (i.e., exergame intervention) or the control group (i.e., usual care). The primary outcome will include global cognition assessed with the Quick Mild Cognitive Impairment Screen (Qmci) [251]. As secondary outcomes, domain-specific assessments for the evaluation of the key neurocognitive domains (as defined by Sachdev et al. (2014) [3] in line with DSM-V [5]) of learning and memory, complex attention, executive function, and visuo-spatial skills will be incorporated as recommended [7]. Moreover, brain structure and function will be evaluated by magnetic resonance imaging with the aim to investigate more closely the underlying neural changes responsible for adaptations in cognitive performance. Gait, HRV (and its associations to neurobiological and cognitive changes), and psychosocial factors (i.e., quality of life and levels of depression, anxiety, and stress) will also be assessed. This study will be registered in https://clinicaltrials.gov and the study protocol will be published beforehand.

4.5 Discussion and Conclusion

In this manuscript, the design and development process of novel exergame-based training concepts was illustrated using a step-by-step application of the MIDE-framework. The aim was to elucidate the design, development, and evaluation process of an exergame-based training concept to halt and/or reduce cognitive decline and improve quality of life in older adults with mNCD [57].

The development of novel exergame-based training concepts for older adults with mNCD is greatly facilitated when it is based on a theoretical framework (e.g., the MIDE-framework). Applying this framework resulted in a structured, iterative, and evidence-based approach that led to the identification of multiple key requirements for the exergame design as well as the training components that otherwise may have been overlooked or neglected. This is expected to foster the usability and acceptance of the resulting exergame intervention in "real life" settings. Therefore, it is

strongly recommended to implement a theoretical framework (e.g., the MIDE-framework) for future research projects in line with well-known checklists to improve completeness of reporting and replicability (i.e., CERT-checklist [238] in line with the CONSORT 2010 statement [252, 253]) when serious games for motor-cognitive rehabilitation purposes are to be developed.

4.6 Data Availability Statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author/s.

4.7 Author Contributions

PM and EB were responsible for the conception, literature research, and writing of the manuscript. Both authors revised, read, and approved the submitted version.

4.8 Funding

PM and EB received a grant from the Synapsis Foundation - Alzheimer Forschung Schweiz AFS (Grant-No.: 2019-PI06) for the project ‘Brain-IT’ that was awarded to elaborate and test a novel exergame-based training concept for older adults with mild neurocognitive disorder that shows protective effects or improvements in hippocampal structure and function, cognition and quality of life.

4.9 Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

4.10 Supplementary Material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2021.734012/full#supplementary-material

4.11 Abbreviations

ADL	activities of daily living
ANS	autonomic nervous system
BIOLOOP	biocybernetic adaptation loop
CERT	Consensus on Exercise Reporting Template
CONSORT	Consolidated Standards of Reporting Trials
HOA	healthy older adults
HR	heart rate
HR_{max}	maximal heart rate
HRR	heart rate reserve
HRV	heart rate variability
HRVB	heart rate variability biofeedback
IT	information technology
MCI	mild cognitive impairment
MIDE	Multidisciplinary Iterative Design of Exergames
mNCD	mild neurocognitive disorder
NCD	neurocognitive disorders
OPTIMAL Learning	Optimizing Performance through Intrinsic Motivation and Attention for
PERF-LOOP	performance adaptation loop
PLAT	concept of performance plateau
Qmci	Quick Mild Cognitive Impairment Screen
RCT	randomized controlled trial
TARGETINT	concept of monitoring target intensity
$VO_{2,max}$	maximal oxygen uptake

Chapter

5

Paper 2:

Design Considerations for an Exergame-Based Training Intervention for Older Adults With Mild Neurocognitive Disorder: Qualitative Study Including Focus Groups With Experts and Health Care Professionals and Individual Semistructured In-Depth Patient Interviews

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5.1 Abstract

Background: Exergames have attracted growing interest in the prevention and treatment of neurocognitive disorders. The most effective exergame and training components (i.e., exercise and training variables such as frequency, intensity, duration, or volume of training and type and content of specific exergame scenarios) however remain to be established for older adults with mild neurocognitive disorders (mNCDs). Regarding the design and development of novel exergame-based training concepts, it seems of crucial importance to explicitly include the intended users' perspective by adopting an interactive and participatory design that includes end users throughout different iterative cycles of development.

Objective: This study aimed to determine the capabilities, treatment preferences, and motivators for the training of older adults with mNCD and the perspectives of individuals on training goals and settings and requirements for exergame and training components.

Methods: A qualitative study including expert focus groups and individual semistructured in-depth patient interviews was conducted. Data were transcribed to a written format to perform qualitative content analysis using QCAmap software.

Results: In total, 10 experts and health care professionals (80 % females) and 8 older adults with mNCD (38 % females; mean age 82.4, SD 6.2 years) were recruited until data saturation was observed.

Conclusions: The psychosocial consequences of patients' self-perceived cognitive deterioration might be more burdensome than the cognitive changes themselves. Older adults with mNCD prefer integrative forms of training (such as exergaming) and are primarily motivated by enjoyment or fun in exercising and the effectiveness of the training. Putting the synthesized perspectives of training goals, settings, and requirements for exergames and training components into context, our considerations point to opportunities for improvement in research and rehabilitation, either by adapting existing exergames to patients with mNCDs or by developing novel exergames and exergame-based training concepts specifically tailored to meet patient requirements and needs.

5.2 Introduction

5.2.1 Background

The normal aging process is associated with a decline in physical and cognitive abilities [254, 255]. When the cognitive decline exceeds the normal age-related cognitive decline but is not severe enough to interfere with independence in activities of daily living, it can be classified as *"mild cognitive impairment"* (MCI), representing an intermediate stage of cognitive impairment between the normal aging process and dementia [2, 5-7, 143-145]. The condition MCI has evolved over the last decades [2] and has recently been incorporated in the latest Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-5) and the International Classification of Diseases 11th Revision, referred to as mild neurocognitive disorder (mNCD) [3-6]. The prevalence of mNCD increases with age, while the incidence of mNCD and the progression to dementia is expected to rise, largely because of the globally growing life expectancies and sedentary lifestyles [2, 7, 153-156]. As currently no effective pharmacological interventions for patients with mNCD exist [159], alternative options to prevent and treat neurocognitive disorders are needed. Targeting modifiable risk factors in midlife may hold promise for mitigating or even preventing neurocognitive disorders in later life [14, 185-188]. The modifiable risk factors for mNCD include the presence of vascular risk factors (i.e., metabolic syndrome, hypertension, hyperlipidemia, coronary heart disease, diabetes mellitus, or stroke) [166-168] or a physically or cognitively sedentary lifestyle [169, 170]. Consequently, changes in lifestyle that increase physical and cognitive activity and reduce vascular risk factors are protective against cognitive decline [171-179].

Exergames have gained growing interest to prevent and treat neurocognitive disorders [62, 63]. *"Exergaming is defined as technology-driven physical activities, such as video game play, that requires participants to be physically active or exercise in order to play the game"* [64]. One of the major advantages of exergame-based training is that it is widely accepted by individuals with neurocognitive disorders. In addition, it increases training adherence and engagement by facilitating training motivation and satisfaction [42], which in turn may have a positive effect on the effectiveness of improving cognitive functioning [84]. Furthermore, exergames can be used as a form of simultaneous cognitive-motor training with incorporated cognitive task demands [34]. Meta-analytic evidence suggests that simultaneous motor-cognitive training is the most effective type of training for improving cognition in healthy older adults (HOA) [35, 72] and older adults with mNCD [35, 73, 74]. For exergames specifically, a recent systematic review synthesized evidence from low risk of bias studies showing that there were consistent positive effects favoring exergaming in people with mNCD and dementia [42]. Nonetheless, it is currently difficult to draw reliable conclusions about the effectiveness of exergaming in preventing and treating neurocognitive disorders because of the substantial variations in the exergame-based training used. Therefore, further investigations are needed for the establishment of effective exergame and training components (i.e., exercise and training variables such as the frequency, intensity, duration, or volume of training and the type and content of specific exergame scenarios) for cognitive functioning that can be applied with confidence in evidence-based exergame interventions [62].

Regarding the design and development of novel exergames, it seems crucial to explicitly include the intended users' perspectives [58]. Taking the characteristics, needs, and experiences into account should ensure adequate use and therefore the effectiveness of the solution. Baquero et al [92]

pointed out that an end user-centered methodological design is most often adopted in the development of computer-based training programs for cognitive rehabilitation of older adults with neurocognitive disorders (NCDs). In an ideal case, this process fulfills the international standards for the development of programs including (1) understanding and specifying the context of use (type, characteristics and tasks of users, and physical or social environment), (2) specifying the user requirements, (3) producing design solutions, and (4) evaluating the design [92, 93]. So far, only half of the studies reporting computer-based interventions took the standard 'specification of user requirements' into account [92]. This has led to the recommendation that future studies in this field should use an interactive and participatory design that explicitly includes end users throughout different iterative cycles of development [92]. In short, it is important to systematically and thoroughly investigate the specific user requirements and preferences for an exergame-based training concept before it is designed and developed.

5.2.2 Objectives

This study aimed to determine the capabilities, treatment preferences, and motivators for the training of older adults with mNCD and the perspectives of individuals on training goals and settings and requirements for exergame and training components.

5.3 Methods

5.3.1 Overview

This study is part of the national project 'Brain-IT', which began in August 2020 in Switzerland. The aims of the overall project are (1) to determine the most suitable components for exergame-based training in older adults with mNCD; (2) to explore novel strategies for a real-time adaptive exergame system to individually tailor exergame demands according to users' physical or cognitive capabilities; (3) to incorporate the acquired knowledge into an exergame-based training concept with the aim of halting or reducing cognitive decline and improving quality of life; and (4) to evaluate the effectiveness of the resulting training intervention in older adults with mNCD. The project is guided by a theoretical framework that provides specific guidance in the design, development, and evaluation of exergames for older adults, the *"Multidisciplinary Iterative Design of Exergames (MIDE): A Framework for Supporting the Design, Development, and Evaluation of Exergames for Health"* [57], which provides specific guidance in the design, development, and evaluation of exergames for older adults. This study is part of the first phase of the project, with the aim to specify a *"set of design requirements that includes design considerations, accessibility recommendations, user modeling elements, and technological reflections to be followed in the design and development phase"* [57, 58], and it was combined with an extensive literature review and reflections on technology scoping and sustainability strategy (see steps 4 and 5 of phase 1 of our recently published methodological paper [58]). For the project, the exergame device 'Senso (Flex)' (Dividat AG) was preselected on the basis of (1) our previous research, (2) because this device has already been shown to be feasible and well-accepted in geriatric patients [256] and patients with major neurocognitive disorder [227], and (3) because it is already widely used (and therefore available more widely and for longer term by end users and health care institutions) for motor-cognitive training within geriatric populations, physiotherapies, or rehabilitation clinics in Switzerland. On this basis, this qualitative study was designed to achieve the defined objectives in general; in addition, it also aimed to collect evidence about the previous

experiences of experts or health care professionals with different exergame systems (including the 'Senso (Flex)'). In this way, the project team wanted to collect evidence to make an informed decision whether the specific exergame device was suitable for the project, what possible modifications might be needed to optimize the exergame experience for patients with mNCD, and whether and what alternative exergame devices are suggested by the experts (see subsections of *"(T2) Treatment Experience and Preferences—Previous Experiences with Exergames ('Senso' specifically)"* and *"(T5) Exergame and Training Components—Exergame System and Content"* in the focus group discussions). Other than parts of these 2 sections that include device-specific findings, none of the remaining sections in this manuscript are device specific.

5.3.2 Study Design

A qualitative study was conducted between November 2020 and January 2021, including expert focus groups and patient interviews; both were organized as semistructured, in-depth interviews. Semistructured, in-depth interviews are the most widely used interviewing format for qualitative research and are generally organized around a set of predetermined open-ended questions, with additional questions and discussion points emerging from the dialogue [257]. The study was planned and reported in accordance with the *"consolidated criteria for reporting qualitative research (COREQ)"* [258].

The MIDE Framework [57] guided our approach. On the basis of this framework, we integrated multiple stakeholders into the design and development process including exergaming researchers, clinical experts with different backgrounds, a company representing the exergaming industry, and the end users.

5.3.3 Ethics Approval

All the study procedures were performed in accordance with the Declaration of Helsinki. The study protocol (not registered) was approved by the ETH Zürich Ethics Commission (EK 2020-N-154). All interested individuals were fully informed of the study procedures. The expected benefits and risks of the study were explained by the study investigator, who was also able to answer open questions and clarify individuals' uncertainties. It was further verified that withdrawal was permitted at any time during the study without providing any reason. After sufficient time, suitable individuals willing to participate in the study provided written informed consent and were included in the study. No compensation was provided to the participants.

5.3.4 Participants

Experts

Recruitment aimed at including experts and health care professionals experienced with exergame training of older adults with mNCD, preferably (but not necessarily) with the exergame training system "Senso (Flex)" or similar. For this purpose, Dividat AG was asked to provide a contact list of 10 to 15 external experts and health care professionals with a variety in age, sex, educational level, and experience in therapy of older adults with mNCD, who are not employed by Dividat AG or had received any funds from Dividat AG for their work. All recommended experts and health care professionals were contacted via email between November and December 2020. By applying broad inclusion criteria, a rich spectrum of experts and health care professionals were considered in the

study, which in turn will foster the usability of the resulting program in clinical practice. The specific eligibility criteria comprised the following aspects: (1) experts or health care professionals (e.g., physical therapists, movement therapists, neuropsychologists, or researchers experienced with exergames) experienced with exergame training or with older adults with mNCD; (2) German or English speaking; and (3) age ≥18 years. There were no specific exclusion criteria.

Older Adults With mNCD

Older adults with mNCD were consecutively recruited between November 2020 and January 2021 in collaboration with health care institutions and (memory) clinics in the larger area of Zurich. Leaflets and study information sheets containing researchers' contact details were handed out to suitable patients by their therapists. Suitable patients were identified from medical records and patient registries of memory clinics or from diagnostics that had just been performed. Interested patients were contacted by the research team by telephone or email to clarify or obtain further information about the study procedures and to register interest in participating in the study. Subsequently, all patients were fully informed about the study procedures in a face-to-face meeting at the patient's homes. In addition, patients of interest were screened for eligibility. The eligibility criteria are presented in Table 5-1.

Table 5-1: Description of all eligibility criteria.

Abbreviations: DSM-5®, Diagnostic and Statistical Manual of Mental Disorders 5th Edition, ICD-XI, International Classification of Diseases 11th Revision; mNCD, mild neurocognitive disorder; Qmci, Quick Mild Cognitive Impairment Screen; (s)MCI, (screened for) mild cognitive impairment

Inclusion criteria	Exclusion criteria
Participants fulfilling all the following inclusion criteria were eligible:	The presence of any of the following criteria led to exclusion:
• (1 = mNCD) clinical diagnosis of 'mNCD' according to ICD-XI [6] or DSM-5® [5]) OR (2 = sMCI) patients 'screened for MCI' (sMCI) according to the following criteria: (a) informant (i.e. healthcare professional)-based suspicion of MCI confirmed by (b) an objective screening of MCI based on the German version of the using the Qmci [251] with (b1) a recommended cut-off score for cognitive impairment (MCI or dementia) of < 62/100 [259], while (b2) not falling below the cut-off score for dementia (i.e. < 45/100 [259]). • German speaking	• presence of additional, clinically relevant (i.e. acute and/or symptomatic) neurological disorders (i.e. epilepsy, stroke, multiple sclerosis, Parkinson's disease, brain tumors, or traumatic disorders of the nervous system) • presence of any other unstable or uncontrolled diseases (e.g. uncontrolled high blood pressure, progressing or terminal cancer)

5.3.5 Procedures and Data Collection

Expert Focus Groups

The expert focus groups were moderated by the first author (PM) into groups of up to 5 experts. The moderator was a male doctoral student with a master's degree in Health Sciences and Technology (ETH Zürich, Switzerland), who was trained for qualitative research. Owing to the COVID-19 pandemic, all focus group sessions were held as web-based meetings in the form of Zoom sessions

(Zoom Video Communications), took approximately 60 to 90 minutes to complete, and were audio recorded. Each session started with a short presentation of the background and overall aim of the project. Subsequently, the aim of this study was presented before starting the focus group discussions. The focus group discussions were organized as semistructured, in-depth interviews with open-ended questions to enable open conversations [257]. The exchange was conducted following a focus group guide (Multimedia Appendix 1) structured along 5 topics, each consisting of multiple key questions. First, the capabilities of older adults with mNCD were discussed, in continuation with insights into training goals and outcomes in the perspective of patients as well as therapists. Thereafter, the exchange focused on treatment experiences and preferences as well as motivators for training of older adults with mNCD. Finally, the requirements and optimal components of the exergame-based training were critically discussed. To focus the moderator's attention on participants' verbal and nonverbal communication and because handwritten notes during interviews are considered relatively unreliable, no notes were taken during the focus group sessions [260].

Patient Interviews With Older Adults With mNCD

The patient interviews were conducted individually with each patient by the first author (PM) and either took place at ETH Zürich (Institute of Human Movement Sciences and Sport, Leopold-Ruzicka-Weg 4, 8093 Zürich) or at the patients' homes, depending on the patients' preferences. The interview sessions were held face-to-face in a quiet room with no one present besides the interviewer, the patient, and, if requested, a care professional or partner as personal support for the patient. We did not set a time limit for the interviews but gave all participants enough time to share their views on the topics discussed. On average, each session took approximately 20 to 30 minutes to complete and was audio recorded. Before starting the interview, the background and overall aim of the project as well as the aim of this study were explained to each patient. The interviews were organized as semistructured, in-depth interviews along an interview guide (Multimedia Appendix 1) [257]. The interview guide was not pilot-tested, as it was developed by the first author (PM) in collaboration with the second author (MA), an experienced clinical neuropsychologist. After questioning the patients' capabilities as well as their previous treatment or training experience and preferences, the interview continued with questions about motivators for training and the preferred components of exergame-based training. Open-ended questions were asked to enable an open conversation [257]. To focus the moderator's attention on patients' verbal and nonverbal communication, no notes were taken during the interviews [260]. Finally, the interviewer was prepared to tailor the interview questions and communication style to the patients' capabilities, and in case of higher levels of impairment, to adopt strategies suggested to optimize communication with patients with NCDs [261, 262].

5.3.6 Sample Size

The intended sample size was set at approximately 5 to 10 experts for the focus group sessions and 5 to 10 older adults with mNCD for the patient interviews; however, study participants were consecutively included until data saturation was reached [263].

5.3.7 Data Analysis

First, all audio files were transcribed in written format in Microsoft Word in pseudonymized form. The transcripts were not returned to the participants for corrections or comments. To explore the perspectives of patients and experts or health care professionals, a qualitative content analysis was

performed according to Mayring et al [264, 265] using QCAmap software [265-267]. The first step in the analysis involved repeated readings of the transcripts and listening to the original audio files to gain a better understanding of the conversation content. Second, the type of analysis (i.e., category assignment procedure) was predefined for each of the research questions (i.e., key questions of the interview guide). In case of an inductive category assignment procedure, a selection criterion and level of abstraction were defined for each of the research questions. For deductive category assignments, each research question was operationalized into categories, and a corresponding coding guideline (i.e., category label, category definition, anchor example, and coding rules) was formulated. On the basis of this, all transcripts were coded line-by-line (i.e., including a revision of the category system after a pilot loop). Subsequently, each resulting list of categories was grouped into main categories, and inter- and intra-agreement checks were performed. Finally, the results of each key question were analyzed along the structure (including predetermined themes and topics) of the interview guide that was created according to the guidelines of the MIDE Framework [57]. Thus, the results were structured and analyzed in 2 main themes and 5 topics. First, the section *"user modeling"* that included 3 topics: (T1) capabilities of older adults with mNCD, (T2) treatment experiences and preferences, and (T3) motivators for training. Second, *"therapeutic needs,"* including (T4) training goals and outcomes and (T5) exergame and training components. Within the topic *"(T1) capabilities of older adults with mNCD,"* the described cognitive capabilities and difficulties were classified into the key neurocognitive domains (as defined by Sachdev et al [3]) in line with DSM-V [5] on agreement between the first (PM) and second author (MA; an experienced neuropsychologist). Within the topic *"(T3) motivators for training,"* the motivators for training were coded and analyzed against the background of the 'Self-determination Theory' [189]. The Self-determination Theory [189] accounts for the quality of different levels of motivational regulation in physical activity settings. It is considered useful to gain a better understanding and promote training motivation, enjoyment, and adherence and has demonstrated considerable efficacy in explaining exercise motivation and behavior [190-194]. Data from the qualitative content analysis were combined with quantitative data (i.e., frequency of various statements [f] and in the case of patient interviews, the proportion of patients making a statement [in %]) [263]. The coding and data analysis process was cross-checked to enhance the credibility of the analytic procedure [263].

5.4 Results

5.4.1 Participants

In total, 11 external experts and health care professionals were contacted by the first author (PM). All experts responded and were interested in participating. Two experts could not participate in the focus group sessions because of time constraints. According to the "integrative" contribution of the MIDE Framework, *"perspectives of various stakeholders (e.g., industry partners, data analysts, health care professionals) are considered in the process of designing and developing exergames"* [57]. In accordance with this, the founder of Dividat AG was involved in one of the focus group discussions as an industry representative. In total, 10 experts and health care professionals (80 % females) participated in 1 of the 5 focus group sessions until data saturation was observed and further recruitment was terminated. The focus group sessions were conducted in groups of between 1 (k = 3) and 3 (k = 1) experts (median 1.5) and the moderator (PM). The professional backgrounds of the experts and health care professionals included exergaming researchers (n = 4), physical and

occupational therapists (n = 2), neuropsychologists (n = 2), project manager therapy (n = 1), and founder of an exergaming company (n = 1).

For the patient interviews, 8 patients (38 % females; mean age 82.4, SD 6.2 years; mean level of cognitive functioning, measured by the German Version of the Quick Mild Cognitive Impairment Screen [251], 56.0, SD 8.2) were invited and interviewed until data saturation was observed and further recruitment was terminated. None of the patients refused to participate or dropped out of the study after providing their written informed consent. The demographic characteristics of the patients are summarized in Table 5-2.

Table 5-2: Demographic Characteristics of the Study Population

Abbreviations: SD, Standard Deviation; Qmci, Quick Mild Cognitive Impairment Screen

	Total Sample (n = 8)	
	mean	SD
Age [years]	82.4	6.2
Height [m]	1.71	0.06
Weight [kg]	67.8	10.0
Body mass index [$kg \cdot m^{-2}$]	23.1	2.4
Physical Activity [min/week]	298.8	227.0
Qmci [251] total score [points]	56.0	8.2
Clinical Subtype:		
mNCD due to Alzheimer's Disease	n = 6 (75 %)	
mild Frontotemporal NCD	n = 0 (0 %)	
mNCD with Lewy Bodies	n = 0 (0 %)	
mild vascular NCD	n = 2 (25 %)	

5.4.2 Qualitative Content Analysis Results

T1: Capabilities

The experts described a large variety of impairments observed in older adults with mNCD. The most frequently described impairments referred to cognitive functioning (f = 43), including impairments in the following neurocognitive domains: executive function (f = 23), complex attention (f = 11), learning and memory (f = 7), visuospatial skills (f = 2), language (f = 1), and social cognition (f = 1). These cognitive changes were also described as affecting psychosocial factors (f = 22), mainly by causing psychological distress (f = 9) and feelings of insecurity (f = 2), leading patients to try to hide their impairments from others (f = 2). In addition, an increased fall risk (f = 9) and reduced physical resilience (f = 7) were observed. Although experiencing difficulties in activities of daily living (ADLs; f = 1), patients were described as maintaining their functional independence in ADL (f = 2).

In line with the experts' viewpoint, cognitive deterioration (f = 22, n = 7, 88 %) was frequently described by the patients, mainly affecting learning and memory (f = 11, n = 4, 50 % of patients), executive function (f = 6, n = 4, 50 % of patients), and complex attention (f = 5, n = 2, 25 % of patients), whereas only minor restrictions in physical capabilities and mobility were mentioned (i.e., impaired balance, [f = 2, n = 2, 25 % of patients], reduced gait speed [f = 1, n = 1, 13 % of patients], increased fall risk [f = 9, n = 5, 63 % of patients], fatigue [f = 6, n = 3, 38 % of patients], and joint pain [f = 2, n = 2, 25 % of patients]). ADLs remained preserved in all patients, but the need for coping strategies was mentioned by 4 patients (50 %) to be able to preserve ADLs. From the patients' perspective, the consequences of their self-perceived subjective cognitive decline (f = 8, n = 6, 75 % of patients) with regard to psychosocial factors were most frequently reported (f = 36, n = 8, 100 % of patients), mainly involving psychological distress (f = 13, n = 2, 25 %), feelings of insecurity (f = 6, n = 3, 38 % of patients), depressive symptoms (f = 2, n = 2, 25 % of patients), or fear of repeated falls (f = 3, n = 1, 13 % of patients):

> *"A really tedious thing is that you often can't keep up. For example, in discussions or conversations. [...] You often think about what the other(s) have just said and in the meantime he or she has already continued. That's why you often just don't say anything. Of course, most people like it when you don't say anything (*laughs*). So, these people don't get upset about it. But I am." [P-01]*

> *"I used to go running a lot. I don't do that anymore. But swimming is still fine. In the worst case, I become a drowned corpse, but at least I can't fall while swimming." [P-02]*

> *"I can actually do everything; I just have to be careful because of my dizziness and weakness so that I don't fall. I also have problems with short-term memory. I have to try to remember everything somehow, but I still forget a lot of things." [P-04]*

T2: Treatment Experience and Preferences

Previous Treatment and Training Experiences

To counteract cognitive decline and preserve physical capabilities, mobility, and ADLs, patients have already been on medical training therapy (MTT; f = 3, n = 3, 38 % of patients), have already been on physical therapy (PT; f = 2, n = 2, 25 % of patients), have performed a specific group-based (i.e., f = 1, n = 1, 13 % of patients) or individual (f = 1, n = 1, 13 % of patients) cognitive training or meditation (f = 1, n = 1, 13 % of patients), or have reported to have no experience in any specific therapy or training (f = 1, n = 1, 13 % of patients).

From the patient's viewpoint, MTT and PT were perceived as useful (f = 3, n = 3, 38 % of patients), but patients reported that they would have to do it more consistently to profit from it (f = 2, n = 2, 25 % of patients). Computerized cognitive training (CCT) was also perceived as useful (f = 1, n = 1, 13 % of patients) and reported to be challenging, fun, and enjoyable (f = 2, n = 2, 25 % of patients). Nonetheless, patients reported being insecure about the effectiveness of CCT (f = 2, n = 2, 25 % of patients):

> *"[In response to PT] [...]my gait has improved. I now take slow and long steps and no longer fall over. However, I would definitely have to do it more consistently."* [P-02]

> *"The problem is primarily that my physical therapist only has time for me every 14 days because she is so booked up. Of course, it would be nice if I could go more often. But it is what it is, and I have to live with it."* [P-08]

> *"[Patient explains game tasks of CCT] It's not even that simple. This is all fun and useful. But I don't know if it will do any good. [and] I have no intention of stopping. However, at some point I have to ask myself: "Does is go any further? Or is it just going to stay at what I'm currently able to manage?""* [P-01]

According to the experience of experts and health care professionals, only cognitive forms of training or physical exercises were often experienced as boring over time by older adults with mNCD (f = 2) and required guidance by a therapist (f = 2). More integrative forms of training, including gamified tasks close to everyday life, multimodal animation, and acoustic feedback, were reported to be preferred by patients (f = 4):

> *"It is often the case that patients are completely dependent during strength training, [and] [...]they just kept on exercising and exercising. [...] They often continue the exercises until you stop them."* [E-10: founder of an exergaming company]

> *"Cognitive exercises including "a certain closeness to everyday life and also a multimodal animation[...] and acoustic feedback have been very well received.""* [E-03: neuropsychologist]

Previous Experiences With Novel Technologies

Although being described as skeptical about the use of technological devices, experts perceived older adults with mNCD as ready to use technological devices such as heart rate monitors during training (f = 9), if its usability is ensured:

> *"Well I think using a sensor it's not a problem if the wearable is well designed."* [E-01: exergaming researcher]

> *"Many people would certainly be okay with a Polar chest strap, but a monitor to be worn at the wrist would certainly be preferable. If people are told why these sensors are used and what they are measuring, it should be feasible with the chest sensors as well. It may be difficult with certain older ladies or overweight individuals, but for the average individual this should not be a problem."* [E-03: neuropsychologist]

The experts' perceptions coincided with those of patients. All patients were willing to use a heart rate monitor worn with a chest strap during training, provided it was beneficial for their training. In addition, 75 % (6/8) of patients stated that their PC or television was usable, whereas 25 % (2/8) of patients reported limited usability:

> [Regarding the use of heart rate monitors during training] *"[...]provided it's useful I would be ready to wear such a heart rate monitor without having any reservations at all."* [P-01]

> [About the usability of the television] *"Sure! All you have to do is press the switch. That's still possible."* [P-07]

> [About the usability of the personal computer] *"Yes, using my personal computer works more or less. [...] It is just not something of my generation. I have a computer and I use it, but there are always things I can't do and have to ask my granddaughter."* [P-01]

Previous Experiences With Exergames ['Senso (Flex)' Specifically]

None of the interviewed patients reported any previous experience with exergames in general or with the exergaming system 'Senso (Flex)' specifically. Nonetheless, after a short introduction to the system, all patients stated that they would be willing to try it.

On the basis of the previous experiences of the experts and health care professionals, the interaction with the 'Senso', its overall usability, and the design of the exergames have been described as good (f = 5). Regarding hardware components, minor usability problems have been reported. Patients were observed to unintentionally walk off the middle plate without noticing the feedback on the screen (f = 4), constantly change their focus between the game tasks on the screen and the stepping plate to anticipate and plan their movements (f = 4), or make too small steps to tap on one of the outer stepping plates (f = 1). In addition, the patients needed time to familiarize themselves with the sensitivity of the stepping plate (f = 2):

> *"[...] the 'Senso' is in general well usable and is also very often used."* [E-04: exergaming researcher]
>
> *"The tasks on the 'Senso' are very well designed."* [E-08: project manager therapy]
>
> *"[...] the 'Senso' is already very user friendly, [but] I had a little problem at the beginning of the experiment where people would accidentally go out of the square in the middle of the 'Senso'."* [E-09: exergaming researcher]
>
> *"Most of the time, the patients look down at that very moment and thus do not see the message [on the screen] at all."* [E-07: physical and occupational therapist]

Additional usability issues were reported to be linked to the capabilities of older adults with mNCD. First, it has been described that patients are often cognitively overloaded when trying out new games (f = 1), by the occurrence of an unexpected situation or technical errors (f = 2), or by the cognitive task demands required to interact with the exergame system in general (f = 1), which may limit training duration owing to attentional exhaustion (f = 2):

> *"With new games, patients are often overwhelmed in general, because they don't know what to expect. They often need time to find their way around."* [E-07: physical and occupational therapist]
>
> *"[...] Patients are completely overwhelmed as soon as something unexpected or a technical problem occurs."* [E-03: neuropsychologist]

In contrast, the physical capabilities were reported to not directly affect the usability of the system (f = 4), although some patients experienced difficulties with backward steps (f = 2), and many patients made use of the handrail to reduce the physical strain (f = 6). In some cases, physical limitations (e.g., fatigue and joint pain) resulting from static loading have been reported to limit the training duration (f = 4):

> *"Patients often have problems with backward steps. [and] Patients hold on to the handrail far too often. [...] it is often the case that people hold on because it is simply 'a bit more comfortable."* [E-10: founder of an exergaming company]

> *"Often it is already difficult and tiring for patients to stand for a longer period of time. It is often easier for them to walk. [and] However, it should be noted that this form of fatigue is not necessarily comparable to fatigue caused by physical training. Fatigue does not necessarily come from physical exertion. It is possible that this type of fatigue is caused by the static load and the resulting joint pain."* [E-06: physical and occupational therapist]

When considering the specific games of the exergaming device 'Senso' (video illustrations and explanations of all currently available games can be found at [268]), the simple and clear design structures of the games (f = 4) and the intuitive tasks were reported to be highly appreciated by patients and promote good comprehensibility, which was reported for the games "Simple" (f = 3), "Birds" (f = 3). Nonetheless, there are also games that were reported to cause problems of understanding, in particular the games "Simon" (f = 3), "Tetris" (f = 3), "Habitats" (f = 4), "Targets" (f = 1), and "Snake" (f = 2). These problems may be related to the game instructions (f = 9):

> *"[...] Many people are very happy with simple design structures. This should be maintained at all costs when designing new games for MCI patients. However, [...]some kind of adjustment of the game instructions is definitely needed."* [E-10: founder of an exergaming company]

> *"For patients, a game does not stand out by its great graphics, but by the game tasks as such."* [E-08: project manager therapy]

> *[About problems of understanding the games] "I think the reasons were that they didn't really understand the instructions well."* [E-09: exergaming researcher]

However, it could also be related to the task demands of the games. It was reported that the patients need some time to familiarize themselves with the game to fully understand it (f = 1). According to the experts' experiences, this works well with the games 'Simple' (f = 4), 'Birds' (f = 1), 'Flexi' (f = 1), and in some cases 'Habitats' (f = 1). At the same time, games such as 'Flexi' (f = 1), 'Habitats' (f = 6), 'Hexagon' (f = 3), 'Simon' (f = 6), 'Ski' (f = 4), 'Targets' (f = 12), and 'Tetris' (f = 4) were frequently reported to start at an already (too) challenging level for older adults with mNCD and progress too fast while there is a limited range of games or adaptability of task demands at the lower end of difficulty levels (f = 9). This was mentioned to be mainly apparent for the cognitive task demands (e.g., game speed and task complexity), whereas physical exercise intensity is often (too) low and could be increased (f = 4):

> *"For MCI-patients, some games are predestined to be used with them, such as 'Simple', 'Flexi', 'Birds' and perhaps also 'Habitats'. These games don't put so much time pressure and the feeling of having missed something on patients."* [E-08: project manager therapy]

> *"[...] the increase in the challenge profile from the easiest games ('Simple' and 'Birds') to the next more difficult game is too steep for MCI-patients. For example, the game 'Targets' is too fast for many patients. The game 'Habitats' contains too many stimuli at once, so that the patients no longer know what they have to pay attention to."* [E-07: physical and occupational therapist]

> *"[...] I have the impression that the internal progression, which is responsible for adapting the game demand, sets the lower limit too high and adapts too quickly, so that the cognitive overload becomes visible very quickly, especially in MCI-patients."* [E-08: project manager therapy]

> *"One problem with the 'Senso', in general, is that the physical intensity might well be higher."* [E-05: neuropsychologist]

Overwhelming task demands may cause frustration or refusal of games (f = 6), although the feedback mechanisms to indicate errors work subtle (f = 4). In contrast, games that are perceived as being too easy lead to boredom (f = 2):

> *"For example, the games 'Targets', 'Ski', or 'Hexagon' are very confronting, and patients recognized quite quick: "Okay, I can't do it," and that frustrates patients. [...] Usually, these patients stop in the middle and say something like: "Ah, I don't need that kind of shit." Most of the time, they stop the training session immediately and don't want to continue anymore."* [E-08: project manager therapy]

> *"My observation was that the negative feedback currently used does not demotivate the patients at all. It is also clear to the patients that they need to know when they are making mistakes and whether they are completing the tasks correctly."* [E-04: exergaming researcher]

> *"Some of the negative feedback is so subtle that it is not even noticed."* [E-05: neuropsychologist]

T3: Motivators for Training

The experts described numerous motivators for training older adults with mNCD. The most frequently described motivators can be classified as intrinsically regulated motivators (f = 44), which are directly related to exergames. Excitement, enjoyment, or fun is perceived as a central motivator for performing exergames (f = 4). This was reported to be maintained by the captivating character of exergames (f = 1) and multimodal animation (f = 1), which is supported by specific game components (e.g., game tasks or designs close to everyday life [f = 6] or with personal relations or memories [f = 1] including music or sound effects [f = 8], animals or plants [f = 4], landscapes [n = 1], or colors [f = 1]). In addition, patients were described as intrinsically motivated by gamification (f = 6), the feeling of being optimally challenged (n = 3), or simply by the variation of training (f = 6):

> *"For patients, the focus is primarily on having fun with the games. For example, they [...] liked watching birds and listening to birdsong and felt very motivated by the personal connection. Through these personal memories [...] a whole other level of motivation emerged." [E-08: project manager therapy]*

> *"I think that those people who enjoy playing games are generally captured by the playful and competitive nature of the games. Furthermore, training with exergames is something completely different compared to classical therapy. Patients appreciate this change from the "dry" standard therapy." [E-06: physical and occupational therapist]*

However, when task demands become too high (f = 6) or too low (f = 2), patients have been observed to promptly lose their willingness to perform the exergames, as already reported. External motivators such as social support (e.g., by therapists or caregivers) or group dynamics have also been reported to improve motivation to train (f = 12). Feeling concerned about cognitive deterioration or being confronted by performance classifications can either motivate or induce negative feelings (f = 7). Finally, some patients were also reported to be motivated by the effectiveness of exergames (f = 2) or performance improvements (f = 2):

> *"I consider this social support to be very central. [...] If a relative joins in for motivation or support it can be very valuable."* [E-04: exergaming researcher]

> *"I think there are always patients who don't want to know how well they are performing. Forcing performance feedback on such people can of course be motivating, but it could also be negative and confirm their limitations."* [E-07: physical and occupational therapist]

From the patients' viewpoint, all patients reported that they could primarily be motivated to train regularly by the effectiveness of the training, helping them achieve their individual success (f = 13, n = 8, 100 %). Alternately, patients reported being motivated by their relatives or partners (f = 2, n = 1, 13 %) and enjoyment of exercising (f = 1, n = 1, 13 %). Having to travel to a training facility was reported to have a negative effect on training motivation and adherence (f = 4, n = 1, 13 %):

> *"It would be nice if I could go for a walk in the forest again without falling down. I used to do this four times a week for 75 minutes. It motivates me to train so that I can do this again in the future."* [P-02]

> *"It would motivate me if I could improve my abilities (balance) again. [...] I would like to stay independent and modern, not to be called an old lady."* [P-03]

> *"The success. I no longer need to be motivated. If I set my mind to it, I do it!"* [P-08]

T4: Training Goals and Outcomes

Regarding the training goals, cognitive functioning (f = 19) should be targeted in the training intervention in the experts' viewpoint while also addressing ADLs and mobility (f = 3), addressing physical capabilities (f = 3), and accounting for psychosocial factors (f = 2), such as feelings of insecurity. However, the weighting of the training focus differs significantly between experts in different fields:

> *"[...] higher order processes (i.e. divided attention or the ability to plan) are affected in most patients. Therefore, it is important to focus on these higher order cognitive functions."* [E-05: neuropsychologist]

> *"I think that the coupling of brain functions with physical functions is central. At the same time [...] it is important to focus on what is impaired. If the frontal lobe is impaired, it is certainly important to train executive functions, attention and inhibition."* [E-10: founder of an exergaming company]

> *"Primarily physical activation, especially that people get moving and walk. But also, to train the intuitive way of taking steps. [...] The cognitive aspects of the training have always played a subordinate role for me, but they were usually not decisive for the success of the therapy, as this was often trained differently, and I am not an expert in this."* [E-06: physical and occupational therapist]

When asking experts about the training goals of patients, ADLs and mobility (f = 5) were the most frequently stated in addition to cognition (f = 3) and physical functioning (f = 2). In addition, psychosocial factors (f = 2) have been reported to include socializing or having fun:

> *"I had patients who wanted to continue training because the training made them more confident in their gait. They felt better balance after the training." [E-06: physical and occupational therapist]*

> *"The patients also see the cognitive aspects of the training, of course. [...] We often explain to the patients that falls prevention has a cognitive and physical aspect and that these aspects interact.*

Therefore, the patients mainly go to the training with the aim of improving their gait.“ [E-07: physical and occupational therapist]

“Some people really know what’s going on and they know that they have a disease and that they can prevent or slow down the progression by doing physical activity and exergames. But then others don’t really know that they have cognitive deterioration and they’re just playing a game and having fun without specific training goals.“ [E-09: exergaming researcher]

This is consistent with patients’ viewpoint who most frequently reported improving gait (f = 6, n = 5, 50 %), memory (f = 3, n = 3, 38 %), and balance (f = 2, n = 2, 25 %) as their primary goal to increase their quality of life. In addition, patients reported being more active (f = 1, n = 1, 13 %), increased functional abilities (i.e., cooking; f = 1, n = 1, 13 %), increased strength (f = 1, n = 1, 13 %), or remaining independent in ADLs (f = 1, n = 1, 13 %) as training goals:

“It is mainly the memory. It is memory because it affects a lot of other things.“ [P-01]

“It would be wonderful, if I could go for a walk in the forest again without falling down.“ [P-02]

“I really want to remain independent. I definitely don’t want to become dependent on others.“ [P-05]

“That I can keep things better in my head. That has diminished. That would be nice!“ [P-06]

“I want to have more strength again to increase stability and be able to walk longer.“ [P-08]

T5: Exergame and Training Components

Location

Regarding training location, the experts reported that the patients would either prefer individual training at home (f = 3) or in a mixed setting, including training at home combined with training at a clinic (f = 4). None of the experts stated that patients would prefer exercising at a clinic or training facility in general, as this is often associated with excessive time expenditure. Training at home was reported to be beneficial, because it represents a known environment that makes patients feel more secure. However, the experts also stated that patients may not be capable of performing exercises or exergames independently and therefore need guidance throughout each training session (f = 4) or at least partially (f = 9); for example, when starting up the system or in case of technical problems:

[The advantage of training at home is that] “it’s a known environment and they feel safer at home and also don’t have to travel.” [However,] “I would suggest that the help of a guiding therapist with experience will be necessary.” [E-09: exergaming researcher]

In a previous investigation [...], patients’ feedback was that 70 % could imagine doing the training from home. [...] For MCI-Patients specifically, relatives may be involved. But in general, the need for home-based exergame training is there, I would say. [E-08: project manager therapy]

This is also reflected in the outcomes of the question of whether patients would be capable of performing home-based exergame training; the experts mainly reported that patients are certainly capable (f = 4) or should be capable of considering some concerns (f = 9) to perform such a training program independently at home. The concerns that need to be considered include the improvement of game instructions (f = 2), accessibility of a handrail or similar for safety support (f = 2), and

avoidance of technical problems (f = 2) or the integration of a guided familiarization period (f = 1) or support of a care professional or partner (f = 2):

> *"I think if the system would really work properly then you could use it at home. However, if you just have some minor technical problems is already like a no-go to use it at home at all."* [E-01: exergaming researcher]

> *"It would certainly be good if the patients could complete an accompanied training for a certain period of time in order to facilitate the transfer to training at home."* [E-04: exergaming researcher]

> *"[...] some kind of adjustment of the instructions is needed [...], especially for this patient group and for independent training in the home-based setting. [...] The instructions have to be adapted in such a way that understanding can be achieved without someone having to stand next to the patients all the time."* [E-10: founder of an exergaming company]

Of those patients who responded to the question and had a clear preference regarding the training location, most (6/7, 86 %) patients would clearly prefer to train individually at home, because it is less time consuming and more flexible. One patient did not have a clear preference; she simply wanted to perform the exercises where it was easiest for her and preferred group exercises:

> *"For me, it is important that the training can be done independently at home. If I have to go to the doctor somewhere every time, it's simply too much work."* [P-01]

> *"Preferably at home, if I can. Then I can also choose the time when I want to exercise. I have lived my whole life with a packed schedule. Now I want to be a little freer and more flexible."* [P-03]

Safety

The experts reported an increased risk for falls, as patients with mNCD (1) are easily distractable and (2) have difficulties in self-assessment and impaired planning abilities. Therefore, it was recommended to use the handrail in the beginning to minimize the risk of falls (f = 3), which was also requested by 1 patient. In the case of a home-based exergaming system—which may not have a handrail—thorough and clear safety instructions are recommended (f = 1):

> *"Especially in the beginning, until the patients have understood what it is all about, it is very important to instruct using the handrail."* [E-04: exergaming researcher]

> *"I definitely need a railing to prevent falls during training. I often fall down if I don't have anything to hold on to."* [P-02]

Instruction, Familiarization, and Guidance

As illustrated earlier, certain adaptations are required to enable a more independent use of the exergaming device. First, patients should be familiarized with the exergaming device and the corresponding games considering the following key elements: (1) start at an easy level (f = 7), for example, by using the game "Simple" (f = 4), (2) ensure that patients voluntarily try out the device (f = 3), (3) ensure that you are not too confronting (f = 2), (4) give patients enough time to familiarize with the new task (f = 1), and (5) start with a reaction game, then progress to games for specific domains of neurocognitive function (f = 1):

> *"It is very important to start very slowly and at a low difficulty level until the patients can better assess their abilities on the 'Senso'. […] Since the game 'Simple' waits for a reaction from the individual, it is very suitable to start with."* [E-04: exergaming researcher]

> *"We always start with a reaction game so that the patients can learn the coupling of the cognitive-motor functions and learn to interact with the environment. Later on, we focus on specific cognitive functions."* [E-10: founder of an exergaming company]

Regarding the instructions, some adjustments are needed to improve comprehensibility. Currently, there is instructional text before starting each game. However, patients with mNCD have been reported to have limited comprehension of instructions. Therefore, adaptations are needed in the instructions of exergames in general and for a home-based exergaming system in particular. The experts mainly suggested to use step-by-step (f = 3) instructions based on a combination of visual (i.e., written instruction or video demonstration) and verbal instructions (f = 4) guided by an experienced therapist (f = 1). In case of more severely impaired patients or for home-based exergaming systems, it was suggested that practical demonstrations (f = 2), video instructions (f = 6) or even interactive "trial run" instructions (f = 5) could improve comprehensibility of the games:

> *"The transfer from the written instructions to the understanding of what is to be done in the game is sometimes difficult."* [E-06: physical and occupational therapist]

> *"Personally, I would replace the written instructions with a short (few seconds) video sequence showing the most important functions of the games."* [E-08: project manager therapy]

> *"I would recommend combining visual and verbal instructions. For example, through a visual presentation with additional step-by-step verbal instructions. Verbally we can "pick up" the patients very well and get a feeling whether the patients have understood the instructions."* [E-03: neuropsychologist]

> *"[...], some kind of adjustment of the instructions is needed. [...] It is definitely important to pursue and use these adaptations, especially for this patient group and for independent training in the home-based setting", because "in the case of more severe impairments, it is often necessary to demonstrate the games step by step by yourself. [...] In other gaming systems there is a short test phase with explanations and trial runs [...]. However, this would have to be offered as an option, since most patients will no longer need it after a few sessions."* [E-10: founder of an exergaming company]

Finally, when guiding patients through their training sessions, social support and guidance by a care professional or partner might be beneficial (f = 3). However, it was also mentioned that this might be critical because of personal conflicts or patients' psychological constraints (f = 2):

> *"Family members could play an important role in reminding and motivating patients to complete their training."* [E-06: physical and occupational therapist]

> *"I don't think it's always a good idea to include family members as guidance, because the pressure to perform gets higher for the patients, since they try to hide their impairments from others. A health care professional like a nurse for example or physical therapists would be better than a husband or wife, I think. They already have a lot of fights in the households, because things are not working out as they should."* [E-09: exergaming researcher]

From a patient's perspective, all patients reported that they can imagine training alone, provided they had received thorough instructions and understood their tasks. One patient additionally requested regular support from a care professional or partner:

> *"Yes, I think so. Once I learn that, I'm sure I can do it independently."* [P-03]

> *"If I am supported by you or by my partner, then I can certainly train partly independently."* [P-07]

Exergame System and Content

Previous experiences of older adults with mNCD using the exergaming system 'Senso' are illustrated earlier. Building on this, several game-specific adaptations were suggested by the experts (f = 9):

> *"More time should be provided between the balls so that the flood of information is reduced (it is often overwhelming when several balls are visible on the screen very quickly)."* [E-07 (physical and occupational therapist): for the game 'Targets']

> *"In the initial phase, until patients' have understood all the game tasks [...], the speed must definitely be reduced."* [E-06 (physical and occupational therapist): for the game 'Habitats']

> *"There are already enough opportunities to increase the task difficulty. [...] However, it is very important to note that the game difficulty is adjusted downwards so that it is easier to start the training."* [E-08: project manager therapy]

In addition to these game-specific adaptations, multiple novel game designs and elements have been suggested and discussed by focus groups to address patients' needs optimally. In general, it has been recognized that there is a need for new games specifically targeting the neurocognitive functions of learning and memory (f = 4) and executive functions (i.e., working memory and cognitive inhibition; f = 2). Specific game design suggestions were discussed for such a memory or working memory game. Additional suggestions for new game designs and elements include the use of music, addition of visual reminders to guide patients within the games, or adaptations in performance feedback:

> *"With the 'Senso', a certain spectrum of neurocognitive function domains is covered. However, games for working memory, inhibition or memory are completely missing. In the case of memory, there is currently only one game available specifically targeting the training of short-term memory span."* [E-05: neuropsychologist]

> *"I think music would be very motivating for people with MCI or dementia also if is music from their youth or music they like. It's also been described in the literature that music has so many good effects on people when they have heard a song that they liked before and they are singing that song."* [E-09: exergaming researcher]

> *"In addition, it would be good to include reminders, for example at the edge of the screen, which patients can use for orientation. [...] Additionally, [...] it would certainly be helpful here if the program not only displayed the performance curve, but also provided a reason or explanation."* [E-03: neuropsychologist]

As general requirements when designing new games, the experts recommended using simple graphics and ensuring good contrast (f = 14), a comfortable relation, and good usability of the exergames (f = 4) using easily comprehensible and clearly designed tasks (f = 2) with a certain

closeness to everyday life (f = 7). Multimodal animations, including multisensory feedback (f = 7), should additionally be integrated by focusing on positive reinforcement mechanisms (f = 2) to motivate the patients during exergaming. In addition, it is important that the main task is in the center of the screen (f = 1) and that only elements that are related to the game task are included (f = 5). Moreover, too confronting performance feedback (f = 1) and unexpected appearance or technical problems (f = 2) should be avoided:

> *"It is very important to create a good contrast. [...] It's generally important for the older population to keep the graphic representation as simple as possible, because for older people, the game is not characterized by great graphics, but by the game task as such. The main importance is that the right level of challenge is offered."* [E-08: project manager therapy]

> *"It is much better to present a simple graphic and focus on the aspects that need to be trained. [...] unnecessary graphic gimmicks should be avoided!"* [E-04: exergaming researcher]

> *"It is important to have a main action that is in the center of the screen and to ensure that the player will have primary task in the center. If you put any secondary tasks into the games, it can be confusing for the patients."* [E-02: exergaming researcher]

> *"Spontaneously, I would say that games close to everyday life are more popular. [...] These games were much better received than abstractly structured games ("visual exploration tasks")."* [E-03: neuropsychologist]

> *"My experience so far is that games that are designed to be more relevant to everyday life (and simpler) work better. Therefore, new game designs should be based on what patients know from their everyday lives."* [E-06: physical and occupational therapist]

Training Components

The recommended exercise frequency ranged from 2 (f = 3) to 5 or more (f = 4) training sessions per week, largely dependent on training location and motivation. The recommended session durations ranged from a maximum of 15 to 20 minutes (f = 3) up to 30 minutes (f = 2), with the aim of reaching a moderate exercise volume of approximately 150 minutes per week (f = 1). Shorter sessions and a higher training frequency have been reported to be preferable to reach this training volume, mainly owing to attentional exhaustion:

> *"The more the better! I would prefer shorter training sessions, especially because of attentional exhaustion. Here I would recommend a maximum of 30 minutes and at least 5 sessions a week. This is much better than training for 2 hours at a stretch!"* [E-03: neuropsychologist]

> *"I would recommend a training frequency of 2 - 3x/week. [...] The training duration is difficult to estimate. Some patients are already exhausted after 2 minutes, others can easily train for 20 minutes."* [E-10: founder of an exergaming company]

> *"I think that a training frequency of 3x/week is already (too) much. 2x/week should be possible to arrange. 1x/week definitely works. This may be because three appointments, in combination with other activities, may already be too much for patients. If the training could be done at home, the training frequency could certainly be increased up to 4 - 5x/week. In this case, motivation could still be difficult."* [E-07: physical and occupational therapist]

> *"I would aim for a training volume of 150 min/week. As far as I know, this is considered moderate for older patients. I would consider 100 min/week as the lower limit. A minimum of 3 x per week for 30 min would also be okay at best."* [E-08: project manager therapy]

Exercises requiring a coupling of physical and cognitive functions were described as preferable and should be prescribed domain-specific depending on the patient's abilities:

> *"I think that the coupling of brain functions with physical functions is central. Whether this is ultimately an attention game, or a training of the executive functions is something I don't consider central at the beginning. Of course, it also plays a role here which cognitive functions are impaired. [...] If the frontal lobe is impaired, it is certainly important to train executive functions, attention and inhibition."* [E-10: founder of an exergaming company]

To maintain the training program in the long term (preferably >12 weeks), motivation is a key factor that can be facilitated by the playful character of the exergames and a variation in the choice of games. Nonetheless, patients seem to prefer a certain routine:

> *"Of course, the training should be maintained over a certain amount of time at a stretch. So not just two weeks, but ideally longer (more than 12 weeks). Of course, motivation is also a very central point. If the training is varied and has a playful character, this should be feasible."* [E-03: neuropsychologist]

> *"Patients are generally routine-oriented, which can also be observed in general. Therefore, it is also important to introduce a new game every now and then. The patients primarily prefer the familiar games and should therefore be challenged to a certain variety."* [E-10: founder of an exergaming company]

The physical exercise intensity should be maintained at a light to moderate level, while the focus should be on game complexity that should be challenging but feasible. Game complexity can be varied on multiple levels, for example, (1) stability support (use of handrail with both hands, 1 hand, or no support), (2) stepping direction, (3) game choice and tasks included, (4) game duration, or (5) game speed:

> *"Adding new games. I always start with the game 'Simple' and sometimes in the first session I also introduced 'Birds' when I think it would be possible. If not, then I will do it the next session. If somebody is really performing well and understanding all the instructions, then I also progress to the game 'Targets' and even 'Birds'."* [E-09: exergaming researcher]

> *"I also often started with just stepping movements forward [...] and included the step direction to the right at a later timepoint."* [E-10: founder of an exergaming company]

> *"We have a routine that we usually do the training sessions over 3 weeks and do the first 3 sessions with holding, just to get a feel for the games. After that, we gradually go back to holding on with one arm and without holding on."* [E-08: project manager therapy]

From the patients' viewpoint, a high training frequency (mean preferred training frequency 5.21 times per week; n = 7), ranging from 2 times per week (n = 1, 13 %) to daily sessions (n = 4, 50 %)) with short session durations (mean preferred session duration 23.4, SD 10.3 minutes; n = 8), ranging from 10 minutes (n = 1, 13 %) up to 30 minutes (n = 3, 38 %) was preferred. Five of 6 (83 %) patients who responded to the questions about how long they would prefer to do the training stated that they would

prefer to continue the training as long as they profit from it and are able to do it. All patients preferred a training that is individually adapted to apply moderate (4/5, 80 % of patients) to high physical (1/5, 20 % of patients) intensity and moderate (3/5, 60 % of patients) to high (2/5, 40 % of patients) cognitive challenges:

> *"If the device was at home, I would do the training every day."* [P-01]
>
> *"I don't want to make a guarantee now, but I could do a short training session every day for like 20 minutes or so. But I can't promise that I'll do 40 minutes every day, because I also want to do other things. Especially when the weather is nice, I like to go outside. And then I also must do the housework, which also takes time."* [P-03]
>
> *"I think about 30 minutes is good. If it goes on too long or is too strict, then I get tired of it. I don't like that. That would be counterproductive."* [P-05]
>
> *"If I have the device, I could do this training forever. As long as I still have the strength to do it."* [P-02]
>
> *"I would need a bit of a start-up period first. If it's not effective, I'll stop again. Additionally, I don't know how my health will be in the future. But as long as I'm reasonably fit, I'll definitely want to do it."* [P-07]

Individualization

Individualization of the exergame intervention concept should mainly account for two aspects: (1) task type (i.e., choice of exergames to individually focus on neurocognitive functioning; f = 4) and (2) task demands (i.e., adapting the game demands according to the individual capabilities to maintain a challenging but feasible cognitive load; f = 5). In addition, it was recommended to change between games with different task demands to enable the maintenance of attention over the entire training duration (f = 2) and to supervise training exertion (f = 3):

> *"It is important to have a system that will adapt the games according to the participant's performance."* [E-02: exergaming researcher]
>
> *"The physical intensity is often not a problem, and it should primarily be the complexity of the training that is individually adapted so that it is doable and still has a certain physical demand."* [E-10: founder of an exergaming company]
>
> *"[...] We also have to check whether somebody is very fatigued [...]. Sometimes you have to let someone take a rest because they will not always feel when they have to take a rest."* [E-09: exergaming researcher]
>
> [One should] *"[...]alternate between games that focus primarily on performance and less on cognitive aspects with more cognitively demanding games."* [E-08: project manager therapy]

5.4 Discussion

5.4.1 Principal Findings

The objective of this study was to determine the capabilities, treatment preferences, and motivators for training older adults with mNCD, as well as their perspectives on training goals, settings, and requirements for exergames and training components. This will—together and in line with a synthesis of the optimal evidence-based informed decisions—serve as basis for user modeling, determination of therapeutic needs, and definition of a set of requirements for the game design and development process of a novel exergame-based training concept. To the best of our knowledge, this is the first study to systematically and thoroughly investigate user requirements and preferences for an exergame-based training concept before it is designed and developed specifically for older adults with mNCD based on these findings.

