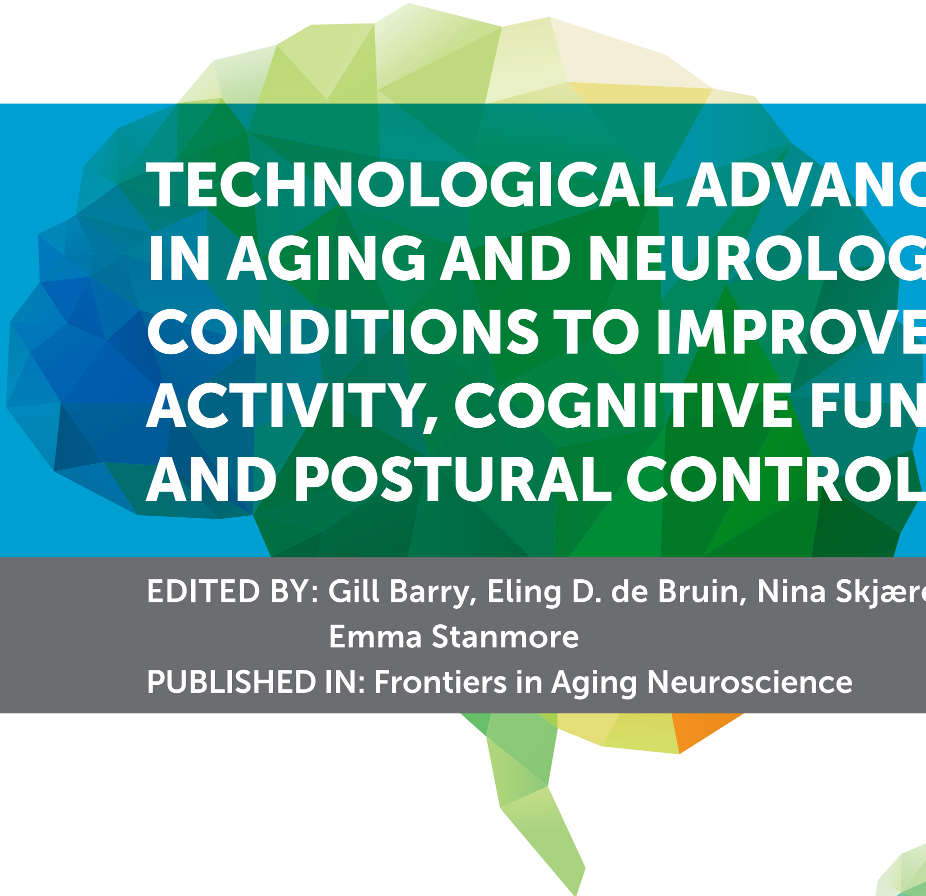

TECHNOLOGICAL ADVANCEMENTS IN AGING AND NEUROLOGICAL CONDITIONS TO IMPROVE PHYSICAL ACTIVITY, COGNITIVE FUNCTIONS, AND POSTURAL CONTROL

EDITED BY: Gill Barry, Eling D. de Bruin, Nina Skjæret-Maroni and Emma Stanmore

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ORIGINAL RESEARCH
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Wearable Devices for Assessing Function in Alzheimer's Disease: A European Public Involvement Activity About the Features and Preferences of Patients and Caregivers

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Background: Alzheimer's Disease (AD) impairs the ability to carry out daily activities, reduces independence and quality of life and increases caregiver burden. Our understanding of functional decline has traditionally relied on reports by family and caregivers, which are subjective and vulnerable to recall bias. The Internet of Things (IoT) and wearable sensor technologies promise to provide objective, affordable, and reliable means for monitoring and understanding function. However, human factors for its acceptance are relatively unexplored.

Objective: The Public Involvement (PI) activity presented in this paper aims to capture the preferences, priorities and concerns of people with AD and their caregivers for using monitoring wearables. Their feedback will drive device selection for clinical research, starting with the study of the RADAR-AD project.

Method: The PI activity involved the Patient Advisory Board (PAB) of the RADAR-AD project, comprised of people with dementia across Europe and their caregivers (11 and 10, respectively). A set of four devices that optimally represent various combinations of aspects and features from the variety of currently available wearables (e.g., weight, size, comfort, battery life, screen types, water-resistance, and metrics) was presented and experienced hands-on. Afterwards, sets of cards were used to rate and rank devices and features and freely discuss preferences.

Results: Overall, the PAB was willing to accept and incorporate devices into their daily lives. For the presented devices, the aspects most important to them included comfort, convenience and affordability. For devices in general, the features they prioritized were appearance/style, battery life and water resistance, followed by price, having an emergency button and a screen with metrics.

The metrics valuable to them included activity levels and heart rate, followed by respiration rate, sleep quality and distance. Some concerns were the potential complexity, forgetting to charge the device, the potential stigma and data privacy.

Conclusions: The PI activity explored the preferences, priorities and concerns of the PAB, a group of people with dementia and caregivers across Europe, regarding devices for monitoring function and decline, after a hands-on experience and explanation. They highlighted some expected aspects, metrics and features (e.g., comfort and convenience), but also some less expected (e.g., screen with metrics).

Keywords: Alzheimer's disease, dementia—Alzheimer disease, wearable sensors devices, public involvement, caregivers, technology acceptance and perception, technology acceptance and adoption, internet of the things

HIGHLIGHTS

What was already known about this topic

- Remote monitoring technologies are promising to improve the current care of people with dementia in several aspects, such as timely assessment and intervention.
- The adoption and acceptance of technology by people with dementia is challenging.
- Several studies have investigated potential barriers to the adoption of the proposed health remote technologies through phone interviews and online questionnaires.

What this study added

- The Public Involvement (PI) activity included focused discussion, hands-on experimentation and detailed presentation of several candidate devices for people with dementia and their caregivers.
- Members of the RADAR-AD Patient Advisory Board (PAB) were given tools specifically designed to rate and rank the various features of the devices presented to them, by order of preference, as well as metrics and aspects of devices in general.
- Each device comes with its own peculiarities and combination of features, so people with dementia and their caregivers need to drive the selection process of the devices to be used in clinical research and future trials, including the RADAR-AD project study.

INTRODUCTION

Current estimates suggest that there are around 9 million of people living with dementia across Europe (Alzheimer Europe, 2020) of which the most prevalent one is Alzheimer's Disease (AD) dementia. In addition, the current conceptualization of AD has been extended to encompass the full spectrum of the disease, including both pre-dementia, i.e., preclinical and prodromal AD or Mild Cognitive Impairment (MCI) due to AD, and dementia phases (Alzheimer's dementia) (Alzheimer Europe, 2020). An important aspect of the diagnosis, in AD and other dementias, is functioning, where current assessment methods rely mostly on self-report and observation by the caregivers. While this information is important, it requires considerable effort and time and still may be inaccurate. Therefore, existing traditional monitoring methods could be complemented by remote, objective, non-intrusive and relatively effortless monitoring, using technology.

Technology for Older Community-Dwelling People With Dementia

The absence of objective data to assess the daily function of people with dementia could be addressed by several advances in digital technology for monitoring and analysis. Objective remote monitoring using digital technology could complement existing methods and lead to more accurate and timely assessment as well as more efficient clinical trials, proposing more effective interventions and ultimately improving both short and long-term care. Developing remote monitoring solutions and adapting them to the needs of people with dementia and their caregivers could, therefore, allow them to live independently at home for longer, support their caregivers and support decisions of healthcare professionals easily and timely, while promoting "aging in place" (American Planning Association and the National Association of County and City Health Officials, 2009).

Remote monitoring technologies (RMTs) can include one or many of the following components: smartphones, Apps, Internet of Things (IoT) sensors, both wearable and ambient smart home solutions, biomedical devices coupled with analytics. Smartphones, can help assess social behavior, via monitoring calls, text messages, or internet browsing, since mobile phone usage by elders is increasing (Anderson and Perrin, 2017), as do the applications of smartphones for health (Joe and Demiris, 2013). Meanwhile, wearable smart devices and remote health monitoring solutions have also been increasing in popularity over the last decade, especially for elders in general and people with dementia in particular (Lazarou et al., 2016, 2019; Megges et al., 2018). More specifically, smart home healthcare solutions can significantly delay nursing home admission (Kim et al., 2017) and promote safety monitoring and care of older adults through mobile devices (Albert et al., 2012; Lazarou et al., 2016, 2019), wearables (Carrino et al., 2012; Al-Shaqi et al., 2016) and other types of sensors (Mahoney et al., 2007; Mihailidis et al., 2008; Aloulou et al., 2013; Hawley-hague et al., 2014; Stucki et al., 2014; Piau et al., 2015; Lazarou et al., 2019). Smartwatches and wristbands are blooming in the electronics retail market. Their purpose primarily is to monitor daily activity and lifestyle including movement and sleep, in order to promote health and well-being. More research-oriented devices can measure activity levels, stress, heart rate, gait and other vital signs.

User Acceptance of Technology

While technology seems to be a promising solution, its adoption is often challenging for end-users, especially older people and healthcare professionals. Technology experts tend to select devices based only on their desire to record the most appropriate signals with the highest granularity and precision. However, the same devices might be quite uncomfortable, heavy and too complicated for users, diminishing the outcome and the success of a study, which is particularly important in the case of people with dementia. Thus, the technology selection process should involve both people with dementia and their caregivers, who will daily operate such technologies. The number of different devices and possibilities increases every year, resulting in a variety of factors that might affect developers, such as data heterogeneity, manufacturer communication standards and programming interfaces, but also the end-users, such as shapes, materials, battery life, design, functionality, precision, and range (Boll et al., 2018). All these parameters should be considered, when selecting proper devices for monitoring users or for examining the potential adoption from them, especially in the case of treating people with AD. Thus, the feedback from the people with dementia as well as their caregivers introduces a valued end-user perspective in the selection process, with parameters that might otherwise be overlooked.