The results of our qualitative study, which included focus groups with 10 experts or health care professionals and individual semistructured, in-depth interviews with 8 older adults with mNCD, yielded the following key findings: (1—capabilities) from a patients' viewpoint, the psychosocial consequences of their self-perceived cognitive deteriorations might be more burdensome than the cognitive changes themselves; (2—treatment preferences) more integrative forms of training (such as exergaming) including gamified tasks close to everyday life, multimodal animation, and acoustic feedback are preferred by patients. None of the interviewed patients reported any previous experience with exergaming, but all patients described the handling of different technologies as feasible despite some challenges and were willing to try out exergaming; (3—motivators for training) from the expert's viewpoint, the most frequently described motivators to train can be classified as intrinsically regulated motivators such as excitement, enjoyment, or fun in exercising that is maintained by the captivating character of exergames supported by specific game components (e.g., game tasks or designs close to everyday life or with personal relations or memories including music or sound effects, animals or plants, landscapes, or colors); the feeling of being optimally challenged; and the variation of training. All patients reported that they could primarily be motivated by the effectiveness of the training, helping them to achieve success on an individual basis; (4—training goals and outcomes) the most important training goals of older adults with mNCD include improvements in ADLs and mobility (gait and balance) and memory, because these outcomes were described as central to improving their quality of life; (5—exergame and training components) the use of home-based exergames as a form of simultaneous-incorporated motor-cognitive training should be prescribed with a domain-specific training focus depending on a patient's cognitive abilities, a high training frequency (4-5 training sessions per week), short session durations (20-25 minutes), and individual adaption and progression of task type and demands to reach a light to moderate level of physical intensity and a challenging but feasible game complexity. To maintain the training program in the long term (preferably >12 weeks), motivation is a key factor and should be facilitated by the playful character of the exergames, variation in the choice of games, and ensuring that the patients are optimally challenged. To make home-based training interventions feasible, multiple factors that need to be considered were identified. Patient-friendly game instructions are needed, while the accessibility of a handrail or similar for safety support, avoidance of technical problems, and the integration of a guided familiarization period or support from a care person need to be ensured to make home-based exergame training feasible. As general requirements for exergame design, simple

graphics with good contrast and easily comprehensible and clearly designed tasks with a certain closeness to everyday life should be used. Multimodal animations, including multisensory feedback that focuses on positive reinforcement mechanisms, should be integrated to motivate patients during exergaming. In addition, it is important that the main task be in the center of the screen and that only elements that are related to the game task are included. Moreover, confronting performance feedback and unexpected appearances or technical problems should be avoided.

5.4.2 Capabilities of Older Adults With mNCD

A variety of cognitive changes mainly affecting the neurocognitive domains of learning and memory, complex attention, and executive function were discussed by the focus groups and mentioned by the patients, whereas no serious restrictions on physical capabilities, mobility, and ADLs were reported. This is in line with DSM-5 [5]. According to the definition of mNCD, modest (i.e., for mNCD, performance typically lies in the 1-2 SD range) deterioration in cognitive functioning can be observed, whereas the capacity for independence in everyday activities is preserved [5]. However, from the patient's perspective, the most prominent consequences of their disorder were described as affecting psychological factors, mainly by causing psychological distress, feelings of insecurity, and depression. It is well known that depression and anxiety are common in older adults with mNCD [241, 242]. In addition, patients with depression have higher rates of conversion to dementia, indicating that depression is an important risk factor for cognitive decline and progression to dementia. This emphasizes the importance of assessing depressive symptoms in older adults with mNCD [242].

5.4.3 Treatment Experience and Preferences

Most of the interviewed patients had already gained experience with different treatment or training approaches to counteract cognitive decline and preserve physical capabilities, mobility, and ADLs. Although MTT, physiotherapy, and CCT were perceived as useful, the patients reported being insecure about the effectiveness of these approaches or that they would have to (be able to) do it more consistently to profit from it, which was described to be limited by the availability of therapists. More integrative forms of training, including gamified tasks close to everyday life, multimodal animation, and acoustic feedback, were reported to be preferred by patients.

This is in line with the literature, showing that *"research involving older adults has found that CCT programs are associated with high satisfaction levels, and that they are also a feasible option for individuals with MCI, with equal or better adherence rates when compared with traditional cognitive training"* [111, 269, 270]. This is also evident in the use of exergames. Exergame-based training interventions are widely accepted in individuals with mNCD, and exergames increase or enhance participants' motivation to engage in rehabilitation activities [42]. This is also reflected by the adherence rates to different types of exercises in patients with mild to major NCD. Recent systematic reviews and meta-analyses synthesized mean adherence rates of 70 % [86] for physical exercise interventions, whereas the mean adherence rate was higher for exergame-based interventions at 84 % [44]. To the best of our knowledge, there is no systematic review that has synthesized adherence rates to CCT. However, Turunen et al [271] investigated adherence to a long-lasting multidomain CCT among a sample of 631 older adults at risk of dementia. It was shown that only 20 % of participants completed at least half of their CCT sessions, and only 12 % of participants completed all (maximal number of training sessions = 144) of their training sessions. In addition, 37 % of the

participants did not train at all, whereas *"previous use of computers, better memory, being married/cohabiting, and positive study expectations were independently associated with the greater probability of starting the CCT. Previous computer use was the main determinant of the number of CCTs completed after the training was initiated"* [271]. Therefore, when comparing these findings, it appears that exergame-based interventions have the highest adherence rates among different training programs. This is consistent with findings in HOAs, where adherence to technology-based training programs was higher than that to traditional training programs, independent of study site or level of supervision [88]. This finding may be largely explained by the high level of enjoyment in using technology-based physical exercise programs [88]. Technology-based training systems offer several advantages over traditional training programs that may contribute to a more enjoyable exercise experience. For example, exergames can provide real-time feedback and positive reinforcement while exercising and can monitor performance over time [88]. In addition, exergames enable individual real-time adaptivity of physical and cognitive task demands according to the participants' performance or physiological response (e.g., heart rate and brain activity), which is considered a key advantage of serious video games (such as exergames) [80, 217, 218]. In fact, the findings of our study suggest that applying an optimal challenge is central to promote the use of exergames in patients with mNCD in the long term.

When considering the experts' previous experience in the use of exergames (i.e., 'Senso') with patients with mNCD, the interaction with the device, its overall usability, and the design of the exergames were described as good. Especially the simple and clear game design structures were reported to be highly appreciated by patients and to promote good task comprehensibility. Various minor usability issues were reported, including difficulties in the interaction with the exergame training system 'Senso' (e.g., unintendingly walk off the middle plate without noticing the feedback on the screen), but mainly, usability issues that related to capabilities of older adults with mNCD (e.g., limited comprehensibility of the game instructions) were reported. These usability issues need to be considered and addressed when developing a training concept specifically for older adults with mNCD. Nevertheless, it is important to emphasize that these are only minor usability issues, and only minor refinements are required to optimize the exergame experience. This is also illustrated by recent studies showing that exergame-based training programs using the "Senso" are feasible; usable; and widely accepted in different populations including community-dwelling older adults [272], geriatric inpatients [256], and patients with major NCD [227], chronic stroke [273], or multiple sclerosis [274]. Therefore, when designing and developing an exergame-based training concept specifically for older adults with mNCD, these refinements should primarily target the adaptability and individualization of task demands and the optimization of the instruction of the exergames.

5.4.4 Motivators for Training

The motivating factors most frequently described by experts were classified as intrinsic motivators. These were described as being maintained by the captivating character of exergames and promoted by specific game components such as game tasks or designs close to everyday life or with a personal relation or memory, including music or sound effects, animals or plants, landscapes, or colors. In addition, patients were described to be intrinsically motivated by gamification and the feeling of being optimally challenged. From a patient's perspective, the effectiveness of the training, which helped them achieve their individual success, was clearly the most prominent motivator.

This is consistent with reports in the literature. More autonomous forms of motivation can be promoted by various factors, although these factors may vary depending on the population. For example, a small case-control study compared the motivational factors for using a balance exergame platform between healthy younger and older adults. It was shown that *"older adults were more intrinsically motivated by the joy of playing and extrinsically motivated by the perceived health effects (physical and cognitive), with less regard for the in-game rewards"* [204]. To provide effective interventions to promote physical activity [205] in patient with NCDs, a new theoretical model has recently been introduced. This theoretical model is based on the review of existing theories that explain behavior change in relation to physical activity in HOA, which were then adapted and integrated to a new theoretical model called the 'PHYT in dementia' [205]. In this framework, several additional key elements for promoting behavioral changes in physical activity have been proposed. These consist of self-efficacy, including embarrassment (e.g., supervision of activity had a negative impact on engagement in the intervention), personal concerns (e.g., fear of falling), and routine (e.g., flexible integration of physical activity intervention into daily life regarding place and time of performance), as well as appropriate challenges [205]. A detailed awareness of participant motivators is required, especially for the preference that the routine can be performed at home and at different times during the day [205], because self-determined motivation may be a central aspect of adherence to home-based training programs [202].

5.4.5 Training Goals and Outcomes

The interviewed experts recommended to mainly target cognitive functioning when developing a training concept for older adults with mNCD, while ADLs and mobility, physical capabilities, and psychosocial factors should also be accounted for. This is consistent with the patients' viewpoint that most frequently reported improving gait and memory as their primary training goals to increase their quality of life.

Similar results have been documented in the literature. According to a survey of patients who completed a multicomponent behavioral intervention for patients with MCI and their caregivers, quality of life was the most important outcome priority for patients with MCI, followed by self-efficacy, depression, basic ADLs, memory-based ADL, anxiety, and memory performance [206].

5.4.6 Exergame and Training Components

The use of exergames as a form of simultaneous-incorporated motor-cognitive training is recommended, which should be prescribed domain-specifically, depending on a patient's cognitive abilities. Previous studies applying exergame-based motor-cognitive training in older adults with mNCD or MCI have used commercially available exergame systems [270, 275-280] or exergames that were specifically developed for patients with mNCD or MCI [281-284], which comprised sensor-based stepping platforms [278], video camera-based or wireless remote device systems [270, 275, 279, 281, 283], or exergames that were controlled using a cycle ergometer or similar [276, 277, 280, 282, 284]. The training programs can be classified as simultaneous-additional [276, 277, 280, 282] or simultaneous-incorporated [270, 275, 278, 279, 281, 283, 284] motor-cognitive training that was applied targeting one [277, 284] or multiple [270, 275, 276, 278-283] neurocognitive domains, including complex attention [270, 275, 276, 278-283], executive functions [270, 275, 276, 278-284], learning and memory [275, 277-279, 281-283], or visuospatial skills [270, 281, 283]. Only one of

these studies applied training that individually prescribed content on the basis of a patient's cognitive abilities [280]. However, it has not been performed or reported in a reproducible manner.

Therefore, so far and to the best of our knowledge, 11 studies have been published that investigated exergame-based motor-cognitive training in older adults with mNCD or MCI. Most of these studies designed or used exergames that could be classified as simultaneous-incorporated motor-cognitive training. Incorporating cognitive tasks into motor tasks may be more beneficial for consolidating neuroplasticity [34], because (1) it leads to greater (motor) cognitive improvements, (2) it is closer to daily life situations, (3) no prioritization effects occur, which can be observed in motor-cognitive training with additional cognitive tasks, and (4) multiple sensory systems are stimulated at the same time, which may provide an optimal basis for cognitive processes such as learning [34]. Meta-analytic evidence suggests that simultaneous motor-cognitive training is the most effective type of training for improving cognition in HOA [35, 72] and in older adults with mNCD [35, 73, 74]. Nevertheless, it remains to be evaluated whether the incorporation of cognitive tasks into exercise or training interventions indeed results in more distinct effects on cognitive performance compared with simultaneous motor-cognitive training with a non-task-relevant secondary cognitive task [34]. Finally, there seems to be room for improvement regarding the domain-specific prescription of the training content, considering a patient's cognitive abilities and the adaptation and development of exergames specifically for patients with mNCD. This may be especially relevant when considering the large heterogeneity in the clinical symptoms of older adults with mNCD. Remarkably, most previous studies applying exergame-based motor-cognitive training in older adults with mNCD or MCI have used commercially available exergame systems [270, 275-280], in which the training content does not specifically target patients with mNCD. This is consistent with the findings of HOA. In a systematic review, Valenzuela et al [88] emphasized that in HOA, most studies used commercially available exergame systems. It was argued that these systems may be difficult to use for those with little or no experience with technology, because these systems often lack clear instructions, present too much graphical information, and have not been designed and developed to provide optimal training components for the target population and aims of the studies in which they were used [88]. In fact, all previous studies applying exergame-based motor-cognitive training in older adults with mNCD or MCI have used exergames with complex 2D or 3D virtual environments [270, 275-284]. This may not be optimal because the limitation that such systems may be difficult to use for those with little or no experience with technology could be even more pronounced in patients with mNCD, as these patients are easily distracted and quickly overwhelmed by the task demands. Indeed, according to the recommendations of the interviewed experts, it is beneficial to focus on the aspects that need to be worked on by implementing easily comprehensible and clearly designed exergame tasks and to only present elements that are directly related to the game tasks while avoiding unnecessary graphical information or distractors.

According to the recommendations of the interviewed experts, the training program should be maintained over the long term (preferably ≥12 weeks). A training frequency of 2 to 5 or more training sessions per week was recommended, largely depending on the training location and motivation. In addition, it is recommended to reach a moderate training volume of approximately 150 minutes per week. To reach this training volume, shorter training sessions and a higher training frequency should be applied, because longer training sessions might lead to attentional exhaustion in this group of patients. Therefore, the experts recommended session durations between 15 and 20 minutes up to

a maximum of 30 minutes. Previous studies applying exergame-based motor-cognitive training in older adults with mNCD or MCI have prescribed training programs over durations of 5 weeks [281], 6 weeks [275, 278, 282, 284], 12 weeks [280, 283], 3 months [277, 279], 24 weeks [270], or 6 months [276]. The prescribed training frequency was 1 time per week [270], 2 times per week [278, 280, 283], 2 to 3 times per week [279], 3 times per week [281, 282], 3 to 5 times per week [276, 277, 284], or 5 times per week [275] with session durations of 15 min [283], 18 - 30 min [278], 20 to 80 min [281], 25 to 30 min [275], 20 to 40 min [277], 30 to 45 min [284], 40 to 45 min [282], 45 min [276], 60 min [280], 90 min [270], or not reported [279], resulting in a weekly training volume of 30 min [283], 36 to 60 min [278], 60 to 200 min [277], 90 min [270], 90 to 225 min [284], 100 to 145 min [281], 120 min [280], 120 to 135 min [282], 125 to 150 min [275], 135 to 225 min [276], or not reported [279]. Therefore, most of these studies prescribed a training volume that was in line with the recommendations of the experts in this study. However, the session durations often exceeded the experts' recommendations, whereas the training frequency was lower than recommended. To avoid attentional exhaustion of the patients during training, future training concepts might consider prescribing shorter session durations while increasing the training frequency to achieve a similar training volume per week. This might actually improve the effectiveness of the intervention because higher training frequencies have already been shown to promote the effectiveness of physical (i.e., ≥ 4 times per week) [120] and cognitive training (i.e., > 3 times per week) [109], while shorter session durations (i.e., ≤ 30 minutes) [120] of physical exercise have been shown to exert more pronounced training effects. These findings might also apply to simultaneous motor-cognitive training. A meta-analysis revealed that training frequency is a significant moderator of the effects of physical and motor-cognitive training interventions on cognitive functioning, favoring higher training frequencies (≥ 5 times per week) in a mixed population of HOA and patients with mNCD [119]. Finally, a high training frequency (approximately 5 times per week) with short session durations (approximately 20 minutes) would also match the preferences of the interviewed patients in this study.

The experts reported that the training should preferably be individually carried out at the patients' homes, not only because it represents a known environment that makes patients feel more secure and represents a less-confronting environment for them (because they do not have to hide their impairments from others when training alone), but also to allow higher training frequencies. Nonetheless, to ensure that training in patients' homes is feasible, multiple factors need to be considered. For example, improvements in game instructions are required, a handrail or similar needs to be made available to allow safety support during training, and technical problems must be avoided. In addition, a guided familiarization period and part-time supervision or support from a care professional or partner should be integrated to make the transfer to home-based exergaming easier. Previous studies applying exergame-based motor-cognitive training in older adults with mNCD or MCI have administered individual [275] or group-based [270, 280, 283] training sessions, and the training setting (i.e., individual vs group sessions) has not been clearly reported [276-279, 281, 282, 284]. The training sessions were conducted at the hospital [275], in a nursing home [278], at day-care centers or memory clinics [283], at a centrally located church [270], at patients' homes [277, 284], or the training location was not clearly reported [276, 279-282]. The training sessions were supervised by a therapist [275, 278, 280], or supervision was not reported [270, 276, 277, 279, 281-284]. Consistent with summarized previous studies applying exergame-based motor-cognitive training in older adults with mNCD or MCI, most cognitive training programs to date have also been conducted in group sessions [285]. However, most of our interviewed patients clearly stated that they

would prefer to train individually at home or with the support of a care professional or partner. Therefore, it might be worthwhile to put more effort into designing and developing exergames that can be used individually at home. This would possibly also reduce the barriers of patients with mNCD to engage in exergame-based training programs in the long term.

Regarding training demands, the experts recommended focusing on game complexity to ensure a challenging but feasible cognitive demand. Physical exercise intensity should be maintained at a light to moderate level. To allow individualization of the cognitive demand in training, two main aspects should be considered: (1) task type (i.e., choice of exergames to individually focus on neurocognitive functioning) and (2) task demands. To allow individualization of task demands, the following factors should be varied based on the experts' recommendations: (1) stability support (use of handrail with both hands, one hand, or no support), (2) stepping direction, (3) game choice and tasks included, (4) game duration, or (5) game speed. Previous studies applying exergame-based motor-cognitive training in older adults with mNCD or MCI have applied relatively effortful, high cognitive demands [276], low [281] to moderate [280-282] physical exercise intensities, or have not reported the physical [270, 275-279, 283, 284] or cognitive [270, 275, 277-284] exercise load or training progression in a clearly reproducible way. This exemplifies the fact that the optimal cognitive load for motor-cognitive training remains unknown. To the best of our knowledge, there has only been 1 meta-analysis to date that compared the effects of training interventions on cognitive functioning in relation to different task complexities and found no difference between simple and complex cognitive games [96]. Therefore, further investigations are needed to identify the optimal cognitive training demands and optimize the monitoring and progression of training programs. For physical exercise intensity, the recommendations of the interviewed experts are in line with those of previous studies applying exergame-based motor-cognitive training in older adults with mNCD or MCI. This also matches the analysis of the moderating variables of the training parameters that influence the effectiveness of the interventions. Based on meta-analytic results from motor-cognitive training in older adults with mNCD, moderate physical training intensity [73] has been shown to be most effective in improving cognitive function. Finally, moderate physical exercise intensity would also match the preferences of the patients interviewed in this study.

5.4.7 Implications for Research

Our findings serve as a basis for user modeling, determination of therapeutic needs, and definition of a set of requirements for the game design and development of novel exergame-based training concepts. To increase the probability that the resulting training will be deemed feasible in future clinical practice, these considerations should be integrated to guide the decision process for the most suitable exergame design and intervention components when developing novel exergames and exergame-based training concepts.

5.4.8 Limitations

The outcomes of this qualitative study must be interpreted with some caution, considering the following limitations. First, none of the interviewed patients with mNCD belonged to the clinical subtypes of mild frontotemporal NCD or mNCD with Lewy bodies. Depending on the clinical subtypes and the associated clinical pictures of the patients, different findings may have emerged from patient interviews. However, a substantial fraction (i.e., ≥ 60 %) of mild or major NCD is attributable to

Alzheimer disease, whereas mild vascular NCD is the second most common cause of NCD after Alzheimer disease; frontotemporal NCD only accounts for approximately 5 % of cases [5]. Therefore, the included study population appeared to be representative of these clinical subtypes. Second, owing to difficulties in recruiting patients, those screened for MCI according to predefined criteria were recruited in addition to patients with a clinical diagnosis of mNCD, which increased the heterogeneity of the study population. By contrast, in our project, we aimed to develop an individualized exergame-based training concept not only to treat clinically diagnosed patients with mNCD but also to prevent progression to dementia in individuals at risk who might not have been diagnosed (yet). Third, owing to the COVID-19 pandemic, all focus group sessions were held as web-based meetings. Face-to-face focus group sessions might have promoted livelier exchanges and may have led to additional insights.

5.5 Conclusions

The psychosocial consequences of patients' self-perceived cognitive deterioration may be more burdensome than the cognitive changes themselves. Older adults with mNCD prefer integrative forms of training (such as exergaming) and are primarily motivated by enjoyment or fun in exercising and the effectiveness of the training. Putting the synthesized perspectives of training goals, settings, and requirements for exergames and training components into context, our considerations point to opportunities for improvement in research and rehabilitation, either by adapting existing exergames to patients with mNCD or by developing novel exergames and exergame-based training concepts specifically tailored to meet patient requirements and needs.

5.6 Acknowledgments

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5.7 Data Availability

The data supporting the findings of this study are available from the corresponding author (PM) on reasonable request.

5.8 Authors' Contributions

PM was responsible for the conception and protocol development of this study under the supervision of EDdB. MAO contributed to the study conception. PM was responsible for the recruitment of participants, data collection, data analysis, and writing of the manuscript. Data coding and analysis was cross-checked by MAO. All authors have contributed to the revision of the manuscript. All authors have read and approved the submitted version.

5.9 Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest. Dividat AG was asked to suggest suitable participants for the expert focus group discussions by providing a contact list of experts and health care professionals, as the company is well connected with institutions for geriatric populations, physiotherapies, and rehabilitation clinics in Switzerland. Therefore, we were able to identify experts and health care professionals who experienced exergame training with older adults with mild neurocognitive disorder. Experience was preferred with the exergame training system "Senso (Flex)" or similar. In addition, the founder of Dividat AG was partaking in one of the focus group discussions as an industry representative in line with the Multidisciplinary Iterative Design of Exergames framework. Dividat AG had no other role in the study and did not play any role in the design and conduct of the study; they also did not play any role in the data analyses, interpretation, or decision to submit results.

5.10 Multimedia Appendix

The Multimedia Appendix for this article can be found online at:
https://jmir.org/api/download?alt_name=games_v11i1e37616_app1.docx&filename=9853a6c08fe12b2e7d6fc7deb845b2f2.docx

5.11 Abbreviations

ADL	activities of daily living
CCT	computerized cognitive training
DSM-5	Diagnostic and Statistical Manual of Mental Disorders 5th Edition
HOA	healthy older adults
MCI	mild cognitive impairment
MIDE	Multidisciplinary Iterative Design of Exergames
mNCD	mild neurocognitive disorder
MTT	medical training therapy
NCD	neurocognitive disorders
PT	physical therapy

Chapter

6

Paper 3:

Feasibility, Usability, and Acceptance of 'Brain-IT' - A Newly Developed Exergame-Based Training Concept for the Secondary Prevention of Mild Neurocognitive Disorder: A Pilot Randomized Controlled Trial

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6.1 Abstract

Background: Exergames provide a promising new approach to implement simultaneous motor-cognitive training, which may support preventing the decline in cognitive functioning in older adults who have a mild neurocognitive disorder (mNCD).

Objective: To evaluate feasibility, system usability, and acceptance of 'Brain-IT', a newly developed training concept combining exergame-based motor-cognitive training and heart rate variability (HRV) guided resonance breathing for the secondary prevention of mNCD.

Methods: A pilot randomized controlled trial (RCT) with an allocation ratio of 2:1 (i.e., intervention:control) was conducted. The control group proceeded with usual care. The intervention group performed a 12-week training according to the 'Brain-IT' training concept implemented with the 'Senso Flex' (Dividat AG) exergaming system in addition to usual care. Feasibility and usability outcomes were analyzed using descriptive statistics. User acceptance was analyzed qualitatively and using Friedman analysis of variance (ANOVA), as well as Wilcoxon signed-rank tests.

Results: Eighteen participants (77.3 ± 9.8 years; 44.4 % females) were included. On average, we recruited 2.2 participants per month, and 35.3 % of the individuals contacted were included. The intervention group had an attrition rate of 20 % and mean adherence and compliance rates of 85.0 and 84.1 %, respectively. The mean system usability score, measured with the system usability scale, was 71.7. High levels of exergame enjoyment, an increase in exergame enjoyment, and internalization of training motivation with large effect sizes ($p = 0.03$, $r = 0.75$ and $p = 0.03$, $r = 0.74$, respectively), as well as acceptable perceived usefulness, were observed. Preliminary data on the effects of the 'Brain-IT' training are promising.

Conclusions: The feasibility and usability of the 'Brain-IT' training are acceptable. However, frequent occurrences of technical problems and difficulties in using the exergame training system were identified as barriers to performing the 'Brain-IT' training. To optimize feasibility, either improvements or alternative solutions are required in the hardware and software of the exergame used to implement the 'Brain-IT' training. The 'Brain-IT' training itself was well-accepted by older adults who have mNCD. Therefore, the effectiveness of the 'Brain-IT' training concept should be investigated in future studies.

6.2 Introduction

6.2.1 Background

Preventing disabilities due to cognitive impairment has been declared a public health priority by the World Health Organization [286]. Potentially modifiable risk factors for cognitive impairment include diabetes mellitus [11-13, 168], hypertension [11-13, 168], obesity [11-13], depression [11-13, 242], physical [11-13] or cognitive inactivity [11], and smoking [11-13, 287]. Estimates suggest that up to half of the world's cases of Alzheimer's disease (AD) - the leading cause of mild-to-major neurocognitive disorders (m-MNCDs) [5] - may be attributable to modifiable risk factors [11, 12]. Lifestyle changes that target these risk factors may hold promise for slowing down cognitive decline or reducing the risk of developing dementia [14, 15]. Physical inactivity is associated with most of the other modifiable risk factors [11]. As an example, physical exercise is effective in reducing cardiovascular risk factors [19] and improving depression [20] across a very wide range of populations, including mNCD [21]. Therefore, increasing physical activity may have an impact on m-MNCD prevalence [11]. Additionally, mental stimulation helps build a 'cognitive reserve', which enables individuals to continue functioning at a "normal" level, despite experiencing neurodegenerative changes [11, 25, 26]. In line with the 'guided-plasticity facilitation' framework [32-34], combining physical and cognitive training seems the most effective type of training for improving cognitive functioning in older adults who have mNCD [35, 73, 288, 289]. There are different forms of combined motor-cognitive training, including 'sequential', 'simultaneous-additional', and 'simultaneous-incorporated' motor-cognitive training [34]. Incorporating cognitive task(s) into motor task(s) (i.e., "simultaneous-incorporated" motor-cognitive training) seems to be the most promising approach in terms of stabilizing neuroplasticity effects [34]. This prediction is supported by recent meta-analytic evidence, showing that simultaneous motor-cognitive training was most efficacious for improving cognitive functioning in individuals who have mNCD [35].

Technological innovations (e.g., exergames) provide new options to engage older adults who have mNCD in simultaneous motor-cognitive training [39]. *"Exergaming is defined as technology-driven physical activities, such as video game play, that requires participants to be physically active or exercise in order to play the game."* [40]. Among the key advantages of exergaming compared to conventional motor-cognitive training is that exergames are highly accepted in individuals who have mNCD and increase or enhance participants' motivation to engage in rehabilitation activities [42]. This is of high relevance because motivation (especially intrinsic motivation) has been identified as a key factor for promoting positive behavioral changes [43] (e.g., adherence to exercise) in different populations, including healthy adults [194-197, 290], healthy older adults [194, 199, 200], and also in individuals with chronic diseases (including cognitive impairment) [205, 291]. As a result, adherence to exergame-based training is typically high in older adults who have m-MNCD [42, 44]. Furthermore, exergaming offers *"the unique opportunity for patients to interact in an enriched environment, providing structured, scalable training opportunities augmented by multi-sensory feedback to enhance skill learning and neuroplasticity through repeated practice"* [41], an additional advantage compared to conventional motor-cognitive training.

Previous systematic reviews and meta-analyses have synthesized consistent positive effects on cognitive functioning favoring exergaming in people who have m-MNCD, although there is considerable variation in exergame-based training [42]. However, most previous studies applying

exergame-based motor-cognitive training in individuals who have mNCD (earlier called 'mild cognitive impairment' (MCI) and incorporated as mNCD into latest Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-5) and the International Classification of Diseases 11th Revision (ICD-XI) [2-6] have used commercially available exergame systems [270, 275-279], which are not specifically designed with purpose beyond play, also referred to as 'serious game' [65, 66]. Valenzuela et al. (2018) argued that commercially available systems may be (too) difficult to use for those with little or no experience with technology because these systems often lack clear instructions, present too much graphical information, and have not been designed and developed to provide optimal training components for the target population and aims of the studies in which they were used [88]. This points to opportunities for improvement in research and rehabilitation by adapting existing exergames or developing novel exergames and exergame-based training concepts specifically tailored to the requirements and needs of individuals who have mNCD [45]. So far, only a few studies have used exergames or exergame-based training concepts that were specifically developed for individuals who have mNCD [281-284] or older adults who have varied motor and cognitive deficits (including individuals who have mNCD) [292]. These were shown to be safe (no training-related adverse events reported) [284, 292], acceptable, and enjoyable [282], while the exergame devices used were shown to have acceptable usability [281]. These exergames and exergame-based training concepts were developed in collaboration between a research laboratory and a software company [284] or based on theoretical considerations [292] reported in the literature [293]. However, the development process has not been transparently reported [281-284, 292].

When designing and developing (exergame-based) training concepts, taking the intended users' characteristics, needs, experiences, and perspectives into account seems of crucial importance to ensure the quality and use of the final training concept [58, 78, 92]. More specifically, a user-centered approach should be adopted [78, 92], whereas the *"central focus should be the inclusion and active participation of end users from the initial stages of development"* [92]. Recently, a theoretical framework was introduced that recommends an interactive and participatory design that explicitly includes end users as well as multidisciplinary teams throughout different iterative cycles of development [92]. This theoretical framework, the *"Multidisciplinary Iterative Design of Exergames (MIDE): A Framework for Supporting the Design, Development, and Evaluation of Exergames for Health"* [57], provides comprehensive, integrative, and specific guidance in the design, development, and evaluation of exergames for older adults on basis of an integrated and multifaceted approach [57].

6.2.2 Prior work

On this basis, a novel exergame-based training concept was developed specifically for older adults who have mNCD with the aim to halt and/or reduce cognitive decline and improve quality of life. The training concept was developed on the basis of a structured, iterative, and evidence-based approach based on the MIDE framework [57]. This process allowed the identification of multiple key requirements for exergame design as well as training characteristics that have formed the basis for determining components of the resulting training concept [45, 58]. A detailed description of the rigorous, structured, iterative, and evidence-based design and development process, as well as the resulting 'Brain-IT' training concept, was published previously [58]. Applying such an interactive and participatory design and development process aimed to ensure that the training concept meets the

requirements and needs of older adults who have mNCD which fosters feasibility, usability, and acceptance of the approach in “real life” [58].

6.2.3 Objectives

The primary objective of this study was to evaluate the feasibility, system usability, and acceptance of the ‘Brain-IT’ project and the ‘Brain-IT’ training concept - a newly developed training concept combining exergame-based motor-cognitive training and HRV-guided resonance breathing for the secondary prevention of mNCD. As a secondary objective, the effects of the ‘Brain-IT’ training on global cognitive functioning, domain-specific cognitive functioning, resting-state cortical activity, spatiotemporal parameters of gait, psychosocial factors, and resting cardiac autonomic regulation were explored.

6.3 Materials and methods

6.3.1 Trial design and study setting

A two-arm, prospective, parallel-group, pilot randomized controlled trial with a 2:1 allocation ratio (i.e., intervention:control) including older adults who have mNCD was conducted between July 2021 and June 2022. The control group proceeded with usual care as provided by (memory) clinics where the participants were recruited. The intervention group performed a 12-week training according to the ‘Brain-IT’ training concept in addition to usual care (see Section Interventions). Unequal randomization was chosen because this pilot trial *“involves new, not established interventions and one of the aims might then be to gain experience in delivering the intervention, in which case it is often better to have as many participants receiving the intervention as is feasible”* [294]. The study was registered at clinicaltrials.gov (NCT04996654) and was reported according to *“The Consolidated Standards of Reporting Trials (CONSORT) 2010 statement: extension to randomized pilot and feasibility trials”* [294] (Supplementary material 1).

After recruitment and providing written informed consent (see Section *“Recruitment“*), participants were screened on eligibility (see Section *“Eligibility criteria”*), and pre-measurements were scheduled for all eligible participants. Pre- and post-measurements took place at ETH Hönggerberg (Auguste-Piccard-Hof 1, CH-8093 Zurich) within 2 weeks before starting and after completing the intervention period. All measurements were led by two investigators of our research team trained in the application of the measurement techniques and protocols. Pre- and post-measurements were scheduled to take place at approximately the same time of the day (± 2 h) for each participant. To minimize the influence of transient confounding effects on HRV, all participants were additionally instructed verbally and in writing to follow a normal sleep routine the day before the experiment, to avoid intense physical activities and alcohol consumption within 24 h before measurements, and to refrain from coffee, or caffeinated drinks, as well as food consumption at least 2 h before measurements [295]. After completing pre-measurements, participants were randomly allocated to the intervention or control group and were instructed about their respective intervention procedures (see Section *“Interventions“*). For participants in the intervention group, the exergame device was installed at their homes; they received safety instructions and were familiarized with the exergame training system. Subsequently, the ‘Brain-IT’ training was started (see Section *“Intervention Group“*).

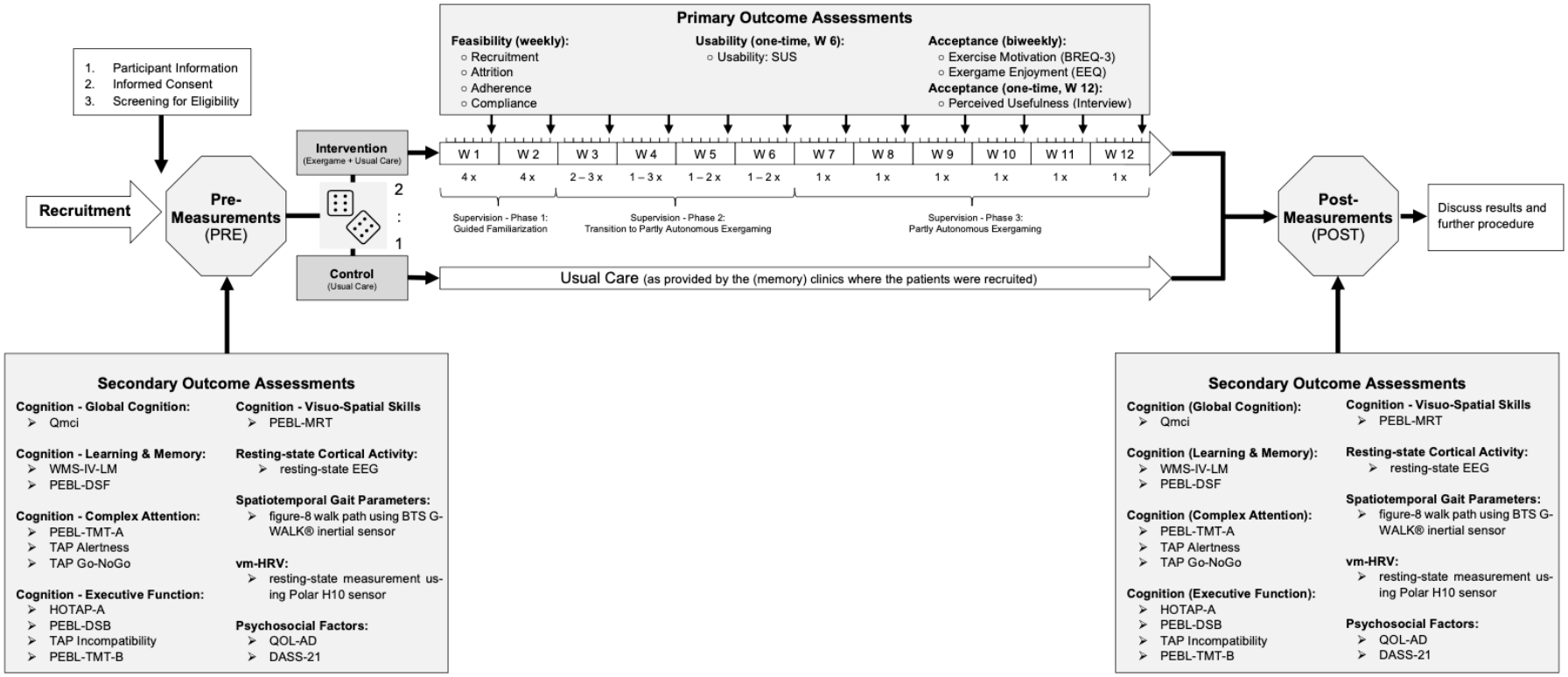

Figure 6-1: Graphical overview of all study procedures. The cubes are used to illustrate the randomization process [variable block randomization (i.e., block sizes = 3, 6) with a 2:1 allocation ratio (intervention:control) stratified by sex, as described in the Section Randomization]. Qmci, Quick Mild Cognitive Impairment Screen; WMS-IV-LM, Subtest "Logical Memory" of the Wechsler Memory Scale—fourth Edition; PEBL, Psychology Experiment Building Language; DSF, Digit Span Forward; DSB, Digit Span Backward; TMT-A and B, Trail Making Test Part A and B; TAP Alertness, Subtest "Alertness" of the Test of Attentional Performance; TAP Go-NoGo, Subtest "Go-NoGo" of the Test of Attentional Performance; TAP Incompatibility, Subtest "Incompatibility" of the Test of Attentional Performance; HOTAP-A, HOTAP Picture-Sorting Test Part A; MRT, Mental Rotation Task; QOL-AD, Quality of Life-Alzheimer's Disease; DASS-21, Depression, Anxiety and Stress Scale-21; vm-HRV, vagally mediated Heart Rate Variability; SUS, System Usability Scale; BREQ-3, German Version of the Behavioral Regulation in Exercise Questionnaire; EEQ, Exergame Enjoyment Questionnaire.

After completing the 12-week intervention period, post-measurements were performed for both groups.

No compensation was granted to participants, but detailed feedback on individual performance as well as the study outcomes in general was provided at the end of the study. All study procedures were carried out in accordance with the Declaration of Helsinki. The study protocol was approved by the ETH Zurich Ethics Committee (EK 2021-N-79). Figure 6-1 summarizes the study procedures and outcome measures.

6.3.2 Important changes to the trial design and study setting after commencement

The study was planned as single-blinded (i.e., outcome evaluator of pre- and post-measurements blinded to group allocation) pilot RCT. Due to COVID-19-related delays in recruiting participants, the study period had to be extended. This resulted in personnel changes in the team of study investigators. Consequently, blind keeping of outcome assessors was only possible for approximately half of post-measurements.

Recruitment

Older adults who have mNCD were recruited between July 2021 and June 2022 in collaboration with (memory) clinics in the larger area of Zurich. Suitable individuals were either identified from medical records and patient registries of (memory) clinics or from recent diagnostics performed by their medical doctors or therapists authorized to search medical records. Alternatively, suitable individuals were identified by an informant (i.e., healthcare professionals)-based suspicion of MCI (see Section *“Eligibility Criteria“*). Identified individuals were verbally informed about the existence of the study and received leaflets from their physicians/therapists containing key information about study participation and the researchers' contact details. In case the individuals were interested in being informed about the study in detail, they were asked to provide consent to share their contact details with the research team and were contacted by phone or e-mail by a trained investigator of the study team. In case of initial interest in participating in the study, all interested subjects were fully informed about the study procedures in-person (at the interested persons' home or at the study center (ETH Hönggerberg), depending on their preferences) by providing verbal explanations and an information sheet. After sufficient time for consideration (i.e., at least 24 h after handing out the study information sheet, but on average around 1 week), suitable individuals willing to take part in the study provided written informed consent in a second in-person meeting. Subsequently, participants were fully screened on eligibility (see Section *“Eligibility criteria“*), and pre-measurements were scheduled.

6.3.4 Eligibility criteria

All eligibility criteria are detailed in Table 6-1.

Table 6-1: Description of all eligibility criteria.

Inclusion criteria:	Exclusion criteria:
Participants fulfilling all the following inclusion criteria were eligible:	The presence of any of the following criteria led to exclusion:
• (1 = mNCD) clinical diagnosis of 'mild neurocognitive disorder' according to International Classification of Diseases 11th Revision (ICD-XI) [6] or the latest Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-5®) [5]) OR (2 = sMCI) individuals screened for mild cognitive impairment (sMCI) according to the following criteria: (a) informant (i.e., healthcare professionals)-based suspicion of mild cognitive impairment (MCI) confirmed by (b) an objective screening of MCI based on the German Version of the Quick Mild Cognitive Impairment Screen (Qmci) [251] with (b1) a recommended cut-off score for cognitive impairment (MCI or dementia) of < 62/100 [259], while (b2) not falling below the cut-off score for dementia (i.e., < 45/100 [259]), while (c) activities of daily living remain intact (judged by the referring healthcare professionals). • fully vaccinated against coronavirus (SARS-CoV-2) with a Swiss Federal Office of Public Health (FOPH)-approved vaccine[296] • German speaking • age ≥ 50 years • able to stand for at least 10 min without assistance	• mobility impairments (i.e., gait, balance) that prevent experiment participation • presence of additional, clinically relevant (i.e., acute and/or symptomatic) neurological disorders (i.e., epilepsy, stroke, multiple sclerosis, Parkinson's disease, brain tumors, or traumatic disorders of the nervous system) • presence of any other unstable or uncontrolled diseases (e.g., uncontrolled high blood pressure, progressing or terminal cancer) Additional Covid-19-specific exclusion criteria: Coronavirus Disease 2019 (Covid-19) specific risk factors (according to the Swiss FOPH) were additional exclusion criteria. In case of Covid-19 specific exclusion criteria, participation in the study was only allowed when the participants' treating physician provided written informed consent allowing participation in the study despite the presence of Covid-19 specific exclusion criteria. Covid-19 specific exclusion criteria included: • high blood pressure (self-reported; systolic ≥ 140 mmHg and/or Diastolic ≥ 90 mmHg) • Chronic respiratory condition • uncontrolled type 2 Diabetes • Condition or therapy that weakens the immune system • unstable cardiovascular disease • Cancer (present and/or under treatment) • Serious obesity (body mass index ≥ 40 kg/m^2)

6.3.5 Interventions

Control group

The control group proceeded with usual care as provided by the (memory) clinics where participants were recruited. Usual care of mNCD typically includes treating medical conditions other than mNCD (e.g., diabetes mellitus and depressive symptoms), controlling comorbidities (e.g., hypertension and obesity), and managing risk factors (e.g., smoking habits and physical and cognitive inactivity). With this regard, usual care may include medication, recommendations for changing lifestyle habits (e.g., living a cognitively, physically, and socially active life), physiotherapy to treat specific health problems such as back pain or mobility problems, occupational therapy, or day clinic visits. Usual care is highly individual, which varies between (memory) clinics where participants are recruited, and it is unclear whether participants comply with the recommendations of their clinicians. Therefore, details about all structured and/or guided usual care activities as well as medication intake were assessed in both the intervention and the control groups.

Intervention group

Participants in the intervention group performed a 12-week training in addition to their usual care (as provided by the (memory) clinics where participants are recruited). The training was prescribed according to our 'Brain-IT' training concept. This training concept represents a guideline for applying a combination of exergame-based motor-cognitive training and HRV-guided resonance breathing by standardizing the training characteristics (e.g., training frequency, intensity, and duration), as well as the structure and content of training, whereas the exergame device and the specific games used within each of the defined neurocognitive domains can be replaced by alternative exergames. Our training concept is implemented using the 'Senso (Flex)' (Dividat AG, Schindellegi, Switzerland, CE certification pending; see Figure 6-2 left side). This platform was found suitable to implement our training concept [45] and is a widely used means for motor-cognitive training within geriatric populations, physiotherapies, or rehabilitation in Switzerland. The original 'Brain-IT' training concept has recently been published with sufficient detail to allow full replication (i.e., consider Supplementary file 3 of [58]). To ensure replicability, the 'Brain-IT' training concept was planned and reported using the Consensus on Exercise Reporting Template (CERT) [238].

For an overview, the 'Brain-IT' training concept consists of an individually adapted multi-domain exergame-based simultaneous motor-cognitive training with incorporated cognitive tasks combined with HRV-guided resonance breathing. It is adopted with a deficit-oriented focus on the neurocognitive domains of (1) learning and memory, (2) executive function, (3) complex attention, and (4) visuospatial skills. Each participant was instructed to train ≥ 5x/week for ≥ 21 min per session resulting in a weekly exercise volume of ≥ 105 min. All training sessions were planned to take place at participants' homes using the 'Senso Flex' hardware. The 'Senso Flex' is a home-based version of the 'Senso' (Dividat AG, Schindellegi, Switzerland; CE certification; see the right side of Figure 6-2). It consists of a 1.11 m x 0.99-m rollable mat that is plugged into the portable computer and a frontal television (or other screen) at home. Both systems divide the pressure-sensitive stepping area into five fields: (1) center (home position), (2) front, (3) right, (4) back, and (5) left. The device detects participants' position and timing of movements to interact with different game scenarios that are programmed in the Dividat training software. Weight shifting, walking on the spot, and steps in four directions (i.e., front, right, back, and left) enable interaction with and control of virtual exergame scenarios that are displayed on a screen right in front of the participant. Visual, auditory, and somatosensory (vibrating platform; only available on the 'Senso') feedback is provided in real-time to enrich the game experience. Various games are available to train different neurocognitive domains (for more detail on how the device is implemented in our training concept, see [58]).

As per the 'Brain-IT' training concept [58], 19 - 24 training sessions were supervised by a designated investigator who instructed and oversaw the participants' use of the exergame device, ensured safety protocols were followed [e.g., ensuring that there were no hard objects (e.g., couch table) within the potential drop zone, determining the appropriate level of stability support using walking sticks, handrail or similar], and ensured adherence to the 'Brain-IT' training concept. All deviations from the 'Brain-IT' training concept were reported.

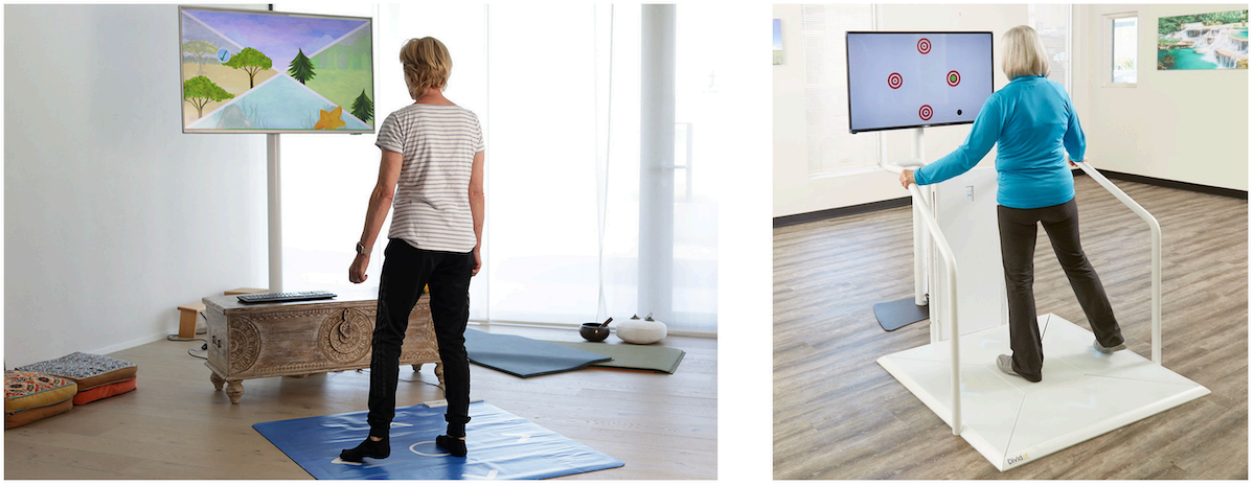

Figure 6-2: Exergame Device used as means to implement the "Brain-IT" training concept in this study: "Senso Flex" for home-based use (left side) and its stationary version ["Senso" for stationary use in physiotherapies, nursing homes, or rehabilitation clinics (right side)]. Photos provided by Dividat AG.

6.3.6 Outcomes

Primary outcomes

Feasibility

The feasibility of the 'Brain-IT' project and the 'Brain-IT' training was assessed with respect to recruitment, adherence, compliance, and attrition. These endpoints were recorded by a recruitment protocol, automatically assessed in the exergame training software (i.e., adherence and compliance protocol), and detailed electronic case report forms (CRFs) throughout the study period. Feasibility outcomes and their calculation are defined in Table 6-2. Adherence is usually calculated as *"the proportion between the number of sessions attended and the number of sessions offered, reported in percentage"* [86]. To ensure that participants who trained more than the prescribed minimum frequency did not compensate for lower adherence and compliance rates in other participants or training weeks in which they trained less, mean adherence and compliance rates were calculated as the average of each participant's weekly adherence/compliance with a maximum of 100 %. Reasons for non-adherence, non-compliance, and dropouts were recorded. A traffic light system with quantitative thresholds was used as a guideline to judge feasibility and progression (Figure 6-3).

Quantitative thresholds for each feasibility criterion were determined based on an educated guess before starting recruitment as follows: To reach a green light (= acceptable), the mean value of the feasibility outcome (F_{mean}) needed to exceed (for attrition rate: fall below) the pooled average of comparable [i.e., exergame or alternatively (combined) physical and/or cognitive exercise) intervention studies based on a recent (within the last 10 years) systematic synthesis of evidence in older adults who have m-MNCD (defined as first threshold (T1)]. The variance of the pooled average was used to determine the lower acceptable threshold [defined as the second threshold (T2)]. In case the mean value of the feasibility outcome fell below (for attrition rate: exceeded) T2, a red light (= unacceptable) was assigned. For values ranging between T1 and T2, an orange light (= conditionally acceptable) was assigned.

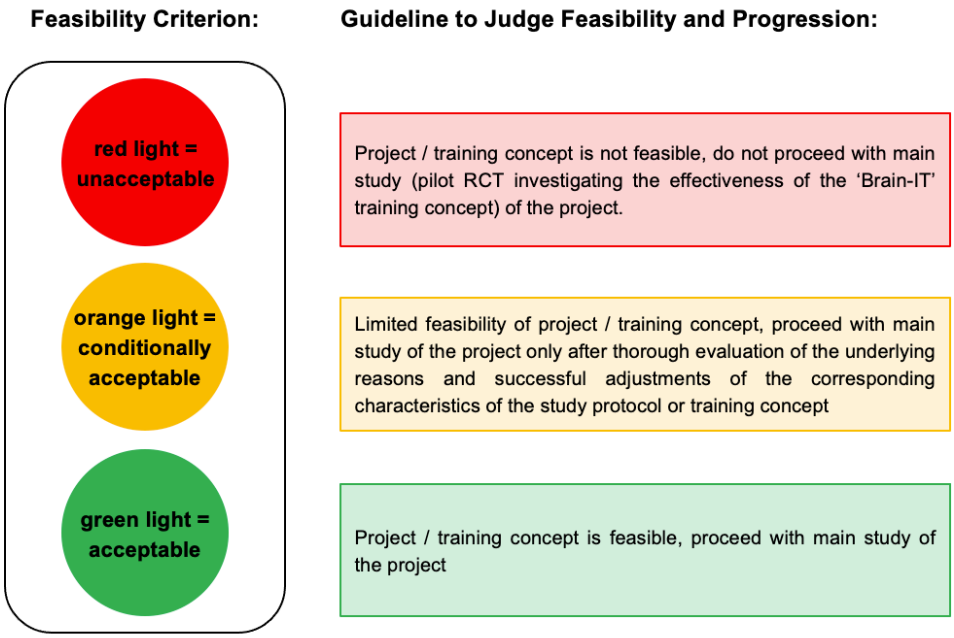

Figure 6-3: Traffic light system as a guideline to judge feasibility and progression.

The ability to recruit sufficient eligible participants within an appropriate timeframe is crucial for the feasibility of a future RCT. An absolute recruitment rate of at least six eligible participants per month was considered optimal, while two eligible participants per month were considered a minimal requirement for the 'Brain-IT' project. Regarding the relative recruitment rate, a median of 26 % (range: 3.4 - 59 %) was determined for exergame-based training in individuals who have mNCD in the studies analyzed in [42]. Based on this information, T1 was set to 6/month for the absolute recruitment rate and 25 % for the relative recruitment rate. T2 was set to 2/month for the absolute recruitment rate and 5 % for the relative recruitment rate. Adherence and compliance to exergame-based training are typically high in healthy older adults (HOA) [88] and older adults who have m-MNCD [42, 44]. For individuals who have m-MNCD, mean adherence rates of 70 % (standard deviation = 21, range = 16 - 100 %) [86] up to 90 % (10th percentile = 79 %; 90th percentile = 99 %) [84] and a median compliance rate of 75 % (range: 16 - 100 %) [86] to physical training were synthesized. For exergame-based training, a mean adherence rate of 84 % (range 69 - 100 %) was reported [44] and a median compliance rate of 70 % (range: 56 - 100 %) was determined for the studies analyzed in [42]. Based on this information and considering the high training frequency prescribed in this study, T1 was set to 75 % and T2 to 50 % for both adherence and compliance. Regarding attrition, a mean attrition rate of 17 % (range 0 - 59 %) [86] was synthesized for physical training and 15 % (range: 0 - 31 %) [44] for exergame-based training in individuals who have m-MNCD. Based on this information, T1 was set to 20 % and T2 to 40 %.

The resulting traffic light system with quantitative thresholds as a guideline to judge feasibility and progression is illustrated in Table 6-2.

Table 6-2: Traffic Light System with Quantitative Thresholds as Guideline to Judge Feasibility and Progression

Abbreviations: REC_{ab}, absolute recruitment rate; REC_{rel}, relative recruitment rate; ADH, adherence rate; COMP, compliance rate; ATT, attrition rate

Feasibility Outcome:	Calculation:	Feasibility Criteria:		
		green light = acceptable	orange light = conditionally acceptable	red light = unacceptable
Recruitment (absolute):	absolute recruitment rate (REC_{ab}) [] = number of included and eligible participants recruited per month	$REC_{ab} \geq 6$/month	6/month ≤ $REC_{ab} \geq$ 2/month	$REC_{ab} \leq 2$/month
Recruitment (relative):	relative recruitment rate (REC_{rel}) [%] = number of contacted individuals / number of included and eligible participants	$REC_{rel} \geq 25$ %	25 % ≤ $REC_{rel} \geq 5$ %	$REC_{rel} \leq 5$ %
Adherence:	adherence rate (ADH) [%] = number of training sessions attended / total number of training sessions offered; calculated as the average of each participants weekly adherence with a maximum of 100 %	ADH ≥ 75 %	75 % ≤ ADH ≥ 50 %	ADH ≤ 50 %
Compliance:	compliance rate (COMP) [%] = training duration attended [min] / total training duration offered [min]); calculated as the average of each participants weekly adherence with a maximum of 100 %	COMP ≥ 75 %	75 % ≤ COMP ≥ 50 %	COMP ≤ 50 %
Attrition:	attrition rate (ATT) = number of drop-outs / number of included participants who were randomly allocated to the intervention or control group and started the intervention period	ATT ≤ 20 %	20 % ≤ ATT ≥ 40 %	ATT ≥ 40 %

Usability

Usability was assessed by self-report using the validated German version of the System Usability Scale (SUS) [297, 298], which is a valid and reliable scale for evaluating newly developed devices and systems [297-299]. It is a frequently used scale for the evaluation of software products and also (exer)games and provides a global view of subjective assessments of usability [300]. A total score was calculated according to the scoring guidelines of the SUS. Total SUS scores range between 0 and 100, whereas higher scores indicate better usability. [297] A total SUS score of ≥70 was defined as a criterion for “acceptable” usability [301].

Acceptance

User acceptance of the newly developed exergame-based training concept was assessed with respect to exergame enjoyment, training motivation, and perceived usefulness.

Exergame enjoyment was assessed biweekly by self-report using the Exergame Enjoyment Questionnaire (EEQ) [302]. The German version of the EEQ was used, which has shown good internal consistency and is responsive to changes in differing conditions of exergame enjoyment [303]. A total score was calculated according to the scoring guidelines, resulting in a minimum score of 20 and a maximum score of 100. A higher score reflects greater enjoyment of playing the exergame [303].

Training motivation was assessed by self-report using the German translation [304] of the revised [305] Behavioral Regulation in Exercise Questionnaire (BREQ) [306], a widely used, valid, and reliable measure of training motivation [194, 305-308] along the Self-Determination Continuum [189, 306]. As an outcome measure, the self-determination index (SDI) was calculated as described in [309]. The SDI ranges between -24 and +24, whereas higher positive values represent a higher degree of self-determined motivation [309].

Perceived usefulness was evaluated after the last supervised training session based on individual interviews, organized as semi-structured in-depth interviews [257] along with an interview guide (Supplementary material 2). In addition to perceived usefulness, the interview guide also contained questions about participants' experiences with the training and desired adaptations of the training concept and/or the exergame device. With this, we aimed to collect data for justifying specific modifications of the 'Brain-IT' training concept and/or the exergame device based on the participants' perspectives. Data collection and analysis were done similarly to the methods described in a previous qualitative study within the 'Brain-IT' project [45], which included qualitative content analysis according to Mayring et al. [264, 265] performed using QCAmap software [265-267].

Secondary outcomes

As secondary outcomes, changes in global cognitive functioning and key neurocognitive domains [as defined in [3] in line with DSM-5 [5] and according to recommendations [7]] of (1) learning and memory, (2) complex attention, (3) executive function, and (4) visuospatial skills, as well as resting-state cortical activity, spatiotemporal parameters of gait, psychosocial factors [i.e., quality of life (QoL), and levels of depression, anxiety, stress], and cardiac vagal modulation [resting vagally mediated HRV (vm-HRV)] were assessed. An overview of all secondary outcome measures is provided in Table 6-3. Details on specific assessments and measurement conditions of all secondary outcomes are provided in Supplementary material 3.

Table 6-3: Overview of all secondary outcome measures, outcome variables and interpretation guide.
↑ = higher values/an increase over time indicate better functioning/improvement in the respective study endpoint
↓ = lower values/a decrease over time indicate better functioning/improvement in the respective study endpoint

Abbreviations: PEBL, Psychology experiment building language; vm-HRV = vagally-mediated heart rate variability

Outcome Measures:		Outcome Variables:	Interpretation Guide:
Primary:	Global Cognition		
	Quick Mild Cognitive Impairment Screen [251, 310]	total point score []	improvement = ↑
Secondary	Learning and Memory		
	Subtest 'logical memory' of the Wechsler Memory Scale - fourth edition [311, 312]	total point score part 1 - free recall []	improvement = ↑
		total point score part 2 - free recall []	improvement = ↑
		total point score part 2 - recognition []	improvement = ↑
	PEBL Digit Span Forward [313-315]	total point score []	improvement = ↑
		maximum span []	improvement = ↑

	Complex Attention		
	PEBL Trail Making Test - Part A [313]	completion time [s]	improvement = ↓
		number of errors []	improvement = ↓
	Subtest 'Alertness' of the Test of Attentional Performance [316]	median reaction time for condition A [ms]	improvement = ↓
		median reaction time for condition B [ms]	improvement = ↓
	Subtest 'Go-NoGo' of the Test of Attentional Performance [316]	median reaction time [ms]	improvement = ↓
		number of errors []	improvement = ↓
	Executive Function		
	HOTAP picture-sorting test part A [317]	combi score (i.e., sum of the points divided by the time they needed to arrange the cards) [points · min^{-1}]	improvement = ↑
	PEBL Digit Span Backward [313-315]	total point score []	improvement = ↑
		maximum span []	improvement = ↑
	Subtest 'Incompatibility' of the Test of Attentional Performance [316]	median reaction time condition 'compatible' [ms]	improvement = ↓
		median reaction time condition 'incompatible' [ms]	improvement = ↓
		number of errors [] condition 'compatible' [ms]	improvement = ↓
		number of errors [] condition 'incompatible' [ms]	improvement = ↓
	PEBL Trail Making Test - Part B [313, 315]	completion time [s]	improvement = ↑
		number of errors []	improvement = ↑
	Visuospatial Skills		
	PEBL Mental Rotation Task [313, 315, 318]	median reaction time of correct answered trials [ms]	improvement = ↓
		performance (number of correct answered trials) []	improvement = ↑
Secondary	**Resting-state Cortical Activity**		
	resting awake state measurement (two repeats of two minutes eyes closed, two minutes eyes opened, resulting in a total measurement duration of eight minutes) using a high-density 64-channel electroencephalography system (eego sport, ANT Neuro, Enschede, The Netherlands). The electrode placement scheme by ANT Neuro (an extension to the 10/20 and 10/10 systems) was used [319].	Mean beta (13 - 30 Hz) frequency band amplitude power of Cz [uV^2/Hz]	improvement = ↓
		Mean theta (4 - 8 Hz) frequency band amplitude power of T7 [uV^2/Hz]	improvement = ↓
		Mean theta (4 - 8 Hz) frequency band amplitude power of T8 [uV^2/Hz]	improvement = ↓
		Mean theta (4 - 8 Hz) frequency band amplitude power of FT7 [uV^2/Hz]	improvement = ↓
		Mean theta (4 - 8 Hz) frequency band amplitude power of FT8 [uV^2/Hz]	improvement = ↓
		Phase synchrony index of alpha (8 - 13 Hz) frequency between Fp2-C4 []	improvement = ↑
		Phase synchrony index of alpha (8 - 13 Hz) frequency between F7-T6 []	improvement = ↑
		Phase synchrony index of alpha (8 - 13 Hz) frequency between T3-T6 []	improvement = ↑
		Phase synchrony index of alpha (8 - 13 Hz) frequency between T5-T6 []	improvement = ↑

Spatiotemporal Parameters of Gait		
Instrumented gait analysis using a figure of eight walking path [320] at preferred walking speed using BTS G-WALK® (BTS Bioengineering S.p.A., Garbagnate Milanese, Italy) inertial sensor attached with semi-elastic belt to the lower back of the participant.	walking speed [$m \cdot s^{-1}$]	improvement = ↑
	stride duration [ms]	improvement = ↓
	stride length [cm]	improvement = ↑
	stance phase duration [% stride duration]	improvement = ↓
	swing phase duration [% stride duration]	improvement = ↑
	single support time [%]	improvement = ↑
	double support time [%]	improvement = ↓
Psychosocial Factors		
Quality of Life-Alzheimer's Disease [321-323]	Overall Score []	improvement = ↑
Depression, Anxiety and Stress Scale-21 [324-328]	Overall Score - Subscale Depression []	improvement = ↓
	Overall Score - Subscale Anxiety []	improvement = ↓
	Overall Score - Subscale Stress []	improvement = ↓
Resting vagally-mediated Heart Rate Variability		
5 min resting vm-HRV measurement with heart rate monitor (Polar M430) and sensor (Polar H10) analyzed using Kubios HRV Premium (Kubios Oy, Kuopio, Finland, version 3.4) [329]	mean R-R time interval [ms]	improvement = ↑
	Root Mean Square of Successive RR interval differences []	improvement = ↑
	percentage of successive RR intervals that differ by more than 50 ms [%]	improvement = ↑
	absolute power of the high-frequency (0.15 - 0.4 Hz) band [ms^2]	improvement = ↑
	relative power of the high-frequency (0.15 - 0.4 Hz) band [nu]	improvement = ↑
	Poincaré plot standard deviation perpendicular to the line of identity [ms]	improvement = ↑
	Parasympathetic Nervous System Tone Index []	improvement = ↑

Other endpoints

Safety endpoint variables

A protocol was kept for all (serious) adverse events [(S)AEs].

Baseline factors

Baseline factors were collected through demographic data including age, sex, height, weight, body mass index (BMI), years of education, physical activity behavior (i.e., time spent in at least a moderate level of physical activity per week), medication intake (yes/no), and etiological subtype (i.e., mainly mNCD due to AD, mild frontotemporal NCD, mNCD with Lewy Bodies, or mild vascular NCD).

6.3.7 Sample size

The sample size was justified based on the rules of thumb of Julious et al. (2005), who recommended a minimum sample size of 12 per group for pilot or feasibility studies [330]. As described in the Section *"Trial design and study setting"*, the focus of this study was on investigating the primary outcomes in

the group receiving our new 'Brain-IT' training. Considering the 2:1 allocation ratio, we targeted a sample size of 12 for the intervention and six for the control group, leading to a total sample size of n = 18. To ensure an adequate number of participants in the study, a safety margin for an attrition rate of up to 40 % (criterion for orange light; see the Section *"Feasibility"*) was chosen. Based on these considerations, we aimed to recruit a total of 18 - 25 participants.

6.3.8 Randomization

Sequence generation

Participants were randomly allocated to the intervention or control group. A variable block randomization (i.e., block sizes = 3, 6) with a 2:1 allocation ratio (intervention:control) stratified by sex was used.

Allocation concealment mechanism

To ensure allocation concealment, the random allocation was computer-generated using a validated variable block randomization model implemented in the data management system Castor EDC (Ciwit BV, Amsterdam, The Netherlands) [331].

Implementation

The randomization process was set up by PM before starting the recruitment of participants. PM was also in charge of the enrollment of participants. Participants were randomly assigned to the intervention or control group by the investigator assigned as the responsible person for supervision and correspondence with the respective participant after completing pre-measurements.

6.3.9 Data management

All involved study investigators were thoroughly trained for all study procedures according to the Guidelines of Good Clinical Practice (GCP) and in line with detailed working instructions. The principal investigator was in charge of methodological standards and quality of data collection using the data management system Castor EDC (Ciwit BV, Amsterdam, The Netherlands). Range checks for data values were pre-programmed for data entry in eCRFs. All data entries were cross-checked by a second study investigator before export for analysis. To minimize bias during the assessment of all outcome measures, detailed working instructions were prepared that included standardized measurement procedures and standardized instructions for participants for all measurements.

6.3.10 Blinding

As clarified in the Section Important changes to the trial design and study setting after commencement, the study was planned as a single-blinded pilot RCT. However, we were not able to keep all outcomes assessors blinded due to COVID-19-related delays in recruiting participants. For all data assessed throughout the intervention period (i.e., only applicable for the intervention group), blinding of investigators was not possible. Blinding of participants was also not possible since usual care was used as a control intervention.

6.3.11 Participant retention

Once a participant was included, a trained investigator was assigned as the person responsible for supervision and correspondence with the respective study participant and made all reasonable efforts to achieve the participant's retention in the study. Examples include providing written information sheets and reminders about study appointments, involving carers or relatives as personal support for study participants, and providing assistance with travel to the study center. Specifically, in the intervention group, each participant was provided with a detailed training manual that was individually adapted to the participants' setup to help them use the training system correctly [with photographs and explanations for each step from starting the system to training completion, including a colored step-by-step identification of required elements (cables and buttons)]. Furthermore, the study team provided telephone support in case of technical difficulties or comprehension problems for unsupervised training sessions.

6.3.12 Statistical methods

Statistical analysis was executed using R Version R 3.6.2 GUI 1.70 El Capitan build (7735) (© The R Foundation) in line with RStudio Version 2022.07.1 (RStudio, Inc.). For demographics and primary outcomes (except user acceptance), all collected data were included (i.e., including data on dropouts up to the timepoint of their withdrawal). For user acceptance, only data of participants who completed the study were analyzed. For all secondary outcomes, a modified intention-to-treat analysis was performed (i.e., data from all participants who completed pre- and post-measurements, regardless of protocol adherence, were included in the data analysis). Questionnaire scores were regarded as ordinal data. Data were reported as mean ± standard deviation for parametric data, median (interquartile range) for non-parametric data, and the frequency of various statements (f) and the proportion of participants making a statement (in %) for qualitative data.

For all outcomes, descriptive statistics were computed first. The normal distribution of data was checked using the Shapiro-Wilk test. The level of significance was set to $p \leq 0.05$ (two-sided, uncorrected).

For all demographic variables, between-group differences (i.e., intervention vs. control) were tested using an independent t-test or Mann-Whitney U-test in case the data were not normally distributed. Between-group differences in categorical variables were tested using Fisher's exact test. Feasibility and usability outcomes were analyzed using descriptive statistics and according to predefined criteria (see Section Primary outcomes). User acceptance was analyzed qualitatively (i.e., perceived usefulness) and based on a Friedman ANOVA to evaluate the effect of time on exergame enjoyment and training motivation. Additionally, a Wilcoxon signed-rank test was performed to evaluate whether there was a difference in median exergame enjoyment and training motivation between the first and the last measurement. To discover whether effects were substantive, effect sizes r were calculated [332, 333] and interpreted to be small ($0.1 \leq r < 0.3$), medium ($0.3 \leq r < 0.5$), or large ($r > 0.5$) [334].

For all secondary outcomes, the assumption of homogeneity of variance was checked using Levene's test. In case all assumptions for ANCOVA were met, effects of the addition of the ‘Brain-IT’ training to usual care as compared to usual care were analyzed using an ANCOVA with pre-measurement values as covariate for the predicting group factor and post-measurement values as outcome variable [333]. In case not all assumptions were met, Quade's non-parametric ANCOVA was used. To

discover whether effects were substantive, partial eta-squared (η^2_p) effect sizes including 90 % confidence intervals were calculated, according to recommendations for pilot trials [335]. Because this pilot RCT is not adequately powered for all secondary outcomes, the interpretation of secondary outcomes focused on the effect size estimates, as recommended by Lee et al. (2014) [335]. Effect sizes were interpreted to be small ($0.01 \leq \eta^2_p < 0.06$), medium ($0.06 \leq \eta^2_p < 0.14$), or large ($\eta^2_p > 0.14$) [334].

Statistical analysis was done by PM after data collection was completed. No interim analysis was performed.

6.4 Results

6.4.1 Recruitment and participant flow

A summary of the participant flow through the study is illustrated in Figure 6-4. Recruitment was stopped after the planned minimum sample size of 18 participants was reached. Of the 18 included participants, 13 were clinically diagnosed with mNCD and five fulfilled the criteria defined for sMCI. In the intervention group, nine participants started their training at home as planned and one participant was allowed to perform the training at the study center (ETH Hönggerberg) using the ‘Senso’ because there was not enough space for the exergame device at the participants' home. Three minor adverse events (falls in participants' homes with bruises, but no more serious injuries) were recorded, all of which occurred in the intervention group (in two different participants, one of whom has mild frontotemporal NCD). All AEs were unrelated to the ‘Brain-IT’ training.

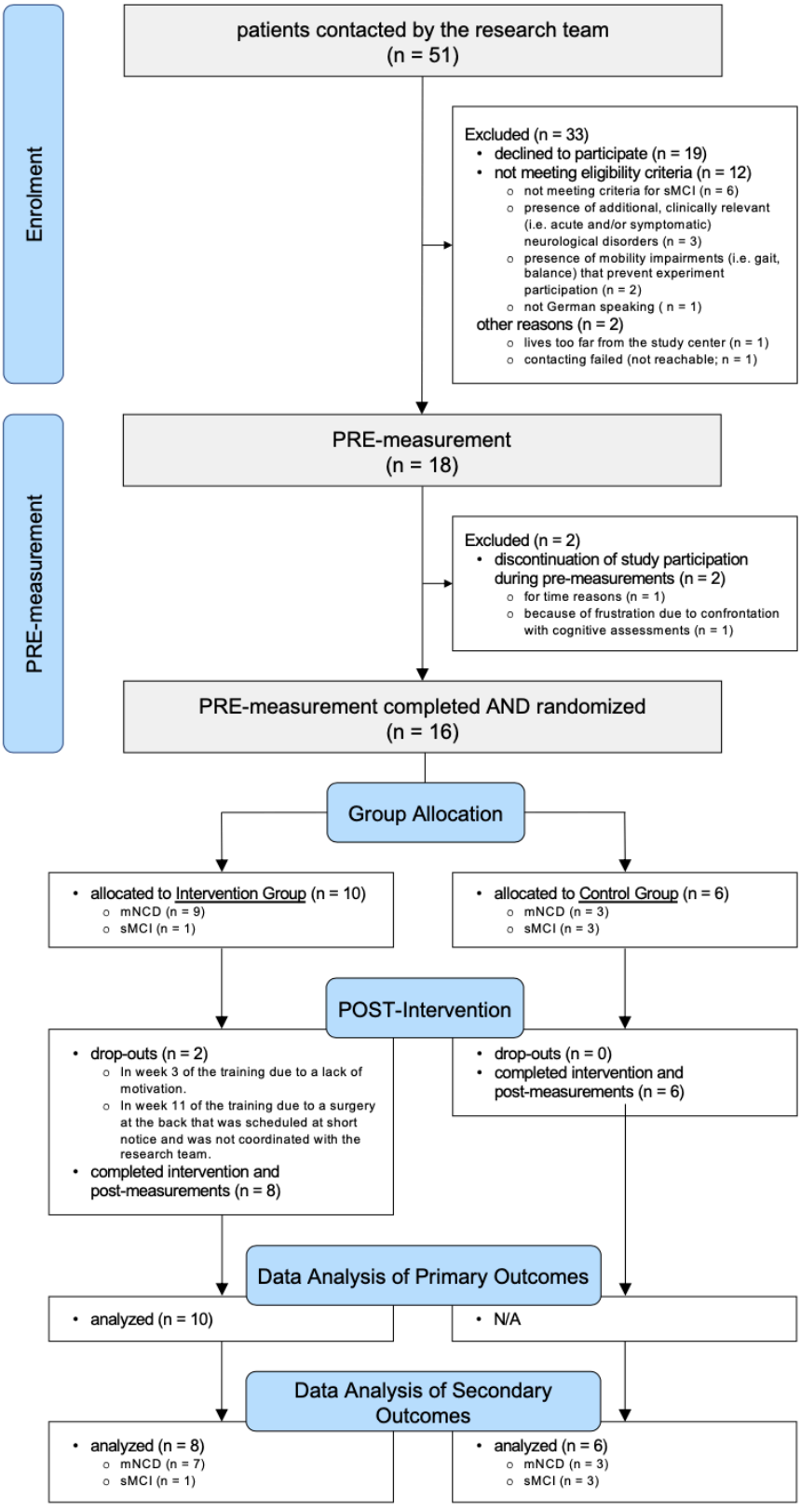

Figure 6-4: Summary of the participant flow throughout the study. mNCD, clinically diagnosed mild neurocognitive disorder; sMCI, screened for mild cognitive impairment.

6.4.2 Baseline data

Demographic characteristics of participants are summarized in Table 6-4. There were no significant between-group differences.

Table 6-4: Demographic Characteristics of the Study Population

(1) t-statistics for the between-group differences tested with an independent t-test or Mann-Whitney U test in case the data are not normally distributed;
(2) p-values for the between-group differences tested with an independent t-test or Mann-Whitney U test in case the data are not normally distributed, or Fisher's exact test for categorical variables.

Abbreviations: SD, Standard Deviation;

	Group: Exergame (n = 10)		Group: Usual Care (n = 6)		Between-Group Difference	
	mean	SD	mean	SD	t-test statistics(1)	p-value(2)
Age [years]	79.9	7.6	73.7	12.9	t(7.14) = 1.076	0.317
Sex [number of females (%)]	3 (30.0)	N/A	4 (66.7)	N/A	N/A	0.302
Education [years]	13.2	4.2	13.2	1.2	t(11.13) = 0.024	0.982
Body mass index [$kg \cdot m^{-2}$]	23.1	2.2	26.4	3.2	t(7.92) = - 2.265	0.054
Physical Activity [min/week]	233.0	200.7	425.0	253.4	t(8.78) = - 1.582	0.149
Clinical Subtype:						
mNCD due to Alzheimer's Disease	n = 7 (70 %)		n = 4 (66.6 %)			1.000
mild frontotemporal NCD	n = 1 (10 %)		n = 0 (0 %)			1.000
mNCD with Lewy Bodies	n = 0 (0 %)		n = 0 (0 %)			1.000
mild vascular NCD	n = 2 (20 %)		n = 2 (33.3 %)			0.604

6.4.3 Delivery of the interventions

Type of usual care activities

For participants who completed the study, 75 % of participants in the intervention group and 83 % of participants in the control group reported that they received one or more structured or guided usual care activities(s) during study participation. Details on types of usual care activities are summarized in Table 6-5. Additionally, one participant in the intervention group had a stationary rehabilitation stay for 3 weeks focusing on gait and balance due to polyneuropathy. During the stay, the participant was able to continue with the 'Brain-IT' training.

Table 6-5: Type of Usual Care Activities

(1) Medical training therapy is prescribed by a doctor and guided and partly supervised by physiotherapists. It typically includes resistance, cardiorespiratory endurance, and balance exercises.
(2) Volume = time per training session [min] multiplied by frequency of training [times/week].
(3) p-values for the between-group differences tested with Fisher's exact test for categorical variables.

Type of Usual Care Activities	Proportion of Participants having received the respective Intervention during Study Participation		Between-Group Difference
	Group: Exergame (n = 8)	Group: Usual Care (n = 6)	p-value(3)
regular medication intake	n = 6 (75 % of participants)	n = 4 (66.7 % of participants)	1.000
physiotherapy	n = 2 (25 % of participants); median volume(2) = 60 min/week	n = 1 (16.7 % of participants); volume = 50 min/week	1.000
occupational therapy	n = 1 (12.5 % of participants); volume = 60 min/week	n = 0 (0 % of participants)	1.000
medical training therapy (1)	n = 2 (25 % of participants); median volume = 60 min/week	n = 1 (16.7 % of participants); volume = 75 min/week	1.000
(computerized) cognitive training	n = 1 (12.5 % of participants); volume = 30 min/week	n = 2 (33.3 % of participants); median volume = 285 min/week	0.539

Actual delivery of the intervention

Participants who completed the training performed on average 54.4 ± 13.0 training sessions resulting in an average training volume of 1,128.3 ± 266.0 min over the 12-week intervention period. On average, 21.4 ± 1.1 training sessions were supervised by our study team. Average heart rates during the 'facilitation', 'guidance', and 'coherence' phases were 96.9 ± 8.4 bpm, 86.2 ± 5.9 bpm, and 83.5 ± 5.9 bpm, respectively. No relevant deviations from the 'Brain-IT' training concept were reported.

6.4.4 Primary outcomes

Feasibility

The first participant was contacted on 2 July 2021. The 18th participant was included on 11 March 2022. This results in an absolute recruitment rate of 2.2 participants per month. Out of the 51 individuals contacted by the study team, 18 were included in the study. This results in a relative recruitment rate of 35.3 %. Two dropouts occurred in the intervention group, resulting in an attrition rate of 20 %. The mean adherence rate to the training was 85.0 ± 21.4 %. Detailed information on weekly adherence including the type and proportions of reasons for non-adherence is illustrated in Figure 6-5. "Other reasons" for non-adherence included organizational challenges (e.g., one participant went into a stationary clinic for 3 weeks and the training equipment first had to be transported to the clinic for the participant to be able to continue training).

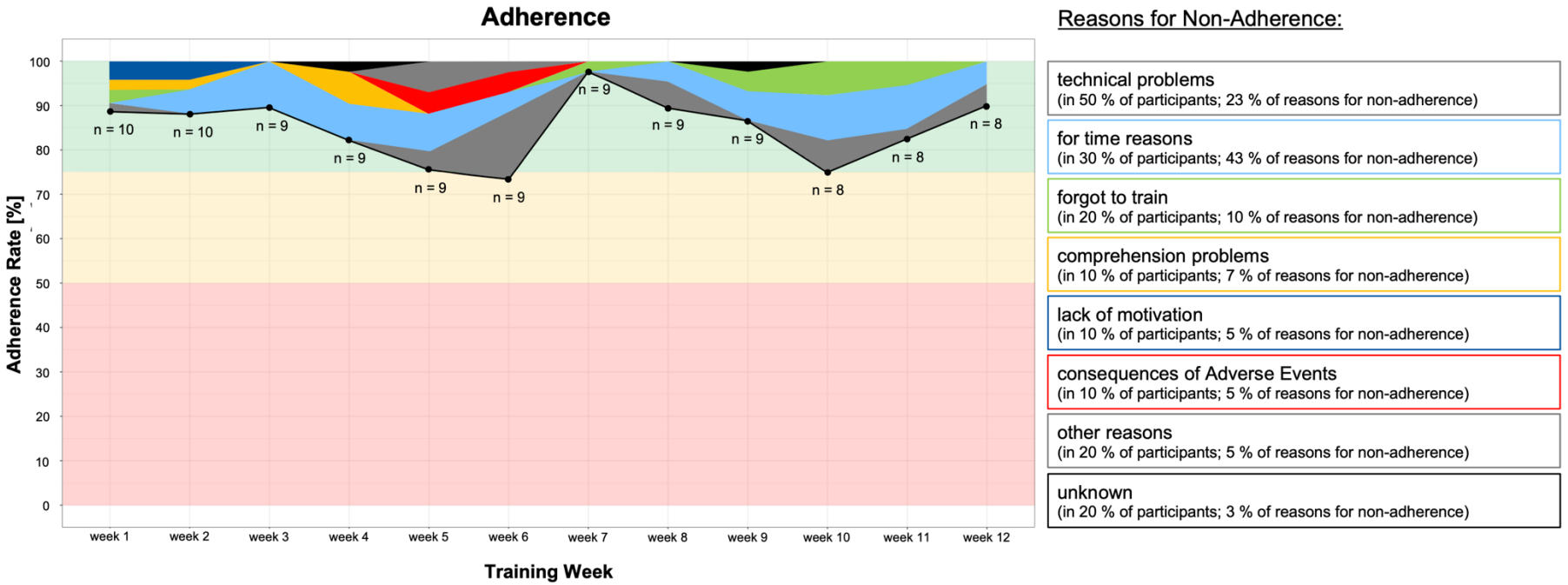

Figure 6-5: Detailed information on weekly adherence including the type and proportions of reasons for non-adherence as well as the predefined traffic light system with quantitative thresholds as guidelines to judge feasibility indicated in red, orange, and green (see the Section *"Feasibility"* or Table 6-1).

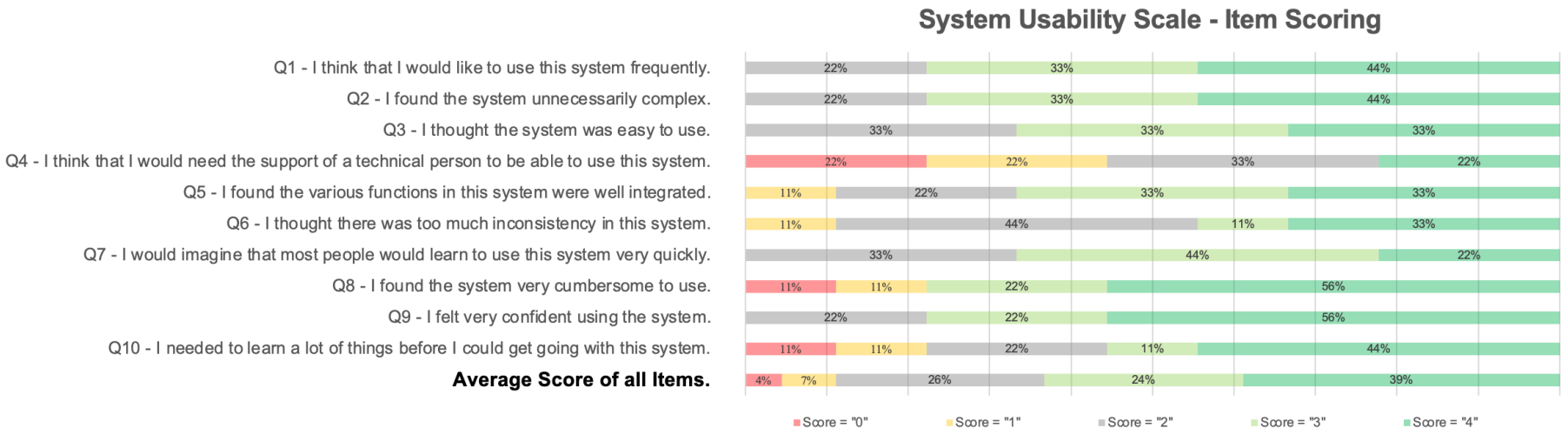

Figure 6-6: Details on item scoring of the system usability scale.

The mean compliance rate to the training was 84.1 ± 21.6 %. In total, 13 training sessions were started but not completed. Of these, reasons for non-compliance included (1) accidentally stopping the training by staying on the back plate of the exergame device for too long (in 40 % of participants; 71 % of reasons for non-compliance), (2) technical problems (in 20 % of participants; 21 % of reasons for non-compliance), or (3) unknown (in 10 % of participants; 8 % of reasons for non-compliance).

Usability

The mean system usability score was 71.7 ± 15.4. Details on item scoring are illustrated in Figure 6-6. The highest score was reached in question nine *("I felt confident using the system"*, mean = 3.3 points). The lowest score was reached in question four *("I think that I would need the support of a technical person to be able to use this system"*, mean = 1.8 points).

Acceptance

Biweekly scores on exergame enjoyment are illustrated in Figure 6-7. There was no main effect of time on exergame enjoyment [$\chi^2(5) = 8.52$, $p = 0.13$]. Exergame enjoyment was rated significantly ($p = 0.03$) higher in week 12 (median = 78.0) compared to week 2 (median = 72.0), with a large ($r = 0.75$) effect size.

Biweekly scores on training motivation are illustrated in Figure 6-8. There was a significant effect of time on training motivation [$\chi^2(5) = 11.31$, $p = 0.04$]. The SDI was significantly ($p = 0.03$) higher in week 11 (median = 16.5) compared to week 1 (median = 12.38), with a large ($r = 0.74$) effect size.

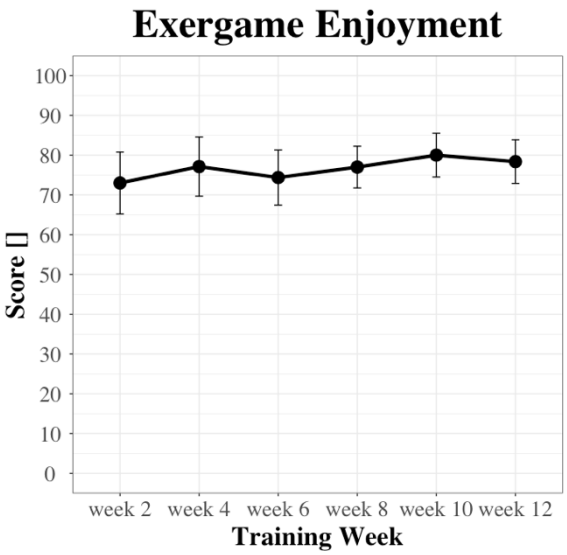

Figure 6-7: Biweekly scores on exergame enjoyment.

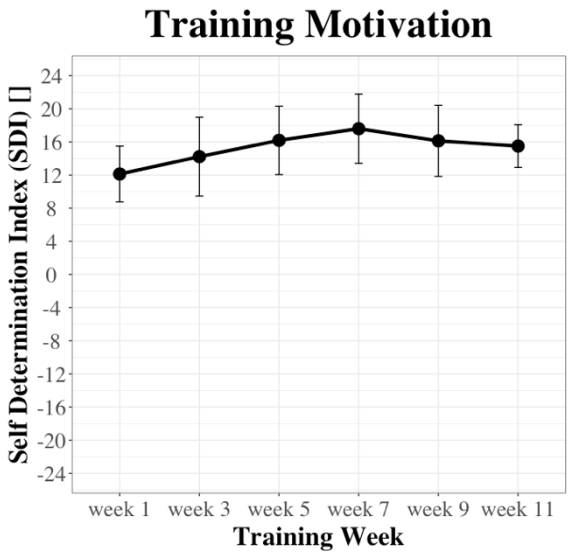

Figure 6-8: Biweekly scores on training motivation.

According to the qualitative in-depth interviews, all participants reported to have perceived the training as useful. Six participants (75 % of interviewed participants) described perceived changes in cognitive functioning, physical abilities, and/or wellbeing in response to training. Participants had difficulties describing the perceived changes. Those perceived changes that were described are summarized in Table 6-6.

Table 6-6: Summary of the perceived changes that were described by the participants in the semi-structured interviews. Perceived changes in cognitive functioning were classified into the key neurocognitive domains (as defined by [3] in line with DSM-V [5]).

Abbreviations: f, frequency of various statements; n, number of participants making a specific statement; IADL, instrumental activities of daily living

	Perceived changes described by the participants as a response to the question *"Do you feel any changes (e.g., mental and physical abilities, well-being) as a result of the training? If so, how exactly do these changes manifest themselves?"*	
	Positive changes (perceived stabilization/improvements)	Neutral/negative changes (perceived (continued) deterioration)
Cognitive Functioning (Overall)	f = 13, n = 5 (62.5 % of participants)	f = 1, n = 1 (12.5 % of participants)
Global Cognition	f = 3, n = 3 (37.5 % of participants)	no statements
Learning and Memory	f = 1, n = 1 (12.5 % of participants)	f = 1, n = 1 (12.5 % of participants)
Complex Attention	f = 6, n = 3 (37.5 % of participants)	no statements
Executive Function	f = 2, n = 1 (12.5 % of participants)	no statements
Visuospatial skills	no statements	no statements
Social Cognition	f = 1, n = 1 (12.5 % of participants)	no statements
Language	no statements	no statements
Physical Functioning	f = 3, n = 3 (37.5 % of participants)	f = 1, n = 1 (12.5 % of participants)
Coupling of Brain-Body Functioning	f = 3, n = 2 (25 % of participants)	no statements
Risk for Falls	f = 1, n = 1 (12.5 % of participants)	no statements
Fear of Falling	f = 1, n = 1 (12.5 % of participants)	no statements
Mood and Well-being	f = 9, n = 3 (37.5 % of participants)	no statements
Transfer-Effects to IADL	f = 3, n = 2 (25 % of participants)	no statements

> *"It's difficult to describe because the physical and mental functions are always connected in the end. I feel improvements in both areas. If I can think better and faster, then I can also react faster physically. That is very important for me. I also notice that when I go for a walk and use public transport. I always have to anticipate and react very quickly. [...] That works better and faster. I even dare to overcome a certain height when I get off the bus. Earlier, I was terrified that I wouldn't make it and would fall. That also went better. I can generally adjust better to such situations. That is very important. Because I know: If I have my 17th fall, it's not good. I also see certain things more positively. Now I'm also happy about little things again and don't demonize everything that doesn't work or didn't work out."* (P-84932328)

> *"I was always very cheerful after the training. So, it had a positive effect on my wellbeing, that's for sure."* (P-3223376)

Participants reported positive experiences with specific games [f = 7, n = 4 (50 % of participants)] and that the training has brought some structure into everyday life [f = 2, n = 2 (25 % of participants)]. The training dosage was perceived as good [f = 1, n = 1 (12.5 % of participants)] and the training varied [f = 1, n = 1 (12.5 % of participants)].

> *"I found the game with the shopping list [game "Shopping Tour'] to be a good exercise to train the memory. Or also the one with the sounds [game 'Simon' and 'Simon_numbered']. [...] The training has also given a structure to everyday life, which was very good."* (P-37740093)

> *"The game 'Habitats' was the one I liked the most. And in general, that the training allowed me to move. I like to move a lot. But the combination with the mind, that's actually what I liked most."* (P-77422816)

Fifty percent of participants would like to continue with the training as it is. The remaining participants would like to continue the training but only if it is effective (n = 1, 12.5 % of participants) and/or if adjustments are made to the training or the exergame device (n = 4, 50 % of participants). These adjustments include a drastic reduction in technical problems (n = 3, 37.5 % of participants) and/or improvements in monitoring and individualized adaptation of task demands (n = 1, 12.5 % of participants). None of the participants reported that they definitely did not want to continue the training.

> *"I would have loved to continue the training. […] Of course, I would be willing to pay to use the system. I really believe that it helps me a lot and improves my quality of life. […] But because of the frustration caused by the technical problems, I don't want to continue. If it wasn't for the technical problems, I would have liked to continue. The structure and volume of the training itself was good and the training was varied."* (P-68113192)

> *"Yes, I would like to continue the training. But you have to be able to measure better whether the performance remains constant or whether you improve or deteriorate a little. It has to be measurable. There was just too much that didn't work [technically]."* (P-05558066)

For the training to be optimal, participants reported that technical problems must be solved [f = 4, n = 3 (37.5 % of participants)], that changes in performance over time should be regularly discussed [f = 2, n = 2 (25 % of participant)], and that individualized adaptation of task demands is improved [f = 2, n = 2 (25 % of participant)].

> *"It would be beneficial to discuss the results with a professional every week. I partly had the feeling that it was miserable again today and of course it would be nice to hear if it was the opposite. These discussions would help to know how things are going and whether my memory has progressed or rather regressed."* (P-53458467)

Additionally, one participant suggested that the effort required to start up the system and start training should be reduced. Finally, one participant suggested specific adaptations of existing games, and three participants suggested that new and/or additional games should be offered.

6.4.5 Secondary outcomes

The results of the 'TAP Incompatibility' were excluded from analysis because many participants had comprehension problems, which led to invalid results. The remaining results of secondary endpoints are summarized in Table 6-7 in detail. In short, the intervention group improved their score in global cognitive functioning from 52.8 ± 11.7 points at pre-measurements to 59.8 ± 11.0 points at post-measurements, while the control group showed a decline from 60.1 ± 8.0 points to 58.9 ± 6.7 points. There was a medium, but non-significant effect [$F(1, 11) = 0.96$, $p = 0.35$, $\eta^2_p = 0.080$], in favor of the intervention group. Regarding domain-specific cognitive functioning, there were small favorable effects on learning and memory and visuospatial skills in favor of the intervention group, small-to-medium favorable effects on executive functioning in favor of the intervention group, and mixed findings on effects on complex attention. Regarding resting-state cortical activity, participants in the intervention group showed changes in the direction of the brain functions of HOAs in the post-intervention EEG measurements when using beta amplitude power and alpha phase synchrony as analysis methods. Regarding spatiotemporal parameters of gait, there were no relevant between-group effects on walking speed and stride length, although walking speed decreased within the intervention group. There was a moderate effect on stride duration in favor of the control group and small-to-moderate favorable effects on gait parameters that indicate a more stable gait (i.e., an increase in swing time and single support time, and a decrease in stance phase duration and double support time) in favor of the intervention group. Regarding psychosocial factors, there was a small favorable effect on quality of life and depression in favor of the intervention group, a moderate favorable effect on stress in favor of the intervention group, and no relevant between-group effects on anxiety. Regarding resting cardiac autonomic regulation, there were no relevant between-group effects. None of the effects were statistically significant.

Table 6-7: Statistics for all secondary outcomes. Normality distribution of data was checked using the Shapiro-Wilk test and Q-Q-plots. The level of significance was set to $p \leq 0.05$ (two-sided, uncorrected). The assumption of homogeneity of variance was checked using Levene's test. In case all assumptions for analysis of covariance (ANCOVA) were met, effects of the addition of the 'Brain-IT' training concept to usual care as compared to usual care were analyzed using an ANCOVA with the pre-measurement value as covariate for the predicting group factor and the post-measurement value as outcome variable [333]. In case not all assumptions were met, Quade's non-parametric ANCOVA was used. To discover whether effects are substantive, partial eta-squared (η^2_p) effect sizes were calculated for all primary and secondary outcomes. Effect sizes were interpreted to be small ($0.01 \leq \eta^2_p < 0.06$), medium ($0.06 \leq \eta^2_p < 0.14$) or large ($\eta^2_p > 0.14$) [334].

(1) = missing data due to comprehension problems of the test;
(2) = missing data because the measurement had to be stopped due to attentional exhaustion of the participant;
(3) = missing data due to technical problems with the measurement device;
(4) = missing data due to insufficient data quality

Abbreviations: Qmci, Quick Mild Cognitive Impairment Screen; WMS-IV-LM, subtest 'logical memory' of the Wechsler Memory Scale- fourth edition; PEBL, Psychology experiment building language; DSF, Digit Span Forward; DSB, Digit Span Backward; TMT-A and B, Trail Making Test Part A and B; TAP Alertness, subtest 'Alertness' of the Test of Attentional Performance; TAP Go-NoGo, subtest 'Go-NoGo' of the Test of Attentional Performance; TAP Incompatibility, subtest 'Incompatibility' of the Test of Attentional Performance; HOTAP-A, HOTAP picture-sorting test part A; MRT, Mental Rotation Task; MRI, magnetic resonance imaging; IADL, Instrumental Activities of Daily Living; QOL-AD, Quality of Life-Alzheimer's Disease; DASS-21, Depression, Anxiety and Stress Scale-21; vm-HRV, vagally-mediated heart rate variability; SD, standard deviation; IQR, interquartile range; n, sample size; ANCOVA, analysis of covariance; η^2_p [90 % CI], partial eta-squared [90 % confidence interval]

Outcome:	Check of Assumptions and Type of Analysis:		Group: Exergame			Group: Usual Care			ANCOVA Statistics:		
			PRE-measurement	POST-measurement	sample	PRE-measurement	POST-measurement	sample			
	All assumptions for parametric analysis met?	AND type of analysis	mean ± SD or median (IQR)	mean ± SD or median (IQR)	n	mean ± SD or median (IQR)	mean ± SD or median (IQR)	n	p-Value	F-Value	η^2_p [90 % CI]
Part 1 - Cognitive Functioning											
1.1 Global Cognition											
Qmci Total Score []	✓	parametric	52.8 ± 11.7	59.8 ± 11.0	8	60.1 ± 8.0	58.9 ± 6.7	6	0.348	0.961	0.080 [0, 0.348]
1.2 Learning and Memory											
WMS-IV-LM Score Part 1 []	x	non-parametric	26.0 (21.0)	30.0 (17.0)	8	24.0 (6.0)	26.0 (3.5)	6	0.646	0.223	0.020 [0, 0.246]
WMS-IV-LM Score Part 2 []	x	non-parametric	6.0 (12.5)	6.5 (8.5)	8	9.5 (4.8)	5.5 (14.5)	6	0.843	0.041	0.004 [0, 0.152]
WMS-IV-LM Score Part 2 - Recognition []	✓	parametric	15.6 ± 3.7	15.9 ± 3.4	8	17.7 ± 3.3	17.6 ± 2.0	6	0.738	0.117	0.011 [0, 0.210]
DSF Total Score []	x	non-parametric	5.0 (2.3)	7.0 (1.5)	6[1, 2]	8.0 (1.5)	7.5 (2.5)	6	0.992	0.000	0.000 [0, 0.000]
DSF Maximal Span []	✓	parametric	3.8 ± 1.3	5.2 ± 1.3	6[1, 2]	5.8 ± 1.5	5.2 ± 1.5	6	0.830	0.049	0.005 [0, 0.162]

1.3 Complex Attention											
TMT-A - Completion Time [s]	x	non-parametric	38.0 (26.1)	39.4 (6.1)	7[2]	45.66 (10.7)	39.0 (16.4)	6	0.370	0.882	0.081 [0, 0.341]
TMT-A - Number of Errors []	x	non-parametric	1.0 (3.0)	1.0 (3.5)	7[2]	1.0 (1.5)	1.5 (2.5)	6	0.426	0.690	0.065 [0, 0.321]
TAP Alertness (Condition A) - RT [ms]	x	non-parametric	310.0 (165.0)	373.8 (191.9)	8	261.5 (51.5)	243.2 (34.5)	6	0.155	2.330	0.175 [0, 0.444]
TAP Alertness (Condition B) - RT [ms]	x	non-parametric	299.5 (148.8)	355.2 (111.6)	8	277.5 (66.1)	256.8 (56.2)	6	0.093	3.377	0.235 [0, 0.494]
TAP Go-NoGo - RT [ms]	x	non-parametric	456.5 (181.8)	566.9 (162.0)	8	430.0 (63.0)	423.5 (77.7)	6	0.082	3.671	0.250 [0, 0.506]
TAP Go-NoGo - Number of Errors []	✓	parametric	3.3 ± 2.4	2.1 ± 2.0	8	2.2 ± 1.9	3.0 ± 1.3	6	0.223	1.672	0.132 [0, 0.404]
1.4 Executive Functioning											
HOTAP-A Combi-Score [points/min]	✓	parametric	3.9 ± 2.0	4.7 ± 2.5	8	5.4 ± 1.8	5.8 ± 1.7	6	0.939	0.006	0.001 [0, 0.030]
DSB Total Score []	x	non-parametric	4.5 (3.3)	4.3 (1.5)	6[1, 2]	6.0 (2.3)	6.0 (2.3)	6	0.998	0.000	0.000 [0, 0.000]
DSB Maximal Span []	x	non-parametric	3.5 (1.0)	4.0 (0.8)	6[1, 2]	4.6 (1.8)	4.0 (0.8)	6	0.387	0.827	0.084 [0, 0.335]
TMT-B - Completion Time [s]	x	non-parametric	185.9 (124.8)	111.8 (107.9)	7[2]	86.4 (47.3)	66.6 (23.7)	6	0.362	0.913	0.084 [0, 0.344]
TMT-B - Number of Errors []	x	non-parametric	7.0 (16.0)	2.0 (9.0)	7[2]	5.0 (9.0)	1.5 (3.3)	6	0.952	0.004	0.000 [0, 0.000]
1.5 Visuospatial Skills											
MRT - RTs [ms]	x	non-parametric	3,471 (1,879)	3,082 (601)	7[2]	4,431 (2,737)	3,653 (1,918)	6	0.187	2.009	0.167 [0, 0.426]
MRT - Score []	✓	parametric	45.0 + 8.7	49.1 ± 9.1	7[2]	44.8 ± 11.9	44.7 ± 11.1	6	0.182	2.054	0.170 [0, 0.428]
Part 2 - EEG											
2.1 Amplitude Power:											
Beta (13 - 30 Hz) power of Cz [uV^2/Hz]	✓	parametric	0.72 ± 0.44	0.42 ± 0.41	4[3, 4]	0.34 ± 0.24	0.81 ± 0.31	4[3]	0.384	0.911	0.154 [0, 0.379]
Theta (4 - 8 Hz) power of T7 [uV^2/Hz]	x	non-parametric	0.36 (0.24)	0.87 (0.19)	5[3, 4]	0.54 (0.18)	0.84 (1.21)	4[3]	0.828	0.052	0.009 [0, 0.165]
Theta (4 - 8 Hz) power of T8 [uV^2/Hz]	x	non-parametric	0.33 (0.16)	0.92 (0.32)	5[3, 4]	0.32 (0.35)	0.36 (1.88)	4[3]	0.397	0.833	0.122 [0, 0.336]
Theta (4 - 8 Hz) power of FT7 [uV^2/Hz]	x	non-parametric	0.31 (0.42)	0.68 (0.67)	6[3]	0.40 (0.38)	0.36 (0.71)	4[3]	0.337	1.062	0.132 [0, 0.358]
Theta (4 - 8 Hz) power of FT8 [uV^2/Hz]	x	non-parametric	0.37 (0.52)	1.28 (1.69)	6[3]	0.22 (0.25)	0.07 (0.30)	3[3, 4]	0.075	4.632	0.436 [0, 0.541]

2.2 Phase Synchrony:											
Alpha (8 - 13 Hz) Fp2-C4 []	x	non-parametric	0.41 (0.04)	0.42 (0.04)	6[3]	0.43 (0.01)	0.42 (0.02)	4[3]	0.762	0.099	0.014 [0, 0.201]
Alpha (8 - 13 Hz) F7 - T6 []	x	non-parametric	0.42 (0.02)	0.43 (0.04)	6[3]	0.42 (0.11)	0.46 (0.19)	4[3]	0.337	1.060	0.132 [0, 0.357]
Alpha (8 - 13 Hz) T3 - T6 []	x	non-parametric	0.44 (0.39)	0.71 (0.59)	6[3]	0.43 (0.02)	0.46 (0.06)	4[3]	0.596	0.309	0.042 [0, 0.265]
Alpha (8 - 13 Hz) T5 - T6 []	x	non-parametric	0.42 (0.03)	0.43 (0.44)	6[3]	0.43 (0.12)	0.43 (0.16)	4[3]	0.540	0.414	0.056 [0, 0.284]
Part 3 - Gait											
Walking Speed [$m \cdot s^{-1}$]	x	non-parametric	1.22 (0.26)	1.00 (0.27)	7[3]	1.15 (0.50)	1.15 (0.30)	6	0.964	0.002	0.000 [0, 0.000]
Stride Duration [ms]	x	non-parametric	1,070 (195)	1,130 (155)	7[3]	1,040 (120)	1,045 (88)	6	0.289	1.254	0.111 [0, 0.374]
Stride Length [cm]	x	non-parametric	123.0 (9.0)	118.0 (18.5)	7[3]	116.0 (36.3)	114.5 (30.0)	6	0.905	0.015	0.002 [0, 0.091]
Stance Phase Duration [% stride duration]	✓	parametric	61.0 ± 3.0	61.0 ± 2.1	8	60.3 ± 1.8	61.5 ± 2.0	6	0.334	1.022	0.085 [0, 0.354]
Swing Phase Duration [% stride duration]	✓	parametric	39.0 ± 3.0	39.0 ± 2.1	8	39.7 ± 1.8	38.5 ± 2.0	6	0.333	1.024	0.085 [0, 0.354]
Single Support Time [%]	✓	parametric	39.2 ± 2.9	39.0 ± 2.0	8	39.6 ± 2.0	38.6 ± 2.1	6	0.499	0.488	0.042 [0, 0.295]
Double Support Time [%]	✓	parametric	10.8 ± 2.9	10.9 ± 2.0	8	10.3 ± 1.9	11.5 ± 2.0	6	0.370	0.875	0.074 [0, 0.340]
Part 4 - Psychosocial Factors											
Quality of Life (QoL-AD) []	x	non-parametric	36.0 (5.8)	36.5 (10.3)	8	36.5 (7.3)	36.0 (3.0)	6	0.746	0.110	0.010 [0, 0.206]
DASS-21 - Depression []	x	non-parametric	4.5 (2.5)	2.5 (4.5)	8	3.0 (5.0)	3.0 (4.8)	6	0.822	0.053	0.005 [0, 0.167]
DASS-21 - Anxiety []	x	non-parametric	2.5 (2.8)	1.0 (1.25)	8	1.0 (0.75)	1.0 (1.5)	6	0.919	0.011	0.001 [0, 0.069]
DASS-21 - Stress []	x	non-parametric	5.0 (4.5)	4.0 (3.5)	8	3.0 (0.75)	4.5 (3.25)	6	0.335	1.016	0.085 [0, 0.353]
Part 5 - Heart Rate Variability											
mRR [ms]	x	non-parametric	804.0 (216.5)	737.0 (217.7)	6[3]	852.0 (136.0)	797.0 (100.0)	5[3]	0.508	0.481	0.057 [0, 0.294]
RMSSD [ms]	x	non-parametric	27.1 (40.0)	25.2 (41.5)	6[3]	8.3 (6.0)	6.1 (7.2)	5[3]	0.789	0.076	0.009 [0, 0.186]
pNN50 [%]	x	non-parametric	4.6 (37.4)	9.7 (26.5)	6[3]	0.0 (0.0)	0.0 (0.0)	5[3]	0.928	0.009	0.001 [0, 0.054]
HF [ms^2]	x	non-parametric	92.5 (793.6)	289.5 (557.3)	6[3]	23.0 (44.0)	9.0 (57.0)	5[3]	0.453	0.623	0.072 [0, 0.313]
HFnu [nu]	✓	parametric	55.1 ± 23.0	39.4 ± 29.7	6[3]	66.2 ± 23.5	57.8 ± 18.1	5[3]	0.412	0.750	0.086 [0, 0.327]
SD1 [ms]	x	non-parametric	19.2 (28.4)	17.85 (29.4)	6[3]	5.8 (4.3)	4.3 (5.1)	5[3]	0.789	0.076	0.009 [0, 0.186]
PNS-Index []	x	non-parametric	0.02 (1.06)	- 0.59 (1.65)	6[3]	- 1.04 (1.0)	- 1.35 (0.62)	5[3]	0.929	0.009	0.001 [0, 0.237]

6.5 Discussion

This study evaluated the feasibility, system usability, and acceptance of the 'Brain-IT' project and the 'Brain-IT' training concept - a newly developed training concept combining exergame-based motor-cognitive training and heart rate variability (HRV)-guided resonance breathing for the secondary prevention of mNCD. The results suggest that (1) the 'Brain-IT' project is feasible (with amendments to the study protocol that allow increasing the absolute recruitment rate); (2) the 'Brain-IT' training is feasible for older adults who have mNCD, indicated by acceptable adherence, compliance, and attrition rates. However, frequent occurrences of technical problems and difficulties in using the 'Senso Flex' training system were identified as barriers to performing the 'Brain-IT' training; (3) the 'Senso Flex' is usable as a means to implement the 'Brain-IT' training concept for older adults who have mNCD, indicated by an acceptable mean system usability score; (4) the 'Brain-IT' training was well-accepted by older adults who have mNCD, indicated by a high level of exergame enjoyment, increases in exergame enjoyment and internalization of training motivation with large effect sizes from the first to the last measurement, and an acceptable perceived usefulness; and (5) preliminary data on the effects of the 'Brain-IT' training are promising.