Older people, their family and caregivers can face considerable stress with the newly introduced technological components (Laguna and Babcock, 1997; Dyck et al., 1998; Tung and Chang, 2007). Most of the time, older adults express technology-related concerns, while the perceived benefits of technology might be more abstract to them. The most common barriers in the adoption of technology by older people are: familiarity and access, need for assistance, trust, privacy implications, design, reduced dexterity, precision, and physical issues (Fischer et al., 2014; Peek et al., 2014; Khosravi and Ghapanchi, 2015; Liu et al., 2016; Yusif et al., 2016; Zhao et al., 2018; Alshahrani et al., 2019). On the other hand, the most highlighted benefits of technology used by older people are: safety, perceived usefulness, independence, and reduced "burden" on family and caregivers (Peek et al., 2014). A crucial component to integrate and accept technology in real-life situations (e.g., at home) is to design and develop user-friendly user interfaces (UIs), to facilitate user interactions with the system (Liu and Yang, 2014). In this direction, the interaction of users with technology that takes into account their concerns and preferences has been shown to empower and engage them more in their care (Villalba-Mora et al., 2015).

Existing Explorative Studies for Technology Adoption

Several exploratory studies have investigated potential barriers in the adoption of RMTs through constructive questionnaires. A recent study, using Theory of Planned Behavior (TPB), explored the potential intention of adult children to use online health information for their aging parents (Bao et al., 2017), and its findings showed that they are willing to use such technological solutions. Another study, using TPB, investigated the potential adoption of mobile health services (Deng et al., 2014) and found that perceived value and behavior control, resistance to change and attitude can be precursors for using mobile health services for the middle-aged group, while additional traits such as self-actualization need and technology anxiety found to affect the behavior intention of older participants. An exploratory study examined the attitude and acceptance of women in Singapore, above 50 years of age, toward a mobile phone-based intervention through a phone survey (Xue et al., 2012). They found that the women were likely to adopt the proposed solution if it was considered as useful and easy-to-use. A questionnaire survey identified that the main factors that affect the acceptance of health technology by people with chronic conditions were: attitude toward technology, perceived usefulness, ease of learning and availability, social support, and perceived pressure (Sun and Rau, 2015). Another paper-based questionnaire survey found that the most important factors underlying the acceptance of technology by older adults were: satisfaction, perceived usability, support availability, and public acceptance (Wang et al., 2011). Furthermore, in (Wong et al., 2012), the authors evaluated the user's intention to use different systems for elders (i.e., the Medication Reminder, Dr. Ubiquitous, Sharetouch, and Intelligent Watch), by administering a modified technological acceptance model (TAM) questionnaire. The participants who used the Intelligent Watch showed the greatest willingness and satisfaction, while the ones who used Dr. Ubiquitous revealed little eagerness regarding the perceived ease of use. More long-term studies investigated commercially available RMTs (Giger et al., 2015), showing that the developed TAM questionnaire revealed that the elders as well as their caregivers and their friends responded positively regarding acceptance. Finally, another study explored attitudes and perceptions of contactless ADL monitoring across 15 older people, and found that they would easily integrate the suggested technology into their daily life (Claes et al., 2015). However, various concerns were outlined related to the operation and the pricing of the proposed contactless monitoring technology.

Commonalities and Differences

In general, exploratory studies so far have focused on the adoption of the suggested technological solutions by older people and their caregivers without presenting them the device characteristics and particular features in detail. Yet, an earlier review study encouraged professionals and caregivers to describe concrete benefits and technological advances to the older people in order to minimize technology-related concerns, while also giving them the opportunity to try out the technology in a risk-free environment (Peek et al., 2014). Another study clearly states that ease of use cannot really be self-reported and actual use is hard to be determined, since the participants cannot conceptualize and visualize themselves using the technology unless they have used it before (Xue et al., 2012). The study concludes that "it may be more enlightening to observe users through focus groups, by trying out a prototype interface."

Based on that, the present Public Involvement (PI) activity involves people with dementia and their caregivers who are members of a Patient Advisory Board (PAB). It also employs a hands-on approach where different solutions are demonstrated, presented in detail with respect to features and offered to participants to test them before collecting feedback. Furthermore, most studies explore either a single demonstrated technology or general features and preferences, whereas this PI activity is part of a device selection process, where several candidate devices were presented. Moreover, in contrast to most studies, the group included participants from several countries from Europe who are members of a PAB of a large European IMI-funded project. The PAB members are men and women with different types of dementia, different stages and experiences, and their caregivers. The composition of the PAB can be found online[1].

Furthermore, in comparison with the exploratory studies so far, most of which describe technology to participants via brochures, online questionnaires or verbally, the present study gives the opportunity to participants to experience and feel the devices hands-on in order to better understand and prioritize particular features based on their preferences. Additionally, the majority of exploratory studies have been focused on the older age dwelling population in general and not particularly on people with dementia. Also, in most studies participants completed the questionnaires themselves (e.g., via telephone or given a paper-pencil questionnaire) without someone being present and explaining possible questions. Another drawback of existing surveys is that they mainly provide a general description of several multi-purpose technological devices (e.g., PC, digital camera, video recorder, and mobile phone) without including tailored questions for a particular type of a device, applications and features of it, relying the answers solely on the appearance and the practical use of them.