6.5.1 Feasibility

Recruitment

Our main difficulty in recruitment was the ability to find reliable and committed clinical collaboration partners. This may be explained by the highly competitive nature of research with individuals who have mNCD in Switzerland and/or the COVID-19 pandemic. As a result, not enough individuals could be reached out to, although the number of individuals who have m-MNCD in Switzerland is high [336]. Many of the individuals contacted by the study team participated in the study. Our relative recruitment rate is above average when compared to the literature [i.e., a median recruitment rate of 26 % (range: 3.4-59 %) was determined for exergame-based training in individuals who have mNCD in the studies analyzed in [42]]. This suggests that our study protocol is feasible without further adjustments with regard to the relative recruitment rate.

Adherence and compliance

Despite their conservative calculation, the adherence and compliance rates found in this study were higher compared to the average pooled adherence rates of comparable intervention studies [42, 44, 84, 86]. Previous (pilot) RCTs investigating exergame-based training in older adults who have mNCD on average found slightly lower adherence and compliance rates. In particular, adherence rates of 78 % (approximated by the reported average number of training sessions per week divided by the target training frequency of 5x/week) [276] and 79.2 % (calculated by dividing the number of played sessions vs. the number of planned sessions) [283] and compliance rates of 88.5 % (calculated by dividing total play duration vs. planned minimal training time) [283] and 55.5 % (calculated from reported exercise time divided by the defined activity goal) [337] were reported. The remaining studies reported training adherence [275, 278, 282] or compliance [275, 276, 278, 282] insufficiently. Overall, our results are in line with previous findings that adherence to exergame-based training is typically high in older adults who have m-MNCD [42, 44].

Most previous exergame-based [276, 283] or conventional [84, 86, 280] training studies including older adults who have mNCD and reporting adherence prescribed one-on-one supervision of training [84, 86, 280], or did not report supervision [276, 283], opposed to that we expected our participants to train partly independently. Therefore, participants had to remember and motivate themselves to do their training. They managed to do this extremely well, as adherence rates stayed high throughout the intervention period with gradually reduced supervision over time. This is promising because home-based and partly unsupervised training allows a time and cost-efficient way of training. Furthermore, it is preferred by older adults who have mNCD [45] and older adults in general [88, 338], and reduces barriers to exercise [45, 88]. Next to a lack of time and inability to travel to the training facility, difficulties in using technology are among the most prevalent reasons for discontinuing technology-based training programs [88]. Our good results in training adherence and compliance might also be because the 'Brain-IT' training concept with some of the exergames included in the training was purpose-developed specifically for older adults who have mNCD guided by the MIDE-Framework [57, 58]. As reported in more detail in the 'Brain-IT' training concept [58], the training concept included individual supervision (including telephone support of the study team in case of technical difficulties or comprehension problems), a familiarization phase of 2 weeks, was individually tailored, included visual and auditory feedback in real-time to enrich the game experience, and was designed to support to overcome known exercise barriers. Additionally, each participant was provided with an individually adapted training manual. All these elements are support strategies with theoretical underpinnings (programs based on behavior change theories) that may help promote training adherence and should therefore be considered when planning training concepts in older adults who have mNCD [91].

In the following iterative research step, further improvements regarding training adherence and compliance should be considered. Fifty percent of participants experienced technical problems (e.g., network errors, software problems, or difficulties in handling the exergame device), ranking as the second most common reason for non-adherence. Non-compliance was entirely explained by technical problems. An additional potentially preventable reason for non-adherence was comprehension problems at the beginning of the 'Brain-IT' training. These two issues have been identified in a qualitative study conducted in the first phase of the 'Brain-IT' project as key issues as well [45, 58]. Details of all identified issues together with suggestions on how to resolve these were communicated to the company providing the 'Senso Flex' after completing the qualitative study and again after completing this study. So far, we are unaware whether the technical problems and difficulties in handling the device were addressed. Importantly, we only reported technical problems that hindered participants from starting a training session in non-adherence. Occurrence of technical problems during training, however, was far more common and mainly included problems with the sensitivity of the sensors hindering interaction with the device and orientation problems on the device (i.e., participants unintentionally leave the middle plate because it is too small, is not properly marked on the 'Senso Flex', and participants do not notice the feedback to return to the middle plate on the screen). These technical problems did not result in early termination of the training session in most cases; however, they did lead to frustration among participants. This negatively influenced the will to continue using the system in future in some participants. Regarding the second key issue of comprehension problems, up to now, an instructional text is displayed before starting each game. However, individuals who have mNCD often have difficulties understanding written instructions and transferring these to the actual tasks. Therefore, more patient-friendly instructions (e.g., step-by-step

video instructions or interactive “trial-run” instructions that combine visual and verbal instructions) should be offered. [45] As the company providing the ‘Senso Flex’ has been unable to change this item, we have alternatively focused on practical demonstrations and provided each participant a detailed training manual that complements instructions provided by the exergame device. This solution is suboptimal because it requires participants to switch between the exergame device and the training manual while the training manual does not allow to offer the described more patient-friendly types of instructions. Future iterations should examine whether alternative hardware and software solutions provide more feasible options to implement the ‘Brain-IT’ training concept. To facilitate this process, we will modify the ‘Brain-IT’ training concept and add specific information that allows the training concept to be adapted to other hardware and software solutions. A possible solution to circumvent some of the technical problems would be the consideration of alternative peripherals. Recent research shows an increased use of camera-based systems and virtual or augmented reality headsets, which offer a wealth of new possibilities for optimizing these interventions [339].

Attrition

The attrition rate found in this study was similar to the average pooled attrition rate of comparable intervention studies [44, 86]. Previous (pilot) RCTs investigating exergame-based training in older adults who have mNCD also found similar attrition rates of 9 % [275, 337], 20 % [278, 282], and 55 % [277], or reported attrition insufficiently [283]. Reasons for discontinuing the training and/or dropping out in these studies included time reasons [277], inappropriate task difficulty [277], voluntary withdrawal [337], medical conditions unrelated to the training [277, 278], or reasons independent from the training [282]. In our study, similar reasons for dropping out were reported. One of the dropouts in our study would have been preventable with better communication with the recruitment partner. The respective recruiting partner was informed, and measures were taken to improve communication between recruiting partners and the study team.

6.5.2 Usability

We found a considerably lower system usability score compared to a similar pilot study with older people that found a mean SUS score of 83.6 ± 13.7 points. The latter study differed regarding participants' lower mean age (73.0 years), not having any cognitive impairment, and using the ‘Senso’ instead of the ‘Senso Flex’. Consistent with the results of this study, the lowest score was found in question four [256]. The fact that a substantial proportion of our participants reported needing technical support to use the system in our study is problematic for a home-based training system aimed to be used (partly) independently. This needs to be addressed in further iterative development steps. Study investigators supervising participants indicated that the need for technical support stems from the effort required to start up the system and start training and in the occurrence of technical problems. This is mirrored in the feedback of one participant in the semi-structured interviews and through the reported technical difficulties and comprehension problems. These issues were anticipated based on the results of our qualitative study [45]. To overcome these anticipated issues, we implemented support strategies specifically for the participants in the training group (as described in the Section *“Participant retention“*). Although these strategies were experienced as helpful by participants and should, therefore, be maintained in future studies, some further support should be considered. Because technical problems are in general overwhelming to individuals who have mNCD

[45], they need to be drastically reduced to improve system usability. This would potentially reduce participants' dependence on study personnel. Additionally, providing more patient-friendly instructions might help to reduce comprehension problems discussed in the Section *"Adherence and compliance"*.

6.5.3 Acceptance

Our findings on acceptance of our training are consistent with previous research showing that exergames may increase or enhance motivation to engage in rehabilitation activities [42]. Motivation (especially intrinsic motivation) is a key factor for promoting positive behavioral changes [43] (e.g., adherence to exercise) in older adults with or without cognitive impairment [194, 199, 200, 205, 291]. More autonomous forms of motivation refer to engagement in a task based on intrinsic motivators such as exercise enjoyment or personal importance to perform the exercises [43]. Intrinsic motivation of individuals who have mNCD can be mainly promoted by excitement, enjoyment, or fun at exergaming. These factors can be supported through specific game components and the feeling of being optimally challenged. Additionally, individuals who have mNCD are motivated by the perceived effectiveness of training. [45] This is in line with findings for HOA, which showed that older adults were motivated by perceived health effects as well as the joy of playing exergames [204]. Exercise enjoyment has been described as *"an optimal psychological state (i.e., flow) that leads to performing an activity primarily for its own sake and is associated with positive feeling state"* [340]. Based on our results, it seems fair to say that our interactive and participatory design and development process of the 'Brain-IT' training concept [58] resulted in an enjoyable training experience promoting internalization of training motivation and high levels of perceived usefulness. This observation might also explain the high levels of adherence to the training, because higher adherence rates to technology-based exercises may be largely explained by high levels of enjoyment [88]. However, despite the increase in motivation over time, we also observed a slight decrease in motivation after week 7. The study investigators who supervised participants indicated that this decline was mainly due to increasing frustration with technical problems. From participants' perspectives, solving the technical problems, improving the individualized adaptation of task demands, and adding a regular discussion of changes in performance are among the most important required modifications. A considerable proportion of participants would only like to continue training provided technical problems are drastically reduced, emphasizing the importance of addressing the issues.

Regarding improvements in the individualized adaptation of task demands, we relied on the exergame device's performance outcomes, as explained in detail in the 'Brain-IT' training concept [58]. However, this did not always work properly with the device used. The system offers an internal progression algorithm that theoretically allows to individually progress task demands in real-time according to these performance outcomes. However, this algorithm has not (yet) been scientifically validated [58] and was found unsuitable for individuals who have cognitive impairment [45]. Therefore, we relied on predefined progression rules based on visually analyzing performance curves, as described in more detail in the 'Brain-IT' training concept [58]. This approach worked well for games that were newly developed or adapted within the 'Brain-IT' project (mainly the games in the neurocognitive domain of learning and memory) because the games include precision parameters or provide a summed point score identical to validated cognitive assessments. For other games, we used mean reaction time [ms] to monitor performance over time as the other performance variables were found unsuitable [58]. However, reaction times were highly variable, making it difficult

to visually read out a performance plateau. Future research should focus on more reliable parameters, preferably with a strong background in sports science or neuroscience. Because such parameters are not available for most of the games currently offered on the 'Senso (Flex)', the games should either be adapted to meet these requirements or alternative hardware and software solutions should be developed and/or investigated to improve monitoring and individualized adaptation of task demands. Regarding a regular discussion of performance, further investigations are required to elaborate on the optimal solution for individuals who have mNCD. In our qualitative study, we have reported mixed findings on how to deal with performance feedback, because performance feedback can be motivating for some individuals whereas for others it may induce negative feelings by confronting them with their limitations. In case performance feedback is given (as is currently the case with the 'Senso (Flex)' system), it is imperative that the program presents not just a performance curve, ideally depicted as a rolling average rather than individual performance scores, but also provides a reason or explanation of changes in performance over time (which the company offering the 'Senso Flex' is not (yet) able to provide) [45].

6.5.4 Effects of the training

The observed medium effect on global cognition is slightly higher compared with pooled evidence of exergame-based training in older adults who have mNCD on global cognition, which reported small [35]-to-medium [75] effects favoring the intervention. Additionally, the observed medium effect size is slightly higher compared with pooled evidence of simultaneous motor-cognitive training with reported small [35, 62]-to-medium [73, 341] effect sizes. Most other secondary outcomes also point in the direction of favorable effects of the addition of the 'Brain-IT' training to usual care. Although these preliminary data must be interpreted with caution due to the limitations of our study, these results are in line with the literature pointing to the direction that favorable effects are achievable in cognitive ([42, 62, 75, 275, 276, 341-343], physical [42, 343], and psychosocial [343] functioning with exergame-based training in individuals who have mNCD. As a follow-up, the effectiveness of our 'Brain-IT' training concept is currently being investigated in an RCT [clinicaltrials.gov (NCT05387057); see study protocol [61]].

6.5.5 Limitations

The outcomes of this pilot RCT should be interpreted with caution considering the following limitations: First, the sample size was small. We stopped recruitment after reaching the planned minimum sample size of 18 participants because reaching out to potential study participants was the main difficulty in our study (as discussed in the Section Recruitment). Subsequently, there was one dropout in the intervention group at week 10 and one participant withdrew from the study during pre-measurement. As a result, the actual sample size is slightly below the recommended sample size for pilot or feasibility studies [330]. However, at the time when we included the 18th participant, it was evident that all remaining feasibility outcomes exceeded the quantitative thresholds for acceptable feasibility. Therefore, we decided to stop recruitment, evaluate all results, revise our 'Brain-IT' training concept as well as the study procedures, and start planning the next phase of our project (see [61] in line with [58]). Second, usual care activities were assessed by participants' self-report. To counteract possible biased information, the study team asked specific questions about whether participants engaged in typical usual care activities (as described in the Section *"Control group"*) and actively involved participants' proxies when collecting this information. Third, as part of usual care

activities, it was only assessed whether participants had a regular intake of medications. No further details were collected because the effects of the 'Brain-IT' training were only a secondary outcome of this study. However, for future studies investigating the effectiveness of the addition of the 'Brain-IT' concept to usual care, details on medication intake (i.e., type and dosage of medication) as well as changes in medication during the study are required and will be assessed [61]. Fourth, all preliminary data on the effects of the addition of the 'Brain-IT' training concept to usual care must be interpreted with caution because the statistical analysis for secondary outcomes was underpowered, groups were unbalanced, and the control group achieved better results in various tests during pre-measurements. In addition, because we investigated the addition of the 'Brain-IT' training to usual care, and because usual care activities were provided by the (memory) clinics where the participants were recruited, we were not able to standardize contact times, which may have affected some of our findings.

6.6 Conclusion

The 'Brain-IT' project is feasible provided the absolute recruitment rate can be increased in future studies. The feasibility and usability of the 'Brain-IT' training concept implemented with the 'Senso Flex' are acceptable. However, frequent occurrences of technical problems and difficulties in using the exergame training system were identified as barriers to performing the 'Brain-IT' training. To optimize the feasibility of the 'Brain-IT' training with the 'Senso Flex' device, improvements in hardware and software are necessary. In particular, the occurrence of technical problems must be drastically reduced. The device's software should be adapted to provide more patient-friendly instructions and more reliable performance parameters to optimize task comprehensibility as well as monitoring and individualized adaptation of task demands. Alternative hardware and software solutions should be developed and/or investigated to provide more feasible options for implementing 'Brain-IT' training. The 'Brain-IT' training itself was well-accepted by older adults who have mNCD. Therefore, the investigation of the effectiveness of the 'Brain-IT' training concept in a future RCT is warranted.

6.7 Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: https://doi.org/10.5281/zenodo.7428378.

6.8 Ethics statement

The studies involving humans were approved by ETH Zurich Ethics Committee ETH Zurich Office of Research Weinbergstrasse 11 WEC E 15/17 8092 Zürich. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

6.9 Author contributions

PM was responsible for the conception of the study under the supervision of EB. PM was responsible for participant recruitment, data collection, statistical analysis, and writing the manuscript. HP contributed to EEG data collection and analysis. All authors contributed to the revisions of the manuscript, read, and approved the submitted version of the manuscript.

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6.12 Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

6.13 Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2023.1163388/full#supplementary-material

6.14 Abbreviations

(S)AEs	(Serious) Adverse Events
AD	Alzheimer's Disease
ADAS-Cog	Alzheimer's Disease Assessment Scale-Cognitive Subscale

ANOVA	Analysis of Variance
ANCOVA	Analysis of Covariance
BREQ	Behavioral Regulation in Exercise Questionnaire
BMI	Body Mass Index
CERT	Consensus on Exercise Reporting Template
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus Disease 2019
DSB	Digit Span Backward
DSF	Digit Span Forward
DSM-5	Diagnostic and Statistical Manual of Mental Disorders 5th Edition
EEQ	Electroencephalography
EEQ	Exergame Enjoyment Questionnaire
F_{mean}	Mean Value of the Feasibility Outcome
FOPH	Federal Office of Public Health
HOA	Healthy Older Adults
HOTAP-A	HOTAP Picture-Sorting Test Part A
HRV	heart rate variability
ICD-XI	International Classification of Diseases 11th Revision (ICD-XI)
MCI	Mild Cognitive Impairment
MIDE	Multidisciplinary Iterative Design of Exergames
mNCD	mild Neurocognitive Disorder
m-MNCD	mild to Major Neurocognitive Disorder
MRT	Mental Rotation Task
PEBL	Psychology experiment building language
Qmci	Quick Mild Cognitive Impairment Screen

QoL-AD	Quality of Life-Alzheimer's Disease
QoL	Quality of Life
RCT	Randomized Controlled Trial
SDI	Self Determination Index
sMCI	screened for Mild Cognitive Impairment
SMD	Standardized Mean Difference
SUS	System Usability Scale
T1	First Threshold
T2	Second Threshold
TAP	Test of Attentional Performance
TAP Alertness	Subtest “Alertness” of the Test of Attentional Performance
TAP Go-NoGo	Subtest “Go-NoGo” of the Test of Attentional Performance
TAP Incompatibility	Subtest “Incompatibility” of the Test of Attentional Performance
TMT-A	Trail Making Test - Part A
TMT-B	Trail Making Test - Part B
vm-HRV	vagally mediated Heart Rate Variability
WMS-IV-LM	Subtest “Logical Memory” of the Wechsler Memory Scale - fourth edition
η^2_p	partial eta-squared

Chapter

7

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Paper 4:

Effectiveness of an Individualized Exergame-Based Motor-Cognitive Training Concept Targeted to Improve Cognitive Functioning in Older Adults With Mild Neurocognitive Disorder: Study Protocol for a Randomized Controlled Trial

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7.1 Abstract

Background: Simultaneous motor-cognitive training is considered promising for preventing the decline in cognitive functioning in older adults with mild neurocognitive disorder (mNCD) and can be highly motivating when applied in the form of exergaming. The literature points to opportunities for improvement in the application of exergames in individuals with mNCD by developing novel exergames and exergame-based training concepts that are specifically tailored to patients with mNCD and ensuring the implementation of effective training components.

Objective: This study systematically explores the effectiveness of a newly developed exergame-based motor-cognitive training concept (called 'Brain-IT') targeted to improve cognitive functioning in older adults with mNCD.

Methods: A 2-arm, parallel-group, single-blinded randomized controlled trial with a 1:1 allocation ratio (i.e., intervention: control), including 34 to 40 older adults with mNCD will be conducted between May 2022 and December 2023. The control group will proceed with the usual care provided by the (memory) clinics where the patients are recruited. The intervention group will perform a 12-week training intervention according to the 'Brain-IT' training concept, in addition to usual care. Global cognitive functioning will be assessed as the primary outcome. As secondary outcomes, domain-specific cognitive functioning, brain structure and function, spatiotemporal parameters of gait, instrumental activities of daily living, psychosocial factors, and resting cardiac vagal modulation will be assessed. Pre- and postintervention measurements will take place within 2 weeks before starting and after completing the intervention. A 2-way analysis of covariance or the Quade nonparametric analysis of covariance will be computed for all primary and secondary outcomes, with the premeasurement value as a covariate for the predicting group factor and the postmeasurement value as the outcome variable. To determine whether the effects are substantive, partial eta-squared (η^2_p) effect sizes will be calculated for all primary and secondary outcomes.

Results: Upon the initial submission of this study protocol, 13 patients were contacted by the study team. Four patients were included in the study, 2 were excluded because they were not eligible, and 7 were being informed about the study in detail. Of the 4 included patients, 2 already completed all premeasurements and were in week 2 of the intervention period. Data collection is expected to be completed by December 2023. A manuscript of the results will be submitted for publication in a peer-reviewed open-access journal in 2024.

Conclusions: This study contributes to the evidence base in the highly relevant area of preventing disability because of cognitive impairment, which has been declared a public health priority by the World Health Organization.

Trial Registration: ClinicalTrials.gov NCT05387057;
https://clinicaltrials.gov/ct2/show/NCT05387057

International Registered Report Identifier (IRRID): DERR1-10.2196/41173

7.2 Introduction

7.2.1 Background

Aging is typically accompanied by structural [254, 344] and functional [254, 345, 346] brain changes associated with a gradual decline in physical [347] and cognitive [344, 345, 348] abilities. Decline in cognitive functioning exists on a continuum from healthy aging to pathological conditions, such as 'mild cognitive impairment' (MCI) or 'dementia' [2, 7, 145]. MCI has evolved over the last decades [2] and was incorporated in the latest Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-V) and the International Classification of Diseases 11th Revision, as mild neurocognitive disorder (mNCD) [3-6]. Although slightly different definitions have been used in the literature, the core criteria remain [2, 7]. According to DSM-V, mNCD is characterized by: *"(A) Evidence of modest cognitive decline from a previous level of performance in one or more cognitive domains [...]; (B) cognitive deficits do not interfere with the capacity for independence in everyday activities [...]; (C) Cognitive deficits do not occur exclusively in the context of delirium. (D) Cognitive deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia)"* [5]. In individuals with mNCD, deterioration in episodic memory and executive function represent the most prevalent cognitive impairment [149] and are associated with structural [7, 349] and functional [7, 349, 350] brain changes. In addition to cognitive decline, individuals with mNCD may also experience problems in motor function [351, 352], impaired balance [352], a higher fall risk [351, 353], or difficulties in everyday functioning [143, 354, 355]. However, individuals with mNCD retain their capacity for independence in everyday activities [5].

In 2021, over 55 million people were living with major neurocognitive disorder (MNCD; also referred to as 'dementia' [12]) [1]. The pooled prevalence of mNCD increases with age and is estimated to be approximately 16 % [154], more than twice as high as the prevalence of MNCD [1, 356]. The global increase in life expectancy [357] and insufficient levels of physical activity [358] serve as important risk factors for cognitive decline [145, 153, 154, 169, 170] and are expected to boost the incidence and prevalence of mild to major neurocognitive disorders (MNCD). Moreover, individuals with mNCD are at an increased risk of developing dementia. The annual conversion rate of mNCD to MNCD is approximately 4.9 % in community settings and 9.6 % in specialist clinical settings [158]. Between 14 % (clinical population) and 31 % (community-based cohort) revert to normal cognitive function [160]. Nonetheless, the pooled progression rate is estimated to be 34 %, which is more than twice as high as the pooled reversion rate of 15 % [154]. Consequently, the worldwide prevalence of dementia is expected to nearly double over the next 20 years [356]. To counteract this development, the World Health Organization has declared the prevention of disabilities caused by cognitive impairment a public health priority [286].

Individuals with mNCD may represent an optimal target population for pharmacological and nonpharmacological interventions [7]. However, no pharmacological treatment that effectively decelerates or prevents the progression from mNCD to MNCD or decreases the impact of cognitive decline on functioning exists [159, 359-361]. The American Food and Drug Administration recently approved a new but controversial pharmacological agent (aducanumab) to treat individuals with mNCD due to Alzheimer disease (AD) [362, 363]. In Europe, Biogen Netherlands BV withdrew its application for marketing authorization of Aduhelm for the treatment of early stages of AD due to insufficient data [364]. Evidence for other pharmacological treatment options (e.g., cholinesterase

inhibitors, antihypertensive, anti-inflammatory, or lipid-lowering medication, or hormone therapies) and nutritional supplements is largely insufficient and does not support their use for improving cognitive performance, slowing down cognitive decline, or reducing the risk of developing dementia [129, 180-184]. Several nonpharmacological interventions, such as lifestyle changes that target modifiable risk factors such as diabetes mellitus [11, 168, 365], hypertension [11, 168, 365], obesity [11], depression [11, 242], physical [11, 169] or cognitive inactivity [11, 170], or smoking [11, 287], may hold promise for slowing down cognitive decline or reducing the risk of developing dementia [14]. It has been estimated that up to half of the world's cases of AD, the leading cause of m-MNCDs [5] - may be attributable to these 7 potentially modifiable risk factors [11]. A 10 % - 25 % reduction in these risk factors is estimated to reduce AD prevalence by up to 3 million individual cases worldwide [11]. As physical inactivity is associated with most other modifiable risk factors, an increase in physical activity is believed to have an impact on m-MNCD prevalence [11]. In addition, the theory of cognitive reserve suggests that, *"education and mental stimulation throughout life may lower risk of AD and dementia by helping to build a 'cognitive reserve' that enables individuals to continue functioning at a 'normal' level despite experiencing neurodegenerative changes"* [11, 25, 26]. According to recent network meta-analyses, nonpharmacological interventions targeting modifiable risk factors, such as physical and cognitive exercises, outperform pharmacological therapies [113, 366]. It can be hypothesized that a shift from pharmacological to nonpharmacological interventions with multi-domain treatment strategies, including physical exercises and cognitive stimulation, may lead to better results [145, 159].

Aerobic training [84, 127, 128] and multicomponent physical exercises [120, 127, 128] are beneficial exercise modes for cognition in patients with NCDs, whereas cognitively engaging exercises appear to have the strongest effect on cognition [72, 73]. Combined motor-cognitive training seems to be the most effective type of training for improving cognitive functioning in older adults with mNCD [35, 73, 288, 289]. These findings are consistent with the 'guided-plasticity facilitation' framework [32-34]: physical exercise enhances brain metabolism and promotes neuroplastic processes, whereas these changes in brain plasticity are guided by cognitive stimulation [32, 33, 70]. Combined motor-cognitive training can be categorized into 'sequential', 'simultaneous-additional', and 'simultaneous-incorporated' motor-cognitive training [34]. Incorporating cognitive tasks into motor tasks is more beneficial than "classical" dual-task approaches or sequential motor-cognitive training in terms of stabilizing neuroplasticity effects [34].

Technological innovations (e.g., exergames) provide new options to engage older adults with mNCD in (simultaneous-incorporated) motor-cognitive training [39]. *"Exergaming is defined as technology-driven physical activities, such as video game play, that requires participants to be physically active or exercise in order to play the game"* [40]. When exergames are specifically designed and implemented with a purpose beyond play, it is a 'serious game' [65, 66]. Exergame-based interventions are highly accepted in individuals with mNCD and increase training adherence and engagement by facilitating training motivation and satisfaction [42]. Furthermore, exergaming offers *"the unique opportunity for patients to interact in an enriched environment, providing structured, scalable training opportunities augmented by multi-sensory feedback to enhance skill learning and neuroplasticity through repeated practice"* [41], an additional advantage compared with conventional motor-cognitive training. There are consistent positive effects on cognitive functioning, favoring exergaming in people with m-MNCD [42]. Nonetheless, it is currently difficult to draw reliable

conclusions about the effectiveness of exergaming in preventing and treating neurocognitive disorders because of the substantial variations in exergame-based training [42]. Gavelin et al (2021) synthesized smaller effects on cognitive outcomes for exergaming (standardized mean difference [SMD] 0.13, 95 % CI -0.22 to 0.44) compared with sequential (SMD 0.25, 95 % CI -0.05 to 0.55) or simultaneous (SMD 0.45, 95 % CI 0.11 to 0.78) motor-cognitive training in individuals with mNCD compared with passive control groups [35]. To the best of our knowledge, 11 studies have investigated exergame-based motor-cognitive training in older adults with mNCD [270, 275-284]. Most of these studies used commercially available exergame systems [270, 275-280], where the training content was not specifically developed for individuals with mNCD. In addition, only one of these studies applied training that individually prescribed content based on a patient's cognitive abilities [280]. This may explain the small effect findings of Gavelin et al (2021), and points to opportunities for improvement in the application of exergames in individuals with mNCD by developing novel exergames and exergame-based training concepts that ensure the implementation of effective training components specifically tailored to the requirements and needs of individuals with mNCD [45]. It seems fair to state that purpose-developed exergames and exergame-based training concepts specifically targeting individuals with mNCD and implementing effective training components will have larger effects on individuals with mNCD.

7.2.2 Prior Work

We developed an exergame-based motor-cognitive training concept ('Brain-IT') specifically for older adults with mNCD. It was developed using the *"Multidisciplinary Iterative Design of Exergames: A Framework for Supporting the Design section, Development, and Evaluation of Exergames for Health"* [57]. The target group, therapists, and experts from different fields were involved in the development process to ensure that the training met the requirements and needs of older adults with mNCD and to foster the usability and acceptance of the approach in "real life." This interactive and participatory design and development process allowed the identification of the key requirements for exergame design as well as the training characteristics. These formed the basis for determining the components of the resulting 'Brain-IT' training concept. It ensures the implementation of effective training components and is specifically tailored to the requirements and needs of older adults with mNCD. A detailed description of this design and development process is outlined in a previously published methodological paper that contains our complete training concept with sufficient details to allow full replication [58].

The original 'Brain-IT' training concept was already shown to be feasible, usable, and highly accepted in our pilot feasibility randomized controlled trial (RCT), including a small sample of older adults with mNCD (n = 18) [60]. Minor modifications were incorporated to further optimize the 'Brain-IT' training concept, making it applicable for the systematic evaluation of effectiveness in samples of older adults with mNCD.

7.2.3 Explanation and Choice of Comparators

According to a recent systematic review summarizing worldwide available clinical practice guidelines and consensus statements, recommendations for the treatment and management of individuals with mNCD can be classified into 4 categories: interventions for risk reduction, pharmacological interventions, nonpharmacologic interventions, and counseling. Recommendations for

nonpharmacological interventions mainly include physical and cognitive activity interventions; however, the specific training characteristics (e.g., frequency, intensity, type, volume, and progression) are not specified. [8]

In line with these recommendations, in Switzerland, usual care for mNCD typically includes treating medical conditions other than mNCD (e.g., diabetes mellitus and depressive symptoms), controlling comorbidities (e.g., hypertension and obesity), and managing risk factors (e.g., smoking habits and physical and cognitive inactivity). In this regard, usual care may include medication, recommendations for changing lifestyle habits (e.g., living a cognitively, physically, and socially active life), physiotherapy to treat specific health problems, such as back pain or mobility problems, occupational therapy, or day clinic visits. This justifies the selection of usual care as the control intervention.

7.2.4 Objectives and Hypotheses

This study explores the effectiveness of the 'Brain-IT' training in improving global cognitive functioning in older adults with mNCD. With this, we aim to obtain a sufficiently precise estimate of the treatment effect to minimize the sample size needed for a future full-scale RCT.

Null Hypothesis (H_0): In older adults with mNCD, the addition of the 'Brain-IT' training to usual care has no significant effect on global cognitive functioning compared with usual care.

Alternative Hypothesis (H_A): In older adults with mNCD, the addition of the 'Brain-IT' training to usual care results in differing effects on global cognitive functioning compared with usual care.

As secondary objectives, the effects of the 'Brain-IT' training on (a) domain-specific cognitive functioning (i.e., learning and memory, complex attention, executive function, and visuospatial skills), (b) brain structure and function, (c) spatiotemporal parameters of gait, (d) instrumental activities of daily living (IADL), and (e) psychosocial factors (i.e., QoL [quality of life], and levels of depression, anxiety, and stress), and (f) cardiac vagal modulation (i.e., resting vagally-mediated heart rate variability [vm-HRV]) in older adults with mNCD as compared with usual care will be explored. (B) Brain structure and function will be evaluated to explore the possible underlying neural changes in training in relation to adaptations in cognitive performance. The following hypotheses are formulated for the remaining outcomes:

Null Hypothesis (H0): In older adults with mNCD, the addition of the 'Brain-IT' training to usual care has no significant effect on (a) domain-specific cognitive functioning, (c) spatiotemporal parameters of gait, (d) IADL and (e) psychosocial factors (i.e., QoL, and levels of depression, anxiety, stress), and (f) cardiac vagal modulation (resting vm-HRV) compared with usual care.

Alternative Hypothesis (HA): In older adults with mNCD, the addition the 'Brain-IT' training to usual care results in differing effects on (a) domain-specific cognitive functioning, (c) spatiotemporal parameters of gait, (d) IADL, (e)

psychosocial factors (i.e., QoL, and levels of depression, anxiety, and stress), and (f) cardiac vagal modulation (resting vm-HRV) compared with usual care.

The rationale and description of the specific hypotheses for (c) spatiotemporal parameters of gait are explained in more detail in the section *"Methods - Outcomes - Secondary Outcomes - Spatiotemporal Parameters of Gait"*.

7.3 Methods

This study protocol (version 1.0; July 20, 2022) was developed in accordance with established guidelines from the *"SPIRIT 2013 Statement: Defining Standard Protocol Items for Clinical Trials"* [367, 368] (see the checklist in Multimedia Appendix 1).

7.3.1 Ethics Approval

All the study procedures will be performed in accordance with the Declaration of Helsinki. The study protocol was approved by the Ethics Committees of Zurich and Eastern Switzerland (EK-2022-00386).

7.3.2 Trial Design and Study Setting

A 2-arm, prospective, parallel-group, single-blinded (i.e., outcome evaluator of pre- and postintervention measurements blinded to group allocation) RCT with a 1:1 allocation ratio (i.e., intervention: control), including 34 to 40 older adults with mNCD, will be conducted between May 2022 and December 2023. The control group will proceed with usual care as provided by the (memory) clinics where the patients are recruited, while the intervention group will perform a 12-week training intervention according to the 'Brain-IT' training concept in addition to usual care (see section *"Methods - Interventions"*). The study was registered at clinicaltrials.gov before the start of patient recruitment (NCT05387057; date of registration: May 18, 2022; see Table 7-1 for details) and will be reported according to *"The Consolidated Standards of Reporting Trials (CONSORT) 2010 statement"* [369] and elaboration paper [370]. The study setup is multicentric (Zurich and St. Gallen) and national (Switzerland).

Table 7-1: Overview of trial registration data

Data category	Information
Primary registry and trial identifying number	ClinicalTrials.gov; NCT05387057
Date of registration in primary registry	18 May, 2022
Secondary identifying numbers	N/A
Source(s) of monetary or material support	Stiftung Synapsis - Demenz Forschung Schweiz
Sponsor-Investigator	Prof. Dr. Eling D. de Bruin Laboratory of Motor Control and Learning Institute of Human Movement Sciences and Sport ETH Zurich Leopold-Ruzicka-Weg 4 CH-8093 Zurich eling.debruin@hest.ethz.ch

	AND Department of Health Eastern Switzerland University of Applied Sciences Vadianstrasse 29 CH-9000 St. Gallen eling.debruin@ost.ch
Contact for public queries	Patrick Manser; Laboratory of Motor Control and Learning - Institute of Human Movement Sciences and Sport, ETH Zurich, Zurich, Switzerland; patrick.manser@hest.ethz.ch
Contact for scientific queries	Patrick Manser; Laboratory of Motor Control and Learning - Institute of Human Movement Sciences and Sport, ETH Zurich, Zurich, Switzerland; patrick.manser@hest.ethz.ch
Public title	Effectiveness of a Novel Exergame-Based Training Concept for Older Adults with Mild Neurocognitive Disorder
Scientific title	Effectiveness of an Individualized Exergame-based Motor-Cognitive Training Concept Targeted to Improve Cognitive Functioning in Older Adults with Mild Neurocognitive Disorder - A Randomized Controlled Trial
Countries of recruitment	Switzerland
Health condition(s) or problem(s) studied	Older adults with mild Neurocognitive Disorder
Intervention(s)	Control Group: The control group will proceed with usual care as provided by the (memory) clinics where the patients are recruited. Intervention Group: Participants in the intervention group will perform a twelve-week training intervention according to the newly developed 'Brain-IT' training concept in addition to their usual care.
Key inclusion and exclusion criteria	Key Inclusion criteria: • (1 = mNCD) clinical diagnosis of 'Mild Neurocognitive Disorder' OR (2 = sMCI) patients screened for mild cognitive impairment (sMCI) • German speaking • able to stand at least for 10 min without assistance Exclusion criteria: • mobility impairments that prevent experiment participation • presence of additional, clinically relevant (i.e. acute and/or symptomatic) neurological disorders • presence of any other unstable or uncontrolled diseases (e.g. uncontrolled high blood pressure, progressing or terminal cancer)
Study type	Study Type: Interventional Primary Purpose: Prevention Study Phase: N/A Interventional Study Model: Randomized, Parallel Assignment Masking: Single blind
Date of first enrolment	22 June 2022
Target sample size	40
Recruitment status	Recruiting
Primary outcome(s)	Changes in global cognitive functioning [Time Frame: Both, the pre- and the post-measurements of the primary outcome measurement will take place within two weeks prior to starting or after completing the intervention.]

Key secondary outcomes	• Changes in Learning and Memory • Changes in Complex Attention • Changes in Executive Function • Changes in Visuospatial Skills • Changes in Brain Structure and Function • Changes in Spatiotemporal Gait Parameters • Changes in Instrumental Activities of Daily Living • Changes in Psychosocial Factors • Changes in vagally-mediated Heart Rate Variability For all secondary outcomes: [Time Frame: Both, the pre- and the post-measurements of the primary outcome measurement will take place within two weeks prior to starting or after completing the intervention.]

After recruitment and providing written informed consent (see section *"Methods - Recruitment"*), participants will be screened on eligibility (see section *"Methods - Eligibility Criteria"*), and premeasurements will be scheduled for all eligible participants. Pre- and postintervention measurements will take place within 2 weeks before starting and after completing the intervention. For participants recruited in Zurich, preintervention measurements will take place at ETH Hönggerberg (Robert-Gnehm-Platz 1, CH-8093 Zurich). For participants recruited in St. Gallen, premeasurements will take place at the Eastern Switzerland University of Applied Sciences (Vadianstrasse 29, CH-9000 St Gallen). The measurements will take approximately 90 minutes. For all participants with no contraindications to magnetic resonance imaging (MRI), an additional appointment to conduct an MRI scan (duration: approximately 1 hour [including preparation]) at University Hospital Zurich (Rämistrasse 100, CH-8006 Zurich) will be scheduled. All measurements will be led by 2 investigators from our research team trained in the application of the measurement techniques and protocols. Pre- and postintervention measurements will be scheduled to occur at approximately the same time of the day (± 2 h) for each participant. To minimize the influence of transient confounding effects on HRV, all participants will additionally be instructed verbally and in writing to follow a normal sleep routine the day before the experiment, to avoid intense physical activity and alcohol consumption within 24 hours before measurements, and to refrain from coffee- or caffeinated drinks as well as food consumption at least 2 hours before measurements [295]. After completing premeasurements, participants will be randomly allocated to the intervention or control group and will be instructed about their respective intervention procedures (see section *"Methods - Interventions"*). For participants in the intervention group, the exergame device will be installed in their homes; they will receive safety instructions and will be familiarized with the exergame training system. Subsequently, the study intervention will be started (see section *"Methods - Interventions - Intervention Group"*). After completing the 12-week intervention period, postintervention measurements will be performed for both groups. No compensation will be granted to the participants, but detailed feedback on individual performance as well as the study outcomes in general will be provided at the end of the trial. Figure 7-1 summarizes the study procedures.

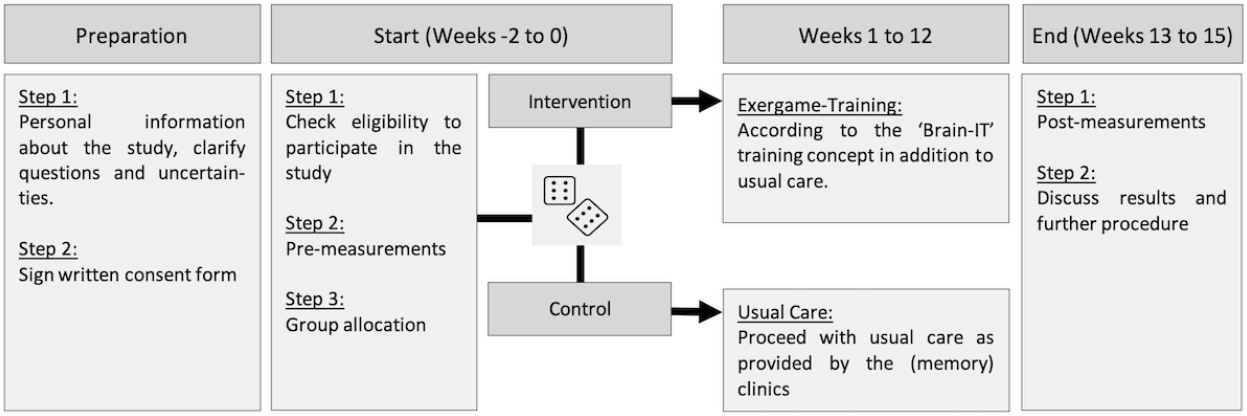

Figure 7-1: Graphical overview of the study procedures. The cubes are used to illustrate the randomization process (variable block randomization (i.e., block sizes = 4, 6, 8) with a 1:1 allocation ratio stratified by sex and per institute (study center), as described in section *"Methods - Randomization"*).

7.3.3 Recruitment

Older adults with mNCD will be recruited between May 2022 and September 2023 in collaboration with (memory) clinics in a larger area of Zurich and St. Gallen. Suitable patients will either be identified from medical records and patient registries of (memory) clinics, or from recent diagnostics performed by medical doctors or therapists authorized to search for medical records. Alternatively, suitable patients will be identified by an informant (i.e., health care professionals) based on suspicion of MCI in one of their patients (see *"Methods - Eligibility Criteria"* section). Identified patients will be verbally informed about the study and will receive leaflets by their physicians or therapists containing key information about study participation and researchers' contact details. If patients are interested in being informed about the study in detail, they will be asked to provide consent to share their contact details with the research team and will be contacted by phone or email by a trained investigator of the study team. In case of initial interest in participating in the study, all interested subjects will be fully informed about the study procedures in-person (at the interested persons' home or at one of the study centers, depending on their preferences) by providing verbal explanations and an information sheet. After sufficient time for consideration (i.e., at least 24 hours after handing out the study information sheet, but on average around 1 week), suitable patients willing to participate in the study will provide written informed consent in a second in-person meeting with one of the trained investigators of the study team at the home of the interested persons or at one of the study centers. After providing written informed consent, participants will be fully screened for eligibility (see section *"Methods—Eligibility Criteria"*), and premeasurements will be scheduled.

7.3.4 Eligibility Criteria

All eligibility criteria are detailed in Table 7-2.

Table 7-2: Description of all eligibility criteria.

Abbreviations: Covid-19, Coronavirus Disease 2019; DSM-5®, Diagnostic and Statistical Manual of Mental Disorders 5th Edition, ICD-XI, International Classification of Diseases 11th Revision; mNCD, mild neurocognitive disorder; Qmci, Quick Mild Cognitive Impairment Screen; (s)MCI, (screened for) mild cognitive impairment

Inclusion criteria	Exclusion criteria
Participants fulfilling all the following inclusion criteria were eligible:	The presence of any of the following criteria led to exclusion:
• (1 = mNCD) clinical diagnosis of 'mNCD' according to ICD-XI [6] or DSM-5® [5]) OR (2 = sMCI) patients 'screened for MCI' (sMCI) according to the following criteria: (a) informant (i.e. healthcare professional)-based suspicion of MCI confirmed by (b) an objective screening of MCI based on the German version of the using the Qmci [251] with (b1) a recommended cut-off score for cognitive impairment (MCI or dementia) of < 62/100 [259], while (b2) not falling below the cut-off score for dementia (i.e. < 45/100 [259]). • German speaking • able to stand at least for 10 min without assistance	• mobility impairments (i.e. gait, balance) that prevent experiment participation • presence of additional, clinically relevant (i.e. acute and/or symptomatic) neurological disorders (i.e. epilepsy, stroke, multiple sclerosis, Parkinson's disease, brain tumors, or traumatic disorders of the nervous system) • presence of any other unstable or uncontrolled diseases (e.g. uncontrolled high blood pressure, progressing or terminal cancer) Covid-19 specific risk factors (according to the Swiss Federal Office of Public Health) are additional exclusion criteria. In case of Covid-19 specific exclusion criteria, participation in the study will only be allowed when the patients' treating physician provides written informed consent allowing participation in the study despite the presence of Covid-19 specific exclusion criteria. Covid-19 specific exclusion criteria include: • high blood pressure (self-reported; systolic ≥ 140 mmHg and/or Diastolic ≥ 90 mmHg) • Chronic respiratory condition • uncontrolled type 2 Diabetes • Condition or therapy that weakens the immune system • unstable Cardiovascular Disease • Cancer (present and/or under treatment) • Serious obesity (body mass index ≥ 40 kg/m^2)

7.3.5 Interventions

Control Group

The control group will proceed with the usual care provided by the (memory) clinics where the patients are recruited. As described in section *"Introduction - Choice of comparators"* and based on clinical practice guidelines [8], in Switzerland, usual care is highly individual, varies between (memory) clinics where patients are recruited, and it is unclear whether patients comply with the recommendations of their clinicians. Therefore, details about all structured or guided usual care activities or both, as well as medication intake, will be assessed in both the intervention and control groups. If there are relevant between-group differences in usual care, these differences will be accounted for in the analysis and discussion of results.

Intervention Group

Participants in the intervention group will perform a 12-week training intervention in addition to their usual care (as provided by the [memory] clinics where patients were recruited). The training will be prescribed according our 'Brain-IT' training concept. This motor-cognitive training concept represents

a guideline for applying exergame-based motor-cognitive training by standardizing the training characteristics (e.g., training frequency, intensity, and duration) as well as the structure and content of the training, whereas the exergame device and the specific games used within each of the defined neurocognitive domains can be replaced by alternative exergames. In this project, our training concept was implemented using the 'Senso (Flex)' (Dividat AG). This platform was found to be suitable for the 'Brain-IT' training [45] and is a widely used means for motor-cognitive training within geriatric populations, physiotherapy, and rehabilitation in Switzerland. The original 'Brain-IT' training concept has recently been published with sufficient detail about the exergame components as well as the exercise and training characteristics (i.e., including all predefined levels of task demands as well as the detailed progression rules) to allow full replication (i.e., consider supplementary file 3 of [58]). Some minor modifications were implemented in the 'Brain-IT' training concept for use in this study, based on the findings of our pilot feasibility RCT [60]. This will be complemented in cases in which suitable new games become available throughout the study. The final (modified) 'Brain-IT' training concept will be published with the manuscript reporting the results of this study, and will additionally provide specific information that would theoretically allow adaptation of the training to other hardware and software solutions. To ensure replicability, the 'Brain-IT' training concept was planned and will be reported using the Consensus on Exercise Reporting Template [238].

For an overview, the 'Brain-IT' training concept consists of individually adapted multidomain exergame-based simultaneous motor-cognitive training with incorporated cognitive tasks that is adopted with a deficit-oriented focus on the neurocognitive domains of (1) learning and memory, (2) executive function, (3) complex attention, and (4) visuospatial skills. Each participant is instructed to train 5 times per week for 24 minutes per session, resulting in a weekly training volume of 120 minutes. All training sessions are planned to take place at participant's homes using the 'Senso Flex' hardware (Dividat AG; CE certification pending; see left side of Figure 7-2). The 'Senso Flex' is a home-based version of the 'Senso' (Dividat AG; CE certification; see right side of Figure 2). It consists of a 1.11×0.99 m rollable mat that is plugged into a portable computer and a frontal television (or other screen) at home. Both systems divide the pressure-sensitive stepping area into five fields: (1) center (home position), (2) front, (3) right, (4) back, and (5) left. The device detects the participants' position and timing of movements to interact with different game scenarios programmed in the training software. Weight shifting, walking on the spot, and steps in 4 directions (i.e., front, right, back, and left) enable interaction with and control of the exergame scenarios displayed on a frontal screen. Visual, auditory, and somatosensory (vibrating platform; only available on the 'Senso') feedback is provided in real time to enrich the game experience. Various games are available for training different neurocognitive domains (more details on how the device is implemented in our training concept have been provided [58]).

Adherence to the training will be monitored for the intervention group (i.e., exergame training; see section *"Outcomes - Other Outcomes - intervention group")*, and participants will be actively motivated and reminded to adhere to the training by the person responsible for supervision and correspondence with the respective study participant. Upon the request of participants, training can be paused for a maximum of 2 weeks (e.g., because of holidays).

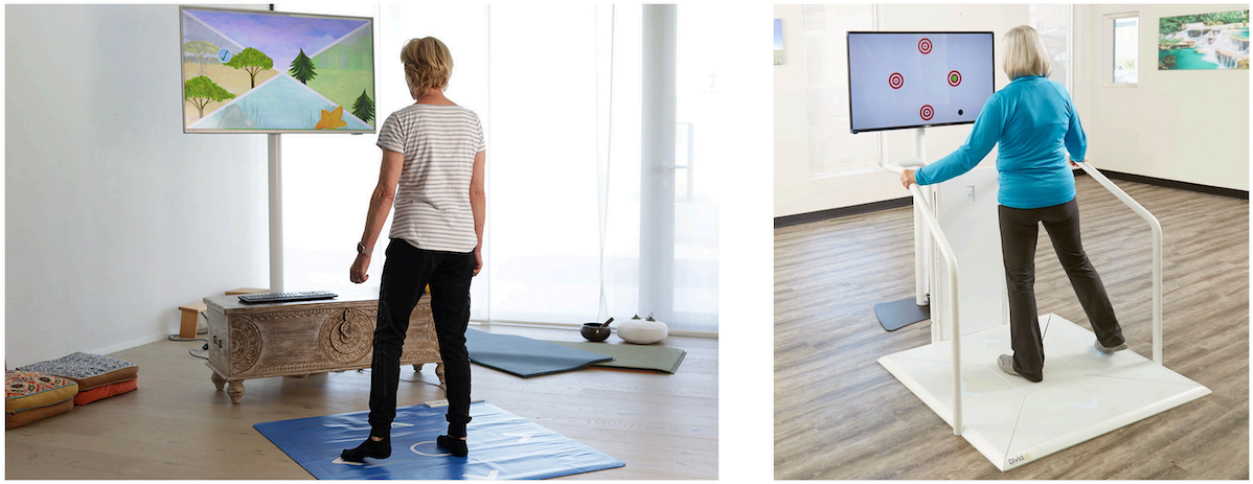

Figure 7-2: Exergame Device used as means to implement the 'Brain-IT' training concept in this study: 'Senso Flex' for home-based use (left side) and its stationary version ('Senso') for stationary use in physiotherapies, nursing homes, or rehabilitation clinics (right side). Photos provided by Dividat AG.

7.3.6 Outcomes

Overview

To ensure comparability of the study outcomes, global cognitive functioning will be assessed as the primary outcome. As secondary outcomes, domain-specific assessments evaluating the key neurocognitive domains (as defined in [3] in line with DSM-V [5] and according to recommendations [7]) of (1) learning and memory; (2) complex attention; (3) executive function; and (4) visuospatial skills, as well as brain structure and function, spatiotemporal parameters of gait, IADL, psychosocial factors (i.e., QoL, and levels of depression, anxiety, and stress), and cardiac vagal modulation (resting vm-HRV) will be assessed. Table 7-3 provides an overview of all endpoints.

Table 7-3: Overview of all primary and secondary outcome measures, outcome variables and interpretation guide.
↑ = higher values/an increase over time indicate better functioning/improvement in the respective study endpoint
↓ = lower values/a decrease over time indicate better functioning/improvement in the respective study endpoint

Abbreviations: PEBL, Psychology experiment building language; (f)MRI, (functional) magnetic resonance imaging; IADL = instrumental activities of daily living; vm-HRV = vagally-mediated heart rate variability

Outcome Measures		Outcome Variables	Interpretation Guide
Primary	Global Cognitive Functioning		
	Quick Mild Cognitive Impairment Screen [251, 310]	total point score []	improvement = ↑
Secondary	Learning and Memory		
	Subtest 'logical memory' of the Wechsler Memory Scale - fourth edition [311, 312]	total point score part 1 - free recall []	improvement = ↑
		total point score part 2 - free recall []	improvement = ↑
		total point score part 2 - recognition []	improvement = ↑
	PEBL Digit Span Forward [313-315]	total point score []	improvement = ↑
		maximum span []	improvement = ↑

Complex Attention		
PEBL Trail Making Test - Part A [313]	completion time [s]	improvement = ↓
	number of errors []	improvement = ↓
Subtest 'Go-NoGo' of the Test of Attentional Performance [316]	median reaction time [ms]	improvement = ↓
	number of errors []	improvement = ↓
Executive Function		
HOTAP picture-sorting test part A [317]	combi score (i.e. sum of the points divided by the time they needed to arrange the cards) [points · min^{-1}]	improvement = ↑
PEBL Digit Span Backward [313-315]	total point score []	improvement = ↑
	maximum span []	improvement = ↑
PEBL Trail Making Test - Part B [313, 315]	completion time [s]	improvement = ↓
	number of errors []	improvement = ↓
Visuospatial Skills		
PEBL Mental Rotation Task [313, 315, 318]	median reaction time of correct answered trials [ms]	improvement = ↓
	performance (number of correct answered trials) []	improvement = ↑
Brain Structure and Function		
3D isotropic T1-weighted MRI scan	grey matter volume of defined key regions of interest [mm^3]	improvement = ↑
	white matter volume of defined key regions of interest [mm^3]	improvement = ↑
Diffusion Tensor Imaging MRI scan	mean diffusivity of defined key regions of interest []	improvement = ↓
	Fractional anisotropy of defined key regions of interest []	improvement = ↑
Resting State T*2-weighted Blood Oxygen Level-Dependent fMRI	Individual functional connectivity maps between the hippocampal seed and the defined key regions of interest []	improvement = ↑
Task-based T*2-weighted Blood Oxygen Level-Dependent fMRI	Individual functional connectivity maps between the hippocampal seed and the defined key regions of interest []	improvement = ↑
Spatiotemporal Parameters of Gait		
Instrumented gait analysis using a figure-8 walking path [320] at preferred walking speed using BTS G-WALK® (BTS Bioengineering S.p.A., Garbagnate Milanese, Italy) inertial sensor attached with semi-elastic belt to the lower back of the participant.	walking speed [m · s^{-1}]	improvement = ↑
	stride duration [ms]	improvement = ↓
	stride length [cm]	improvement = ↑
	stance phase duration [ms]	improvement = ↓
	swing time [ms]	improvement = ↓
	single support time [ms]	improvement = ↓
	double support time [ms]	improvement = ↓
Instrumental Activities of Daily Living (IADL)		
Amsterdam IADL Questionnaire [371]	T- score []	improvement = ↑
Psychosocial Factors		
Quality of Life-Alzheimer's Disease [321-323]	Overall Score []	improvement = ↑
Depression, Anxiety and Stress Scale-21 [324-328]	Overall Score - Subscale Depression []	improvement = ↓
	Overall Score - Subscale Anxiety []	improvement = ↓

		Overall Score - Subscale Stress []	improvement = ↓
	Resting vagally-mediated Heart Rate Variability		
	5 min resting vm-HRV resting measurement with heart rate monitor (Polar M430) and sensor (Polar H10) analyzed using Kubios HRV Premium (Kubios Oy, Kuopio, Finland, version 3.4) [329]	mean R-R time interval [ms]	improvement = ↑
		Root Mean Square of Successive RR interval differences []	improvement = ↑
		percentage of successive RR intervals that differ by more than 50 ms [%]	improvement = ↑
		absolute power of the high-frequency (0.15 - 0.4 Hz) band [ms^2]	improvement = ↑
		relative power of the high-frequency (0.15 - 0.4 Hz) band [nu]	improvement = ↑
		Poincaré plot standard deviation perpendicular to the line of identity [ms]	improvement = ↑
		Parasympathetic Nervous System Tone Index []	improvement = ↑

Primary Outcome

The German version of the quick mild cognitive impairment (Qmci) screen will be used to assess global cognitive functioning [251, 310]. The Qmci has been validated against the standardized Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog) [251, 372], which is considered the gold standard for assessing the efficacy of antidementia treatments [373-375]. The Qmci was shown to *"correlate strongly, significantly and correspondingly over time to the standardized ADAS-cog and that both are equally sensitive with similar responsiveness to deterioration over time"* [372], *"suggesting that the Qmci could be substituted for a more detailed neuropsychological instrument in clinical trials"* [251, 372]. Furthermore, it is accurate in differentiating mNCD from normal cognition and MNCD [372]. In this regard, it has also been externally validated and has shown a higher level of accuracy, sensitivity, and specificity than commonly used tests such as the (Standardised) Mini Mental State Exam ([S]MMSE) and the Montreal Cognitive Assessment for detecting cognitive impairment (MCI and dementia) [376]. In comparison to the (S)MMSE and Montreal Cognitive Assessment, the Qmci includes a more detailed scoring system and a logical memory task that allows the Qmci to detect more subtle cognitive abnormalities and avoid ceiling effects [376]. Qmci was scored as the point rate out of a maximum score of 100. It consists of 6 subtests: orientation (10 points), registration (5 points), clock drawing (15 points), delayed recall (20 points), verbal fluency (20 points), and logical memory (30 points) [310, 377]. Qmci will be administered and evaluated according to published guidelines [310].

To the best of our knowledge, the smallest unit of clinically meaningful change has not yet been determined for the Qmci. However, changes in Qmci scores were very similar to changes in standardized ADAS-cog scores. Longitudinal data of more than 360 patients with m-MNCD were analyzed for responsiveness of the Qmci and the standardized ADAS-cog [378] by calculating standardized response mean from baseline to scores obtained at 1, 3, 6, 9, and 12 months. The mean change between months 1 and 12 was 5 points (SD 7.56) for the standardized ADAS-cog scores, and 5.41 points (SD 10.02) for the Qmci. The paired-samples t test showed no statistically significant difference in standardized response means for standardized ADAS-cog and Qmci (t_{357}=0.32; p = 0.75) [372]. Therefore, it is anticipated that the smallest units of clinically meaningful changes between these 2 measures are similar. For the standardized ADAS-cog, the minimal clinically relevant change is estimated to be 3 points for individuals with mNCD compared with ≥4 points based on previous recommendations made by a consensus committee of the Food and Drug

Administration for patients in more advanced stages [379, 380]. Therefore, it is assumed that a change of ≥ 3 points in the Qmci score can be regarded as a clinically meaningful change.

Secondary Outcomes

Learning and Memory

Learning and memory will be assessed using the German version of the subtests 'logical memory' of the Wechsler Memory Scale - fourth edition (WMS-IV-LM) [311, 312] and a computerized version of the digit span forward (DSF) test (psychology experiment building language [PEBL; PEBL-DSF]) [313-315].

The WMS-IV-LM measures auditory verbal contextual learning and memory with excellent reliability and validity [312]. The validated older adults battery (aged 65 years or older) of the German version of the WMS-IV-LM [311, 312, 381] will be used for all participants. The test will be instructed, conducted, and evaluated according to the standardized administration and scoring manual [311]. During the 20 to 30 minutes retention phase, unrelated assessments (e.g., gait analysis, questionnaires) will be performed that do not interfere with memory.

The PEBL-DSF test assesses immediate recall and will be executed using the PEBL Test battery software [version 2.1 (2), with default settings] [313-315]. Participants were required to remember and repeat the digit sequences presented on the screen. Span length covers 2 to a maximum of 8 digits. For each digit span, 2 trials will be presented before increasing the sequence length (in case at least one of the 2 trials is completed correctly). For every correct replication of a digit sequence, 1 point will be scored, summing up to a total point score. In addition, the length of the longest correctly repeated digit sequence will be recorded as the maximum span. Instructions will be presented on the screen and will be explained verbally to each participant before starting the test.

Complex Attention

Complex attention will be assessed using a computerized version of the Trail Making Test—Part A (PEBL-TMT-A) [313, 315] and the subtest 'Go-NoGo' of the Test of Attentional Performance (test of attentional performance [TAP] Go-NoGo) [316].

The TMT-A is a valid and reliable neuropsychological test for assessing psychomotor processing speed and visuo-perceptual abilities [382-387]. A computerized version of the TMT-A PEBL Test battery software [version 2.1 (2), with default settings] will be used [313, 315, 388]. Participants will be verbally instructed, and a short practice session will be conducted before starting the test. The completion time will be limited to 300 seconds. Completion times (seconds; including time for error correction) and the number of errors will be measured.

The TAP (version 2.3.1, PSYTEST, Psychologische Testsysteme, Herzogenrath, Germany) is a valid and reliable computerized test battery to assess various attentional and executive functions [316, 389], with norm values for healthy older adults provided by the supplier [316, 390]. The TAP Go-NoGo will be used to assess selective attention and inhibition. The test form "1 of 2" will be instructed, conducted and evaluated according to the standardized protocol of the manufacturer. The median reaction time and number of errors will be measured. [316]

Executive Function

Executive function will be assessed considering planning (i.e., using the HOTAP picture-sorting test part A [317]), working memory (i.e., using a computerized version of the Digit Span Backward test; PEBL Digit Span Backward [PEBL-DSB]) [313-315], and cognitive flexibility (i.e., using a computerized version of the Trail Making Test-Part B [PEBL-TMT-B] [313, 315]).

HOTAP picture-sorting test part A [317] will be used to measure planning ability. A set of photo cards containing actions typical of everyday life (e.g., making coffee, washing clothes, and grocery shopping) will be presented. Participants will be verbally instructed to sort photo cards on which the individual substeps of these typical everyday actions are depicted. The test will be conducted according to the manufacturer's standardized protocol. The outcome variable is a combination score calculated as the sum of points divided by the time needed to arrange the cards. [317]

The PEBL Digit Span Backward (PEBL-DSB) [313-315] test will be used to assess the short-term working memory capacity. It will be instructed, administered, and scored identical to the PEBL-DSF, but participants will have to remember and repeat the digit sequences in reverse order.

The TMT-B is a valid and reliable neuropsychological test for assessing cognitive flexibility [382-387]. It consists of 25 randomly allocated circles distributed over a sheet of paper. A computerized version of the TMT-A (PEBL Test battery software [version 2.1 (2), with default settings]) will be used [313, 315, 388]. It will be instructed, administered, and scored identical to the PEBL-TMT-A.

Visuospatial Skills

Visuospatial skills will be tested using a computerized version of the classic Shepard and Metzler mental rotation task [391]. The PEBL-Mental Rotation Task (PEBL-MRT) will be executed using PEBL Test battery software [version 2.1 (2), with default settings] [313, 315, 318]. Instructions will be presented on the screen and will be explained verbally to each participant before starting the task. Pairs of differently rotated 2D polygons will be presented simultaneously on the screen. Participants need to decide as quickly as possible whether the 2 presented objects are identical (i.e., pressing <Lshift> on the keyboard) or different (i.e., pressing <Rshift> on the keyboard). Median reaction time of correct answered trials as well as performance (number of correct answered trials) are an indicator for mental rotation ability [318, 391]. Trials with reaction times less than 0.2 seconds or greater than 13 seconds will be excluded from the data analysis [318].

Brain Structure and Function: Data Acquisition

Brain structure and function will be evaluated by MRI using a 3.0 Tesla Philips whole-body scanner (Philips Medical Systems, Best, and Netherlands) to explore possible underlying neural changes of training in relation to adaptations in cognitive performance. Only participants having no contraindications to MRI (i.e., any MRI-incompatible metallic parts within the body, metallic or electronic implants [e.g., heart pacemaker, brain pacemaker, and cochlear implants], and strong claustrophobia) will be measured. During measurements (duration=approximately 35 min), participants will lay comfortably in the MRI scanner and will be asked to avoid head movements. Data will be collected according to the Canadian Dementia Imaging Protocol (CDIP) [392] for comparison with other studies. The CDIP was developed to harmonize MRI acquisitions in the context of studying primary and secondary causes of morbidity of neurodegeneration in a wide range of neurological

pathologies related to aging [392]. First, the following parts of the core CDIP will be applied: anatomical imaging (1.) and connectivity and functional imaging (2. - 3.) [392]:

- a 3D isotropic t_1-weighted (t_1w) scan (duration = 6.5 minutes) for assessing fine anatomical detail and brain atrophy (voxel size = 1.0 × 1.0 × 1.0 mm^3) with an acceleration factor of 2 (TFE-Sense: 2);
- diffusion tensor imaging (DTI; duration = 6 minutes) for assessment of white matter microstructural integrity and connectivity, with resolution 2.0 × 2.0 × 2.0 mm^3, a minimum of 30 uniformly distributed directions with b = 1000 second/mm^2, (EPI-Sense 2-32 directions; we use the vendor-provided directions set), and an acceleration factor of 2; and
- a resting state fMRI (duration = 9 minutes) for assessment of functional networks and pathways using a T^*_2-weighted blood oxygen level-dependent-sensitive sequence, with resolution of 3.5 × 3.5 × 3.5 mm^3, repetition time = 2110 milliseconds, 300 volumes over time, and slice order = ascending.

During resting-state fMRI data acquisition, participants will be asked to fixate on a cross displayed on the screen. At the end of this scan, participants must respond to written instructions by button press to check whether they were awake during the measurement.

In addition, task-based (event-related) fMRI measured with an episodic memory task (face-occupation matching task; duration: approximately 10 min) will be conducted. The face-occupation matching task was described in [393] and has been used in fMRI [394]. It was shown to robustly activate the hippocampus bilaterally and provide a differential signal for correct and incorrect trials [394]. The task was adapted specifically for older adults with mNCD [395] and will be run in PsychoPy (version 3.2.4) [396]. It includes 6 rounds, each containing (1) an encoding phase, (2) a retention phase, and (3) a retrieval phase including a cued recall task and a recognition task (see Figure 7-3 for an overview).

Figure 7-3: Graphical overview of the episodic memory task (face-occupation matching task).

During the encoding phase, 5 face-occupation pairs will be presented in each round in a randomized order. A total of 30 face-occupation pairs (15 different face-occupation combinations) will be presented (Figure 3). Photographs of unfamiliar faces of older adults with neutral expressions were derived from the FACES database [397] and will be equally balanced over sex. Each face-occupation pair will be shown for 3.5 seconds. To ensure that participants view both faces and occupations, they will be asked to indicate whether each respective occupation "suits" (i.e., pressing a button with their right index finger) or does not suit the presented face (i.e., pressing a button with their right middle finger).

During the retention phase, 5 silhouettes will be presented in randomized order in each round. A total of 30 silhouettes will be presented. Each silhouette will be shown for 3.5 seconds. Participants will be asked to indicate by button press whether each silhouette corresponds to a woman (pressing a button with their right index finger) or a man (pressing a button with their right middle finger).

In the retrieval phase, a cued-recall task will be performed followed by a recognition task. In the cued recall task, participants will be asked to decide which of 2 educational degrees (i.e., study [pressing a button with their right index finger] or apprenticeship [pressing a button with their right middle finger]) the previously encoded occupation of the person matched. In the recognition task, participants will have to decide between correct and distractor occupation via a button press (right index finger or right middle finger). For both the tasks, the response window will be 3.5 seconds. The photographs will be presented in the same order as those in the encoding phase.

The same recording parameters as in resting-state fMRI will be used. There are 4 alternative task conditions (i.e., other face-occupation pairs). The task condition will be randomly allocated using random.org [398], while ensuring that 2 different conditions are used in the pre- and postintervention measurements for each participant.

Brain Structure and Function: Data Analysis

Processing and volumetric segmentation of t_1w morphological data is performed using the longitudinal pipeline of the FreeSurfer software package (version 7.2.0 or newer with default parameters) [399, 400], as described in [401]. Gray matter volumes and WMVs are determined for the following key regions of interest (ROIs): total brain (i.e., total brain volume without ventricles [brainsegvolnotvent] from the aseg file), hippocampus, dorsolateral prefrontal cortex, PFC, and anterior cingulate cortex (ACC). Similar to Anderson-Hanley et al [276], we will combine the following regions to obtain the defined key ROIs of the dorsolateral prefrontal cortex, PFC, and ACC, because these are not directly extracted using the FreeSurfer software package: dlPFC=frontal middle gyrus and sulcus from the Destrieux et al [402] atlas; ACC=rostral and caudal anterior cingulate cortices from the Desikan et al [403] atlas; PFC=ACC+medial orbitofrontal and transverse frontopolar regions [404].

DTI data will be processed using the TractoFlow pipeline [405, 406], a diffusion MRI tractography processing pipeline based on Nextflow [407] and Singularity [408], for human brain tractography reconstruction. In patients with m-MNCD, DTI abnormalities are concentrated in the posterior regions, whereas the most reported regions of DTI alterations are the temporal lobes, with a particular emphasis on the parahippocampal white matter and posterior cingulum [409, 410]. Therefore, MD and FA will be calculated for the parahippocampal white matter and posterior cingulum, defined as

key ROIs for this study. In addition, tract-based spatial statistical analysis will be performed to study white matter changes at voxel-to-voxel (whole-brain) levels. Tract-based spatial statistical analysis is based on a general linear model and will be performed using FSL's randomization tool [411] with 5000 permutations to correct for multiple comparisons (P<.05, corrected). All results will include threshold-free cluster enhancement [412]. The threshold-free cluster enhancement correction method is somewhat similar to cluster-based thresholding but is generally more robust and avoids the need for an arbitrary initial cluster-forming threshold. Two contrasts will be computed at the individual and group levels, testing for positive and negative differences in FA and MD parameters pre- and postintervention. We will include age and sex as key covariates in the general linear model.

Data of resting state and task-based fMRI will be preprocessed to minimize data artifacts from thermal noise of MRI, system noise of the MR hardware, and subject-related noise resulting mostly from head motion [413]. The preprocessing steps will include slice time correction, motion correction, coregistration, and spatial smoothing (Gaussian kernel with 7 mm full width at half maximum) of the signal [414]. For functional connectivity (FC) analysis, preprocessed resting-state functional data will be analyzed using the latest release of the Functional Connectivity Toolbox (currently CONN 21a; [415, 416]) in SPM12. The CONN utilizes a component-based noise correction method (CompCor) that increases selectivity and sensitivity and allows a higher degree of interscan reliability [417]. In addition to the described preprocessing steps, a band-pass filter (0.01-0.1 Hz) will be applied to remove linear drift artifacts and high-frequency noise. The CONN also accounts for outlier data points and movement time courses as nuisance regressors. The 6 motion parameters, WM and CSF, will be included as regressors of no interest, thereby reducing noise and signals that are unlikely to reflect neuronal activity related to FC. Age and sex will be included as key covariates of no interest. Significance was set at P<.05 with Family Wise Error-level correction for multiple comparisons (with P < 0.05 2-sided false-discovery rate correction) [416].

Bilateral hippocampal masks were selected as seeds from an Anatomical Automatic Labeling template [418]. Individual FC maps for the hippocampal seed will then be generated based on correlations between the mean signal time course within each seed region and the rest of the brain, similar to Suo et al 2016 [419], with the following selected key ROIs (i.e., brain regions related to cognitive functioning, similar to Zhong et al [420]): precuneus or posterior cingulate cortex, medial prefrontal cortex, medial temporal lobe, angular gyrus, lateral temporal cortex, and medial, lateral, and inferior parietal cortex.

Spatiotemporal Parameters of Gait

Spatiotemporal parameters of gait will be evaluated to explore whether the addition of the 'Brain-IT' training to usual care effectively improves gait. The gait of individuals with mNCD differs from that of healthy controls in terms of (among others; 1) slower single-task gait speed at the preferred walking speed (m/s) [352, 421], (2) longer stride duration (ms) [352, 421], (3) shorter stride length (cm) [352, 421], (4) longer stance time (ms) [421], (5) longer swing time (ms) [421], (6) longer single support time (ms) [421], and (7) longer double support time (ms) [421]. Furthermore, individuals with mNCD typically show greater variability and coefficient of variation of gait parameters compared with cognitively healthy individuals [421].

According to the literature summarized above, we assume that an effective intervention leads to an (1) increase in single-task gait speed at the preferred walking speed, (2) decrease in stride duration, (3) increase in stride length, (4) decrease in stance time, (5) decrease in swing time, (6) decrease in single support time, and (7) decrease in double support time.

On the basis of this, we have elaborated our alternative hypotheses in more detail. It is hypothesized that in older adults with mNCD, the addition of the 'Brain-IT' training to usual care results in differing effects on (c1) single-task gait speed at the preferred walking speed, (c2) stride duration, (c3) stride length, (c4) stance time, (c5) swing time, (c6) single support time, and (c7) double support time compared with usual care.

Spatiotemporal gait parameters will be assessed using a BTS G-WALK (BTS Bioengineering SpA, Garbagnate Milanese, Italy) inertial sensor attached with semielastic belt to participants' lower back. The BTS G-WALK sensor delivers valid [422-424] and reliable [422, 425] spatiotemporal gait parameters. All the acceleration data will be sampled at a frequency of 100 Hz. Data will be transmitted for analysis through Bluetooth 3.0, connection to the software program BTS G-Studio (BTS Bioengineering SpA, Italy). A gait-analysis protocol consisting of a figure of 8 walking path (i.e., distance between cones of approximately 8 m) will be applied [320]. At least 50 consecutive gait cycles are required to ensure the reliability of the spatial and temporal parameters of gait variability [426]. Therefore, participants will perform 5 to 10 repetitions of the figure of 8 walking path at the preferred walking speed, depending on their walking speed and stride length. Comparative quantitative reference values for healthy older adults are available [427].

IADL Functioning

IADL functioning will be assessed using the Amsterdam IADL questionnaire short version, German for Switzerland, which has demonstrated good psychometric properties [371]. In addition, the original version of the Amsterdam IADL questionnaire was sensitive to longitudinal changes [428] and has been recommended for use in research settings [429]. The closest informant (e.g., spouse, child, or friend) will fill out the questionnaire twice (within 2 weeks before the study participant starts or completes the intervention). Each item is scored on a 5-point Likert scale ("no difficulty" to "unable to perform"). Scoring is based on the item response theory. Item response theory latent trait levels are transformed to a T-score, with a range from 20 to 80, a mean of 50, and an SD of 10. A higher t score indicates better functioning. [371]

Psychosocial Factors

QoL will be evaluated in interview format using the Quality of Life-Alzheimer Disease (QOL-AD) scale [321]. The QOL-AD is a valid and reliable self-report 13-item scale assessing various domains of QOL in cognitively impaired patients [321, 430]. The German version of the QOL-AD scale, which has high test-retest reliability and good construct validity [322, 323] will be used. Administration and evaluation will follow standardized instructions [323, 431]. Comparable values are available for individuals with mNCD [432].

Levels of depression, anxiety and stress will be assessed using the short version of the Depression, Anxiety and Stress scale-21 (DASS-21) [324-326]. The DASS-21 has high reliability and good convergent and discriminant validity [324, 433]. The validated German version of the DASS-21 will

be administered and scored according to guidelines and scoring template [327, 328]. Normative data of the 3 subscales are available and suggest cut-off scores of 10, 8, and 15, indicating significant depression, anxiety, or stress, respectively [327]. Comparative values for individuals with mNCD are available [434].

Cardiac Vagal Modulation (Resting Vagally-Mediated Heart Rate Variability)

To determine resting vm-HRV, all participants will be instructed to sit in a comfortable position on a chair without speaking, both feet flat on the floor with knees at a 90º angle, hands on the thighs (i.e., palms facing upward), and eyes closed [295]. Measurements will be performed in a quiet room with dimmed light at room temperature. Data will be collected using a heart rate monitor (Polar M430) and sensor (Polar H10). The initial acclimatization phase will last for 5 minutes followed by a 5-minute resting measurement, the recommended standard duration for short-term recordings [295, 435]. The start of the resting measurement will not be announced to the participants [295].

For resting HRV measurements, a sampling rate of 1000 Hz will be used to provide a temporal resolution of 1 milliseconds for each RR interval [436]. R-R data recordings will directly be transmitted to the Kubios HRV Premium (Kubios Oy, Kuopio, Finland, version 3.4) for analysis. Kubios HRV is a scientifically validated software for HRV analysis and has achieved the gold standard status in research [329, 437-439]. The automatic beat correction algorithm and noise handling provided by the software will be used to correct for artifacts or ectopic beats. This algorithm has been validated for measurements at rest. [437] After removing interbeat-interval time series nonstationarities by detrending analysis using the smoothness priors method approach (settings: detrending method=smoothing priors, Lambda = 500, f_c = 0.035 Hz), the mean values of mainly vagal-mediated HRV indices will be calculated for each segment. For this purpose, the mean R-R time intervals (mRR; ms), root mean square of successive RR interval differences (ms), percentage of successive RR intervals that differ by more than 50 milliseconds (%), absolute power of the high-frequency (0.15 - 0.4 Hz; high frequency [HF]) band (ms^2), relative power of HF (in normal units; HF [n.u.] = HF [ms^2] / (total power [ms^2] - very low frequency; 0.00 - 0.04 Hz [ms^2]), and Poincaré plot SD perpendicular to the line of identity (SD1; ms) will be considered [295, 435, 440-442]. In addition, the parasympathetic nervous system tone index (parasympathetic nervous system index) will be calculated to compare parasympathetic nervous system activity with normal resting values [442].

Other Endpoints

Safety Endpoint Variables

A protocol will be kept of all (serious) adverse events.

Baselie Factors

Baseline factors are collected through demographic data, including age, sex, height, weight, BMI, years of education, physical activity behavior (i.e., measured with the German version of the International Physical Activity Questionnaire Short Form - short form [443, 444] and analyzed according to published guidelines for data processing and analysis of International Physical Activity Questionnaire Short Form - short form [445]), clinical subtype (i.e., mNCD due to AD, mild Frontotemporal NCD, mNCD with Lewy Bodies, or mild vascular NCD), medication intake, and changes in medication intake between pre- and postintervention measurements.

Adherence and Compliance Protocol

For the intervention group (i.e., exergame training):

- Adherence Protocol (number of sessions completed per week per participant; automatically assessed in the Exergame Training Software) to calculate the mean adherence rate (%) = number of training sessions attended / total number of training sessions offered; calculated as the average of each participant's weekly adherence with a maximum of 100 %.

- Compliance Protocol (training time completed per week per participant; automatically assessed in the Exergame Training Software) to calculate the mean compliance rate (%) = training duration attended (min) / total training duration offered (min), calculated as the average of each participant's weekly compliance, with a maximum of 100 %.

7.3.7 Participant Timeline

Table 7-4 provides an overview of the participant timeline.

Table 7-4: Participant Timeline.
Abbreviations: Qmci, Quick Mild Cognitive Impairment Screen; WMS-IV-LM, subtest 'logical memory' of the Wechsler Memory Scale- fourth edition; PEBL, Psychology experiment building language; DSF, Digit Span Forward; DSB, Digit Span Backward; TMT-A and B, Trail Making Test Part A and B; TAP Go-NoGo, subtest 'Go-NoGo' of the Test of Attentional Performance; HOTAP-A, HOTAP picture-sorting test part A; MRT, Mental Rotation Task; MRI, magnetic resonance imaging; IADL, Instrumental Activities of Daily Living; QOL-AD, Quality of Life-Alzheimer's Disease; DASS-21, Depression, Anxiety and Stress Scale-21; vm-HRV, vagally-mediated heart rate variability

Time	> - 2 days before Pre-Measurements	> - 1 day before Pre-Measurements	week -1 to 0	week 1 - 12	week 13 to 14	week 15
Visit	Information	Consent and Screening	Pre-Measurements	Intervention Period	Post-Measurements	Post-Information
Location	at the interested persons' home or at one of the study centers, depending on their preferences	at the interested persons' home or at one of the study centers, depending on their preferences	at one of the study centers	at the participants' homes	at one of the study centers	at the participants' homes or at one of the study centers, depending on their preferences
Oral and written information	✓					
Written informed consent		✓				
Inclusion-/exclusion criteria		✓				
Primary Outcome: Qmci (~ 5 min)			✓		✓	
Secondary Outcomes: • WMS-IV-LM (~ 15 min) • PEBL-DSF and DSB (~ 5 min) • PEBL-TMT-A and B (~ 5 min) • TAP Go-NoGo (~ 5 min) • HOTAP-A (~ 5 min) • PEBL-MRT (~ 5 min) • MRI-Scan (~ 60 min) • Gait Analysis (~ 5 min) • IADL (~ 15 min) • QOL-AD (~ 5 min) • DASS-21 (~ 5 min) • resting vm-HRV (~ 12 min)			✓		✓	
Baseline Factors (~ 5 min)			✓			
Safety Endpoints			✓	✓	✓	
Adherence and Compliance to the Training Protocol				✓		
Study Intervention				✓ (study visits only applicable for exergame-group)		
Discuss Individual Results						✓

7.3.8 Sample Size

The optimal sample size was justified based on Whitehead et al [446], and the following assumptions: the future main (full-scale) RCT will be planned with identical design and primary outcome as this study, with a two-sided type 1 error rate of 5 % and a statistical power of 80 %.

Our pilot feasibility RCT revealed a medium effect size (η^2_p = 0.080) [60]. The observed medium effect size is slightly higher than the pooled evidence of exergame-based or combined motor-cognitive training interventions in older adults with NCD on global cognitive functioning. For exergame-based interventions in individuals with mNCD, Wang et al (2019) reported a medium SMD of 0.57 (P = 0.21, 95 % CI −0.32 to 1.47; k = 1; n = 20, compared with cognitively active control) [75], while Gavelin et al (2021) reported an SMD of 0.13 (P > 0.05, 95 % CI −0.22 to 0.48; k = 2; n = 109, compared with passive control) [35]. Stanmore et al (2017) reported a small pooled effect of Hedges g=0.340 (P = 0.02, 95 % CI 0.06 - 0.62; k = 6; n = 193) for patients with cognitive impairment [62]. Further meta-analytic results for individuals with mNCD are limited to simultaneous motor-cognitive training with reported small-to-medium effect sizes, including SMDs of 0.45 [73], 0.48 [141], 0.531 [73], and 0.69 [341]. On the basis of this, a medium effect size of a SMD of 0.5 seems reasonable and is anticipated. This leads to a justified optimal sample size of n = 14 per arm.

In our pilot feasibility RCT, we observed an attrition rate of 20 % [60]. This is consistent with recent systematic reviews synthesizing mean attrition rates of 17 % (range, 0 to 59 %) [86] in physical training interventions, 10 % for combined motor-cognitive training interventions [78], and 15 % (range 0 % - 31 %) [44] for exergame-based interventions for patients with m-MNCD. Therefore, an attrition rate of 20 % is anticipated. To ensure an adequate number of participants, a wide upper safety margin for an attrition rate of up to 40 % is selected.

On the basis of these considerations, we will aim to recruit 17 to 20 older adults with mNCD per group, leading to a total sample size of 34 to 40. This will provide a sufficiently precise estimate of the treatment effect to minimize the sample size needed for a future full-scale RCT [446].

7.3.9 Randomization

Sequence Generation

Participants will be randomly allocated to the intervention or control group. Variable block randomization (i.e., block sizes = 4, 6, and 8) with a 1:1 allocation ratio stratified by sex and institute (study center) will be used.

Allocation Concealment Mechanism

To ensure allocation conceaalment, random allocation will be computer generated using a validated variable block randomization model implemented in the data management system Castor EDC (Ciwit BV) [331].

Implementation

Randomization process will be set up by PM before starting patient recruitment. PM will also oversee the enrollment of participants. Participants will individually be assigned to the intervention or control group by the investigator responsible for supervision and correspondence with the respective study

participant after completing premeasurements. Randomization allocation can be viewed in eCRFs by investigators who have been assigned right to do so. The eCRF is implemented in the Castor EDC data management system [331]. None of the investigators performing postintervention measurements will have access rights to view the randomization allocation in eRCFs.

7.3.10 Blinding

Outcome evaluators of pre- and postintervention measurements will be blinded to the group allocation (single blinding). To ensure blinding and blind-keeping of outcome assessors, detailed study-specific guidelines for all relevant procedures related to blinding and blind-keeping of outcome assessors have been established, which will be followed by all involved study investigators. For data assessed throughout the intervention period (i.e., only applicable to the intervention group), blinding of investigators is not possible. The blinding of participants will also not be possible because usual care will be used as a control intervention.

7.3.11 Participant Retention

Once a patient is included, a trained investigator will be assigned as the person responsible for supervision and correspondence with the respective study participant and will make all reasonable efforts to achieve participant's retention in the study. Examples include providing written information sheets and reminders about study appointments, involving carers or relatives as personal support for study participants, and providing assistance with travel to the study center. Specifically, in the intervention group, each participant is provided with a training manual that is individually adapted to ensure that they use the training system correctly.

7.3.12 Data Management

All study investigators will be thoroughly trained for all study procedures according to the Guidelines of Good Clinical Practice and in line with detailed working instructions and a data management plan (Multimedia Appendix 1). In short, local principal investigators are in charge for methodological standards and quality of data collection using data management system Castor EDC (Ciwit BV) [331]. The data management plan specifies standard procedures for data management, evaluation, and storage. All data entries will be cross-checked by a second investigator before exporting for analysis. Range checks for data values were preprogrammed for data entry into the eCRFs. To minimize bias during the assessment of all clinical outcome measures, detailed working instructions were prepared, including standardized measurement procedures and standardized instructions of participants for all measurements.

7.3.13 Statistical Methods

Statistical analysis will be executed using R (The R Foundation), in line with RStudio (RStudio Inc). For demographics as well as training adherence and compliance, all collected data will be included (i.e., including data of dropouts up to the time point of their withdrawal). For primary and all secondary outcomes, the data of all participants who completed pre- and postintervention measurements, regardless of protocol adherence, will be included in the statistical analyses. Questionnaire scores will be regarded as ordinal data. Data will be reported as mean (SD) values for continuous parametric data and median (IQR) values for continuous nonparametric data.

For all outcomes, descriptive statistics will be computed first. Normality distribution of data will be checked using the Shapiro-Wilk test. The level of significance will be set to $P \leq 0.05$ (2-sided, uncorrected).

For all demographic variables, between-group differences (i.e., intervention vs control) will be tested using an independent t test or Mann-Whitney U test in case the data are not normally distributed. For primary and secondary outcomes, the assumption of homogeneity of variance will be checked using Levene test. In case all assumptions for a 2-way analysis of covariance (ANCOVA) are met, effectiveness of the 'Brain-IT' training will be analyzed using a two-way ANCOVA with the premeasurement value as covariate for the predicting group factor and the postmeasurement value as outcome variable. [333] If not all assumptions are met, the Quade nonparametric ANCOVA will be used. Because of the stratification by sex in the randomization process, no sex-specific statistical analysis will be computed. However, if there are relevant between-group differences in sex distribution or other demographic variables, these will be included in the statistical analyses as additional covariates. To determine whether the effects are substantive, partial eta-squared (η^2_p) effect sizes will be calculated for all primary and secondary outcomes. Effect sizes will be interpreted as small ($0.01 \leq \eta^2_p < 0.06$), medium ($0.06 \leq \eta^2_p < 0.14$), or large ($\eta^2_p > 0.14$) [334].

Statistical analysis will be performed by PM after data collection is completed. As this is a small-scale RCT, no interim analysis will be performed.

7.3.14 Monitoring

External monitoring will be performed at three time points: (1) before starting recruitment (site initiation visit); (2) after inclusion of 10 participants (routine monitoring visit); and (3) after completing all postintervention measurements and database lock (close-out visit) by Dr Ruud Knols (Physiotherapy and Occupational Therapy Research Centre, Directorate of Research and Education, University Hospital Zurich). Monitoring activities will be performed according to the ICH-GCP and according to a detailed monitoring plan that is based on adaptations of the 'Monitoring Plan Template' of the Swiss Clinical Trial Organization to meet study-specific requirements.

7.3.15 Ethics and Dissemination

Research Ethics Approval and Protocol Amendments

The study protocol was approved by the Ethics Committees of Zurich and Eastern Switzerland (EK-2022-00386). Any substantial amendment to the study protocol will have to be approved by the Ethics Committees of Zurich and Eastern Switzerland, and the trial registration at clinicaltrials.gov (NCT05387057) will be updated accordingly. Any substantial amendments to the study protocol that may occur after publication of this study protocol will be reported in the final publication of the study results.

Consent or Assent

As described in detail in section *"Methods - Recruitment"*, suitable patients willing to take part in the study will provide written informed consent in a second in-person meeting with one of the trained investigators of the study team at the interested persons home or at one of the study centers, depending on their preferences.

Confidentiality

Measures to ensure data confidentiality are detailed in the data management plan (Multimedia Appendix 1).

Access to Data

As detailed in the data management plan (Multimedia Appendix 1), anonymized data sets from this project that underpin a publication will be deposited in the Zenodo repository and made public after completing data collection.

Ancillary and Posttrial Care

In the event of study-related damage or injuries, the liability of the institution ETH Zurich provides compensation, except for claims arising from misconduct or gross negligence. Insurance is covered by ETH Zurich public liability insurance (Police Nr 30/4.078.362 of 'Basler Versicherung AG'). After completion of study participation, all participants will be offered to use the training device at their own responsibility, either by purchasing a 'Senso Flex' (if market launch of the 'Senso Flex' has already taken place at that time) or by using a 'Senso' in one of a nearby physiotherapies, nursing homes or rehabilitation clinics offering the system.

Dissemination Policy

Each participant will be informed of their personal results by providing a written report summarizing the patients' relevant results. The report will be handed out in person and explained by a trained investigator to ensure that the patients understand their results. In addition, upon request, an information letter will be sent to participants at the end of the study to inform them about the findings obtained in this study.

A manuscript of the results will be published in a peer-review open-access journal as well as on ResearchGate and original data sets will be made available in a publicly accessible repository. Standard journal authorship criteria will be applied; there will be no use of professional writers. In addition, the results of this study will be disseminated via open-access journal articles and conference presentations to inform health care professionals, the public, and other relevant groups about the study results and the knowledge gained.

7.4 Results

Upon the initial submission of this study protocol, 13 patients were contacted by the study team. Four patients were included in the study, 2 were excluded because they were not eligible, and 7 were being informed about the study in detail. Of the 4 included patients, 2 already completed all premeasurements and were in week 2 of the intervention period. Data collection is expected to be completed by December 2023. A manuscript of the results will be submitted for publication in a peer-reviewed open-access journal in 2024.

7.5 Discussion

7.5.1 Principal Findings

This RCT will systematically evaluate the effectiveness of a newly developed nonpharmacological exergame-based training targeted at improving cognitive functioning in older adults with mNCD. The results of this study should provide information on whether the addition of our modified and improved exergame-based training (according to the 'Brain-IT' training concept) to usual care is effective in improving global cognitive functioning, and a future full-scale RCT is warranted. The study will thus contribute to the evidence base in prevention of disability because of cognitive impairment, which has been declared a public health priority by the World Health Organization [286].

7.5.2 Comparison With Prior Work

Technological innovations (e.g., exergames) provide new options to engage older adults with mNCD in (simultaneously-incorporated) motor-cognitive training [39]. So far, only 1 study has applied exergame-based training that was individualized content-wise based on the cognitive abilities of older adults with mNCD [280]. Furthermore, most previous studies used commercially available exergame systems [270, 275-280], where the training content was not specifically developed for individuals with mNCD. These studies have shown rather limited effects on global cognitive functioning [35], although combined motor-cognitive training seems to be the most effective type of training for improving cognition in older adults with mNCD [35, 73, 288, 289].

7.5.3 Limitations

There are some limitations to this RCT that must be mentioned. First, we will only explore the effectiveness of the addition of the 'Brain-IT' training concept to usual care. In line with this, the sample size for this RCT was justified to provide a sufficiently precise estimate of the treatment effect to minimize the sample size needed for a future full-scale RCT [446]. As a result, the statistical analyses will most probably be insufficiently powered, and confirmatory studies are needed following this study. Second, usual care interventions are assessed by self-report of patients. To counteract possible biased information, the study team will ask specific questions about whether participants are engaged in typical usual care interventions (as described in section *"Methods and Materials - Interventions - Control Group"*) and actively involve participants' proxies when collecting this information. Third, patients screened for MCI according to predefined criteria are recruited in addition to patients with a clinical diagnosis of mNCD, which will increase the heterogeneity of the study population. In line with this, in our project, we aim to investigate an individualized exergame-based training concept not only to treat clinically diagnosed patients with mNCD but also to prevent progression to dementia in individuals at risk who might not have been diagnosed (yet).

7.6 Conclusions

This study will contribute to the evidence base in the highly relevant area of prevention of disability because of cognitive impairment, which has been declared a public health priority by the World Health Organization.

7.7 Acknowledgments

This sponsor-investigator initiated study is funded by Synapsis Foundation—Dementia Research Switzerland (grant 2019-PI06) and 'Gebauer Stiftung', and financially supported by 'Fondation Dalle Molle'. 'Senso Flex' training systems are provided free of charge by Dividat AG for the duration of the study. Neither the funder nor Dividat AG played any role in the design of this study, nor did they play any role in the collection, management, analysis, and interpretation of data, writing of the report, or decision to submit the report for publication.

7.8 Authors' Contributions

PM was responsible for the conception and writing of the study protocol under the supervision of EdB. LM and AS contributed to magnetic resonance imaging methodology, and FB contributed to the recruitment strategy and eligibility criteria for participants. All authors have contributed to the revision of the manuscript. All authors have read and approved the submitted version of the manuscript.

7.9 Conflicts of Interest

None declared.

7.10 Multimedia Appendix

The Multimedia Appendix for this article can be found online at:
https://jmir.org/api/download?alt_name=resprot_v12i1e41173_app1.pdf&filename=32a29d7e6f9885d815b9350ff6416a3c.pdf&__hstc=178719527.fa0b4465ba21d3a13ad01413adac48f4.1704192024719.1704874607982.1704989379694.4&__hssc=178719527.1.1704989379694&__hsfp=4015062042

7.11 Abbreviations

ACC	anterior cingulate cortex
AD	Alzheimer disease
ADAS-cog	Alzheimer's Disease Assessment Scale-Cognitive Subscale
ANCOVA	analysis of covariance
CDIP	Canadian Dementia Imaging Protocol
DASS-21	Depression, Anxiety and Stress Scale-21
DSF	digit span forward
DSM-V	Diagnostic and Statistical Manual of Mental Disorders 5th Edition

DTI	diffusion tensor imaging
FC	functional connectivity
HF	high frequency
IADL	instrumental activities of daily living
MCI	mild cognitive impairment
MNCD	major neurocognitive disorder
mNCD	mild neurocognitive disorder
MRI	magnetic resonance imaging
PEBL	psychology experiment building language
Qmci	quick mild cognitive impairment
RCT	randomized controlled trial
ROI	region of interest
SMD	standardized mean difference
TAP	test of attentional performance

Chapter

8

Paper 5:

‘Brain-IT’ - exergame training with biofeedback breathing in neurocognitive disorders

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Full Reference:

not yet available, submitted on 26 February 2024 and currently under review in the journal *“Alzheimer’s & Dementia®: The Journal of the Alzheimer’s Association”* that is published by Wiley Periodicals LLC on behalf of Alzheimer’s Association.

8.1 Abstract

Introduction: The combination of exergame-based motor-cognitive training with resonance breathing guided by heart rate variability biofeedback (HRV-BF) targets various relevant mechanisms of action to alleviate the pathological state in mild neurocognitive disorders (mNCD).

Methods: This randomized controlled trial (RCT) investigated the effectiveness of adding this novel intervention approach to usual care in mNCD. The individualized intervention was delivered via the 'Brain-IT' training concept, which was iteratively co-designed, tested, and refined with patient and public involvement.

Results: We observed statistically significant effects with large effect sizes for global cognitive performance, immediate verbal recall, and delayed verbal recall in favor of the intervention group. 55 % of participants showed a clinically relevant improvement in response to training.

Discussion: Confirmatory RCTs are warranted to investigate whether the observed improvements in cognitive performance translate to affecting the rates of progression to or onset of dementia and test the implementation of the training in clinical practice.

Trial registration: ClinicalTrials.gov NCT05387057;

https://clinicaltrials.gov/ct2/show/NCT05387057

8.3 Background

The global prevalence of dementia is projected to increase dramatically, making it a key challenge for aging societies. To mitigate this impending escalation, it is imperative to implement sustainable and effective measures aimed at averting its progression. [1] Individuals at an early stage of the disorder (mild cognitive impairment (MCI) or mild neurocognitive disorder (mNCD) [4]) may represent an optimal target population for secondary prevention [7].

Where physical frailty can be seen as emerging from dysregulation of multiple interconnected physiological and biological systems that cross a threshold to critical dysfunction, thus severely compromising homeostasis [28], a similar phenomenon can be assumed for cognitive frailty. Several studies have reported the interactions between neuro-immune, immune-metabolic and neuro-metabolic pathways [29], which also bears relevance for individuals with Alzheimer's disease (AD) [30, 31]. Consequently, holistic interventions that have multisystem effects are expected to be more promising to remedy cognitive impairment than interventions targeted at replenishing single systems.

Combined physical and cognitive training was recently recommended for the secondary prevention of mNCD by a collaborative international guideline [22]. Physical exercise is proposed to alleviate the pathological state of mNCD, which is characterized by an abnormal accumulation of proteins, excessive oxidative stress, metabolic disorder, and neuroinflammation within the brain, via distinct mechanisms of action [23, 24, 35] that also lead to an improvement of brain structure and function [23, 24, 32-34] and help maintain or increase cognitive reserve [12, 24]. Cognitive exercises support and stabilize these neuroplastic processes, facilitating the survival and integration of new neuronal structures in brain circuits [32-34]. The simultaneous execution of physical and cognitive exercises has positive synergistic effects and is currently considered most effective for improving cognitive performance in individuals with mNCD [32-35].

For older adults with mNCD specifically, it is imperative to also consider that these individuals often have disrupted self-regulatory capacity to flexibly adapt to daily life challenges [46]. This capacity is supported by the central autonomic networks (CAN), which can be viewed as an integrated component of an internal regulatory system in which the brain controls visceromotor, neuroendocrine, and behavioral responses that are critical for goal-directed behavior, adaptability, and health [47]. Therefore, interventions should be designed holistically to also target this network specifically.

This could be achieved by combining simultaneous motor-cognitive training with resonance breathing guided by heart rate variability biofeedback (HRV-BF). HRV-BF aims to increase cardiac autonomic control, enhance homeostatic regulation, and regulate emotional state [48-50]. An increased cardiac autonomic control increases vagal afferent transmission to the forebrain and activate and stimulate brain regions relevant for cognitive adaptations (such as the prefrontal cortex) [48, 50]. HRV-BF or paced breathing (at resonance frequency) is effective in improving cardiac autonomic control [50, 51], cognitive functioning (in particular executive functions) [52, 53], and emotional regulation [50, 53] (i.e., by decreasing symptoms of depression [50, 53, 54], anxiety [50, 54, 55], and stress [54, 55]) across different age groups and in clinical populations. Moreover, there is evidence supporting a causal role of cardiac autonomic control in modulating plasma AD-related biomarkers [56].

Although HRV-BF has been suggested useful as a complementary treatment [53], its combination with simultaneous motor-cognitive training remains to be investigated. In light of a holistic approach that maximizes transferability to clinical practice, this new intervention approach should be implemented using technological innovations, such as exergames [40]. Exergames offer a standardized and scalable method for training and can be designed to provide an optimal environment with enriched multi-sensory feedback to enhance skill acquisition and neuroplasticity [41] in a motivating environment [42] that promotes positive behavioral changes [43] and typically resulting in high training adherence [42]. As a result, exergames are currently considered more promising than conventional training approaches [137, 447, 448].

This is the first randomized controlled trial (RCT) aiming to investigate the effectiveness of the combination of exergame-based motor-cognitive training with HRV-BF delivered via an individualized exergame-based training concept (called 'Brain-IT') in individuals with mNCD.

8.4 Methods

8.4.1 Prior Work

In the project 'Brain-IT', we systematically designed and developed a novel training concept ('Brain-IT') specifically for older adults with mNCD that addresses the proposed mechanism of action described in the introduction.

The projects' methodology [58] followed the guidelines of the Medical Research Council for the development and evaluation of complex interventions [449] as well as the Multidisciplinary Iterative Design of Exergames (MIDE) – Framework [57]. The 'Brain-IT' project was structured in three phases. In phase 1, we systematically combined a comprehensive literature synthesis [58] with qualitative research including primary end users (older adults with mNCD), secondary end users (physiotherapists, occupational therapists, healthcare professionals), exergaming researchers, as well as experts from the exergaming industry [45] to specify a set of design requirements for the 'Brain-IT' training concept. In phase 2, possible concepts for the exergame-based training concept were co-designed and elaborated based on the set of design requirements defined in phase 1. The first prototype of the resulting 'Brain-IT' training concept [58] then entered the iterative cycle of feasibility, usability, safety and acceptance testing and integrating study results for further development based on co-design until an "acceptable" solution was achieved. The results of this process revealed that the resulting 'Brain-IT' training is feasible, usable, safe, and highly accepted by older adults with mNCD and preliminary data on the effects of the 'Brain-IT' training are promising [60]. This study is part of phase 3 of the project.

8.4.2 Objectives and Hypotheses

This study evaluated the effectiveness of adding 'Brain-IT' training to usual care in improving global cognitive performance in older adults with mNCD compared to usual care alone. As secondary objectives, the effects of the 'Brain-IT' training on: (1) domain-specific cognitive functioning (i.e. learning and memory, complex attention, executive function, and visuospatial skills), (2) spatiotemporal parameters of gait, (3) instrumental activities of daily living (IADL) and (4) psychosocial factors (i.e. quality of life (QoL), and levels of depression, anxiety, stress), and (5)

cardiac vagal modulation (i.e. resting vagally-mediated heart rate variability (vm-HRV)) in older adults with mNCD as compared to usual care were explored. The specific hypotheses were detailed in the published study protocol [61]. Additionally, the study protocol states that we aimed to evaluate brain structure and function to explore possible underlying neural changes of the training in relation to adaptations in cognitive performance. Because details on the methods for these analyses are dependent on the results on cognitive performance reported here, these will be reported separately in focused manuscripts.

8.4.3 Explanation and Choice of Comparators

As detailed in the study protocol [61], we have chosen to compare the addition of the 'Brain-IT' training to usual care versus usual care alone as a comparator. This decision is based on the alignment of recommended treatment and management of individuals with mNCD in Switzerland with available global clinical practice guidelines and consensus statements [8].