Aim of the PI Activity

The aim of this PI activity is to guide the decision about device selection for the wearables to be used in the clinical trials of the RADAR-AD project[2]. The RADAR-AD project aims to improve the assessment of AD through digital biomarkers extracted from the use of smartphones, wearables, and smart home sensors with respective apps and analytics tools. The RADAR-AD trials focus on remote assessment of people with dementia while at the same time offering support to their informal caregivers. Tier 1 of the study focuses on using wearable devices continuously throughout the day and several apps during the observational period and at baseline and last visit to clinic. More specifically, our study examined several diverse wearables and considered also the acceptance or not of particular devices through an open session involving both people with dementia and caregivers.

This paper focuses on understanding the unique preferences, needs and concerns of people with dementia and caregivers at the core of a device selection process for a wearable in the framework of the RADAR-AD trials. The selection of wearables presented to the users is not limited only to specific devices available in the market nor are the features and preferences extracted from them. As such, it aims to serve as a guide for any future trial involving people with dementia and caregivers.

The process for the PI activity and its steps are illustrated in **Figure 1**. People with dementia and caregivers first highlighted particular features tailored to the disease, memory, and other functional impairments, as, for example, the necessity for a waterproof device or a sound or blinking light notification to remind users to charge the device. Then, an optimization process identified the best compromise between the most technologically advanced and user-accepted devices to satisfy both parties. Thus, the present PI activity described in this paper explored some of the potential concerns and requirements relevant to both people with dementia and their caregivers through a user-centered approach. Additionally, we examined four specific brands/models of wearables and deducted results about participants' preferences.

This paper is structured as follows. In section Introduction, we present a general background about the concept of health-related technologies and other studies in the field of technology adoption from older adults. Section Materials and Methods provides details on the PAB PI activity and the presentation and feedback collection process designed for this work. Section Results presents the results and descriptive statistics, while section Discussion considers discussion, limitations, comparisons of results with similar approaches, and suggestions for future research. Finally, section Conclusion presents conclusions drawn.

MATERIALS AND METHODS

Participants and Setting

All members of the PAB were members of the European Working Group of People with Dementia (EWGPWD) European Working Group of People with Dementia - Alzheimer Europe, which comprises of people from different countries across Europe. Its members have been diagnosed and informed of their diagnosis[3] and play an active role in collaborative research projects, such as in RADAR-AD. The members of the EWGPWD had all agreed to be members of the RADAR-AD PAB and will be referred to hereafter as PAB members. The PAB was a diverse group composed of 11 people with different kinds of mild to moderate dementia (mainly Alzheimer's dementia, one person with frontotemporal and one person with vascular dementia) and 10 carers from 11 different countries, namely, from the Czech Republic, Bosnia and Herzegovina, the Republic of Ireland, England/Wales, Scotland, Portugal, Belgium, Sweden, Finland, Austria, and Germany.

Given that the PAB involves members of the public in the design and development of research to act as advisers, providing valuable knowledge and expertise based on their experience of a health condition or as a carer/caregiver, the PI activity does not raise ethical concerns and, thus, does not require ethical approval,

[1] About the PAB: https://www.radar-ad.org/patient-engagement/patient-advisory-board/about-pab.

[2] The RADAR-AD Project: https://www.radar-ad.org/.

[3] https://www.radar-ad.org/patient-engagement/patient-advisory-board/general-members-pab.

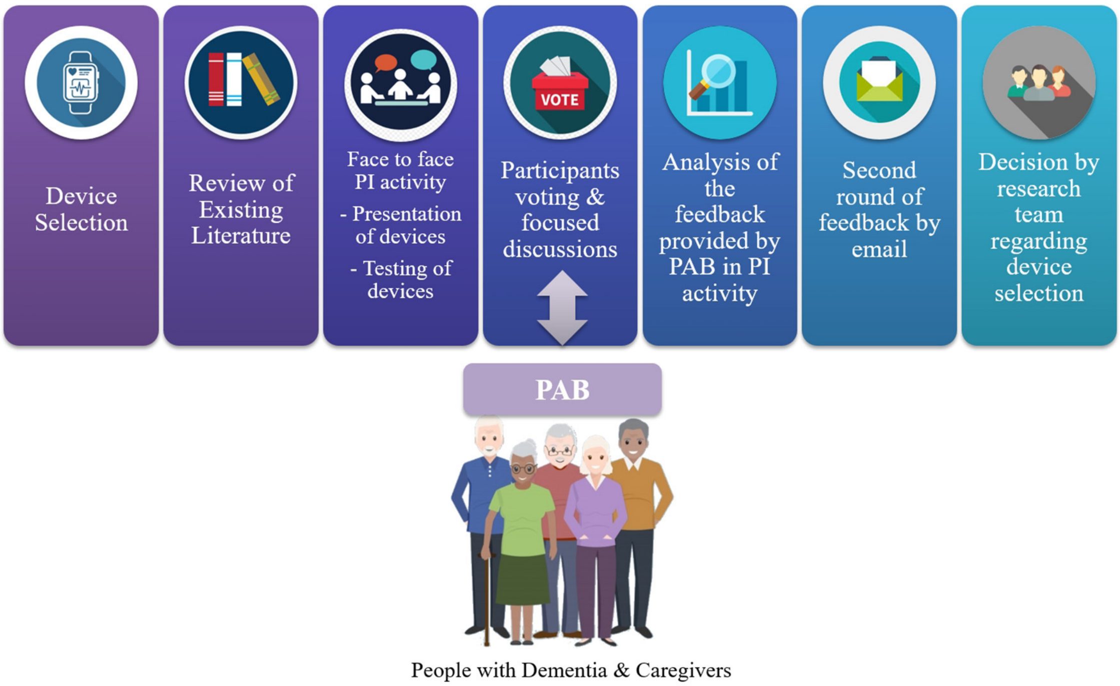

FIGURE 1 | The framework of the study centered around people with dementia and their caregivers.

according to the National Health Services (NHS) Health Research Authority[4]. In detail, and with respect to those guidelines: (i) the PAB involves members of the public for assurances on aspects of the design of future research, making it more relevant to the people it is trying to help, helping to define what is acceptable to participants and improving their experience; (ii) the PI activity involves the PAB in the research process with or by the public and not to, about or for them; and (iii) the public is involved in identifying and prioritizing research topics, plays the role of a research advisory group, identifies outcome measures which are meaningful and relevant to patients and comments on the feasibility of the research design including the burden of participants and the levels of risk/distress they may be exposed to.

The PI activity took place during the first RADAR-AD PAB meeting in Luxemburg on 18 April 2019. In total, 21 ($N = 21$) PAB members took part. In order to present the devices, support, and collect feedback more efficiently and effectively, the PAB was divided into three groups—round tables of seven people and one facilitator—researcher. The three groups were at the same room and were asked the same questions/tasks. The three facilitators were researchers, familiar with the technology and applications in AD. Two members of Alzheimer Europe supported all three groups when needed. We asked all PAB members whether they wished to take part in the session and gave them verbal and written information about the activity prior to the meeting. All agreed to participate in this PI activity, with anonymity and confidentiality by all researchers. The input provided by the participants during the activity was anonymized and stored locally (offline).

The researchers explored a vast number of lifestyle wearables and sports wearables available in the market as well as some more research-oriented wearabels, paying particular attention to a range of characteristics such as their size and weight (e.g., from light and comfortable size to heavier), more feature-rich alternatives (e.g., several icons and choices), accuracy and battery life. For the purpose of the PI activity, four devices were selected which represented four different combinations of those parameters. To minimize possible biases participants did not know the marketed names of the four devices (they were refered to as Bracelet 1, 2, 3, and 4). The accuracy of the devices was known from previous experimental evaluation studies (Stavropoulos et al., 2020). Being representatives means that some devices can be replaced in the future with alternatives of similar properties and features. The selected devices were:

- **Bracelet 1—**measures steps, sleep and heart rate (HR), high accuracy, light, high comfort, 7-day battery life, monochrome touchscreen, and waterproof
- **Bracelet 2—**measures steps, sleep, HR and 3D movement (XYZ accelerometer), high accuracy, bulkier, soft, 2-day battery life, and color touchscreen
- **Bracelet 3—**measures steps and sleep, average accuracy, the lightest (is a wristband), 7-day battery life, and no screen

[4]https://www.invo.org.uk/wp-content/uploads/2016/05/HRA-INVOLVE-updated-statement-2016.pdf.