8.4.4 Protocol and Registration

The study protocol for this RCT was prepared in accordance with established guidelines from the *"SPIRIT 2013 Statement: Defining Standard Protocol Items for Clinical Trials"* [367, 368] and published previously [61]. In this manuscript, key information is reported to adhere to the latest version of the *"Consolidated Standards of Reporting Trials (CONSORT) Statement for Randomized Trials of Nonpharmacologic Treatments"* [450] (supplementary file 1). For full reproducibility, please also refer to the study protocol [61].

Important changes to the trial design and study setting after commencement

Recruitment was extended by six weeks. This allowed us to stop recruitment only once we had complete data on the primary outcome for the planned minimum sample size of 34 participants. Other than that, there were no changes to the published study protocol or deviations from it.

8.4.5 Ethics Approval

All the study procedures were performed in accordance with the Declaration of Helsinki. The study protocol was approved by the Ethics Committees of Zurich and Eastern Switzerland (EK-2022-00386).

8.4.6 Overview of the Trial Design, Participants, and Interventions

A two-arm, prospective, parallel-group, single-blinded (i.e. outcome evaluator of pre- and post-measurements blinded to group allocation) RCT with a 1 : 1 allocation ratio (i.e. intervention : control) including older adults with mNCD was conducted between May 2022 and February 2024. The study was registered at clinicaltrials.gov prior to the start of patients' recruitment (NCT05387057; date of registration: 18 May, 2022) The study setup was multicentric (Zurich and St. Gallen) and national (Switzerland).

Individuals with mNCD were recruited between May 2022 and October 2023 in collaboration with (memory) clinics in the larger area of Zurich and St. Gallen. Suitable patients were either identified from medical records and patient registries of (memory) clinics or from recent clinical diagnostics performed by their medical doctors or therapists authorized to search medical records. Alternatively,

suitable patients were identified by an informant (i.e. healthcare professionals)-based suspicion of MCI of one of their patients. To ensure diversity, equity and inclusion, all patients referred to us by the clinical recruitment partners were fully considered for participation in the study. After recruitment and providing written informed consent, participants were screened on eligibility (full list of eligibility criteria see study protocol [61]), and pre-measurements were scheduled for all eligible participants.

Pre- and post-measurements took place at one of our study sites (ETH Hönggerberg, Zurich and Eastern Switzerland University of Applied Sciences, St. Gallen) within two weeks prior to starting and after completing the intervention. The measurements took approximately 90 min. All participants having no contraindications to magnetic resonance imaging (MRI) had an additional appointment to conduct an MRI scan (duration: approximately one hour (including preparation)) at University Hospital Zurich. All measurements were led by two investigators of our research team trained in the application of the measurement techniques and protocols. Pre- and post-measurements were scheduled to take place at approximately the same time of the day (± 2 h) for each participant. To minimize the influence of transient confounding effects on vm-HRV, all participants were additionally instructed verbally and in writing to follow a normal sleep routine the day before the experiment, to avoid intense physical activities and alcohol consumption within 24 h before measurements, and to refrain from coffee – or caffeinated drinks as well as food consumption at least 2 h before measurements [295].

After completing pre-measurements, participants were randomly allocated to the intervention or control group and were instructed about their respective intervention procedures. The control group proceeded with usual care as provided by the (memory) clinics where the patients were recruited. For participants in the intervention group, the exergame device was installed at their homes, they got a safety instruction and were familiarized with the exergame training system and then started with their twelve-week training intervention according to the ‘Brain-IT’ training concept in addition to usual care. The ‘Brain-IT’ training concept represents a guideline for applying a combination of exergame-based motor-cognitive training and HRV-BF training by standardizing the training characteristics (e.g., training frequency, intensity, and duration), as well as the structure and content of training, whereas the exergame device and the specific games used within each of the defined neurocognitive domains can be replaced by alternative exergames. To ensure replicability, the ‘Brain-IT’ training concept was planned and reported according to the Consensus on Exercise Reporting Template (CERT) [238] and provides specific instructions on how to adapt the ‘Brain-IT’ training concept to other hardware and software solutions (see supplementary file 2).

For an overview, the ‘Brain-IT’ training consists of a personalized and individually adapted multi-domain exergame-based simultaneous motor-cognitive training with incorporated cognitive tasks combined with HRV-BF training. It is adopted with a deficit-oriented focus on the neurocognitive domains of (1) learning and memory, (2) executive function, (3) complex attention, and (4) visuospatial skills. Each participant was instructed to train ≥ 5x/week for ≥ 24 min per session resulting in a weekly training volume of ≥ 120 min. All training sessions took place at participants' homes. As per the ‘Brain-IT’ training concept [58], 19 - 24 training sessions were supervised by a designated investigator who instructed and oversaw the participants' use of the exergame device, ensured safety protocols were followed [e.g., ensuring that there were no hard objects (e.g., couch table) within the potential drop zone, determining the appropriate level of stability support using walking sticks, handrail or similar], and ensured adherence to the ‘Brain-IT’ training concept. All deviations from the ‘Brain-IT’ training concept were reported. In this project, we used technology of

Dividat AG (i.e., 'Senso Flex' (Dividat AG, Schindellegi, Switzerland; hardware: prototype version 2, software: version 22.4.0-360-gf9df00d5b), Polar (i.e., heart rate monitor (Polar M430) and sensor (Polar H10)), and Kubios (Kubios HRV Premium (Kubios Oy, Kuopio, Finland, version 3.4)) to implement our training concept. For more detail on how the specific technologies are used to implement our training concept, consider the full revised 'Brain-IT' training concept (supplementary file 2).

After completing the twelve-week intervention period, post-measurements were performed for both groups. An individual report of their results was provided to each participant and discussed with them personally. In addition, viable options for continuing (or, for the control group, starting) 'Brain-IT' training outside of the study were carefully explored and identified, and we provided support for their implementation. No compensation was granted to participants, but detailed feedback on individual performance as well as the study outcomes in general was provided at the end of the trial. When possible, caregivers were actively involved in helping participants travel to the study centers for measurements and reminding them to adhere to the training plan.

8.4.7 Overview of Outcomes

An overview of all outcome measures is provided below. Details for all specific assessments and measurement conditions are provided in the published study protocol. Due to the journal's stipulations on the maximum number of references, all references to the respective assessments are also provided in the published study protocol [61].

Primary Outcome

As primary outcome, changes in global cognitive performance were assessed using the validated German version [451] of the Quick mild cognitive impairment screen (Qmci) [251, 310]. The Qmci comprises six subtests: orientation (10 points), registration (5 points), clock drawing (15 points), delayed recall (20 points), verbal fluency (20 points), and logical memory (30 points), was scored as a point rate out of a maximum score of 100 [310], and was shown to be sensitive for changes in cognitive performance over time [372]. The Qmci was administered and evaluated according to published guidelines [310]. A clinically meaningful change was defined as a change in ≥ 3 points in the Qmci score [61].

Secondary Outcomes

As secondary outcomes, key neurocognitive domains (as defined in [3] in line with the Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-5) [5] and according to recommendations [7, 452]) of (1) learning and memory, (2) complex attention, (3) executive function, and (4) visuospatial skills, spatiotemporal parameters of gait, psychosocial factors (i.e., QoL, and levels of depression, anxiety, stress), and cardiac vagal modulation (resting vm-HRV) were assessed.

As defined in the published study protocol [61], **learning and memory** was assessed using the German version of the subtests 'logical memory' of the Wechsler Memory Scale - fourth edition (WMS-IV-LM) and a computerized version of the Digit Span Forward test (Psychology experiment building language (PEBL)-Digit Span Forward (PEBL-DSF)). **Complex attention** was assessed using a computerized version of the Trail Making Test – Part A (PEBL-TMT-A) and the subtest 'Go-

NoGo' of the Test of Attentional Performance (TAP Go-NoGo). **Executive Functions** were assessed considering planning abilities (i.e. using the HOTAP picture-sorting test part A (HOTAP-A)), working memory (i.e. using a computerized version of the Digit Span Backward test (PEBL Digit Span Backward (PEBL-DSB)), and cognitive flexibility (i.e. using a computerized version of the Trail Making Test – Part B (PEBL-TMT-B)). **Visuo-spatial skills** were tested with a computerized version of the classic Shepard and Metzler's mental rotation task, that was executed using PEBL Test battery software (version 2.1 (2); with default settings). **Spatiotemporal gait parameters** were assessed using a BTS G-WALK® (BTS Bioengineering S.p.A., Garbagnate Milanese, Italy) inertial sensor gait-analysis protocol consisting of a figure-8 walking path (i.e. distance between cones approximately 8 m). **IADL functioning** was assessed by report of the closest informant (e.g., spouse, child, or friend) using the Amsterdam IADL Questionnaire short version German for Switzerland. **QoL** was evaluated in interview format using the validated German version of the Quality of Life-AD (QOL-AD) scale. **Levels of depression, anxiety, and stress** were assessed using the validated German version of the Depression, Anxiety and Stress Scale-21 (DASS-21). **Resting vm-HRV** was assessed in accordance recommendations for experiment planning, data analysis, and data reporting using a heart rate monitor (Polar M430) and sensor (Polar H10). Data were analyzed in Kubios HRV Premium (Kubios Oy, Kuopio, Finland, version 3.4) using the validated beat correction algorithm and noise handling provided by the software.

Other Endpoints

Safety Endpoint Variables

We kept a protocol of all (serious) adverse events ((S)AEs).

Baseline Factors

Baseline factors were collected through demographic data including age, sex, height, weight, body mass index (BMI), years of education, physical activity behavior (i.e. measured with the German version of the International Physical Activity Questionnaire Short Form - short form (IPAQ-SF) [61]), etiological subtype (i.e. mNCD due to AD, mild Frontotemporal NCD, mNCD with Lewy Bodies, or mild vascular NCD) and medication intake as well as changes in medication intake between pre- and post-measurements.

Adherence Protocol

For the intervention group (i.e. exergame training), we also had an attendance adherence (number of sessions completed per week per participant) and duration adherence (training time completed per week per participant) protocol, which was automatically assessed in the exergame training software). To ensure that participants who trained more than the prescribed minimum frequency did not compensate for lower adherence rates in other participants or training weeks in which they trained less, mean adherence rates were calculated as the average of each participant's weekly attendance and duration adherence with a maximum of 100 % (formulae for calculations see [60]). Reasons for non-adherence and dropouts were recorded.

8.4.8 Sample Size

The sample size was justified based on Whitehead et al. (2016) [446] and the following assumptions: the future main (full-scale) RCT will be planned with identical design and primary outcome as this study, with a two-sided type 1 error rate of 5 % and a statistical power of 80 %. A medium effect size and an attrition rate of 20 % were anticipated. To ensure an adequate number of participants, a wide upper safety margin for an attrition rate of up to 40 % was chosen. Based on these considerations, we aimed to recruit n = 17 - 20 older adults with mNCD per group, leading to a total sample size of N = 34 - 40. This provides a sufficiently precise estimate of the treatment effect to minimize the sample needed for a future full-scale RCT [446].

8.4.9 Randomization

To ensure allocation concealment, each participant was individually assigned to intervention or control group by the investigator assigned as responsible person for supervision and correspondence with the respective study participant after completing pre-measurements. A variable block randomization model (i.e. block sizes = 4, 6, 8) implemented in the data management system Castor EDC (Ciwit BV, Amsterdam, The Netherlands) [331] with a 1 : 1 allocation ratio stratified by sex and per institute (study center) was used.

8.4.10 Blinding

Outcome assessors of the pre- and post-measurements were blinded to group allocation (single blinding). To ensure blinding and blind-keeping of all outcome assessors, detailed study-specific guidelines for all relevant procedures have been established that were strictly followed by all involved study investigators. For data assessed throughout the intervention period (i.e. only applicable for intervention group), blinding of investigators was not possible. Blinding of participants was also not be possible since usual care was used as a control intervention.

8.4.11 Participant Retention

Once a participant was included, a trained investigator was assigned as the person responsible for supervision and correspondence with the respective study participant and made all reasonable efforts to achieve the participant's retention in the study. Examples include providing written information sheets and reminders about study appointments, involving carers or relatives as personal support for study participants, and providing assistance with travel to the study center. Specifically, in the intervention group, each participant was provided with a detailed training manual that was individually adapted to the participants' setup to help them use the training system correctly (with photographs and explanations for each step from starting the system to training completion, including a colored step-by-step identification of required elements (cables and buttons)). Furthermore, the study team provided telephone support in case of technical difficulties or comprehension problems for unsupervised training sessions.

8.4.12 Statistical Methods

Statistical analysis done using R (The R Foundation; version 4.3.1 GUI 1.79 Big Sur Intel build) in line with RStudio (RStudio, Inc.; version 2023.12.1+402 (2023.12.1+402)). We did a modified intention-to-treat analysis (i.e., data of all randomized participants who completed pre- and post-measurements, regardless of protocol adherence, were included in statistical analyses). Questionnaire scores were regarded as ordinal data. Data was reported as mean ± standard deviation for parametric data, and median (interquartile range) for non-parametric data.

For all outcomes, descriptive statistics were computed first. Normality distribution of data was checked using Shapiro-Wilk test. Level of significance was set to $p \leq 0.05$ (two-sided, uncorrected).

For all demographic variables, between-group differences (i.e., intervention vs. control) were tested using an independent t-test or Mann-Whitney U-test in case the data were not normally distributed. Between-group differences in categorical variables were tested using Fisher's exact test. To discover whether the between-group differences were substantive, Pearson's r effect sizes were calculated [333] and interpreted to be small ($0.1 \leq r < 0.3$), medium ($0.3 \leq r < 0.5$) or large ($r > 0.5$) [334].

For the primary and all secondary outcomes, the assumption of homogeneity of variance was checked using Levene's test. In case all assumptions for an analysis of covariance (ANCOVA) were met, the effectiveness of the 'Brain-IT' training was evaluated using an ANCOVA with the pre-measurement value as covariate for the predicting group factor and the post-measurement value as outcome variable. [333] In case not all assumptions were met, Quade's non-parametric ANCOVA was used. To discover whether effects are substantive, partial eta-squared (η^2_p) effect sizes were calculated for all primary and secondary endpoints. Effect sizes were interpreted to be small ($0.01 \leq \eta^2_p < 0.06$), medium ($0.06 \leq \eta^2_p < 0.14$) or large ($\eta^2_p \geq 0.14$) [334].

Statistical analysis was done by P.M. after data collection was completed. No interim, subgroup, or adjusted analyses were performed.

8.5 Results

8.5.1 Recruitment and participant flow

A summary of the flow of participants through the study is shown in Figure 8-1. Recruitment was stopped when we had complete data on the primary outcome for the planned minimum sample size of 34 participants. A total of 41 participants were enrolled, of whom two withdrew consent voluntarily prior to pre-measurements and two dropped out during the intervention (one in each group). As a result, 37 participants (72.8 ± 9.0 years; 30 % females) successfully completed the study. Of these 37 participants, 32 were clinically diagnosed with mNCD and five met the criteria defined for screened for MCI. No deviations from the study protocol regarding initiation of the interventions (within two weeks after completing pre-measurements) were recorded. No intervention-related (S)AEs were recorded.

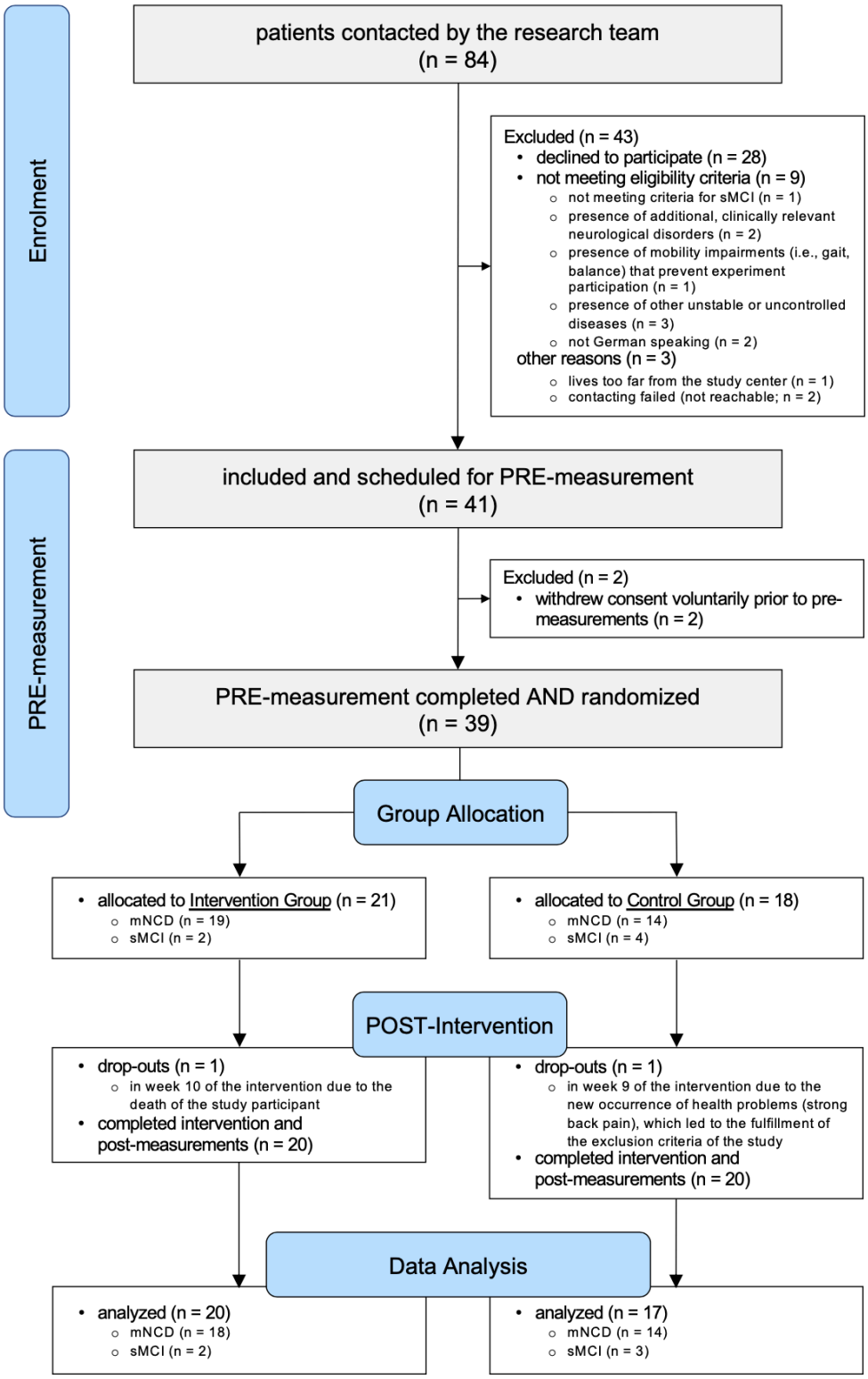

Figure 8-1: Summary of the participant flow throughout the study. mNCD, clinically diagnosed mild neurocognitive disorder; sMCI, screened for mild cognitive impairment.

8.5.2 Baseline data

Table 8-1 summarizes the demographic characteristics of the participants. A moderate effect size was observed for a higher BMI in the intervention group, although the mean/median of both groups fell within the range of a 'healthy' BMI. No other statistically significant between-group differences were found.

Table 8-1: Demographic Characteristics of the Study Population;

Data is reported as mean ± standard deviation for continuous parametric data and median (interquartile range) for continuous non-parametric data.

(1) t-statistics for the between-group differences tested with an independent t-test or Mann-Whitney U test in case the data are not normally distributed;
(2) *P* values for the between-group differences tested with an independent t-test or Mann-Whitney U test in case the data are not normally distributed, or Fisher's exact test for categorical variables.
(3) effect size estimates for the between-group differences tested with an independent t-test (=> effect size Pearson r) or Mann-Whitney U test (=> effect size Spearman rho (r_s)) in case the data are not normally distributed, or Fisher's exact test for categorical variables (=> odds ratio).

* = statistically significant at $p < 0.05$

Abbreviations: mild neurocognitive disorder; IPAQ-SF, International Physical Activity Questionnaire Short Form - short form (IPAQ-SF); IQR, interquartile rage; MET, metabolic equivalent of task; OR, odds ratio; SD, Standard Deviation;

	Group: Exergame (n = 20)	Group: Usual Care (n = 17)	Between-Group Difference		
			test statistics(1)	*P* Value(2)	|effect size|(3)
Age [years]	74.0 ± 8.0	71.8 ± 9.9	t = 1.048	.304	r = 0.192
Sex [% females]	30	29	N/A	.730	OR = 1.44
Body mass index [$kg \cdot m^{-2}$]	24.7 ± 2.3	22.7 (2.4)	W = 249	.017*	r_s = 0.393
Years of education [years]	16.0 ± 3.5	15.5 ± 3.5	t = - 0.025	.981	r = 0.004
IPAQ-SF [$MET \cdot week^{-1}$]	1683 (1735)	1485 (1342)	W = 219	.141	r_s = 0.242
Etiology of mNCD					
mNCD due to Alzheimer's Disease	n = 11 (55 %)	n = 10 (59 %)	N/A	1.00	OR = 0.86
mild frontotemporal NCD	n = 3 (15 %)	n = 0 (0 %)	N/A	.234	OR = ∞
mild vascular NCD	n = 3 (15 %)	n = 5 (29 %)	N/A	.428	OR = 0.43
mNCD with Lewy Bodies	n = 0 (0 %)	n = 1 (6 %)	N/A	.460	OR = 0.00
unclear / not yet determined	n = 3 (15 %)	n = 1 (6 %)	N/A	.460	OR = 0.00

8.5.3 Delivery of the interventions

Type of usual care activities

For participants who completed the study, 100 % of participants in the intervention group and 94 % of participants in the control group reported that they received one or more structured or guided usual care activities(s) during study participation. Details on types of usual care activities are summarized in Table 8-2. There were no statistically significant between-group differences in any of the pharmacological and non-pharmacological interventions. In addition to the interventions listed in the table, one participant in the intervention group underwent surgery for an inguinal hernia and received general anesthesia 9 weeks before the post-measurement. However, the participant was able to resume training after a brief break. In addition, one participant from the control group acquired the 'Senso Flex' device from Dividat AG without informing us, as they were frustrated with the group assignment, and trained with the commercially available software of the device using individualized progression algorithms for 15 minutes per day for about 2.5 months prior to the post-measurements.

Table 8-2: Type of Usual Care Interventions

(1) Medical training therapy is prescribed by a doctor and guided and partly supervised by physiotherapists. It typically includes resistance, cardiorespiratory endurance, and balance exercises.
(2) Fitness training may include the same training content as medical training therapy (i.e., resistance, cardiorespiratory endurance, and balance exercises), but is structured individually and/or with the help of (fitness) coaches
(3) Volume = time per training session [min] multiplied by frequency of training [times/week].
(4) *P* Values for the between-group differences tested with Fisher's exact test for categorical variables.

* = statistically significant at $p < 0.05$

Abbreviations: OR, odds ratio;

Type of Usual Care Activities	Proportion of Participants having received the respective Intervention during Study Participation		Between-Group Difference
	Group: Exergame (n = 20)	Group: Usual Care (n = 17)	*P* Value(4) and OR
Regular Medication Intake (at baseline):	n = 20 (100 % of participants)	n = 15 (88 % of participants)	.204, OR = ∞
Alzheimer's medication:			
- Cholinesterase inhibitors	n = 3 (15 % of participants)	n = 7 (41 % of participants)	p = 0.136, OR = 0.26
Blood Pressure Regulators:			
- Angiotensin-converting enzyme inhibitors	n = 10 (50 % of participants)	n = 7 (41 % of participants)	p = 0.743, OR = 1.41
- Beta-Blockers	n = 3 (15 % of participants)	n = 2 (12 % of participants)	p = 1.00, OR = 1.31
- Calcium Channel Blockers	n = 4 (20 % of participants)	n = 1 (6 % of participants)	p = 0.348, OR = 3.87
- Others	n = 1 (5 % of participants)	n = 1 (6 % of participants)	p = 1.00, OR = 0.85
Cholesterol-Lowering Agents:			
- Cholesterol absorption inhibitor	n = 1 (5 % of participants)	n = 1 (6 % of participants)	p = 1.00, OR = 0.85
- Statins	n = 9 (45 % of participants)	n = 6 (35 % of participants)	p = 0.738, OR = 1.48
Anticoagulants and Antiplatelet Agents:			
- Anticoagulants	n = 3 (15 % of participants)	n = 3 (18 % of participants)	p = 1.00, OR = 0.83
- Antiplatelet agents	n = 8 (40 % of participants)	n = 4 (24 % of participants)	p = 0.319, OR = 2.12
Psychopharmaka:			
- Antidepressants	n = 4 (20 % of participants)	n = 3 (18 % of participants)	p = 1.00, OR = 1.16
- Antipsychotics	n = 1 (5 % of participants)	n = 0 (0 % of participants)	p = 1.00, OR = ∞
Antidiabetic Agents:			
- Glucagon-like peptide-1 receptor agonist	n = 1 (5 % of participants)	n = 0 (0 % of participants)	p = 1.00, OR = ∞
- Insulin	n = 2 (10 % of participants)	n = 1 (6 % of participants)	p = 1.00, OR = 1.75
- Metformin	n = 1 (5 % of participants)	n = 2 (12 % of participants)	p = 0.584, OR = 0.40
- Sodium-glucose transport protein 2 inhibitors	n = 0 (0 % of participants)	n = 1 (6 % of participants)	p = 0.460, OR = 0
- Sulfonylurea antidiabetic agent	n = 2 (10 % of participants)	n = 1 (6 % of participants)	p = 1.00, OR = 1.75
Other medications:			
- Betahistini dihydrochloridumistamine	n = 1 (5 % of participants)	n = 0 (0 % of participants)	p = 1.00, OR = ∞
- Desmopressin	n = 1 (5 % of participants)	n = 0 (0 % of participants)	p = 1.00, OR = ∞
- Estradiol	n = 1 (5 % of participants)	n = 0 (0 % of participants)	p = 1.00, OR = ∞
- Glucocorticoids	n = 3 (15 % of participants)	n = 0 (0 % of participants)	p = 0.234, OR = ∞

- Lamotrigin	n = 0 (0 % of participants)	n = 1 (6 % of participants)	p = 0.460, OR = 0
- Nonsteroidal anti-inflammatory drug	n = 1 (5 % of participants)	n = 0 (0 % of participants)	p = 1.00, OR = ∞
- Metamizole	n = 0 (0 % of participants)	n = 1 (6 % of participants)	p = 0.460, OR = 0
- Mirabegron	n = 1 (5 % of participants)	n = 0 (0 % of participants)	p = 1.00, OR = ∞
- Paracetamol	n = 1 (5 % of participants)	n = 0 (0 % of participants)	p = 1.00, OR = ∞
- Proton pump inhibitor	n = 4 (20 % of participants)	n = 3 (18 % of participants)	p =1.00, OR = 1.16
- Risedronate sodium	n = 1 (5 % of participants)	n = 0 (0 % of participants)	p = 1.00, OR = ∞
- Thyroid hormone replacement	n = 1 (5 % of participants)	n = 1 (6 % of participants)	p =1.00, OR = 0.85
- Trospiumchlorid	n = 1 (5 % of participants)	n = 1 (6 % of participants)	p =1.00, OR = 0.85
- 5-alpha reductase inhibitor	n = 1 (5 % of participants)	n = 0 (0 % of participants)	p = 1.00, OR = ∞
Changes in Medication Intake (during intervention):			
Increase in medication dosage:			
- Antidepressants	n = 1 (5 % of participants)	n = 0 (0 % of participants)	p = 1.00, OR = ∞
- Cholinesterase inhibitors	n = 2 (10 % of participants)	n = 0 (0 % of participants)	p = 0.490, OR = ∞
Decrease in medication dosage:			
- Glucocorticoids	n = 0 (0 % of participants)	n = 1 (6 % of participants)	p = 0.460, OR = 0
New medication(s) and/or medication replacement:			
- Angiotensin-converting enzyme inhibitors	n = 0 (0 % of participants)	n = 1 (6 % of participants)	p = 0.460, OR = 0
- Antidepressants	n = 0 (0 % of participants)	n = 1 (6 % of participants)	p = 0.460, OR = 0
- Antihistamine	n = 1 (5 % of participants)	n = 0 (0 % of participants)	p = 1.00, OR = ∞
- Phosphodiesterase type 5 (PDE5) inhibitor	n = 0 (0 % of participants)	n = 1 (6 % of participants)	p = 0.460, OR = 0
Discontinuation of medication			
- Glucocorticoids	n = 1 (5 % of participants)	n = 0 (0 % of participants)	p = 1.00, OR = ∞
- Statins	n = 1 (5 % of participants)	n = 0 (0 % of participants)	p = 1.00, OR = ∞
Physiotherapy	n = 2 (10 % of participants); median volume[3] = 45 min/week	n = 3 (18 % of participants); median volume = 45 min/week	.644, OR = 0.53
Occupational Therapy	n = 2 (10 % of participants); median volume = 30 min/week	n = 2 (12 % of participants); median volume = 35 min/week	1.00, OR = 0.84
Medical Training Therapy [1]	n = 3 (15 % of participants); median volume = 90 min/week	n = 2 (12 % of participants); volume = 110 min/week	1.00, OR = 1.31
Fitness Training [2]	n = 5 (25 % of participants); median volume = 105 min/week	n = 2 (12 % of participants); median volume = 175 min/week	.417, OR = 2.44
(Computerized) Cognitive Training	n = 2 (10 % of participants); median volume = 65 min/week	n = 4 (24 % of participants); volume = 40 min/week	.383, OR = 0.37
Psychiatric Therapy	n = 0 (0 % of participants);	n = 1 (7 % of participants); median volume[3] = 30 min/week	.474, OR = ∞

Actual delivery of the 'Brain-IT' training

Participants who completed the training performed on average 71.5 ± 26.2 training sessions resulting in an average training volume of 1689 ± 579 min over the 12-week intervention period. On average, 19.5 ± 1.6 training sessions were supervised by our study team. Average attendance and duration adherence rates were 90.0 ± 11.2 % and 89.8 ± 12.2 %, respectively. The reasons for non-attendance adherence were technical problems (in 52 % of participants; 38 % of reasons for non-adherence), for time reasons (in 52 % of participants; 29 % of reasons for non-adherence), interruption of training due to AEs (in 10 % of participants; 12 % of reasons for non-adherence), forgot to train (in 10 % of participants; 2 % of reasons for non-adherence), comprehension problems (in 5 % of participants; 1 % of reasons for non-adherence), other reasons (in 14 % of participants; 10 % of reasons for non-adherence), or unknown (in 19 % of participants; 8 % of reasons for non-adherence). The reasons for early termination of training sessions were that they accidentally stopped the training (with back plate; in 45 % of participants; 40 % of reasons for non-adherence) technical problems (in 20 % of participants; 20 % of reasons for non-adherence), others (in 10 % of participants; 11 % of reasons for non-adherence) or unknown (in 15 % of participants; 29 % of reasons for non-adherence). Due to technical issues with the exergame device, the feedback mechanism for walking on the spot did not function correctly in a substantial number of participants. As a result, the physical exercise

intensity could not be reliably monitored in all participants. Otherwise, no relevant deviations from the 'Brain-IT' training concept were reported.

8.5.4 Primary outcome

Data on the primary outcome is illustrated in Figure 8-2. The intervention group improved their score in global cognitive performance from 58.7 ± 15.2 points at pre-measurements to 62.6 ± 13.5 points at post-measurements, while the control group showed a decline from 55.1 ± 15.9 points to 51.6 ± 15.3 points. There was a statistically significant effect with a large effect size [F(1, 36) = 8.32, p = 0.007, η^2_p [$CI_{90\ \%}$] = 0.197 [0.034, 0.371] in favor of the intervention group. A post-hoc power analysis with G*Power (version 3.1.9.6) [453] revealed a statistical power of 0.832 for this analysis. 55 % of participants in the intervention group and 23 % of participants in the control group were responders, showing a clinically relevant improvement in global cognitive performance.

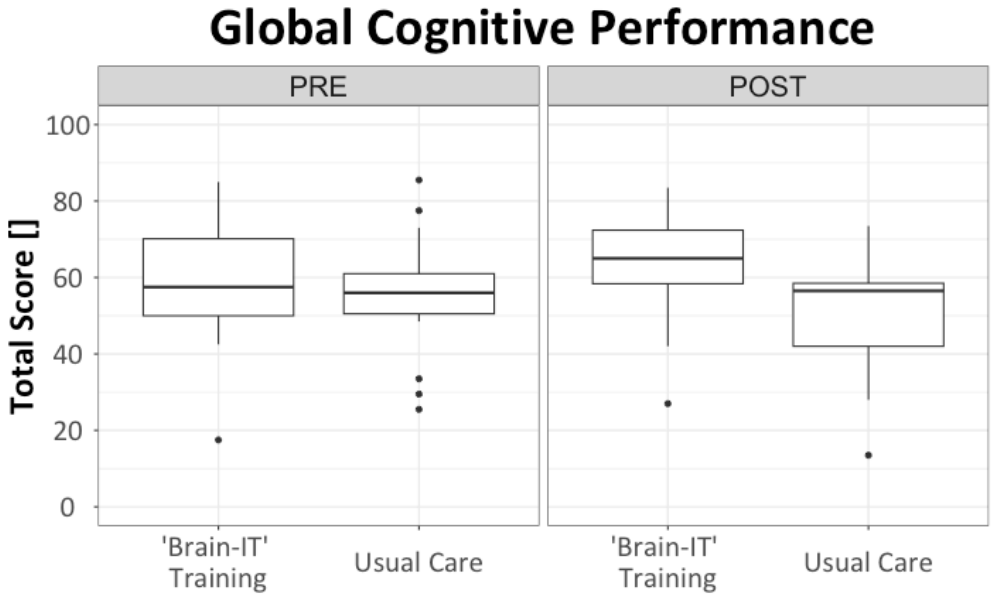

Figure 8-2: Boxplot for the primary outcome, global cognitive performance, measured with the German version of the Quick mild cognitive impairment screen (Qmci).

8.5.5 Secondary outcomes

The results of all secondary endpoints are summarized in Table 8-3 in detail. We observed statistically significant effects with large effect sizes in favor of the intervention group for immediate [F(1, 34) = 5.83, p = 0.022, η^2_p [$CI_{90\ \%}$] = 0.154 [0.013, 0.332] and delayed verbal recall [F(1, 34) = 8.18, p = 0.007, η^2_p [$CI_{90\ \%}$] = 0.204 [0.034, 0.382]. The remaining statistical analyses were underpowered and revealed no consistent effects, despite a statistically significant effect with a moderate effects size for a reduction in double support time in favor of the control group [F(1, 34) = 4.96, p = 0.033, η^2_p [$CI_{90\ \%}$] = 0.134 [0.006, 0.311] and a borderline statistically significant effect with a moderate effects size for an improvement of quality of life in favor of the intervention group [F(1, 36) = 3.64, p = 0.065, η^2_p [$CI_{90\ \%}$] = 0.097 [0, 0.263].

Table 8-3: Statistics for all secondary outcomes. Normality distribution of data was checked using the Shapiro-Wilk test and Q-Q-plots. The level of significance was set to $p \leq 0.05$ (two-sided, uncorrected). The assumption of homogeneity of variance was checked using Levene's test. In case all assumptions for analysis of covariance (ANCOVA) were met, effects of the addition of the 'Brain-IT' training concept to usual care as compared to usual care were analyzed using an ANCOVA with the pre-measurement value as covariate for the predicting group factor and the post-measurement value as outcome variable [333]. In case not all assumptions were met, Quade's non-parametric ANCOVA was used. To discover whether effects are substantive, partial eta-squared (η^2_p) effect sizes were calculated for all primary and secondary outcomes. Effect sizes were interpreted to be small ($0.01 \leq \eta^2_p < 0.06$), medium ($0.06 \leq \eta^2_p < 0.14$) or large ($\eta^2_p > 0.14$) [334].

(1) = Missing data because measurement was aborted due to emotional breakdown.
(2) = Missing data because measurement was not performed due to the psychological/emotional overload of the participant.
(3) = Missing data because measurement was not performed due to lack of test comprehension.
(4) = Missing data because measurement was aborted because the maximum processing time according to the test instructions was reached.
(5) = Missing data because measurement was not performed because participant had knee surgery a few weeks ago and is still undergoing physical therapy, which could introduce bias into the analysis of gait changes over time.
(6) = Missing data due to technical problems with the measurement device;
(7) = Missing data due to unavailability of closed relative of the study participant
(8) = Missing data due to insufficient data quality

Abbreviations: Qmci, Quick Mild Cognitive Impairment Screen; WMS-IV-LM, subtest 'logical memory' of the Wechsler Memory Scale- fourth edition; PEBL, Psychology experiment building language; DSF, Digit Span Forward; DSB, Digit Span Backward; TMT-A and B, Trail Making Test Part A and B; TAP Alertness, subtest 'Alertness' of the Test of Attentional Performance; TAP Go-NoGo, subtest 'Go-NoGo' of the Test of Attentional Performance; TAP Incompatibility, subtest 'Incompatibility' of the Test of Attentional Performance; HOTAP-A, HOTAP picture-sorting test part A; MRT, Mental Rotation Task; MRI, magnetic resonance imaging; IADL, Instrumental Activities of Daily Living; QOL-AD, Quality of Life-Alzheimer's Disease; DASS-21, Depression, Anxiety and Stress Scale-21; vm-HRV, vagally-mediated heart rate variability; SD, standard deviation; IQR, interquartile range; n, sample size; ANCOVA, analysis of covariance; η^2_p [90 % CI], partial eta-squared [90 % confidence interval]

Outcome:	Check of Assumptions and Type of Analysis:		Group: 'Brain-IT' Training			Group: Usual Care			ANCOVA Statistics:		
			PRE-measurement	POST-measurement	sample	PRE-measurement	POST-measurement	sample			
	All assumptions for parametric analysis met?	AND type of analysis	mean ± SD or median (IQR)	mean ± SD or median (IQR)	n	mean ± SD or median (IQR)	mean ± SD or median (IQR)	n	*P* Value	F Value	η^2_p [90 % CI]
Part 1 - Cognitive Functioning											
1.2 Learning and Memory											
WMS-IV-LM Score Part 1 []	✓	parametric	27.7 ± 10.0	29.6 ± 8.7	19(1)	25.1 ± 9.2	23.8 ± 9.9	16(2)	**.022**	5.83	0.154 [0.013, 0.332]
WMS-IV-LM Score Part 2 []	x	non-parametric	8.0 (8.0)	14.0 (14.0)	19(1)	6.5 (9.0)	7.0 (14.5)	16(2)	**.007**	8.18	0.204 [0.034, 0.382]
WMS-IV-LM Score Part 2 - Recognition []	✓	parametric	15.8 ± 3.6	16.5 ± 3.2	18(1, 3)	16.7 ± 2.6	16.2 ± 2.2	15(2, 3)	.164	2.04	0.064 [0, 0.229]
DSF Total Score []	x	non-parametric	6.0 (2.0)	6.0 (3.0)	20	7.5 (2.3)	6.5 (2.0)	16(4)	.865	0.03	0.001 [0, 0.054]
DSF Maximal Span []	x	non-parametric	5.0 (1.0)	4.0 (1.3)	20	5.0 (2.0)	5.0 (1.3)	16(4)	.890	0.02	0.001 [0, 0.043]

1.3 Complex Attention											
TMT-A - Completion Time [s]	x	non-parametric	33.9 (20.7)	35.2 (8.3)	20	31.8 (9.6)	38.9 (17.0)	17	.270	1.26	0.036 [0, 0.176]
TMT-A - Number of Errors []	x	non-parametric	0.0 (2.3)	0.5 (1.3)	20	1.0 (3.0)	0.0 (1.0)	17	.651	0.21	0.006 [0, 0.104]
TAP Go-NoGo - RT [ms]	x	non-parametric	439 (105)	482 (106)	20	412 (140)	448 (112)	17	.665	0.19	0.006 [0, 0.101]
TAP Go-NoGo - Number of Errors []	x	non-parametric	1.5 (3.3)	1.0 (2.0)	20	2.0 (3.0)	1.0 (3.0)	17	.701	0.15	0.004 [0, 0.095]
1.4 Executive Functioning											
HOTAP-A Combi-Score [points/min]	x	non-parametric	4.7 (3.6)	4.6 (3.5)	20	4.7 (3.6)	4.1 (3.5)	16[(2)]	.294	1.14	0.033 [0, 0.174]
DSB Total Score []	x	non-parametric	4.0 (3.0)	3.5 (2.0)	20	4.0 (1.0)	4.5 (1.3)	16[(2)]	.434	0.629	0.019 [0, 0.145]
DSB Maximal Span []	x	non-parametric	3.0 (1.0)	3.0 (1.0)	20	4.0 (1.0)	4.0 (0.3)	16[(2)]	.073	3.42	0.094 [0, 0.262]
TMT-B - Completion Time [s]	x	non-parametric	97.6 (113.1)	103.0 (78.1)	20	112.4 (81.3)	99.5 (90.0)	17	.662	0.20	0.006 [0, 0.104]
TMT-B - Number of Errors []	x	non-parametric	5.0 (4.0)	6.0 (9.5)	20	5.5 (10.8)	3.5 (9.8)	16[(2)]	.381	0.79	0.024 [0, 0.155]
1.5 Visuospatial Skills											
MRT - RTs [ms]	x	non-parametric	4918 (1142)	4761 (1936)	17	3945 (1012)	3778 (2243)	14[(3)]	.714	0.14	0.005 [0, 0.109]
MRT - Score []	✓	parametric	42.2 ± 10.6	45.4 ± 10.0	17	44.4 ± 8.6	46.9 ± 8.0	14[(3)]	.964	0.00	0.000 [0, 0.000]
Part 2 - Gait											
Walking Speed [$m \cdot s^{-1}$]	✓	parametric	0.95 ± 0.13	0.95 ± 0.13	18[(5, 6)]	1.02 ± 0.14	0.96 ± 0.18	17	.248	1.39	0.042 [0, 0.191]
Stride Duration [ms]	x	non-parametric	1095 (60)	1065 (85)	18[(5, 6)]	1060 (140)	1060 (130)	17	.620	0.25	0.008 [0, 0.115]
Stride Length [cm]	✓	parametric	102.8 ± 11.2	102.2 ± 11.2	18[(5, 6)]	107.8 ± 14.5	102.5 ± 14.9	17	.178	1.89	0.056 [0, 0.213]
Stance Phase Duration [ms]	✓	parametric	613.1 ± 67.4	611.8 ± 69.9	18[(5, 6)]	645.5 ± 94.7	617.0 ± 117.0	17	.258	1.33	0.040 [0, 0.188]
Swing Phase Duration [ms]	✓	parametric	415.3 ± 50.6	409.9 ± 46.7	18[(5, 6)]	432.8 ± 56.0	418.8 ± 63.8	17	.644	0.22	0.007 [0, 0.110]
Single Support Time [ms]	✓	parametric	414.7 ± 51.4	409.8 ± 47.7	18[(5, 6)]	433.5 ± 56.6	419.9 ± 63.3	17	.669	0.19	0.006 [0, 0.106]
Double Support Time [ms]	x	non-parametric	98.7 (27.4)	98.1 (21.9)	18[(5, 6)]	101.2 (19.1)	90.4 (23.4)	17	**.033**	4.96	0.134 [0, 0.311]
Part 3 - IADL											
T-Score []	✓	parametric	56.5 (8.5)	58.1 (8.9)	18[(7)]	52.8 (7.9)	55.4 (7.2)	17	.990	0.00	0.000 [0, 0.000]
Part 4 - Psychosocial Factors											
Quality of Life (QoL-AD) []	x	non-parametric	39.0 (5.5)	39.0 (4.3)	20	38.0 (6.0)	38.0 (7.0)	17	.065	3.64	0.097 [0, 0.263]
DASS-21 - Depression []	x	non-parametric	2.0 (5.0)	1.5 (4.0)	20	2.0 (4.0)	1.0 (4.0)	17	.993	0.00	0.000 [0, 0.000]
DASS-21 - Anxiety []	x	non-parametric	2.5 (3.3)	1.5 (3.3)	20	1.0 (2.0)	1.0 (2.0)	17	.996	0.00	0.000 [0, 0.000]
DASS-21 - Stress []	x	non-parametric	3.0 (5.0)	4.0 (3.5)	20	4.0 (6.0)	4.0 (4.0)	17	.279	1.212	0.000 [0, 0.174]

Part 5 - Heart Rate Variability											
mRR [ms]	x	non-parametric	873 (121)	851 (154)	$14^{(6, 8)}$	773 (186)	776 (190)	$12^{(6, 8)}$	.741	0.112	0.005 [0, 0.270]
RMSSD [ms]	x	non-parametric	16.7 (25.7)	13.2 (20.1)	$14^{(6, 8)}$	20.3 (13.7)	21.1 (25.9)	$12^{(6, 8)}$	.591	0.297	0.013 [0, 0.157]
pNN50 [%]	x	non-parametric	1.5 (16.1)	0.4 (7.1)	$14^{(6, 8)}$	1.4 (5.6)	1.3 (17.2)	$12^{(6, 8)}$	.531	0.404	0.017 [0, 0.170]
HF [ms^2]	x	non-parametric	89.0 (452.9)	79.5 (109.8)	$14^{(6, 8)}$	155.5 (156.0)	155.5 (371.5)	$12^{(6, 8)}$	.230	1.524	0.062 [0, 0.251]
HFnu [nu]	x	non-parametric	40.5 (28.0)	36.3 (32.9)	$14^{(6, 8)}$	54.2 (33.9)	65.8 (25.4)	$12^{(6, 8)}$	.126	2.525	0.099 [0, 0.298]
SD1 [ms]	x	non-parametric	11.8 (18.1)	9.4 (14.2)	$14^{(6, 8)}$	14.4 (9.8)	14.9 (18.3)	$12^{(6, 8)}$	.600	0.283	0.012 [0, 0.155]
PNS-Index []	x	non-parametric	-0.67 (1.72)	-1.05 (1.01)	$14^{(6, 8)}$	-1.06 (1.47)	-1.03 (1.99)	$12^{(6, 8)}$	.772	0.086	0.004 [0, 0.111]

8.6 Discussion

This RCT investigated the effectiveness of combining exergame-based motor-cognitive training with HRV-BF delivered through an individualized training concept called 'Brain-IT'. The results provide robust evidence that 'Brain-IT' training is effective for enhancing global cognitive performance, immediate verbal recall, and delayed verbal recall. However, the results regarding near- and far-transfer effects were inconclusive.

8.6.1 Principal Findings

This was the first RCT to examine the effectiveness of combining exergame-based motor-cognitive training with HRV-BF. Therefore, comparisons with previous literature are limited. To the best of our knowledge, there are no studies available that investigated the effects of HRV-BF on cognitive performance in individuals with mNCD so far. Pooled evidence from studies investigating the effects of exergaming in individuals with mNCD found small [35] to medium [75] effects favoring the intervention, which is consistent with pooled evidence of simultaneous motor-cognitive training, which also reported small [35, 62] to medium [73, 341] effect sizes. Based on the large effect size observed, it appears that our exergame-based training may be more effective than previously investigated training concepts. This may reflect our rigorous methodology and the quality of its resulting training concept. Only one of previous study applied exergame training that individually prescribed content on the basis of a patient's cognitive abilities [280]. In contrast, we investigated an evidence-based, purpose-designed and user-centered training concept that was iteratively co-designed, tested, and refined with continuous patient and public involvement, that is individualized and progressed according to predefined progression rules on different levels, and that includes a number of elements and support strategies to facilitate training motivation and self-determined training behavior. Therefore, it seems reasonable to conclude that this extensive groundwork has paid off by showing larger-than-expected effects on the outcomes for which the training was primarily designed. However, it is possible that these effects are partly attributable to our novel intervention approach with the addition of HRV-BF, which may have induced positive synergistic effects.

The literature explains that HRV-BF training increases cardiac autonomic control, which in turn increases vagal afferent transmission to the forebrain and activates brain networks such as the CAN, including the prefrontal cortex. This activation is important for self-regulation and the control of cognitive processes, and helps to restore hemostasis. [48-50] More specifically, electroencephalography studies indicate an increase in alpha power and a decrease in theta power, as well as increased levels of oxygenated hemoglobin in the anterior part of the prefrontal cortex as measured by near-infrared spectroscopy. Furthermore, a study using functional magnetic resonance imaging has shown increased activity in cortical areas such as the prefrontal, motor, and parietal cortices, as well as subcortical structures including the pons, thalamus, sub-parabrachial nucleus, periaqueductal gray, and hypothalamus. [50] The observed effects of HRV-BF on improving cognitive performance, particularly executive functions, have been attributed to these neurophysiological changes [50, 52, 53].

Based on the increased activation and oxygenation of brain regions relevant for cognitive adaptations, it could be hypothesized that HRV-BF enhances receptivity for neuroplastic changes induced by physical and/or cognitive training when combined with simultaneous motor-cognitive

training, similar to the facilitation effects on cognitive adaptations in response to cognitive training performed simultaneously with at least moderate intensity physical exercise [32-34, 454]. However, this hypothesis needs to be specifically tested in future research.

This lack of consistent transfer effects observed in this study may be due to the higher-than-expected baseline performance. Specifically, our study participants' performance was closer to the reference values of healthy older adults than to mNCD for several outcomes, including complex attention (i.e., TMT-A [455], TAP Go-NoGo [456]), executive functions (i.e., TMT-B [455]), and spatiotemporal parameter of gait [457]. We also observed bottom effects for symptoms of depression, anxiety, and stress, which are comparable to the reference values [434]. Consequently, room for improvements in these endpoints was limited. These observations could be explained by a potential selection bias in the recruitment process, as the main reason for non-participation was patient declination (65 % of reasons for non-participation). Individuals with prominent executive deficits and/or gait insecurities may lack confidence in their ability to commit to the study and the 12 weeks of regular and partly independent training it entails. Therefore, future research should aim to implement strategies that further reduce participation barriers for these individuals.

8.6.2 Implications for Research and Clinical Practice

Larger confirmatory RCTs are necessary to draw conclusions about the potential near- and far-transfer effects of the training. Additionally, it is recommended to compare the training with active comparators, including isolated and combined physical and/or cognitive exercises [452], as well as HRV-BF training. Furthermore, future research should investigate whether the observed improvements in cognitive performance translate to affecting the rates of progression to or onset of dementia [22].

In a next step, the implementation of the 'Brain-IT' training concept in clinical practice should be tested. In this regard, it is recommended to adapt and implement the training concept with various hardware and software solutions to overcome current barriers and to further develop and improve technologies to provide an optimal training environment and stimuli [60] in line with a “training first” approach [452]. Consistent with this approach, our training concept was reported using CERT [238] and provides detailed guidance on how to adapt it to other hardware and software solutions. Therefore, the 'Brain-IT' training concept can and should be incorporated as an adjunctive therapy to standard care for improving global cognitive performance and memory of individuals with mNCD.

Previous studies have reported potential neurophysiological benefits induced by exergaming, but further research is required in this area [458-460]. Therefore, it is necessary to further elucidate the underlying biological mechanisms of action. These investigations should then guide further research aimed at further improving the training by providing optimal stimuli to influence the pathological mechanisms of mNCD and ultimately maximize the training’s effectiveness in the secondary prevention of mNCD.

8.6.3 Strengths and Limitations

This RCT had several important strengths. First, the evaluated intervention targets various mechanisms of action to alleviate the pathological state in individuals with mNCD and has been iteratively designed, developed, and evaluated following best practice recommendations of the Medical Research Council [449] as well as the MIDE-Framework [57] with continuous patient and public involvement [45, 58] (see [58] for project's methodology). Second, the study as well as its intervention were strictly planned, conducted, and reported in accordance with established guidelines including the SPIRIT [367, 368], CONSORT [450], as well as CERT [238], to ensure full reproducibility. The study also adhered to several best practice characteristics for exercise/exergame studies, such as blinding of outcome assessors, allocation concealment, modified intention-to-treat analysis, and reporting of all relevant study characteristics to minimize the risk of bias [452, 461]. Third, the study was pre-registered at clinicaltrials.gov (NCT05387057), we submitted the study protocol for publication before starting recruitment [61], and transparently reported any deviations from the published study protocol. Finally, we included various etiologies of mNCD and chose relatively broad eligibility criteria to increase the generalizability of our findings.

The study also has some key limitations that are worth mentioning. First, we originally aimed to only explore the effectiveness of the addition of the 'Brain-IT' training concept to usual care. In line with this, the sample size for this RCT was justified to provide a sufficiently precise estimate of the treatment effect to minimize the sample size needed for a future full-scale RCT [446]. However, we obtained effect sizes for the primary outcome, as well as for immediate and delayed verbal recall, that were larger than expected. This prompted us to conduct a post-hoc power analysis, which confirmed that the statistical analysis for these outcomes was sufficiently powered. Second, our investigation of the addition of the 'Brain-IT' training to usual care was limited by the fact that the (memory) clinics where participants were recruited provided the usual care interventions, making it impossible to standardize contact times. This may have impacted some of our findings. However, comparing an intervention against treatment as usual is a recommended practice for effectiveness studies [449]. Third, usual care interventions were assessed by self-report of patients. To mitigate possible biased information, the study team posed specific questions regarding participants' engagement in typical care interventions and actively involved their proxies in collecting this information. Fourth, patients screened for MCI according to predefined criteria were recruited in addition to patients with a clinical diagnosis of mNCD, which increased the heterogeneity of the study population. However, this is in line with the project's objective to investigate an intervention not only to treat clinically diagnosed patients with mNCD but also to prevent progression to dementia in individuals at risk who might not have been diagnosed (yet). Fifth, women were underrepresented which might limit the generalizability of our findings. Finally, medication changes during the intervention could have potentially introduced bias. Although we did not find any statistically significant differences between the groups in terms of pharmacological or non-pharmacological usual care interventions, 10 % of participants in the intervention group had an increase in their dose of cholinesterase inhibitors and the control group had a substantially larger proportion of participants taking cholinesterase inhibitors throughout the study. Because the evidence for cholinesterase inhibitors suggests only a stabilization or slowing of cognitive decline, not an improvement in cognition as observed in the intervention group [462], this confounding effect played a subordinate role.