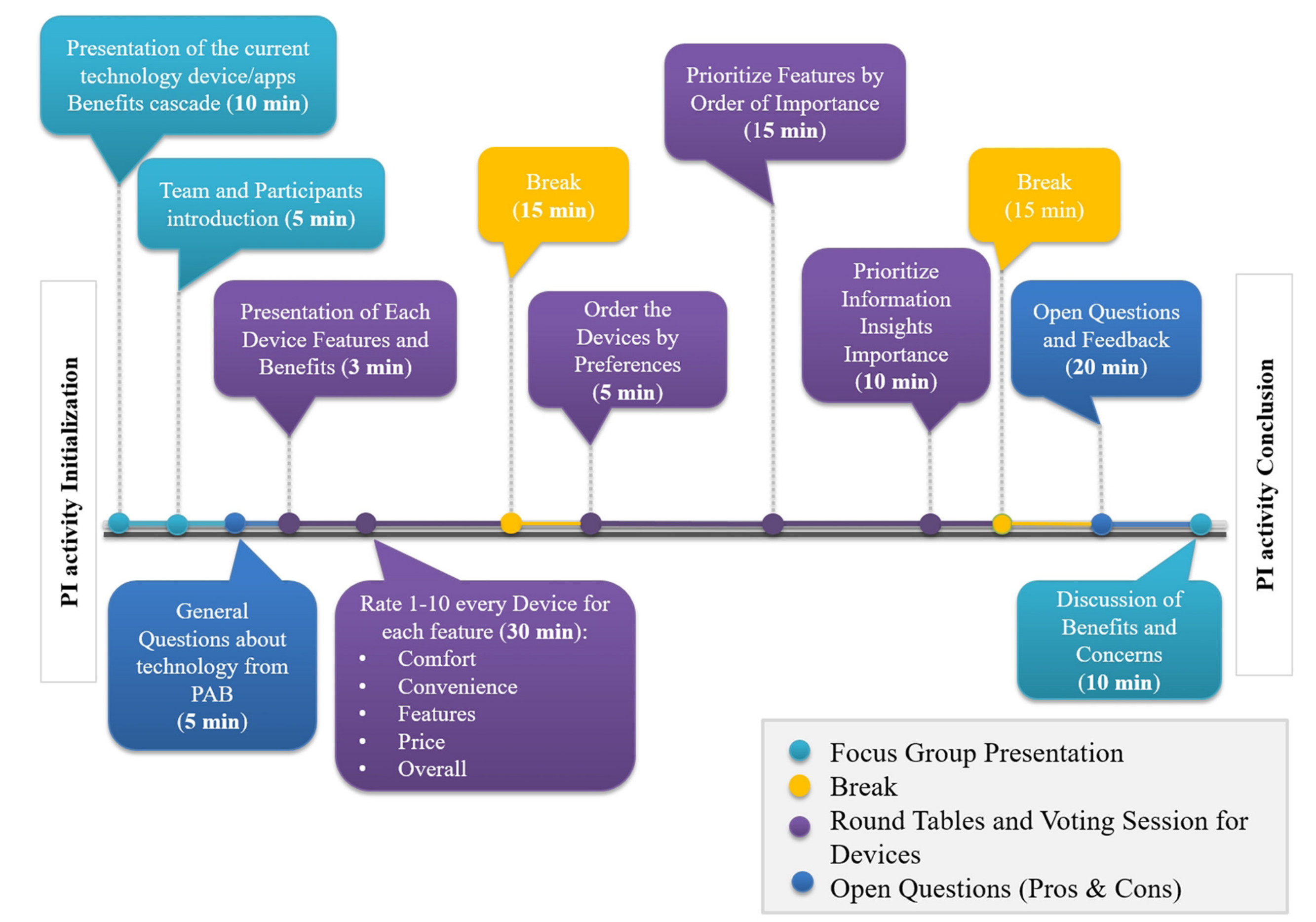

FIGURE 2 | Focus Group process timeline.

- **Bracelet 4—**measures steps, sleep, HR, heart rate variability and perspiration (Galvanic Skin Response—GSR), high accuracy, large and heavy, 1-day battery life, and no screen

The PAB Session

The total duration of the PI activity was around two and a half hours, including a structured voting session and close questions which were quantitatively analyzed as well as general and open discussion. The structure and timeline of the session is illustrated in **Figure 2**. Each activity block is presented in the following subsections. Additionally, **Figure 3** shows the setting, the groups and the materials used during the PAB session. The PAB session was organized as follows:

- Introduction to the RADAR-AD project, the PI aim, current technology status of devices/apps and their potential benefits for the researcher, the clinician and the user
- Presentation and rating of four specific wearable devices and their features
- Ranking devices in order of preference and prioritizing device-independent features and metrics
- Open discussion about the devices and their use

Presentation of Current Device Technology

Initially, the facilitator—researcher and members of Alzheimer Europe presented the general outline of the activity aims and the RADAR-AD study context. Then, the facilitators presented all current technology of the devices, while describing the potential benefits for the researcher, the healthcare professionals and the beneficiaries (people with dementia and caregivers) as described in the literature.

Examining and Evaluating Each Device Separately

Afterwards, a presentation on a projector was shown for each device, listing its main features for the user (battery life, screen, waterproof, etc.) and its value for researchers/clinicians/persons (metrics and accuracy). Then, 2–3 of each device were provided to the round tables for the PAB members to wear and test, e.g., by trying the touchscreen, checking the time and measurements of HR, steps etc. After the presentation of the devices, the facilitators answered questions raised by the PAB. Discussion followed for the pros and cons of the devices and more detailed feedback

FIGURE 3 | The setting, the three groups—round tables and materials used during the PAB Session.

was given. For the voting, each participant was provided with a "device card set," with device depictions printed in color, exactly as shown in **Figure 4**. This would help the participants remember the wearable devices when they are not physically present on their table.

Also, each person was given a "voting card set" with the numbers 1–10. In each voting round, votes were cast—card face-down on the table, counting 1–2–3 and then revealed simultaneously to avoid bias and contribute to fun. More specifically, the PAB was asked to rate every device for each feature from 1 to 10 with regards to (a) *Comfort* while wearing or living with the device at home (Feature: Size, Weight, and Material), (b) *Convenience* while charging it, taking it on and off etc. (Feature: Battery Life, Water-resistance, etc.), (c) *Features* for the user (Feature: Screen with Clock/Alarm, Calls, Steps/Sleep/Calories/HR), (d) *Price* if you were to buy it yourself and value-for-money, and (e) *Overall* device rating. The abovementioned rating was repeated for each of the four bracelets, yielding 20 rates per PAB member. The PAB was then asked why they voted as they did and to expand on the issues further. The total duration of this segment was around 50 min, followed by a 15 min break.

Cross-Device, Feature, and Qualities Ranking

The PAB was asked to rank devices, features, and qualities by arranging the respective card sets from left to right accordingly (left: most preferable, right: least preferable). Firstly, they were asked to order the four wearable devices from the previous segment, by overall preference. Then, a new card set was introduced to examine device features in general, independent of specific device implementations. They were then asked to prioritize the device "feature card set" (**Figure 5A**) from those most to those least important to them: Weight, Size, Material, Battery Life, Water-resistance, Screen with Clock/Alarm, Screen with Calls/SMS, Screen with Steps/Calories/Distance/Sleep/HR, Appearance matching your taste/style, Emergency/Panic Button to call help, and Price. Finally, the "metrics card set" (**Figure 5B**) was introduced so that they could prioritize the various types of measurements that can potentially be provided by devices from most to least important to them (Physical Activity Level, Steps, Calories, Distance, Heart Rate, Respiration Rate, Sleep Duration, Sleep Quality—Light, Deep). The total duration of this segment was around 30 min, followed by a 15 min break.

Open Questions and Feedback

Finally, all PAB members in their round tables had the opportunity to discuss and elaborate about the potential benefits and concerns of using these devices, according to their personal belief. Then the facilitators communicated the results of all the rankings to the PAB members.

RESULTS

Device Selection

Regarding the particular device selection, the participants gave ratings (from 1 to 10) for each aspect and an overall rating for each device. Then they ordered the devices by preference. The results from the voting session are illustrated in **Figure 6** (per Device ratings) and **Figure 7**, while mean values and standard deviation are presented in **Table 1**.

FIGURE 4 | The four wearable devices provided to the participants, as they are depicted on the device card set.

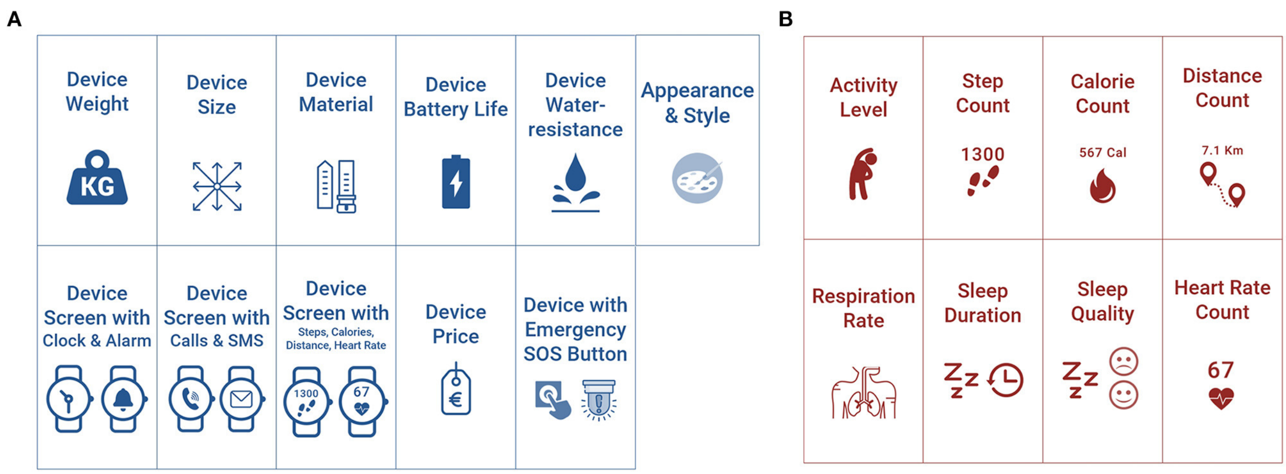

FIGURE 5 | The feature **(A)** and the metrics **(B)** card sets.

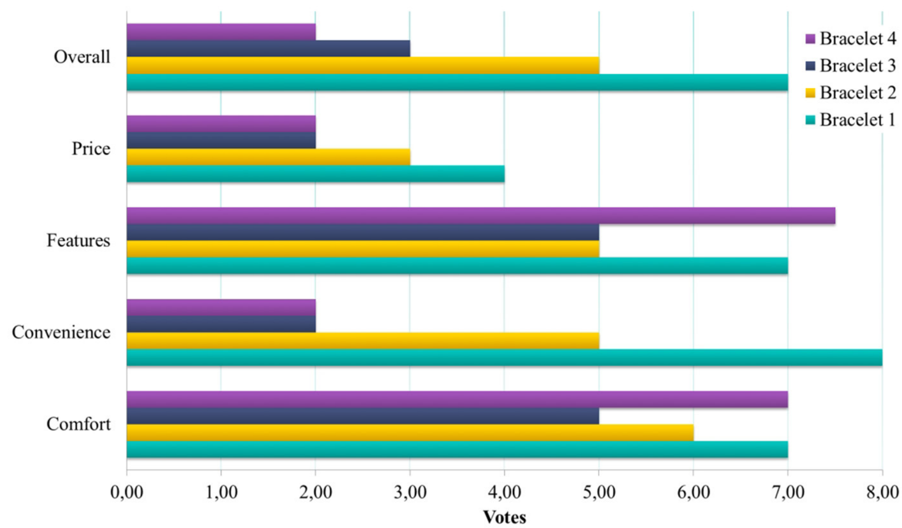

FIGURE 6 | Average rating per device aspect for each of the four bracelets.