8.7 Conclusion

The combination of exergame-based motor-cognitive training with HRV-BF delivered via an individualized exergame-based training concept (called 'Brain-IT') is effective in improving global cognitive performance, immediate verbal recall, and delayed verbal recall. Confirmatory RCTs with larger sample sizes are necessary to draw conclusions about the potential near- and far-transfer effects of the training and to investigate whether the observed improvements in cognitive performance translate to affecting the rates of progression to or onset of dementia. Additionally, the training should be compared to different active comparators, such as isolated and combined physical and cognitive exercises or HRV-BF training. Future research should also test the implementation of the training in clinical practice and further optimize the 'Brain-IT' training concept. In this regard, the underlying biological mechanisms of action should be elucidated to guide further research aimed at further improving the training by providing optimal stimuli to influence the pathological mechanisms of mNCD and ultimately maximize its effectiveness in the secondary prevention of mNCD.

8.8 Acknowledgments

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8.10 Disclosures

8.10.1 Declaration of interest

None.

8.10.2 Author contributions

PM was responsible for the conception of the study under the supervision of EdB. PM was responsible for participant recruitment, data collection, statistical analysis, and writing the manuscript. Both authors contributed to the revisions of the manuscript, read, and approved the submitted version of the manuscript.

8.10.3 Data availability statement

The data sets that were generated and analyzed during the current study are available in the Zenodo repository at https://doi.org/10.5281/zenodo.10695988.

8.11 Abbreviations

(S)AEs	(serious) adverse events
AD	Alzheimer's disease
ANCOVA	analysis of covariance
BMI	body mass index
CAN	central autonomic networks
CERT	Consensus on Exercise Reporting Template
CONSORT	Consolidated Standards of Reporting Trials
DASS-21	Depression, Anxiety and Stress Scale-21
DSB	Digit Span Backward
DSF	Digit Span Forward
DSM-5	Diagnostic and Statistical Manual of Mental Disorders 5th Edition
HOTAP-A	HOTAP picture-sorting test part A
HRV-BF	resonance breathing guided by heart rate variability biofeedback
IADL	instrumental activities of daily living
IPAQ-SF	International Physical Activity Questionnaire Short Form - short form
MCI	Mild Cognitive Impairment
MIDE	Multidisciplinary Iterative Design of Exergames
mNCD	mild Neurocognitive Disorder
MRI	magnetic resonance imaging
MRT	Mental Rotation Task
PEBL	Psychology experiment building language
Qmci	Quick mild cognitive impairment screen

QoL	quality of life
QoL-AD	Quality of Life-Alzheimer's Disease
RCT	randomized controlled trial
TAP	Test of Attentional Performance
TAP Go-NoGo	subtest 'Go-NoGo' of the Test of Attentional Performance
TMT-A	Trail Making Test - Part A
TMT-B	Trail Making Test - Part B
vm-HRV	vagally-mediated heart rate variability
WMS-IV-LM	subtest 'logical memory' of the Wechsler Memory Scale - fourth edition
η^2_p	partial eta-squared

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Chapter

9

General Discussion and Future Prospects

The aim of the 'Brain-IT' project was to design, develop, and evaluate a novel training concept for the secondary prevention of mNCD. Our approach differed from previous research in three main factors: (i) a new intervention approach was introduced by combining purpose-developed and individualized motor-cognitive training with biofeedback-guided resonance breathing; (ii) technology (exergames) was used to implement this new intervention approach in light of a holistic approach that maximizes transferability to clinical practice; (iii) a new methodology was introduced to more systematically involve the perspectives of all relevant stakeholders, especially at the beginning of the project, with the aim of unlocking the project's full potential.

Our results seem to confirm that this extensive groundwork in combination of the innovative intervention approach have paid off by showing larger-than-expected effects on the outcomes for which the training was primarily designed. Notably, we reveal, to the best of our knowledge, as the first research team, that this novel intervention approach of combining exergame training with biofeedback-guided resonance breathing is not only safe, feasible, and highly accepted by individuals with mNCD, but also highly effective in improving cognitive performance. Our study also revealed a striking disparity in the rate of responders between the intervention and control groups, with 55 % of participants in the intervention group showing a clinically relevant improvement in global cognitive performance compared to only 23 % in the control group. It is important to note that the observed response rate in the control group aligns with what can be expected based on existing literature. Approximately 26 % of community-dwelling individuals with mNCD experience spontaneous reversion to normal cognitive functioning over time [154]. However, the substantial difference in the rate of responders between the intervention and control groups further underscores the effectiveness of our intervention and suggests that the addition of 'Brain-IT' training to usual care has a potentially meaningful clinical impact beyond that expected from usual care alone. The high rate of responders observed in the intervention group underscores the clinical relevance and potential utility of the intervention as a viable therapeutic option for individuals with mNCD. The addition of the 'Brain-IT' training to usual care resulted in a clinically relevant improvement in global cognitive performance in more than half of the participants, highlighting its promise as a valuable tool in the management and potential reversal of cognitive decline associated with mNCD.

These findings suggest that the implementation of the 'Brain-IT' training concept in clinical practice should be tested in a next iterative step as an adjunctive therapy to standard care for improving global cognitive performance and memory. Additionally, confirmatory RCTs with larger sample sizes are necessary to draw conclusions about the potential near- and far-transfer effects of the training. Even more importantly, our training concept was developed with the aim of secondary prevention of mNCD. Based on the available data, no conclusions can be drawn yet as to whether this was successful, as we only evaluated functional changes over a relatively short period of time. There is robust evidence that physical exercise, in particular simultaneous motor-cognitive training [35, 62, 73, 341], but also exergaming [35, 75, 463] interventions have a positive effect on cognitive performance in mNCD. However, these effects are typically only small to moderate and there is no high-quality evidence from systematic reviews or single RCTs indicating that physical activity or exercise can delay the onset of dementia in individuals with mNCD [22]. Therefore, although it appears that our training approach may be more effective in improving cognitive reserve than previously investigated training concepts, our findings have the same limitations compared to previous research, and, consequently, *"[…] there is continued uncertainty about the role of physical activity and exercise in slowing the*

conversion to dementia" [22] in mNCD. To overcome this limitation, there is a need for adequately powered RCTs evaluating the effect of training for the prevention of the onset of dementia, considered as primary outcome, in individuals with mNCD.

There is also further room for improvement regarding the design of the intervention. Although, exergame-based training is currently considered a more promising training approach than conventional physical and cognitive training [137, 447, 448] and it is effective in improving cognitive functioning in healthy middle-aged to older adults [452, 464, 465] as well as middle-aged to older adults with a range of clinical conditions, including mild [42, 463] to major [42, 44, 463] neurocognitive disorder, there is often considerable heterogeneity of training outcomes across studies, which can be attributed to the large variation in the design of exergame-based training approaches [447]. To overcome this limitation, it has been suggested that the scientific community should establish a consensus on a protocol that should be followed in future studies [452]. When developing our intervention, we comprehensively synthesized the evidence on moderating effects of specific exercise and training variables (training components) that contribute to the effectiveness of exergame-based training to influence cognitive functioning in the aging population (i.e., healthy older adults with and without cognitive disorders). This evidence synthesis can and should inform future research on the design of physical and/or cognitive training. However, our evidence synthesis was limited mainly to conventional physical and/or cognitive training, because no moderator analyses were available for exergaming specifically at the time. In the meantime, Torre and Temprado (2022) conducted a similar analysis in healthy older adults specifically for combined motor-cognitive training [448] and exergaming [452]. Based on these analyses, they proposed gold standards for the design and evaluation of exergame-based training studies, which are a major step to push the field forward [448, 452].

While these recommendations align with a majority of exercise and training variables that we defined as preferred choice for the 'Brain-IT training concept in the first phase of the project [58], there are also some discrepancies, especially with regard to the training frequency and exercise duration. This may suggest that the optimal training frequency and exercise duration might differ between mNCD and HOA, as it has been reported that a higher training frequency with shorter sessions (15 - 30 min) may be preferable in mNCD to achieve a similar training volume (~ 150 min/week) and prevent attentional exhaustion compared to healthy middle-aged to older adults [45, 58]. However, it could also be related to the important limitations of these analyses. First, both of our analysis relied on a qualitative synthesis of the evidence (i.e., no meta-analysis with moderator or subgroup analyses). Second, the original publications did not provide sufficient information on all specific training components (e.g., training density or level of cognitive demand), which limited the subsequent qualitative analysis of the literature. Third, both of our analysis did not consider other potentially important components of exergame-based training, such as body position during training, training density, level of cognitive demands, training location, specificity of the training, or whether it was delivered in a group or individually.

Therefore, the next logical step to advance the field of research would be to identify in a more robust manner the training components that can influence the effectiveness of exergame-based training to preserve or improve cognitive performance in middle-aged to older adults and evaluate whether these differ between cognitively impaired and healthy populations. To address this, we conducted a systematic review with meta-analysis aiming to provide quantitative evidence of which training

components influence the effectiveness of exergame-based training (**I**ntervention) on cognitive functioning (**O**utcome) in middle-aged to older adults (mean age ≥ 50 years) (**P**articipants) compared to inactive control interventions (i.e. sham control, usual care or lifestyle, or no intervention; **C**omparison). This systematic review and meta-analysis was registered at the international prospective register of systematic reviews (PROSPERO) before starting this systematic review (ID = CRD42023418593; date of registration: 1 May 2023), and is currently under review in the journal 'Ageing Research Reviews'. The results of this review will supplement to the recommendations provided by Torre and Temprado's (2022) [452] for HOA and our earlier recommendations specifically for older adults with mNCD [58] and build a promising basis to further optimize and develop exergame-based training concepts aiming to improve cognitive functioning in MOA.

Furthermore, there is potential for enhancing the technologies utilized in the implementation of the 'Brain-IT' training concept. In addition to the most important factors discussed in detail in chapter 6, future research could benefit from using camera-based or augmented reality systems to capture the body's movements and monitor training fidelity. This could include assessing movement quality and strategies used to maintain postural stability [210]) in addition to training adherence. In order to improve the coherence phase of the training, it is recommended to provide biofeedback during the breathing exercises. While empirical evidence does not suggest that adding biofeedback to coherence breathing would further improve its effectiveness [466], the addition of biofeedback could be gamified to increase engagement and allow for better monitoring of exercise adherence. The potential of biofeedback should also be further explored for the remaining phases of the training, particularly regarding feedback on exercise intensity and movement quality. Ideally, closed-loop feedback systems based on biofeedback should be developed, as already suggested in chapter 4 at the beginning of the project, with the concept of a biocybernetic adaptation loop. Finally, future technological advancements should incorporate the 'Brain-IT' training concept, including the MYCHOICE concept and all other algorithmic decisions previously made by training supervisors, into their software. This will optimize the delivery of the intervention and facilitate its transfer to clinical practice by reducing the time and effort required to follow the 'Brain-IT' training concept.

Finally, as discussed in chapter 8, future research is warranted to (i) specifically test our newly proposed hypothesis that the combination of exergame-based motor-cognitive training with resonance breathing guided by heart rate variability biofeedback (HRV-BF) may have positive synergistic effects by comparing the training with active comparators, including isolated and combined physical and/or cognitive exercises [452], as well as HRV-BF training; and (ii) elucidate the underlying biological mechanisms of action. Regarding the second point, we have collected data of magnetic resonance imaging of the brain that is outside the scope of this doctoral thesis. These ongoing analyses will allow us to explore the possible underlying neural changes in training in relation to adaptations in cognitive performance. In particular, we are interested in changes in grey and white matter volume, white matter microstructural integrity and connectivity, as well as functional connectivity of the hippocampus as well as other frontotemporal key regions of interest. Our data on task-based functional magnetic resonance imaging in particular can aid in distinguishing changes in the network underlying the specifically trained task (e.g., hippocampus in an episodic memory task) from changes in neuronal processing observed outside the task-specific network, where they may play a compensatory role [395]. According to the framework of Herold et al. 2019 [59], these investigations allow us to assess functional ad structural brain changes (level 2) in addition to

changes in cognitive performance (outcome level) and socioemotional changes (e.g., quality of life, symptoms of depression, anxiety, and stress; level 1). However, outcomes on cellular and molecular changes (level 1) are missing in the current project and should be specifically targeted in future research. All these investigations will facilitate a better understanding of the mechanisms of action and provide a stronger foundation for guiding decisions on further research aimed at improving training by providing optimal stimuli to influence the pathological mechanisms of mNCD and ultimately maximize the effectiveness of training in the secondary prevention of mNCD.

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Chapter

10

Supplementary Files

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Supplementary Files to Publication:

'Brain-IT' - exergame training with biofeedback breathing in neurocognitive disorders

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Supplementary File 1 - CONSORT checklist

Table S1: 2017 CONSORT Checklist of Information to Include When Reporting Randomized Trials Assessing nonpharmacologic treatments [450]

Section/Topic:	Item No:	Checklist item:	Reported in section(s):
TITLE AND ABSTRACT:			
	1a	Identification as a randomized trial in the title.	Journal restrictions on the number of characters in the title did not allow this information to be included in the title. Therefore, it is reported in the 'Abstract' section.
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts).	'Abstract'
INTRODUCTION:			
Background and objectives:	2a	Scientific background and explanation of rationale.	'Introduction' and 'Materials and Methods - Prior Work'
	2b	Specific objectives or hypotheses.	'Materials and Methods - Objectives and Hypotheses'; more details in the published study protocol [42]
METHODS:			
Trial design:	3a	Description of trial design (such as parallel, factorial) including allocation ratio. When applicable, how care providers were allocated to each trial group.	'Materials and Methods - Overview of the Trial Design, Participants, and Interventions'; more details in the published study protocol [42]
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons.	'Materials and Methods - Protocol and Registration - Important changes to the trial design and study setting after commencement'; more details in the published study protocol [42]
Participants:	4a	Eligibility criteria for participants. When applicable, eligibility criteria for centers and for care providers.	'Materials and Methods - Overview of the Trial Design, Participants, and Interventions'; more details in the published study protocol [42]
	4b	Settings and locations where the data were collected.	'Materials and Methods - Overview of the Trial Design, Participants, and Interventions'; more details in the published study protocol [42]
Interventions:	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered. Precise details of both the experimental treatment and comparator.	'Materials and Methods - Overview of the Trial Design, Participants, and Interventions'; more details in the published study protocol [42] and supplementary file 2
	5a	Description of the different components of the interventions and, when applicable, description of the procedure for tailoring the interventions to individual participants.	'Materials and Methods - Overview of the Trial Design, Participants, and Interventions'; more details in the published study protocol [42] and supplementary file 2
	5b	Details of whether and how the interventions were standardized.	'Materials and Methods - Overview of the Trial Design, Participants, and Interventions'; more details in the published study protocol [42] and supplementary file 2

	5c	Details of whether and how adherence of care providers to the protocol was assessed or enhanced.	N/A
	5d	Details of whether and how adherence of participants to interventions was assessed or enhanced.	'Materials and Methods - Overview of Outcomes - Other Endpoints - Adherence Protocol'
Outcomes:	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed.	'Materials and Methods - Overview of Outcomes'; more details in the published study protocol [42]
	6b	Any changes to trial outcomes after the trial commenced, with reasons.	N/A
Sample size:	7a	How sample size was determined. When applicable, details of whether and how the clustering by care providers or centers was addressed.	'Materials and Methods - Sample Size'; more details in the published study protocol [42]
	7b	When applicable, explanation of any interim analyses and stopping guidelines.	N/A (see 'Materials and Methods - Statistical Methods'
Randomization:			
Sequence generation:	8a	Method used to generate the random allocation sequence.	'Materials and Methods - Randomization'; more details in the published study protocol [42]
	8b	Type of randomization; details of any restriction (such as blocking and block size).	'Materials and Methods - Randomization'; more details in the published study protocol [42]
Allocation concealment mechanism:	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned.	'Materials and Methods - Randomization'; more details in the published study protocol [42]
Implementation:	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to Interventions.	'Materials and Methods - Randomization'; more details in the published study protocol [42]
Blinding:	11a	If done, who was blinded after assignment to interventions (e.g., participants, care providers, those administering co-interventions, those assessing outcomes) and how.	'Materials and Methods - Blinding'; more details in the published study protocol [42]
	11b	If relevant, description of the similarity of interventions.	N/A
	11c	If blinding was not possible, description of any attempts to limit bias	N/A
Statistical methods:	12a	Statistical methods used to compare groups for primary and secondary outcomes. When applicable, details of whether and how the clustering by care providers or centers was addressed.	'Materials and Methods - Statistical Methods'
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	N/A (see 'Materials and Methods - Statistical Methods'
RESULTS:			
Participant flow (a diagram is strongly recommended):	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome. The number of care providers or centers performing the intervention in each group and the number of patients treated by each care provider or in each center.	'Results - Recruitment and Participant Flow'
	13b	For each group, losses and exclusions after randomization, together with reasons.	'Results - Recruitment and Participant Flow'

	13c	For each group, the delay between randomization and the initiation of the intervention.	'Results - Recruitment and Participant Flow'
	13d	Details of the experimental treatment and comparator as they were implemented.	'Results - Delivery of the interventions'
Recruitment:	14a	Dates defining the periods of recruitment and follow-up.	'Results - Recruitment and Participant Flow'
	14b	Why the trial ended or was stopped.	'Results - Recruitment and Participant Flow'
Baseline data:	15	A table showing baseline demographic and clinical characteristics for each group. When applicable, a description of care providers (case volume, qualification, expertise, etc.) and centers (volume) in each group.	'Results - Baseline Data'
Numbers analyzed:	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups.	Primary Outcome: 'Results - Recruitment and Participant Flow' and 'Results – Primary Outcome' Secondary Outcomes: 'Results – Secondary Outcomes' and 'Table 8-3: Statistics for all secondary outcomes'
Outcomes and estimation:	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval).	Primary Outcome: 'Results – Primary Outcome' Secondary Outcomes: 'Results – Secondary Outcomes' and 'Table 8-3: Statistics for all secondary outcomes'
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N/A
Ancillary analyses:	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	N/A (see 'Materials and Methods - Statistical Methods'
Harms:	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	'Results - Recruitment and Participant Flow'
DISCUSSION:			
Limitations:	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses. In addition, take into account the choice of the comparator, lack of or partial blinding, and unequal expertise of care providers or centers in each group.	'Discussion - Strength and Limitations'
Generalizability:	21	Generalizability (external validity) of the trial findings according to the intervention, comparators, patients, and care providers and centers involved in the trial.	'Discussion - Principal Findings' and 'Discussion - Strength and Limitations'
Interpretation:	22	Interpretation consistent with results, balancing benefits - and harms, and considering other relevant evidence.	'Discussion - Principal Findings' and 'Discussion - Implications for Research and Clinical Practice'
OTHER INFORMATION:			
Registration:	23	Registration number and name of trial registry.	'Abstract' and 'Materials and Methods - Overview of the Trial Design, Participants, and Interventions'
Protocol:	24	Where the full trial protocol can be accessed, if available.	'Materials and Methods - Protocol and Registration'
Funding:	25	Sources of funding and other support (such as supply of drugs), role of funders.	'Sources of Funding'

Supplementary File 2 - refined ‘Brain-IT’ training concept

S2.1 Introduction

This training concept has been developed in the project ‘Brain-IT’. In this project, we designed and developed a novel training concept (‘Brain-IT’) specifically for older adults with mild neurocognitive disorder (mNCD). The ‘Brain-IT’ training concept represents a guideline for applying a combination of exergame-based motor-cognitive training and resonance breathing guided by heart rate variability biofeedback (HRV-BF) training by standardizing the training characteristics (e.g., training frequency, intensity, and duration), as well as the structure and content of training, whereas the exergame device and the specific games used within each of the defined neurocognitive domains can be replaced by alternative exergames.

The projects’ methodology [58] followed the guidelines of the Medical Research Council for the development and evaluation of complex interventions [449] as well as the Multidisciplinary Iterative Design of Exergames (MIDE) – Framework [57]. The ‘Brain-IT’ project was structured in three phases. In phase 1, we systematically combined a comprehensive literature synthesis [58] with qualitative research including primary end users (older adults with mNCD), secondary end users (physiotherapists, occupational therapists, healthcare professionals), exergaming researchers, as well as experts from the exergaming industry [45] to specify a set of design requirements for the ‘Brain-IT’ training concept. In phase 2, possible concepts for the exergame-based training concept were co-designed and elaborated based on the set of design requirements defined in phase 1. The first prototype of the resulting ‘Brain-IT’ training concept [58] then entered the iterative cycle of feasibility, usability, safety and acceptance testing and integrating study results for further development based on co-design until an "acceptable" solution was achieved. The results of this process revealed that the resulting ‘Brain-IT’ training is feasible, usable, safe, and highly accepted by older adults with mNCD and preliminary data on the effects of the ‘Brain-IT’ training are promising [60]. The results on the effectiveness of the ‘Brain-IT' concept were published with the accompanied paper (study protocol [61]; registered at clinicaltrials.gov prior to the start of patients’ recruitment (NCT05387057)).

In the ‘Brain-IT’ project, we used technology of Dividat AG (i.e., ‘Senso Flex’ (Dividat AG, Schindellegi, Switzerland; hardware: prototype version 2, software: version 22.4.0-360-gf9df00d5b), Polar (i.e., heart rate monitor (Polar M430) and sensor (Polar H10)), and Kubios (Kubios HRV Premium (Kubios Oy, Kuopio, Finland, version 3.4)) to implement our training concept. To ensure replicability, the ‘Brain-IT’ training concept was planned and reported according to the Consensus on Exercise Reporting Template (CERT) [238] and provides specific instructions on how to adapt the ‘Brain-IT’ training concept to other hardware and software solutions.

S2.2 Overview of the Exercise and Training Variables

Frequency:	≥ 5x/week
Intensity/Complexity:	monitored and adapted according to predefined progression rules (section S2.4).
Type & Specificity:	combination of exergame-based simultaneous motor-cognitive training with incorporated cognitive tasks and HRV-BF training that is adopted with an individualized (deficit-oriented) focus on (1) learning and memory, (2) executive function, (3) complex attention, and (4) visuo-spatial skills.
Time & Duration:	≥ 24 min/session for ≥ 12 weeks
Volume:	≥ 120 min/week
Variability:	according to the concept of MYCHOICE (section S2.8).
Progression:	according to predefined progression rules (section S2.7).
Density:	In general, training sessions should be performed on different days. If multiple sessions are performed on the same day, recovery time between sessions should be ≥ 4 hours.
Location:	at participant's homes
Guidance & Supervision:	structured in 3 phases starting with a guided familiarization period with the aim to lead participants to being able to train independently in the long-term.

S2.3 Overview of the Training

S2.3.1 Implementation in the Project 'Brain-IT':

The 'Brain-IT' training concept consists of an individualized combination of exergame-based simultaneous motor-cognitive training with incorporated cognitive tasks and HRV-BF training that is adopted with an individualized (deficit-oriented) focus on (1) learning and memory, (2) executive function, (3) complex attention, and (4) visuo-spatial skills. According to the training concept, each participant is instructed to train ≥ 5x/week for ≥ 24 min per session resulting in a weekly training volume of ≥ 120 min. All training sessions are planned to take place at participant's homes using the exergame training system Senso Flex. In case a participant prefers to train at one of the study centers or has not enough space for training with the 'Senso Flex' at home, the participants can be instructed to train with an adapted training frequency of ≥ 3x/week for 24 min per session at one of the study sites using the exergame training system 'Senso' (Dividat AG, Schindellegi, Switzerland; CE certification), but it is still recommended to train at the suggested optimal frequency (≥ 5x/week) and volume (≥ 120 min/week).

The 'Senso Flex' is a home-based version of the 'Senso'. The 'Senso' was developed for stationary use in physiotherapies, nursing homes, or rehabilitation clinics. It consists of a 1.13 m × 1.13 m robust stepping platform built from metal and glass including a handrail for balance support. The stepping platform is connected to a computer and a frontal television screen. In contrast, 'Senso Flex' was developed for home-based use and consists of a 1.11 m x 0.99 m rollable mat as stepping platform that is plugged into the portable computer and a television (or other screen) at home) and can be packed up and put away after training. In both cases, the pressure-sensitive stepping platform is divided into five areas: (1) center (home position), (2) front, (3) right, (4) back, and (5) left. The device detects participants' position and timing of movements (including weight shifting, walking on the spot, and steps in four directions: front, right, back, and left) to interact with different game scenarios, that are programmed in the Dividat training software (i.e. the same training software is used for both types of stepping platforms ('Senso' and 'Senso Flex')). Weight-shifting, walking on the spot, and stepping movements to the four directions enable the interaction and control of the virtual exergame scenarios that are displayed on a screen right in front of the participant. Visual, auditory and somatosensory (vibrating platform; only available on the 'Senso') feedback is provided in real-time in order to enrich the game experience.

The training intervention starts with a familiarization period of two weeks. During this phase, most of the training sessions (i.e. 4 out of 5 sessions) are supervised by our research team. After this initial guided familiarization period, supervision of training sessions is gradually reduced to 1x/week during a four-week transition phase. This transition phase aims to lead participants to being able to train independently. In this transition phase, the amount of supervision of training sessions is individually determined within a predefined range (see Figure 1) in accordance with the capabilities and preferences of the participants. From the 7th week until completion of the training intervention, semi-autonomous training with one supervised training session per week is prescribed for each participant. During independent training sessions, the research team is available by phone to provide help when needed. In case the training sessions need to take place at one of the study sites using the exergame training system 'Senso', the absolute amount of supervision is kept the same, since participants are

instructed to train at ≥ 3x/week but it is still recommended to train at the suggested optimal frequency (≥ 5x/week) and volume (≥ 120 min/week).

S2.3.2 How to adapt the 'Brain-IT' training concept to other hardware and software solutions:

Step 1: Select an exergame device that meets the following criteria:

Step 1a: If you intend to develop a new exergame system to implement the 'Brain-IT' training, follow all the steps of the MIDE-framework [57]. A detailed description of the methodology and the integration of the MIDE-framework into the 'Brain-IT' project can be found in [58].

Step 1b: If you intend to use an existing exergame system to implement the 'Brain-IT' training, make sure it meets all of the following criteria:

- General Criteria:
  - Step-based exergame played in standing position (including treadmill-based exergames)
  - Device is (optimally) suitable for home use.
  - Exergame device provides real-time visual, auditory and/or tactile feedback (i.e. multisensory feedback to be used as a positive reinforcement mechanism)

- Safety requirements:
  - The exergame system provides a handrail or similar for balance support or can be combined with an external balance support device (e.g., walking sticks, harness, mobile handrails) to prevent falls (especially at the beginning of training).

- Usability requirements:
  - Ensure good usability of the exergames. As a rule of thumb, each participant should be able to use the system independently (including setting up and starting training) after the two-week familiarization phase and with the help of a user manual.

- Basic requirements to game design:
  - Provide simple graphics and ensure good contrast (i.e., main task located in the center of the screen AND only elements that are related to the game task are visible).
  - Provide game tasks with a certain closeness to everyday life.
  - Provide easily comprehensible and clearly designed tasks.
  - Avoid unexpected appearings or technical problems.
  - Avoid confronting performance feedback by providing very subtle negative feedback in case of mistakes to help ensure task comprehension.

S2.4 Structure of each Exergame Session

S2.4.1 Implementation in the Project 'Brain-IT':

Throughout the training intervention period, all sessions are prescribed following the same basic structure (see Figure S1). Each session consists of three blocks with 3 phases per block.

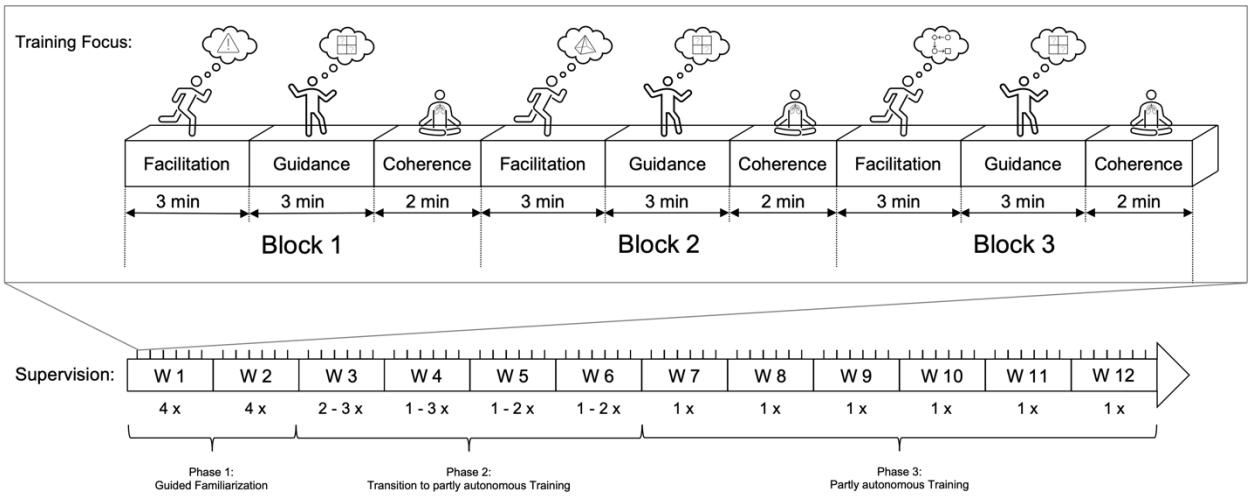


Figure S1: Overview of the exergame-based intervention concept and the basic structure of each exergame session (here as an example for a patient with amnestic-single domain mild neurocognitive disorder with a training focus on learning and memory in week 1).

Phase 1 - Facilitation

Phase 1 - Facilitation aims to apply a moderate physical intensity in the context of challenging but feasible neurocognitive and motoric demands mainly intending to *"trigger neurophysiological mechanisms, which promote neuroplasticity"* [34, 239] while additionally using *"cognitive stimulation […] to "guide" these neuroplastic processes"* [34, 239, 240]. This phase includes games focusing on neurocognitive domains that are least impaired. The external task demands is individually adapted to ensure an appropriate internal training load. More specifically, the internal training load is subdivided into a fixed component (i.e. physical intensity) and a variable component (i.e. neurocognitive (game-) demand). An additional stepping task is used to set the level of physical intensity. It includes walking on the spot at a predefined stepping frequency that is needed to reach a moderate level of physical intensity (i.e. ranging between 40 and 59 % heart rate reserve (HRR) [233])). The stepping frequency is individually determined for each participant (see section 2.7). A battery figure add-on is visible in the center of the screen that provides real-time visual feedback whether the predefined stepping frequency is reached. More specifically, if the predefined minimal required stepping frequency is reached or exceeded, the battery stays at equilibrium or fills. As long as the battery level is above 80 % (indicated by a line), the battery stays green. If the participants' stepping frequency falls below the predefined minimal required stepping frequency, the battery level decreases, and the battery turns orange (40 – 80 %) or red (below 40 %) indicating that the stepping frequency should be increased. On top of this fixed physical intensity, a variable amount of neurocognitive (game-) demands (e.g. game type, task complexity, predictability of required tasks)

is applied. Since the physical intensity is kept constant, changes in the overall internal training load can mainly be attributed to these neurocognitive and motoric (game-) demands and, accordingly, the internal training load can be adjusted on basis of these game characteristics. Therefore, the neurocognitive demands of the exergame are individually adapted in order to ensure an appropriate total internal training load. The monitoring and adaption of the internal training load is based on predefined progression rules for adapting characteristics of external training load (section 2.7).

Phase 2 – Guidance

Phase 2 - Guidance aims to make use of the triggered neurophysiological mechanisms from phase 1 to specifically guide neuroplastic processes of the mainly impaired neurocognitive domain. Therefore, games focusing on the mainly impaired neurocognitive domain for the individual participant (e.g. amnestic single domain => learning and memory) are used. These games focus on cognitive and motoric demands, but not on physical intensity. The cognitive-motoric demands of the exergame (also called 'external load') are individually adapted in order to ensure an appropriate internal training load. The monitoring and adaption of the internal training load will be based on predefined progression rules for adapting characteristics of external training load (section 2.7).

Phase 3 – Coherence

Phase 3 - Coherence integrates HRV-BF training that includes breathing slowly and in a controlled manner and extending the exhalation phase. With this, we specifically activate the vagus nerve and promote the activation of the central autonomous networks in the brain that is important for self-regulation and the control of cognitive processes and helps to restore the balance of various physical systems. The unique combination of this biofeedback-guided breathing training with exergame training forms the core of our training concept. Through physical and cognitive training, we bring various systems in the body out of balance. The breathing training aims to restore this balance and thus offer holistic training. Additionally, this also allows us to account for psychological factors, as patients with mNCD often exhibit depressive symptoms and anxiety, which are in turn important indicators for progression to dementia [241, 242].

HRV-BF training is a behavioral intervention aiming to increase cardiac autonomic control, enhance homeostatic regulation, and regulate emotional state [48-50]. It consists of a regular breathing practice at a specific frequency that is individually determined that produces high amplitude of heart rate variability (HRV), leading to increased cardiac autonomic control. Usually, this resonance breathing frequency is around 6 breaths/min [243]. An increased cardiac autonomic control increases vagal afferent transmission to the forebrain and activate and stimulate brain regions relevant for cognitive adaptations (such as the prefrontal cortex) [48, 50]. HRV-BF or paced breathing (at resonance frequency) is effective in improving cardiac autonomic control [50, 51], cognitive functioning (in particular executive functions) [52, 53], and emotional regulation [50, 53] (i.e., by decreasing symptoms of depression [50, 53, 54], anxiety [50, 54, 55], and stress [54, 55]) across different age groups and in clinical populations. The evidence for older adults (i.e. ≥ 60 years) or patients with cognitive impairments is sparse, but decreases in depression, anxiety, and increases in attentional performance (no sign. difference in executive functioning) have already been reported, suggesting that older adults may benefit from HRVBT much like the younger populations [244]. Moreover, there is evidence supporting a causal role of cardiac autonomic control in modulating plasma AD-related biomarkers [56].

In the 'Brain-IT' project, we did not have the resources to provide each participant with the technology to implement biofeedback throughout the intervention. However, *"so far, no empirical evidence indicates that slow breathing practice with biofeedback offers superior outcomes in terms of vagally-mediated HRV or other health-related outcomes, compared to SPB without biofeedback."* [466] Additionally, *"after initial training some people still achieve better results by following a heart monitor, while others do just as well doing paced breathing at their resonance frequency, once this frequency has been determined by biofeedback, following the second hand on a clock or counting seconds silently"* [4]. Therefore, for the sake of simplicity, made use of this transfer to resonance breathing. Before starting the training intervention, the resonance frequency is determined according to the protocol of Lehrer et al. 2013 (i.e. visit 1 of their protocol) [245]. During the training intervention, HRV-BF training involves breathing for two minutes at a rhythm of 30 % inhale, 10 % hold, 50 % exhale, 10 % hold at the individually predetermined resonance frequency visualized on the screen of the exergame device (i.e. a sun is displayed within a landscape. When the sun gets bigger, the patients breath in. When the sun gets smaller, the patients breath out).

S2.4.2 How to adapt the 'Brain-IT' training concept to other hardware and software solutions:

In general, the structure of the 'Brain-IT' training concept must remain the same (see Figure 1). To implement this, the following adaptations are required in each of the following phases of the training:

Phase 1 – Facilitation:

Various real-time feedback options can be provided in place of the battery number add-on to maintain a moderate level of physical intensity throughout the game. When implementing alternative options, the basic game design requirements (see Section 1.2 Overview of the Training) must be met. Otherwise, no adjustments to this phase are required.

Phase 2 – Guidance:

No adaptations are required for this phase.

Phase 3 – Coherence:

No adaptations are required for this phase. However, alternative (optimally gamified) visualizations can be used to guide participants' breathing patterns as long as the basic requirements for game design (see Section 1.2 Overview of the Training) are met.

S2.5 Overview of Exergames and Trained Neurocognitive Domains

S2.5.1 Implementation in the Project 'Brain-IT':

In this section, an overview of the currently available exergames on the 'Senso (Flex)' that we found suitable for implementation in the 'Brain-IT' project for the training of the neurocognitive domains of complex attention, learning and memory, executive function, and visuo-spatial skills that is provided. Depending on the complexity of the games as such, an earliest start and latest end were predefined that are considered in the progression rules (section 2.7).

Table S1: Overview of the currently available exergames on the 'Senso (Flex)' that we found suitable for implementation in the 'Brain-IT' project for the training of the neurocognitive domains of complex attention, learning and memory, executive function, and visuo-spatial skills

* = secondary classification of a game that focuses on more than one neurocognitive (sub)domains

color coding: black = existing games, green = new games or game elements that were developed in the 'Brain-IT' project

Training Focus	Neurocognitive Domain	Neurocognitive Subdomain	Exergames	Timeframe	
				earliest start	latest end
	Complex Attention	Sustained Attention	'Simple'	W 1	W 8
		Divided Attention	'Divided'	W 2	W 10
		Selective Attention	'Birds'	W 3	W 12
			'Habitats'*	W 5	W 12
		Processing Speed	'Simple'*	W 1	W 8
			'Flexi'*	W 4	W 12
	Learning & Memory AND Working Memory	Free Recall	'Shopping Tour'*	W 1	W 12
		Serial Recall	'Simon_numbered'	W 2	W 12
			'Simon'	W 3	W 12
		Cued Recall	'Steps'	W 4	W 12
		Recognition Memory	'Shopping Tour'	W 1	W 12
		Semantic Memory	N/A	N/A	N/A
		Implicit Learning	N/A	N/A	N/A
		Working Memory	'Nomis_numbered'	W 5	W 12
			'Nomis'	W 6	W 12
	Executive Function	Planning	'Targets'	W 1	W 12
			'Tetris'*	W 6	W 12
		Decision Making	N/A	N/A	N/A
		Inhibition	'Habitats'	W 5	W 12
		Flexibility	'Flexi'	W 4	W 12
			'Evolve'	W 2	W 12
	Visuo-spatial Skills	Visual Perception	'Gears'*	W 1	W 12
			'Tetris'*	W 6	W 12
			'Targets'*	W 1	W 12
		Visuoconstructional Reasoning	'Gears'	W 1	W 12
			'Tetris'	W 6	W 12
		Perceptual-Motor Coordination	N/A	N/A	N/A

S2.5.2 How to adapt the 'Brain-IT' training concept to other hardware and software solutions:

To adapt the 'Brain-IT' training concept to other software and hardware and software solutions, use Table S1 and fill in your existing exergames and/or develop new exergames in collaboration with neuropsychologist(s) and following these rules:

(1) Ideally, there should be at least one exergame available for each of the neurocognitive subdomains.

(2) Each exergame must be categorized into the primary neurocognitive subdomain being trained (and secondary subdomain in the case of a game that focuses on more than one neurocognitive (sub)domain). The categorization must be made by agreement between at least two experienced neuropsychologists to ensure the content validity of the exergames used to train each neurocognitive (sub)domain.

(3) For each game, an earliest and latest start time must be defined. The following steps should be followed, all in agreement with at least two experienced neuropsychologists, to ensure the content validity of the exergames used to train each neurocognitive (sub)domain.

   I. For each neurocognitive domain, rank-order all available games according to their neurocognitive demands.

   II. Allocate the least demanding game for each neurocognitive domain to start in the first week.

   III. Allocate the remaining games consecutively according to their rank-order.

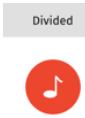
   IV. In general, all games should be kept available until the end of the training to increase the available options of games throughout the training and in line with the concept of MYCHOICE. However, in case the neuropsychologists have good reasons for excluding games earlier in the training (e.g., introductory games that mainly fulfill the purpose of getting patients familiarized with the device, have limited options to increase neurocognitive demands, and where it is expected that they are not challenging enough even for the most impaired patients towords the end of the training), this can be defined accordingly.

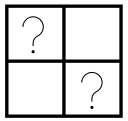
S2.6 Description of Specific Exergames

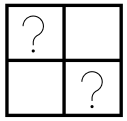
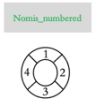
S2.6.1 Implementation in the Project 'Brain-IT':

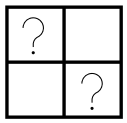
Table S2: Description of the currently available exergames on the 'Senso (Flex)' for the training focus on the neurocognitive domains of complex attention, learning and memory, executive function, and visuo-spatial skills

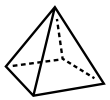
color coding: black = existing games, green = new games or game elements that were developed in the 'Brain-IT' project or related projects in our lab

Neurocognitive Domain	Exergames				
	Name	Main Neurocognitive Subdomain(s)	Description	Parameters to adapt Task Complexity	Feedback Mechanisms (provided after each response)
Complex Attention 		Sustained Attention, Processing Speed	In the game 'Simple', four circles are displayed in grey. As soon as one of the circles turns red, a step needs to be taken in the corresponding direction as fast as possible.	• internal progression algorithm that automatically adapts task difficulty based on game performance in real time • game speed (interstimulus-interval) • variance in interstimulus-interval • response window • predictability (predefined vs. random sequences) • stepping direction(s) • stepping frequency	Positive feedback: 'Positive' vibration (i.e. single short pulse), visual feedback (i.e. wiggling of target, and sound effect (i.e. "ringing bell") Negative feedback: 'Negative vibration' (i.e. multiple strong pulses).
		Divided Attention	In the game 'Divided', four circles are displayed in grey. As soon as one of the circles turns red, or an auditory cue is played (high tone = step forwards, low tone = step backwards), a step needs to be taken in the corresponding direction as fast as possible.	• internal progression algorithm that automatically adapts task difficulty based on game performance in real time • game speed (interstimulus-interval) • variance in interstimulus-interval • response window • predictability (predefined vs. random sequences) • stepping direction(s) • stepping frequency	Positive feedback: 'Positive' vibration (i.e. single short pulse), visual feedback (i.e. wiggling of target, and sound effect (i.e. "ringing bell"). Negative feedback: 'Negative vibration' (i.e. multiple strong pulses).

Complex Attention 		Selective Attention	In the game 'Birds' a feather is displayed in the middle of the screen. The participants' task is to match the feather with a bird and to return the feather to its birds by making a step into the corresponding direction.	• internal progression algorithm that automatically adapts task difficulty based on game performance in real time • game speed (interstimulus-interval) • variance in interstimulus-interval • response window • stepping direction(s) • predictability (predefined vs. random sequences) • stepping frequency	Positive feedback: 'Positive' vibration (i.e. single short pulse), and sound effect (i.e. bird chirping). Negative feedback: 'Negative vibration' (i.e. multiple strong pulses) and sound effect (i.e. muffled sound effect).
Learning and Memory & Working Memory (EF) 		Serial Recall	In the game 'Simon_numbered', a stepping sequence (i.e. indicated by a concurrent lighting up of a sequence of sections with different numbers of a circle and a corresponding sound) has to be memorized and repeated by stepping into the corresponding direction.	• sequence length • stepping direction(s) • stepping frequency	Positive feedback: 'Positive' vibration (i.e. single short pulse), visual feedback (i.e. lighting up of target, and sound effect (i.e. single tone corresponding to color). Negative feedback: 'Negative vibration' (i.e. multiple strong pulses) and sound effect (i.e. muffled sound effect).
		Serial Recall	In the game 'Simon', a stepping sequence (i.e. indicated by a concurrent lighting up of a sequence of sections with different colors of a circle and a corresponding sound) has to be memorized and repeated by stepping into the corresponding direction.	• internal progression algorithm that automatically adapts task difficulty based on game performance in real time • sequence length • stepping direction(s) • stepping frequency	Positive feedback: 'Positive' vibration (i.e. single short pulse), visual feedback (i.e. lighting up of target, and sound effect (i.e. single tone corresponding to color). Negative feedback: 'Negative vibration' (i.e. multiple strong pulses) and sound effect (i.e. muffled sound effect).

Learning and Memory & Working Memory (EF) 		Cued Recall	In the game 'Steps', a stepping sequence (i.e. indicated by a concurrent lighting up of a sequence of sections with different numbers of a square with 9 fields) has to be memorized and repeated by stepping into the corresponding direction at the rhytm of the beat (i.e. indicated by a metronome).	• number of steps per level • maximal number of trials per stepping sequence • start level	Positive feedback: 'Positive' vibration (i.e. single short pulse), visual feedback (i.e. lighting up of target (in green), and sound effect (i.e. single tone corresponding to a number and ascending tone sequence). Negative feedback: visual feedback (i.e. lighting up of target (in orange/red), and sound effect (i.e. descending tone sequence).
		Free Recall, Recognition Memory	In the game 'Shopping Tour, at first, a shopping list is displayed in the center of the screen for the duration of encoding phase. Second, the shopping list will disappear and one item after another will appear on the screen. The users' task is to gather all items (type and quantity) of the shopping list by stepping to the right (i.e. to put the object into the shopping cart) or to the left (i.e. not to buy the product). After each response, a feedback is provided.	• number of items on the list • number of items to be purchased • probability of presented items to be purchased or not (in percent) • probability that items need to be purchased multiple times (in percent)	Positive feedback: Arrow lights up in green light, 'positive' (i.e. single short pulse) vibration and sound effect (i.e. "ringing bell"), cross out items on shopping list and throw out list when successfully completed Negative feedback: Arrow lights up in red light, 'negative vibration' (i.e. multiple strong pulses), and sound effect (i.e. muffled sound effect).
		Working Memory	In the game 'Nomis_numbered', a stepping sequence (i.e. indicated by a concurrent lighting up of a sequence of sections with different numbers of a circle and a corresponding sound) has to be memorized and repeated backwards by stepping into the corresponding direction.	• sequence length • stepping direction(s) • stepping frequency	Positive feedback: 'Positive' vibration (i.e. single short pulse), visual feedback (i.e. lighting up of target, and sound effect (i.e. single tone corresponding to color). Negative feedback: 'Negative vibration' (i.e. multiple strong pulses) and sound effect (i.e. muffled sound effect).

Learning and Memory & Working Memory (EF) 	Nomis 	Working Memory	In the game 'Nomis' (Simon backwards), a stepping sequence (i.e. indicated by a concurrent lighting up of a sequence of sections with different colors of a circle and a corresponding sound) has to be memorized and repeated backwards by stepping into the corresponding direction.	• sequence length • stepping direction(s) • stepping frequency	Positive feedback: 'Positive' vibration (i.e. single short pulse), visual feedback (i.e. lighting up of target, and sound effect (i.e. single tone corresponding to color). Negative feedback: 'Negative vibration' (i.e. multiple strong pulses) and sound effect (i.e. muffled sound effect).
Executive Function 	Targets 	Planning	The game 'Targets' requires the participant to hit incoming red balls in the middle of the target by stepping into the corresponding direction.	• internal progression algorithm that automatically adapts task difficulty based on game performance in real time • game speed (speed multiplier) • stepping direction(s) • stepping frequency	Positive feedback: 'Positive' vibration (i.e. single short pulse), visual feedback (i.e. visual impulse of selected target, and sound effect (i.e. "ringing bell"). Negative feedback: 'Negative vibration' (i.e. multiple strong pulses) and sound effect (i.e. muffled sound effect).
	Habitats 	Inhibition, Selective Attention	In the game 'Habitats', animals move across the four landscapes in the picture. If an animal does not appear in its familiar surroundings, a step needs to be taken in this direction. However, animals shouldn't be disturbed in their natural habitat.	• internal progression algorithm that automatically adapts task difficulty based on game performance in real time • game speed (interstimulus-interval) • variance in interstimulus-interval • task complexity (including inhibition tasks or not) • stepping direction(s) • stepping frequency	Positive feedback: 'Positive' vibration (i.e. single short pulse), visual feedback (i.e. wiggling of target, and sound effect (i.e. animal sounds). Negative feedback: 'Negative vibration' (i.e. multiple strong pulses), sound effect (i.e. muffled sound effect), and visual animation (i.e. animal with speech bubble displaying "Hey!")

Executive Function 		Flexibility, Processing Speed	The game 'Flexi' consists of two parts: Part A: Requires participants to make a step in the direction of the next higher number, starting from the number displayer in the center. Part B: In addition to the task of Part A, a figure appears around the number. It is necessary to make a step in the direction of the next higher number with the opposite pattern.	• task complexity (Part A/B)	Positive feedback: 'Positive' vibration (i.e. single short pulse), and sound effect (i.e. "ringing bell"). Negative feedback: 'Negative vibration' (i.e. multiple strong pulses).
		Flexibility	The task of the game 'Evolve' is to catch targets (blue balls) while avoiding hitting obstacles (red crosses) by controlling an avatar through weight shifting.	• progression that automatically adapts task difficulty based on game performance in real time • game speed (interstimulus-interval) of targets • movement speed of targets • game speed (interstimulus-interval) of obstacles • movement speed of obstacles	Positive feedback: 'Positive' vibration (i.e. single short pulse), and sound effect (i.e. high "blubb" sound). Negative feedback: 'Negative vibration' (i.e. multiple strong pulses) and sound effect (i.e. low "blubb" sound).
Visuo-Spatial Skills 		Visuoconstructional Reasoning, Planning	'Gears' requires the participant to select the correct trace for the corresponding gear wheel of a displayed train.	• complexity of the gear wheels (3 selectable levels) • response window • stepping direction(s) • predictability (predefined vs. random sequences) • animated (rotating wheels) wheels vs. wheels in fixed position • stepping frequency	Positive feedback: 'Positive' vibration (i.e. single short pulse), visual feedback (i.e. visual impulse of selected target, and sound effect (i.e. "ringing bell"). Negative feedback: 'Negative vibration' (i.e. multiple strong pulses) and sound effect (i.e. muffled sound effect).
		Visuoconstructional Reasoning, Planning	'Tetris' requires participants to rotate and move two-dimensional polygons (with varying shapes and colors) dropping one-by-one from top to the bottom. The aim of the game is to arrange complete rows of blocks to form solid horizontal lines, in order to let these lines disappear.	• internal progression algorithm that automatically adapts task difficulty based on game performance in real time • game speed (speed multiplier) • stepping frequency	Positive feedback: 'Positive' vibration (i.e. multiple short pulses) for a full row, visual feedback (i.e. full row disappears), and sound effect (i.e. "ringing bell"). Negative feedback: none

S2.6.2 How to adapt the 'Brain-IT' training concept to other hardware and software solutions:

In Table S2, provide a description of each of the exergames you used to deliver the 'Brain-IT' training.

S2.7 Progression Rules for Monitoring Internal Load and Adapting External Loads

S2.7.1 Phase 1 – Facilitation

Implementation in the Project 'Brain-IT':

As described above, the internal training load is subdivided into the physical exercise intensity of the stepping task and the neurocognitive and motoric (game-) demands of the games in phase 1. Additionally, the level of stability support (holding on to a handrail or similar with both hands, one hand, only two fingers or no stability support) is individually determined to provide a challenging but safe condition. The stepping frequency of the stepping tasks is predetermined for each participant with the aim to reach a moderate level of physical intensity (i.e. ranging between 40 and 59 % heart rate reserve (HRR) [233]). To avoid overload, the participants are introduced stepwise; first, the stepping frequency is determined while the level of neurocognitive demand is held low. Afterwards, the total level of internal training load is monitored and continuously adapted.

Phase 1a - Determination of minimal stepping frequency:

All participants start with a stepping frequency of 100 steps/min and at Level 1 of game demands in the first training session (see section 7). The target physical exercise intensity is determined based on the target heart rate (HR) that is calculated using the Karvonen method with a target intensity of 40 % HRR: $HR_{target} = (HR_{max} – HR_{rest}) \cdot 0.40 + HR_{rest}$ [246, 247]. For this calculation the age-predicted maximal heart rate: $HR_{max} = 208 – 0.7 \cdot age$ and HR_{rest} measured at the pre-measurements is used. The stepping frequency is then increased by 5 steps/min at each training session (to a maximum of 140 steps/min) until the minimal level of physical exercise intensity is reached. The evaluated stepping frequency is then considered as a fixed component of the overall external load. In all subsequent training session, this fixed physical exercise intensity is kept constant and the focus shifts on monitoring and adapting the total internal training load.

Phase 1b – Monitoring and adaptation of total internal training load:

Since the physical intensity in phase 2 is held constant, changes in the overall internal training load can mainly be attributed to the variable level of neurocognitive demand. The level of neurocognitive demand is standardized according to predefined game levels (see section 7). Phase 2 continues with game level 1, until a plateau in performance is reached. A plateau in performance is read out visually guided by the following predefined criteria: (1) a performance increase of less than or equal to 5 % compared to the previous exergame session while (2) there was an increase in performance from session so session over at least the previous three training sessions. The specific performance outcomes for each exergame to take into consideration are underlined in table S3. In case a precision outcome is available (i.e. for the game 'Targets'; precision = number of hits / (number of hits + number of missed targets)), the criterion to progress to the next higher level is to achieve a precision of at

least 90 %. Each time a plateau in performance is reached, the game level is increased by one level. If the participants wishes to have the task demands increased or the staff supervising the participants recognize that an increase in the task demands is feasible, they have the option to override these progression criteria and increase the game level by one (or more) level(s). Additionally, the level of stability support (holding on to a handrail or similar with both hands, one hand, only two fingers or no stability support) is individually determined to reach a challenging but safe condition. Depending on the complexity of the games as such, the earliest start and latest end that were predefined in section 2 that are additionally considered when planning the training sessions.

How to adapt the 'Brain-IT' training concept to alternative exergame devices:

In general, the progression rules for monitoring the internal training load and adapting the external training loads must remain the same as implemented in the 'Brain-IT' project. To adapt the 'Brain-IT' training to other software and hardware and software solutions, use all available exergames filled in Table S1 and fill in Table S3 for each of these games. The game levels and the parameters chosen to reach these levels must be defined by agreement between at least two experienced neuropsychologists, taking into account the following key points:

- Level 1 = Introductory level. Even most impaired patients should be able to play the game while performing the additional stepping task at the first trial without problems to ensure that no overload occurs.
- Level 10 = "healthy functioning" level. The neurocognitive demands, while performing the additional step task, are expected to be challenging but doable for an average healthy older adult.
- The remaining levels are defined to increase neurocognitive demands consecutively and regularly from level to level. This should again be done by agreement between at least two experienced neuropsychologists. It is recommended to consider Gentile's Taxonomy for Motor Learning [467], Neuroplasticity Principles [468], Motor Learning Principles [469], and Training Principles [59, 229] in this regard.

For each game, at least one game metric needs to be chosen or developed that provides a valid and reliable measure for game performance and is sensitive to changes in game performance over time.

In case a scientifically validated progression algorithm that is based on game metric that provides a valid and reliable measure for game performance and are sensitive to changes in game performance over time, this option can be considered instead of the predefined levels. However, it must be ensured, that the patients are not overloaded in the initial training sessions.

S2.7.2 Phase 2 – Guidance

Implementation in the Project 'Brain-IT':

In phase 2, the mainly impaired neurocognitive domain is trained. Therefore, the focus of monitoring and adapting the task demands is on neurocognitive demands (i.e. motor- and cognitive demands that are linked because both change as a function of game complexity). The level of neurocognitive demand is standardized according to predefined game levels (see section 8) for game levels one to nine. The final game level (i.e. Level 10+) is based on an adaptive mode (i.e. internal progression algorithm provided by the Dividat) that automatically adapts task difficulty based on game

performance in real time and aims to adapt the game demands in order to provide an optimal challenge.

All participants start with level 1. Each time a plateau in performance is reached, the game level is increase by one level. A plateau in performance is read out visually guided by the following predefined criteria: (1) a performance increase of less than or equal to 5 % compared to the previous exergame session while (2) there was an increase in performance from session so session over at least the previous three training sessions. The specific performance outcomes for each exergame to take into consideration are underlined in Table S4. In case a precision outcome is available (i.e. for the games 'Shopping Tour' and 'Targets' (precision = number of hits / (number of hits + number of missed targets))), the criterion to progress to the next higher level is to achieve a precision of at least 90 %. If the participants wish to have the task demands increased or the staff supervising the participants recognize that an increase in the task demands is feasible, they have the option to override these progression criteria and increase the game level by one (or more) level(s). Additionally, the level of stability support (holding on to a handrail or similar with both hands, one hand, only two fingers or no stability support) is individually determined to reach a challenging but safe condition. Depending on the complexity of the games as such, the earliest start and latest end that were predefined in section 2 that are additionally considered when planning the training sessions.

How to adapt the 'Brain-IT' training concept to other hardware and software solutions:

In general, the progression rules for monitoring the internal training load and adapting the external training loads must remain the same as implemented in the 'Brain-IT' project. To adapt the 'Brain-IT' training to other software and hardware and software solutions, use all available exergames filled in Table S1 and fill in Table S4 for each of these games. The game levels and the parameters chosen to reach these levels must be defined by agreement between at least two experienced neuropsychologists, taking into account the following key points:

- Level 1 = Introductory level. Even most impaired patients should be able to play the game at the first trial without problems to ensure that no overload occurs.
- Level 10 = "healthy functioning" level. The neurocognitive demands are expected to be challenging but doable for an average healthy older adult.
- The remaining levels are defined to increase neurocognitive demands consecutively and regularly from level to level. This should again be done by agreement between at least two experienced neuropsychologists. It is recommended to consider Gentile's Taxonomy for Motor Learning [467], Neuroplasticity Principles [468], Motor Learning Principles [469], and Training Principles [59, 74] in this regard.

For each game, at least one game metric needs to be chosen or developed that provides a valid and reliable measure for game performance and is sensitive to changes in game performance over time.

In case a scientifically validated progression algorithm that is based on game metric that provides a valid and reliable measure for game performance and are sensitive to changes in game performance over time, this option can be considered instead of the predefined levels. However, it must be ensured, that the patients are not overloaded in the initial training sessions.

S2.8 The concept of MYCHOICE to ensure sufficient variability

S2.8.1 Implementation in the Project 'Brain-IT':

The concept of MYCHOICE describes a self-determined choice of exergames within groups of games for cognitive domains so that the preferences of each participant can be taken into account while the time spent at training each neurocognitive domain is still standardized within participants with the same training focus (i.e. predetermined according to the deficit-oriented focus on the neurocognitive domains as described in section 2). The advantage of this concept is that it promotes self-efficacy, which facilitates training motivation [205]. According to the Optimizing Performance through Intrinsic Motivation and Attention for Learning (OPTIMAL) theory of motor learning, this is expected to enhance performance expectancies which – accompanied with these autonomy-supportive conditions - *"contribute to efficient goal-action coupling by preparing the motor system for task execution"* [248]. This is further proposed *"to facilitate the development of functional connectivity across brain regions, and structural neural connections more locally, that support effective and efficient motor performance and learning"* [248, 249]. With this regard, the exergames were grouped into mainly trained neurocognitive domains of learning and memory, executive function, complex attention, visuo-spatial skills (see Table S1) and each participant gets to choose which game within these groups he prefers to play. Optimally, the participant would get the option to choose between different games on the screen before starting each training session. Since this is not (yet) implemented into the Dividat user interface, alternatively, the research team consecutively plans the training session for each participant based on the participant's preferences.

Depending on the complexity of the games as such, the earliest start and latest end that are predefined in section 2 that have to be considered when planning the training sessions. Therefore, the range for self-determined choices is limited at the start of the training with the aim to provide a certain routine until the participants have familiarized themselves with the game scenarios and are prepared to learn new games step-by-step. Over the course of the training intervention, the number of options to choose from will steadily increase, giving the participants and the research team the opportunity to plan the training sessions according to the individuals' preferences.

S2.8.1 How to adapt the 'Brain-IT' training concept to other hardware and software solutions:

Ideally, no changes to this concept are required if the exergame software allows for the grouping of alternative exergames to train the same neurocognitive (sub)domain and these can be displayed on the interface for selection by the participants before starting or during the training. If this option is not available, the person supervising the participants should consecutively plan the training session for each participant based on the participant's preferences.

S2.9 Game Levels for Phase 1 – Facilitation

Table S3: Game Levels for each Game for Phase 1 – Facilitation

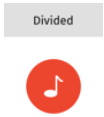
Game	Task Demands											Performance Measures
	Parameter(s)		Conditions & Settings									
			Level 1	Level 2	Level 3	Level 4	Level 5	Level 6	Level 7	Level 8	Level 9	Level 10	
	game speed (interstimulus-interval)		= ½ RW	= ½ RW	= ½ RW	= ½ RW	= ½ RW	= ½ RW	= ½ RW	= ½ RW	= ½ RW	= ½ RW	mean reaction time game score point rate
	response window (RW)		10000 ms	8000 ms	6000 ms	5500 ms	5000 ms	4500 ms	4000 ms	3500 ms	3000 ms	2500 ms	
	predictability (order/time interval)		random	random	random	random	random	random	random	random	random	random	
	stepping direction(s)	↑	90 %	80 %	70 %	60 %	50 %	45 %	40 %	35 %	30 %	25 %	
		→	5 %	10 %	15 %	20 %	22.5 %	22.5 %	25 %	25 %	25 %	25 %	
		←	5 %	10 %	15 %	20 %	22.5 %	22.5 %	25 %	25 %	25 %	25 %	
		↓	0 %	0 %	0 %	0 %	5 %	10 %	10 %	15 %	20 %	25 %	
	game speed (interstimulus-interval)		= ½ RW	= ½ RW	= ½ RW	= ½ RW	= ½ RW	= ½ RW	= ½ RW	= ½ RW	= ½ RW	= ½ RW	mean reaction time game score point rate
	response window (RW)		12000 ms	10000 ms	8000 ms	6000 ms	5500 ms	5000 ms	4500 ms	4000 ms	3500 ms	3000 ms	
	predictability (order/time interval)		random	random	random	random	random	random	random	random	random	random	
	stepping direction(s)	↑	80 %	70 %	60 %	55 %	50 %	45 %	40 %	35 %	30 %	25 %	
		→	10 %	15 %	20 %	20 %	22.5 %	22.5 %	25 %	25 %	25 %	25 %	
		←	10 %	15 %	20 %	20 %	22.5 %	22.5 %	25 %	25 %	25 %	25 %	
		↓	0 %	0 %	0 %	5 %	5 %	10 %	10 %	15 %	20 %	25 %	
	game speed (interstimulus-interval)		= ½ RW	= ½ RW	= ½ RW	= ½ RW	= ½ RW	= ½ RW	= ½ RW	= ½ RW	= ½ RW	= ½ RW	mean reaction time game score point rate
	response window (RW)		10000 ms	8000 ms	6000 ms	5500 ms	5000 ms	4500 ms	4000 ms	3500 ms	3000 ms	2500 ms	
	predictability (order/time interval)		random	random	random	random	random	random	random	random	random	random	
	stepping direction(s)	↑	80 %	70 %	60 %	55 %	50 %	45 %	40 %	35 %	30 %	25 %	
		→	10 %	15 %	20 %	20 %	22.5 %	22.5 %	25 %	25 %	25 %	25 %	
		←	10 %	15 %	20 %	20 %	22.5 %	22.5 %	25 %	25 %	25 %	25 %	
		↓	0 %	0 %	0 %	5 %	5 %	10 %	10 %	15 %	20 %	25 %	

Simon_numbered	sequence length		2	3	3	3	4	4	5	5	6	6	mean reaction time game score point rate
	stepping direction(s)	↑	50 %	50 %	35 %	25 %	35 %	25 %	35 %	25 %	35 %	25 %	
		→	25 %	25 %	25 %	25 %	25 %	25 %	25 %	25 %	25 %	25 %	
		←	25 %	25 %	25 %	25 %	25 %	25 %	25 %	25 %	25 %	25 %	
		↓	0 %	0 %	15 %	25 %	15 %	25 %	15 %	25 %	15 %	25 %	
Simon	sequence length		2	3	3	3	4	4	5	5	6	6	mean reaction time game score point rate
	stepping direction(s)	↑	50 %	50 %	35 %	25 %	35 %	25 %	35 %	25 %	35 %	25 %	
		→	25 %	25 %	25 %	25 %	25 %	25 %	25 %	25 %	25 %	25 %	
		←	25 %	25 %	25 %	25 %	25 %	25 %	25 %	25 %	25 %	25 %	
		↓	0 %	0 %	15 %	25 %	15 %	25 %	15 %	25 %	15 %	25 %	
Shopping Tour	number of items on the list		2	3	3	4	4	5	5	6	6	7	mean reaction time number of items collected number of mistakes precision
	duration of encoding phase		10 s	8 s	6 s	8 s	6 s	7 s	5 s	9 s	6 s	7 s	
	bulking probability		0 %	80 %	60 %	80 %	60 %	60 %	40 %	50 %	40 %	50 %	
	probability of presented items to be purchased or not (in percent)		80 %	70 %	60 %	55 %	50 %	45 %	40 %	35 %	30 %	25 %	
Nomis_numbered	sequence length		2	3	3	3	4	4	4	5	5	6	mean reaction time game score point rate
	stepping direction(s)	↑	50 %	50 %	35 %	25 %	35 %	25 %	35 %	25 %	35 %	25 %	
		→	25 %	25 %	25 %	25 %	25 %	25 %	25 %	25 %	25 %	25 %	
		←	25 %	25 %	25 %	25 %	25 %	25 %	25 %	25 %	25 %	25 %	
		↓	0 %	0 %	15 %	25 %	15 %	25 %	15 %	25 %	15 %	25 %	
Nomis	sequence length		2	3	3	3	4	4	4	5	5	6	mean reaction time game score point rate
	stepping direction(s)	↑	50 %	50 %	35 %	25 %	35 %	25 %	35 %	25 %	35 %	25 %	
		→	25 %	25 %	25 %	25 %	25 %	25 %	25 %	25 %	25 %	25 %	
		←	25 %	25 %	25 %	25 %	25 %	25 %	25 %	25 %	25 %	25 %	
		↓	0 %	0 %	15 %	25 %	15 %	25 %	15 %	25 %	15 %	25 %	
Targets	game speed (speed multiplier)		0.2	0.25	0.3	0.35	0.4	0.45	0.5	0.55	0.6	0.65	game score point rate number of hits number of missed targets
	stepping direction(s)	↑	90 %	80 %	70 %	60 %	50 %	45 %	40 %	35 %	30 %	25 %	
		→	5 %	10 %	15 %	20 %	22.5 %	22.5 %	25 %	25 %	25 %	25 %	
		←	5 %	10 %	15 %	20 %	22.5 %	22.5 %	25 %	25 %	25 %	25 %	
		↓	0 %	0 %	0 %	0 %	5 %	10 %	10 %	15 %	20 %	25 %	
Habitats	game speed (interstimulus-interval)		10000 ms	8000 ms	6000 ms	5500 ms	5000 ms	4500 ms	4000 ms	3500 ms	3000 ms	2500 ms	mean reaction time game score point rate
	response window (RW)		constant	constant	constant	constant	constant	constant	constant	constant	constant	constant	
	task complexity (including inhibition task = yes/no)		no	no	no	yes	yes	yes	yes	yes	yes	yes	
	stepping direction(s)	↑	80 %	70 %	60 %	55 %	50 %	45 %	40 %	35 %	30 %	25 %	
		→	10 %	15 %	20 %	20 %	22.5 %	22.5 %	25 %	25 %	25 %	25 %	
		←	10 %	15 %	20 %	20 %	22.5 %	22.5 %	25 %	25 %	25 %	25 %	
		↓	0 %	0 %	0 %	5 %	5 %	10 %	10 %	15 %	20 %	25 %	

Gears 	response window (RW)		12000 ms	10000 ms	8000 ms	8000 ms	8000 ms	6000 ms	6000 ms	5000 ms	5000 ms	5000 ms	mean reaction time game score point rate
	complexity of the gear wheels (out of 3 levels)		Level 1	Level 1	Level 1	Level 1&2	Level 1&2	Level 1&2	Level 2	Level 2	Level 2&3	Level 3	
	animated (rotating wheels) wheels vs. wheels in fixed position		fixed	fixed	fixed	fixed	animated	animated	animated	animated	animated	animated	
	predictability (order/time interval)		random	random	random	random	random	random	random	random	random	random	
	stepping direction(s)	↑	80 %	60 %	40 %	35 %	35 %	30 %	30 %	25 %	25 %	25 %	
		→	10 %	20 %	25 %	25 %	25 %	25 %	25 %	25 %	25 %	25 %	
		←	10 %	20 %	25 %	25 %	25 %	25 %	25 %	25 %	25 %	25 %	
		↓	0 %	0 %	10 %	15 %	15 %	20 %	20 %	25 %	25 %	25 %	
Tetris 	game speed (speed multiplier)		0.6	0.8	1	1.2	1.3	1.4	1.5	1.6	1.7	1.8	game score

S2.10 Game Levels for Phase 2 – Guidance

Table S4: Game Levels for each Game for Phase 2 – Guidance

Game	Task Demands											Performance Measures
	Parameter(s)		Conditions & Settings									
			Level 1	Level 2	Level 3	Level 4	Level 5	Level 6	Level 7	Level 8	Level 9	Level 10(+)	
	game speed (interstimulus-interval)		= ½ RW	= ½ RW	= ½ RW	= ½ RW	= ½ RW	= ½ RW	= ½ RW	= ½ RW	= ½ RW	= ½ RW	mean reaction time game score point rate
	response window (RW)		6000 ms	5000 ms	4500 ms	4000 ms	3750 ms	3500 ms	3250 ms	3000 ms	2750 ms	adaptive; start level: 2500 ms	
	predictability (order/time interval)		random	random	random	random	random	random	random	random	random	random	
	stepping direction(s)	↑	90 %	80 %	70 %	60 %	50 %	45 %	40 %	35 %	30 %	25 %	
		→	5 %	10 %	15 %	20 %	22.5 %	22.5 %	25 %	25 %	25 %	25 %	
		←	5 %	10 %	15 %	20 %	22.5 %	22.5 %	25 %	25 %	25 %	25 %	
		↓	0 %	0 %	0 %	0 %	5 %	10 %	10 %	15 %	20 %	25 %	
	game speed (interstimulus-interval)		= ½ RW	= ½ RW	= ½ RW	= ½ RW	= ½ RW	= ½ RW	= ½ RW	= ½ RW	= ½ RW	= ½ RW	mean reaction time game score point rate
	response window (RW)		5000 ms	4500 ms	4000 ms	3750 ms	3500 ms	3250 ms	3000 ms	2750 ms	2500 ms	adaptive; start level: 2250 ms	
	predictability (order/time interval)		random	random	random	random	random	random	random	random	random	random	
	stepping direction(s)	↑	80 %	70 %	60 %	55 %	50 %	45 %	40 %	35 %	30 %	25 %	
		→	10 %	15 %	20 %	20 %	22.5 %	22.5 %	25 %	25 %	25 %	25 %	
		←	10 %	15 %	20 %	20 %	22.5 %	22.5 %	25 %	25 %	25 %	25 %	
		↓	0 %	0 %	0 %	5 %	5 %	10 %	10 %	15 %	20 %	25 %	
	game speed (interstimulus-interval)		= ½ RW	= ½ RW	= ½ RW	= ½ RW	= ½ RW	= ½ RW	= ½ RW	= ½ RW	= ½ RW	= ½ RW	mean reaction time game score point rate
	response window (RW)		8000 ms	6000 ms	5500 ms	5000 ms	4500 ms	4000 ms	3500 ms	3000 ms	2500 ms	adaptive; start level: 2000 ms	
	predictability (order/time interval)		random	random	random	random	random	random	random	random	random	random	
	stepping direction(s)	↑	80 %	70 %	60 %	55 %	50 %	45 %	40 %	35 %	30 %	25 %	
		→	10 %	15 %	20 %	20 %	22.5 %	22.5 %	25 %	25 %	25 %	25 %	
		←	10 %	15 %	20 %	20 %	22.5 %	22.5 %	25 %	25 %	25 %	25 %	
		↓	0 %	0 %	0 %	5 %	5 %	10 %	10 %	15 %	20 %	25 %	

Simon_numbered	sequence length		2	3	3	4	4	5	5	6	6	7	mean reaction time game score point rate
	stepping direction(s)	↑	50 %	50 %	35 %	35 %	25 %	35 %	25 %	35 %	25 %	25 %	
		→	25 %	25 %	25 %	25 %	25 %	25 %	25 %	25 %	25 %	25 %	
		←	25 %	25 %	25 %	25 %	25 %	25 %	25 %	25 %	25 %	25 %	
		↓	0 %	0 %	15 %	15 %	25 %	15 %	25 %	15 %	25 %	25 %	
Simon	sequence length		2	3	3	4	4	5	5	6	6	7	mean reaction time game score point rate
	stepping direction(s)	↑	50 %	50 %	35 %	35 %	25 %	35 %	25 %	35 %	25 %	25 %	
		→	25 %	25 %	25 %	25 %	25 %	25 %	25 %	25 %	25 %	25 %	
		←	25 %	25 %	25 %	25 %	25 %	25 %	25 %	25 %	25 %	25 %	
		↓	0 %	0 %	15 %	15 %	25 %	15 %	25 %	15 %	25 %	25 %	
Steps	progression rule defined by the game itself		This game was designed to include over 100 game levels considering a progression in motor load (i.e. execution speed (i.e. stepping frequency (beats per minute) and pattern complexity), and cognitive load (i.e. pattern length) that are described by Giannouli et al. 2020 [470]. All participants will start at level 1 and each training session will start at the final level of the previous training session.										game score point rate number of hits number of missed targets accuracy
Shopping Tour	number of items on the list		2	3	3	4	4	5	5	6	6	7	mean reaction time number of items collected number of mistakes precision
	duration of encoding phase		10 s	8 s	6 s	8 s	6 s	7 s	5 s	9 s	6 s	7 s	
	bulking probability		0 %	80 %	60 %	80 %	60 %	60 %	40 %	50 %	40 %	50 %	
	probability of presented items to be purchased or not (in percent)		80 %	70 %	60 %	55 %	50 %	45 %	40 %	35 %	30 %	25 %	
Nomis_numbered	sequence length		2	3	3	3	4	4	5	5	6	6	mean reaction time game score point rate
	stepping direction(s)	↑	50 %	50 %	35 %	25 %	35 %	25 %	35 %	25 %	35 %	25 %	
		→	25 %	25 %	25 %	25 %	25 %	25 %	25 %	25 %	25 %	25 %	
		←	25 %	25 %	25 %	25 %	25 %	25 %	25 %	25 %	25 %	25 %	
		↓	0 %	0 %	15 %	25 %	15 %	25 %	15 %	25 %	15 %	25 %	
Nomis	sequence length		2	3	3	3	4	4	5	5	6	6	mean reaction time game score point rate
	stepping direction(s)	↑	50 %	50 %	35 %	25 %	35 %	25 %	35 %	25 %	35 %	25 %	
		→	25 %	25 %	25 %	25 %	25 %	25 %	25 %	25 %	25 %	25 %	
		←	25 %	25 %	25 %	25 %	25 %	25 %	25 %	25 %	25 %	25 %	
		↓	0 %	0 %	15 %	25 %	15 %	25 %	15 %	25 %	15 %	25 %	
Targets	game speed (speed multiplier)		0.3	0.4	0.5	0.55	0.6	0.65	0.7	0.75	0.8	adaptive; start level: 0.8	game score point rate number of hits number of missed targets
	stepping direction(s)	↑	90 %	80 %	70 %	60 %	50 %	45 %	40 %	35 %	30 %	25 %	
		→	5 %	10 %	15 %	20 %	22.5 %	22.5 %	25 %	25 %	25 %	25 %	
		←	5 %	10 %	15 %	20 %	22.5 %	22.5 %	25 %	25 %	25 %	25 %	
		↓	0 %	0 %	0 %	5 %	5 %	10 %	10 %	15 %	20 %	25 %	

Habitats 	game speed (interstimulus-interval)		8000 ms	6000 ms	5000 ms	4500 ms	4000 ms	3500 ms	3250 ms	3000 ms	2750 ms	adaptive; start level: 2500 ms	mean reaction time game score point rate
	response window (RW)		constant	constant	constant	constant	constant	constant	constant	constant	constant	constant	
	task complexity (including inhibition task = yes/no)		no	no	no	yes	yes	yes	yes	yes	yes	yes	
	stepping direction(s)	↑	80 %	70 %	60 %	55 %	50 %	45 %	40 %	35 %	30 %	25 %	
		→	10 %	15 %	20 %	20 %	22.5 %	22.5 %	25 %	25 %	25 %	25 %	
		←	10 %	15 %	20 %	20 %	22.5 %	22.5 %	25 %	25 %	25 %	25 %	
		↓	0 %	0 %	0 %	5 %	5 %	10 %	10 %	15 %	20 %	25 %	
Flexi 	task complexity		Part A	Part A & B									mean reaction time game score
Evolve 	game speed (interstimulus-interval) of targets		10000 ms	7500 ms	5000 ms	5000 ms	4000 ms	4000 ms	4000 ms	4000 ms	4000 ms	4000 ms	catches (Level 1-3) collisions precision (Level 4+) points
	movement speed of targets		0	0	0	0.2	0.4	0.6	0.7	0.8	0.9	1	
	game speed (interstimulus-interval) of obstacles		0	0	0	10000 ms	8000 ms	6000 ms	4000 ms	3000 ms	2000 ms	1000 ms	
	movement speed of obstacles		0	0	0	0.2	0.4	0.6	0.7	0.8	0.9	1	
Gears 	response window (RW)		10000 ms	8000 ms	6000 ms	6000 ms	6000 ms	5000 ms	5000 ms	4000 ms	4000 ms	4000 ms	mean reaction time game score point rate
	complexity of the gear wheels (out of 3 levels)		Level 1	Level 1	Level 1	Level 1&2	Level 1&2	Level 1&2	Level 2	Level 2	Level 2&3	Level 3	
	animated (rotating wheels) wheels vs. wheels in fixed position		fixed	fixed	fixed	fixed	animated	animated	animated	animated	animated	animated	
	predictability (order/time interval)		random	random	random	random	random	random	random	random	random	random	
	stepping direction(s)	↑	80 %	60 %	40 %	35 %	35 %	30 %	30 %	25 %	25 %	25 %	
		→	10 %	20 %	25 %	25 %	25 %	25 %	25 %	25 %	25 %	25 %	
		←	10 %	20 %	25 %	25 %	25 %	25 %	25 %	25 %	25 %	25 %	
		↓	0 %	0 %	10 %	15 %	15 %	20 %	20 %	25 %	25 %	25 %	
Tetris 	game speed (speed multiplier)		0.6	0.8	1	1.2	1.3	1.4	1.5	1.6	1.7	adaptive; start level: 1.8	game score

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Chapter

11

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Chapter

12

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First and foremost and most important, I would like to express my deepest appreciation to my supervisor, **Prof. Dr. Eling D. de Bruin**, for giving me the opportunity to join his research group as a doctoral student, for believing in me and my abilities, for cheering for me at presentations at scientific congresses, including his unforgettable cheering when I won the 3 Minute Thesis Competition at the 2023 World Congress of the International Society of Posture & Gait Research, and, most importantly, for the fruitful and very productive collaboration on many projects with the countless fascinating scientific discussions. He was not only my supervisor, but also a mentor who played an invaluable role in promoting my growth as a researcher and as an individual. Reflecting on the past years, it is remarkable to acknowledge the journey I have had the opportunity to experience. I have finally found my professional passion and am thrilled to continue working in academia after completing my doctorate, striving for scientific advancements with fruitful collaborations. My unstoppable curiosity and fascination with conducting research, as well as my desire to contribute to the solution of socially relevant problems, and thereby help people to live a better life, drive me to do so. In this regard, I would also like to thank **Prof. Dr. Katrien de Bock** for providing the environment for me to be able to pursue my doctorate in Elings' group.

A special thanks also goes to all members of my thesis committee, including my supervisors Prof. Dr. Eling D. de Bruin and Prof. Dr. Katrien de Bock, **Prof. Dr. Jess Gerrit Snedeker** as the chair of the examination, as well as **Prof. Dr. Jean-Jacques Temprado** as co-examiner. I appreciate Prof. Dr. Jean-Jacques Temprado's willingness to evaluate my thesis as external expert in the area of my thesis. I am honored to have him on my thesis committee and very much look forward to a fruitful and insightful scientific discussion at my doctoral examination, facilitated by such an experienced and highly renowned professor in our field of research. I would also like to thank **Farida Esther D'Addario** for organizing the doctoral examination as well as other employees from ETH Doctoral Administration, Academic Services department and the Department of Health Sciences and Technology who were involved in providing me the environment to complete my doctorate, especially the study administration, and information technology support.

The success of the project was greatly aided by the invaluable support of numerous master's students who completed research internships and/or master's theses. Across all the side projects associated with the 'Brain-IT' project and the 'Brain-IT' project itself, we conducted 446 measurement sessions with our study participants and supervised more than 600 individual training sessions at the participants' homes; we spent countless hours in critical discussions about the methodology, the results of our studies, or possible explanations for our findings; and, thankfully, we were also able to spend time joyfully celebrating our positive study results and our good teamwork. I would like to wholeheartedly thank each of the involved students, namely, **Robin Mozolowski**, **Karishma Thekkanath, André Groux**, **Lorenzo Einaudi**, **Patricia Groth**, **Kathrin Rohr**, **Chiara Bassi**, **Nadine Decher**, **Anna Riedler**, **Enis Ljatifi**, **Julia Müller**, **Julia Czopek-Rowinska**, and **Wanda Kaiser**.

However, we would not have had that much work without motivated study participants that thankfully agreed to participate in our projects and therefore contributed to the scientific advancement in our field. Across all side projects associated with the 'Brain-IT' project and the 'Brain-IT' project itself, we included a total of 128 study participants, **59 individuals with mild neurocognitive disorder**, **59 healthy older adults**, and **10 experts** (therapists, neuropsychologists, other exergaming researchers, or representatives from the exergaming industry). Notably, the study participants with mild neurocognitive disorder completed an exceptional total of 1939 (!) training sessions, summing up to a total training time of 44,512 min - more than 742 hours of training. Without the willingness and huge investment of time and effort of our study participants, neither the project nor my doctoral thesis, nor the associated master's theses would have been possible. We consider ourselves very privileged to have had the opportunity to work with all of them.

Of course, the project's success was also dependent on the inputs from many project collaborators, including all co-authors and recruitment partners. Most importantly, I would like to thank **Dr. Hanna Poikonen** for her excellent work in teaching me how to analyze data from electroencephalography, **Prof. Dr. phil. Lars Michels** for teaching me how to set-up and conduct measurements of brain magnetic resonance imaging independently and the upcoming data analysis as well as **Dr. Roger Lüchinger** for teaching us in magnetic resonance imaging safety and providing us the environment to conduct our measurements independently and free of charge. I would also thank our monitor, **Dr. Ruud Knols**, for taking the time and doing a great detective work in finding opportunities for improvement in our studies' implementation, giving valuable insight from his own experience with external audits, and helping us to improve our studies' implementation and documentation in line with good clinical practice. With regards to the recruitment partners, a special thanks goes to **Dr. phil. Sandra Loosli**, **Dr. phil. Nicole Schmid**, **Dr. med Filip Barinka**, **Dr. med Robert Koch**, **Dr. med Jeannette Werner**, **Dr. med. Maria Martin Zinnenlauf**, **Dr. med. Stefan Zinnenlauf**, **Dr. med. Sonja Kagerer**, **Dr. Jakob Spyth**, and **Dr. med. Sacha Beck**, who contributed the most for the successful recruitment of all our study participants with mild neurocognitive disorder.

This project would not have been able without the generous funding of **Synapsis Foundation-Dementia Research Switzerland** (grant 2019-PI06) and "**Gebauer Stiftung**", and the financial support of "**Fondation Dalle Molle**." Notably, **Heide Marie Hess**, **Andrea Traber**, **Kevin Duarte Carneiro** from Synapsis Foundation-Dementia Research Switzerland did not only coordinate the funding of our projects, but did a remarkable job in making our research more accessible to other researchers via the yearly Synapsis Forum as well as to the public via the organization of a "Meet the Researchers" event, the co-creation of a promo-video together with us, the publication of multiple articles in the "Synapsis News", as well as the initiation of publications about our project on other platforms (e.g., DeinAdieu, CH-media with Schweiz am Wochenende). In this regard, I would also like to thank **Sabrina Rohner** for writing a wonderful blog article that also covered our project. I would also like to thank **Cornelia Schmid** of (Ringier Axel Springer Switzerland AG) for reaching out to us, interviewing us, and writing an article about our project and the experiences of one of the study participants, as well as photographer **Jonas Weibel** for taking and editing the photos for this article. Finally, I would also like to thank **Dividat AG** for providing the 'Senso Flex' technology and implementing some of our suggestions for further development of the software, both of which helped us to implement our 'Brain-IT' training together with the technologies from Polar and Kubios Oy.

I would also like to express my gratitude to my “doctorate-buddies“, **Simone Huber** and **Julia Seinsche**, for their collaboration on a side project, for our scientific discussions and exchanges about the potential difficulties of our lives as doctoral students, and for providing an environment for me to grow as a researcher. Of course, I would also like to thank my family (especially my mom, **Karin Manser** and my dad, **Urs Manser**) and friends (especially **Matthias Knöri**, **Marco Niederhauser**, **Laura Niederhauser**, and **Anja Stutz**) for cheering for me in all the good times of my life as a researcher, but also providing an open ear and support to me in challenging times or, when once again, the editors or reviewers challenged my patience.

Finally, I am deeply grateful to all those who expressed critical opinions and skepticism about me or my work. Their insights challenged me to dig even deeper to ensure the robustness of my research by providing a good scientific basis for all my decisions. This ultimately further enhanced the quality and integrity of the project and facilitated my personal and professional growth as a researcher. All these contributions therefore indirectly contributed to the success of the project and my journey towards becoming a respected researcher.

ETH zürich

Chapter

13

Curriculum Vitae

Curriculum Vitae

Patrick Manser

Master of Science ETH in Health Sciences and Technology

My current research evaluates the effectiveness of 'Brain-IT' - a newly developed training concept combining exergame-based motor-cognitive training and heart rate variability guided resonance breathing for the secondary prevention of mild neurocognitive disorder.

My key strength is my rigorous iterative methodological approach in designing, developing, and evaluating innovative eHealth intervention concepts. I put a strong emphasis on the involvement of primary and secondary end users together with the close collaboration with multidisciplinary experts. I am experienced in qualitative and quantitative research as well as various interventional and observational study designs. Additionally, I am experienced in a wide range of assessment techniques, including domain-specific neuropsychological assessments, various clinical protocols for (instrumented) physical activity, gait, and mobility analysis (with accelerometry), electroencephalography, and (functional) magnetic resonance imaging.

My ambition is to make transformative contributions to the field through my rigorous methodological approach, to continually adapt my research goals based on the results of this iterative process, and to actively disseminate my findings to facilitate the translation of research into clinical practice. I strive to extend my research to other neurodegenerative and mental disorders. My medium-term goals are to investigate dose-response relationships between intervention characteristics and their effectiveness, to further improve the personalization of eHealth interventions, and to investigate their mechanism of action across different etiologies or subtypes of neurodegenerative and mental disorders.

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ORCiD = 0000-0003-3300-6524

Patrick Manser

- ✓ passionate,
- ✓ reliable,
- ✓ critical-analytical

Health- and Sports-Scientist

with
excellent skills in:

- ✓ methodological rigor
- ✓ project management
- ✓ teamwork

RESEARCH:

Publications[(1)]:	6
Total times cited[(1)]:	30
H-Index[(1)]:	3
Verified Reviews[(2)]:	5

According to (1) Scopus and (2) Publons

CERTIFICATES:

- ✓ Good Clinical Practice 1 - 3
- ✓ Advanced English for Academic Purposes (C1-C2)

LANGUAGES:

German:

English:

HOBBIES:

EDUCATION:

08.2020 - now — **Doctor of Science ETH in Health Sciences and Technology** — ETH Zurich (CH)

project title: **Brain-IT** - Targeting the **Brain** using **I**nformation **T**echnology for Secondary Prevention of mild Neurocognitive Disorder

supervisors: Prof. Dr. Eling D. de Bruin and Prof. Dr. Katrien De Bock

09.2022 - 11.2023 — **Teaching Certificate in Health Sciences and Technology** — ETH Zurich (CH)

final grade: not yet announced / 6.0*

09.2019 - 07.2020 — **Master of Science ETH in Health Sciences and Technology** — ETH Zurich (CH)

final grade: 5.64 / 6.0*

specialization: Human Movement Sciences and Sport

tutor: Prof. Dr. Eling D. de Bruin

09.2016 - 09.2019 — **Bachelor of Science ETH in Health Sciences and Technology** — ETH Zurich (CH)

final grade: 4.81 / 6.0*

PROFESSIONAL EXPERIENCE:

10.2023 – 12.2023
10.2022 – 11.2022
10.2021 – 11.2021 — **Lecturer** — OST – Eastern Swiss University of Applied Sciences

Lecture Series “Human Movement Analysis” and “Evidence-based Intervention Planning“ for Students “Bachelor of Science in Physiotherapy“

02.2020 - 07.2020 — **Master’s Thesis Project** — University Hospital Zurich (CH)

project title: The Reactivity of Heart Rate Variability as a Potential Biomarker and Monitoring Tool to Promote Healthy Ageing - A Systematic Review with Meta-Analysis

final grade: 6.0 / 6.0*

supervisors: Prof. Dr. Eling D. de Bruin and Dr. Ruud Knols

09.2019 - 02.2020 — **Student Research Internship** — ETH Zurich (CH)

- Development of a taxonomy for exergame-based motor-cognitive training in chronic stroke patients
- Planning and organization (including writing of the ethics application) of a pilot intervention study investigating the resulting training taxonomy

07.2017 - 12.2019 — **Research Assistant** — ETH Zurich (CH)

- Extension of the online learning platform for the exercise physiology course at the Exercise Physiology Lab
- Synthesis, preparation, statistical analysis, and interpretation of datasets of the Exercise Physiology Lab
- Assistance in the practical training ‘Sports Physiology’

02.2015 - 05.2017 — **Fitness Instructor** — Update Fitness (CH)

PROFESSIONAL TRAINING:

08.2014 - 07.2015 — **Fitness Instructor** — Update Academy; Uzwil (CH)

final grade: 5.9 / 6.0*

*6.0 is the top mark, 1.0 the lowest. The pass mark is 4.0.

MAIN ACHIEVEMENTS:

1

My main achievement so far is the publication of my first paper of my Doctorate project (see section 'PUBLICATIONS' – publication number 2), which represents a significant paradigm shift in the approach to designing and developing personalized eHealth training concepts. Traditionally, training concepts are developed based on existing evidence and expert suggestions, followed by the adaptation of technological solutions and subsequent evaluation of their effectiveness, acceptance, and patient adherence. However, I advocate for the need of understanding patients' genuine needs for long-term engagement and adherence before embarking on the development of interventions or sophisticated eHealth technologies. This requires involving patients from the very beginning of the project and actively listening to their voices. Only after gaining a deep understanding of their needs should we proceed with the development of customized technologies and interventions.

In this methodological paper, I describe the methodology for the design and development process of novel exergame-based training concepts for older adults on basis of a step-by-step application of a recently published methodological framework in my Doctorate project. This paper emphasizes the importance of systematically involving qualitative research in the process to define a set of design requirements for a training concept before commencing the development process, which deviates from the conventional approach. This achievement highlights my commitment to patient-centered research by specifically considering user perspectives when designing interventions and showcases my methodological rigor for designing novel eHealth training concepts. It demonstrates my innovative approach and contribution to advancing research methodologies.

2

In July 2023, I was honored to receive the prestigious award for the best Three Minute Thesis (3MT®) presentation during the 2023 World Congress of the International Society of Gait and Posture Research. Participation in this highly competitive competition sharpened my ability to succinctly communicate the significance and impact of my research to diverse audiences. The recognition garnered from this victory significantly amplified the visibility and appreciation of my work, solidifying its relevance on a broader scale.

3

In January 2023, I initiated an international collaboration with Dr. Fabian Herold from the Research Group "Degenerative and Chronic Diseases, Movement" at the University of Potsdam. This collaboration marks a milestone in my research career as my first international partnership. Together, we are conducting a systematic review to investigate the components that enhance the effectiveness of exergame-based training on cognitive functioning in middle-aged to older adults (PROSPERO ID: CRD42023418593).

This collaboration not only strengthens our partnership but also contributes to the global scientific community's understanding of the impact of exergames on cognitive functioning. Through our joint efforts, we aim to identify key components and inform future research in this field. This achievement showcases my commitment to rigorous research and collaboration, positioning me as a valuable contributor to the advancement of knowledge in exergame-based interventions.

COMMITTEE WORK:

11.2023 - now

Active Member of the Communications Committee of the International Society of Posture & Gait Research.

HONORS & AWARDS:

07.2023 Award: Winner of the 3 Minute Thesis Competition at the 2023 World Congress of the International Society of Posture & Gait Research

GRANTS & SCHOLARSHIPS:

01.2021 - now I have played an active role in eight grant applications to the Swiss National Science Foundation, the Synapsis Foundation, the European Partnership on transforming health and care systems (Co-fund action under the Horizon Europe Programme), as well as ERA-NET NEURON - The Network of European Funding for Neuroscience Research. Due to my role as a doctoral student, I have not been listed as official main or co-applicant. However, I have experience in coordinating and/or actively participating in the grant writing process.

PUBLICATIONS:

6 Manser, P., Poikonen, H., & de Bruin, E. D. **Feasibility, Usability and Acceptance of 'Brain-IT'-A Newly Developed Exergame-Based Training Concept for the Secondary Prevention of Mild Neurocognitive Disorder: A Pilot Randomized Controlled Trial.** Frontiers in Aging Neuroscience, 15, 1163388. doi: 10.3389/fnagi.2023.1163388

5 Manser, P., Huber, S., Seinsche, J., de Bruin, E. D., & Giannouli, E. (2023). **Development and initial validation of the German version of the Exergame Enjoyment Questionnaire (EEQ-G)**; PLoS One, 18(6), e0286556. doi: 10.1371/journal.pone.0286556

4 Manser, P., Michels, L., Schmidt, A., Barinka, F., & de Bruin, E. D. (2023). **Effectiveness of an Individualized Exergame-Based Motor-Cognitive Training Concept Targeted to Improve Cognitive Functioning in Older Adults With Mild Neurocognitive Disorder: Study Protocol for a Randomized Controlled Trial**; JMIR Res Protoc, 12, e41173. doi: 10.2196/41173

3 Manser, P., Adcock-Omlin, M., & de Bruin, E. D. (2023). **Design Considerations for an Exergame-Based Training Intervention for Older Adults With Mild Neurocognitive Disorder: Qualitative Study Including Focus Groups With Experts and Health Care Professionals and Individual Semistructured In-depth Patient Interviews**; JMIR Serious Games, 11, e37616. doi: 10.2196/37616

2 Manser, P., & de Bruin, E. D. (2021). **Making the Best Out of IT: Design and Development of Exergames for Older Adults With Mild Neurocognitive Disorder - A Methodological Paper**; Front Aging Neurosci, 13, 734012. doi: 10.3389/fnagi.2021.734012

1 Manser, P., Thalmann, M., Adcock, M., Knols, R. H., & de Bruin, E. D. (2021). **Can Reactivity of Heart Rate Variability Be a Potential Biomarker and Monitoring Tool to Promote Healthy Aging? A Systematic Review With Meta-Analyses**; Front Physiol, 12(1133), 686129. doi: 10.3389/fphys.2021.686129

VERIFIED REVIEWS:

5 Santini et al. (January 2024) **A quasi-experimental mixed-method pilot study to check the efficacy of the "SOUND" active and passive music-based intervention on mental wellbeing and residual cognition of older people with dementia and dementia professionals' burnout: a research protocol**; Frontiers in Psychology - Psychology of Aging – manuscript number: 1327272

4 Nagamatsu and Ford (December 2023) **Four weeks of meditation training improves sustained attention in older communitydwelling adults: A proof-of-concept randomized controlled trial**; Frontiers in Aging - Interventions in Aging – manuscript number: 1322705

3 Adelirad et al. (March 2023) **Physical and mental -based training in healthy older adults: evidence from a systematic review and meta-analysis**; Journal of Geriatric Psychiatry and Neurology – manuscript number: JGPN-23-0031

2 Alaa Abd-alrazaq et al. (December 2022) **Serious games for learning among older adults with cognitive impairment: A systematic review and meta-analysis**; Journal of Medical Internet Research (JMIR) Serious Games - manuscript number: 43607-689647

1 Quillion-Dupré et al. (March 2022) **Cognitive training software development for autonomous use by people with neurocognitive disorders: relevance of a multidisciplinary user-centered approach**; Innovation and Research in BioMedical engineering (IRBM) - manuscript number: IRBM-D-21-00359

CONFERENCE CONTRIBUTIONS:

Invited Talks / Invited Symposia (in total: n = 0):

N/A

Oral Presentations (in total: n = 5):

5 Swiss Society of Sports Sciences (SGS) – 15th Annual Conference (7 – 8 February 2024; Zurich, Switzerland);

title: **Brain-IT - Targeting the Brain using Information Technology for Secondary Prevention of mild Neurocognitive Disorder** (a part of the finalist's presentations of the Young Investigator Award); conference abstract available at: https://doi.org/10.36950/2024.2ciss021

4 International Society of Gait & Posture Research (ISPGR) – World Congress 2023 (9 – 13 July 2023; Brisbane, Australia);

title: **Rethinking the Development of Technology-Based Interventions for Secondary Prevention of Cognitive Impairment** (a part of the Three Minute Thesis (3MT®) competition)

3 Mobility and Exercise (MobEx) conference 2022 (13 - 14 May 2022; Heidelberg Academy of Sciences and Humanities, Heidelberg, Germany);

title: **Exergaming for Older Adults with mild Neurocognitive Disorder**

2 Synapsis Forum 2021 – Scientific exchange for researchers investigating Alzheimer's disease and neurodegeneration (8 – 9 November 2021; Gerzensee, Switzerland);

title: **Making the Best out of IT: Design and Development of Exergames for Older Adults with mild Neurocognitive Disorder**

1 Synapsis Forum 2020 – Scientific exchange for researchers investigating Alzheimer's disease and neurodegeneration (24 November 2020; Online Congress (due to the Covid-19 pandemic));

title: **Brain-IT**

Poster Presentations (in total: n = 4):

4 Synapsis Forum 2023 – Scientific exchange for researchers investigating Alzheimer's disease and neurodegeneration (6 – 7 November 2023; Gerzensee, Switzerland);

title: **Diagnostic Accuracy, Reliability, and Construct Validity of the German Quick Mild Cognitive Impairment Screen**

3 International Society of Gait & Posture Research (ISPGR) – World Congress 2023 (9 – 3 July 2023; Brisbane, Australia);

title: **Design, Development, and Evaluation of an Individualized Exergame-based Motor-Cognitive Training Concept for Older Adults with Mild Neurocognitive Disorder**

2 Synapsis Forum 2022 – Scientific exchange for researchers investigating Alzheimer's disease and neurodegeneration (8 – 9 November 2022; Gerzensee, Switzerland);

title: **Feasibility, Usability and Acceptance of a Newly Developed Exergame-Based Training Concept for Older Adults with Mild Neurocognitive Disorder - A Pilot Randomized Controlled Trial**

1 Synapsis Forum 2020 – Scientific exchange for researchers investigating Alzheimer's disease and neurodegeneration (24 November 2020; Online Congress (due to the Covid-19 pandemic));

title: **Brain-IT**

TEACHING ACTIVITIES:

Lectures (in total: n = 3):

10.2023 - 12.2023 Lecture Series *"Human Movement Analysis"* and *"Evidence-based Intervention Planning"* for Students "Bachelor of Science in Physiotherapy" (2 October 2023 to 4 December 2023; Eastern University of Applied Sciences, St.Gallen, Switzerland)

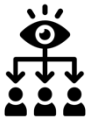
10.2022 - 11.2022 Lecture Series *"Human Movement Analysis"* for Students "Bachelor of Science in Physiotherapy" (10 October 2022 to 14 November 2022; Eastern University of Applied Sciences, St.Gallen, Switzerland)

10.2021 - 11.2021 Lecture Series *"Human Movement Analysis"* for Students "Bachelor of Science in Physiotherapy" (11 October 2021 to 15 November 2021; Eastern University of Applied Sciences, St.Gallen, Switzerland)

Invited Lectures (in total: n = 2):

03.2024 Aix-Marseille University (Research Group of Prof. Dr. Jean-Jacques Temprado - Institute for Movement Science - Faculty of Sport Sciences) - Lecture "*Exercise and Technologies in Secondary Prevention of mild Neurocognitive Disorders"* (26 March 2024; Online)

03.2021 Bern University of Applied Sciences – Lecture *"Design and use of exergames and their influence on physical functioning of Stroke/MCI patients"* (5 March 2021; Online (due to the Covid-19 pandemic)



CO-SUPERVISION OF STUDENTS:

Master's Theses Projects (in total: n = 9):

09.2023 – 03.2024 Wanda Kaiser (Master's Student in Health Sciences and Technology; ETH Zurich); title of the thesis: *"Evaluation of Domain-Specific Exergame Metrics in Older Adults with Mild Neurocognitive Disorder"*

07.2023 – 02.2024 Julia Czopek-Rowinska (Master's Student in Health Sciences and Technology; ETH Zurich); title of the thesis: *"Diagnostic Accuracy of Heart Rate Variability as a Screening Tool for Mild Neurocognitive Disorder"*

05.2023 – 10.2023 Julia Müller (Master's Student in Health Sciences and Technology; ETH Zurich); title of the thesis: *"Effectiveness of a 12-week Exergame-Based Motor-Cognitive Training on Patient-Centered Outcomes in Older Adults With Mild Cognitive Impairment Compared to Usual Care: A Randomized Controlled Trial"*

02.2023 – 08.2023 Enis Ljatifi (Master's Student in Health Sciences and Technology; ETH Zurich); title of the thesis: *"Effectiveness of an Exergame Based Training on Learning and Memory in Older Adults with Mild Cognitive Impairment Compared to Usual Care: A Randomized Controlled Trial"*

08.2022 – 03.2023 Anna Riedler (Master's Student in Health Sciences and Technology; ETH Zurich); title of the thesis: *"The Effect of a 12-Week Exergame Based Motor Cognitive Training on Psychological Factors, Cognitive Functions and Heart Rate Variability in Older Adults With Mild Cognitive Impairment Compared to Usual Care"*

06.2022 – 12.2022 Nadine Decher (Master's Student in Health Sciences and Technology; ETH Zurich); title of the thesis: *"Effects of a 12-Eeek Exergame-based Motor Cognitive Training Concept on Working Memory Function in Older Adults with Mild Cognitive Impairment – a Pilot Randomized Controlled Trial"*

06.2021 - 02.2022 Kathrin Rohr (Master's Student in Health Sciences and Technology; ETH Zurich); title of the thesis: *"Development and Initial Validation of the German Version of the Exergame Enjoyment Questionnaire (EEQ-G)"*

05.2021 - 01.2022 Patricia Groth (Master's Student in Health Sciences and Technology; ETH Zurich); title of the thesis: *"Feasibility, Usability and Acceptance of a Newly Developed Exergame-Based Intervention Concept for Older Adults with Mild Neurocognitive Disorder – A Pilot Randomized Controlled Trial"*

03.2021 - 10.2021 Karishma Thekkanath (Master's Student in Health Sciences and Technology; ETH Zurich); title of the thesis: *"Reliability and Validity of Heart Rate Variability Reactivity as Internal Load Parameter for Exergaming in Older Adults – a Within-Person Trial"*

Research Internships (in total: n = 10):

06.2023 – 09.2023 Wanda Kaiser (Master's Student in Health Sciences and Technology; ETH Zurich); project: *"'Brain-IT' - exergame training with biofeedback breathing in neurocognitive disorders - a RCT"*

03.2023 – 07.2023 Julia Czopek-Rowinska (Master's Student in Health Sciences and Technology; ETH Zurich); project: *"'Brain-IT' - exergame training with biofeedback breathing in neurocognitive disorders - a RCT"*

02.2023 – 04.2023 Julia Müller (Master's Student in Health Sciences and Technology; ETH Zurich); project: *"'Brain-IT' - exergame training with biofeedback breathing in neurocognitive disorders - a RCT"*

11.2022 – 01.2023 Enis Ljatifi (Master's Student in Health Sciences and Technology; ETH Zurich); project: *"'Brain-IT' - exergame training with biofeedback breathing in neurocognitive disorders - a RCT"*

05.2022 – 07.2022 Anna Riedler (Master's Student in Health Sciences and Technology; ETH Zurich); project: *"'Brain-IT' - exergame training with biofeedback breathing in neurocognitive disorders - a RCT"*

03.2022 – 05.2022 Nadine Decher (Master's Student in Health Sciences and Technology; ETH Zurich); project: *"'Brain-IT' - exergame training with biofeedback breathing in neurocognitive disorders - a RCT"*

11.2021 - 02.2022 Chiara Bassi (Master's Student in Health Sciences and Technology; ETH Zurich); project: *"Feasibility, Usability, and Acceptance of 'Brain-IT' - A Newly Developed Exergame-Based Training Concept for the Secondary Prevention of Mild Neurocognitive Disorder: A Pilot Randomized Controlled Trial"*

07.2021 - 03.2022 Lorenzo Einaudi (Master's Student in Physiotherapy; Bern University of Applied Sciences); project: *"Development and initial validation of the German version of the Exergame Enjoyment Questionnaire (EEQ-G)"*

05.2021 - 08.2022 André Groux (Master's Student in Health Sciences and Technology; ETH Zurich); project: *"Feasibility, Usability, and Acceptance of 'Brain-IT' - A Newly Developed Exergame-Based Training Concept for the Secondary Prevention of Mild Neurocognitive Disorder: A Pilot Randomized Controlled Trial"*

02.2021 - 05.2021 Robin Mozolowski (Master's Student in Health Sciences and Technology; ETH Zurich); project: *"Test-Retest Reliability and Validity of vagally-mediated Heart Rate Variability to Monitor Internal Training Load in Older Adults: A within-subjects (repeated-measures) randomized study"*

REFERENCES:

1 **Prof. Dr. Eling D. de Bruin**

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Department of Health Sciences and Technology
Institute of Human Movement Sciences and Sport
Motor Control and Learning Group
HCP H25.1
Leopold-Ruzicka-Weg 4
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Switzerland

Professional relation:
Prof. Dr. Eling D. de Bruin is the supervisor for my Doctorate project and was my tutor during the Masters's Programme.

2 **Dr. phil. Ruud Knols**

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Phone: +41 44 255 88 09

University Hospital Zurich
Directorate of Research and Education
Sonnentalstrasse 25
8600 Dübendorf
Switzerland

Professional relation:
Dr. phil. Ruud Knols is the external monitor for my ongoing randomized controlled trial in my Doctorate project and was supervisor for my master's thesis project.

3 **Prof. Dr. phil. Lars Michels**

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Phone: +41 44 255 49 65

University Hospital of Zurich
Department of Neuroradiology
Frauenklinikstrasse 10
CH-8091
Zurich
Switzerland

Professional relation:
Prof. Dr. phil. Lars Michels is a scientific collaborator of my doctorate project. He is a specialist in (functional) magnetic resonance imaging and responsible for teaching me how to plan and conduct magnetic resonance imaging scans and how to process and analyze the data.