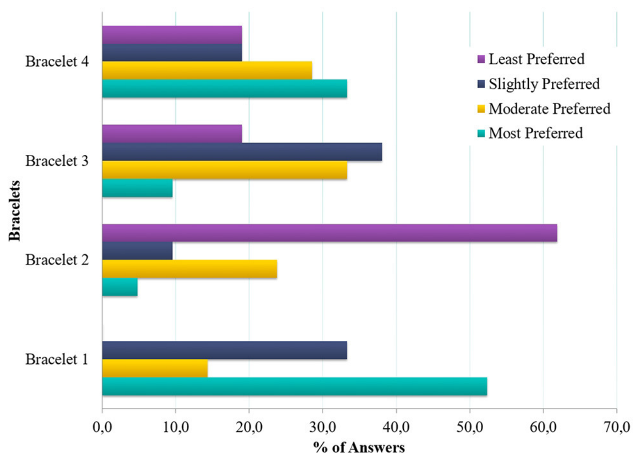

FIGURE 7 | Preferred order of Bracelets: percentage of PAB members who placed each bracelet in each place in an order of preference from 1 (most preferred) to 4 (least preferred).

TABLE 1 | Order of the devices based on preference (% of Answers) and rating per device (Mean and Standard Deviation).

	Bracelet 1	Bracelet 2	Bracelet 3	Bracelet 4
Rating per Device—*M*(*SD*)				
Comfort	7.00 (2.16)	6.00 (2.62)	5.00 (1.71)	7.00 (2.33)
Convenience	8.00 (2.31)	5.00 (2.04)	2.00 (1.20)	2.00 (1.57)
Features	7.00 (2.35)	5.00 (1.74)	5.00 (1.71)	7.50 (2.89)
Price	4.00 (3.10)	3.00 (2.33)	2.00 (1.93)	2.00 (2.56)
Overall	7.00 (1.96)	5.00 (2.10)	3.00 (1.82)	2.00 (2.33)
Order based on Preference—%				
Most Preferred	52.4%	4.8%	9.5%	33.3%
Moderate Preferred	14.3%	23.8%	33.3%	28.6%
Slightly Preferred	33.3%	9.5%	38.1%	19.0%
Least Preferred	0.0%	61.9%	19.0%	19.0%

The PAB favored bracelets that they perceived as convenient, comfortable, and affordable and feature rich. The most high-rated bracelet (Bracelet 1) was also perceived as the most comfortable to wear, convenient (less charging) and affordable. A bracelet that is light to wear and convenient, but does not have a screen feature was less prefered (Bracelet 2). On the contrary the most feature-rich bracelet was the least prefered due to incovenience (frequent charging) and despite being comfortable (Bracelet 4).

Along those lines, most PAB members again selected the bracelet they perceived as the most comfortable, convenient and affordable with enough features (Bracelet 1). A bracelet that is light and comfortable but without a screen was the least preferred here, highlighting the importance for some indication features (Bracelet 2), explored in the next segment.

Metrics and Features

Regardless of device, PAB members ranked "Activity Level" and "Heart Rate" as the most interesting and useful metrics a device could measure. These metrics were ranked in the first place by 33.3 and 19%, respectively. Also, these two metrics were ranked in the first, second, or third place by more than half of the PAB members. Other metrics which also received votes for first place but by fewer people included Sleep Quality, Distance Count and Respiratory Rate (ranked in the first place by 4.8% each). The full order of metrics is shown in **Figure 8**.

The most important feature of a candidate device was: "Appearance and Style," which was ranked in first place by many PAB members (53.8%). This was followed by "Water-Resistance," "Price," and an "Emergency Button" (19% each), "Screen with Steps and Heart Rate metrics" (14.3%) and "Weight," "Material," and a "Screen with Calls and SMS" (9.5 %). Notably, "Battery Life" was ranked second by several PAB members (42.9%), followed by a "Screen with Clock and Alarm" and "Size" (14.3% each).

"Appearance and Style," "Battery life," and "Water resistance" were ranked in first, second, or third place by more than half of the PAB members. The full order of features is shown on **Figure 9**.

Benefits and Concerns—Open Discussion

After the voting and ordering session, PAB members were asked about different existing devices and in particular about the most important aspects to consider when selecting a particular device. Relevant issues were linked to the devices being waterproof, easy to use, comfortable to wear and nice. Many felt the type of information or support the person could gain or have whilst using it was very important (e.g., information about their health such as sleep, heart rate, etc., information about where the person is such as tracking/GPS system, time, and date etc.). Concerns about the devices included that the person could forget to charge the devices, misplace it or lose it and the potential anxiety or distress if the person forgot how to use the device or if the device did not work. **Table 2** shows the key benefits and concerns mentioned by the PAB members regarding the remote monitoring solutions previously described in addition to any other particular feature they would like to be included.

DISCUSSION

This PI activity allowed a great deal of interaction between the PAB members who are "experts by experience" and the researchers. The different features any device might have were also presented to them and ordered by personal importance. In this way, the researchers were able to identify and extract preferences and features absolutely important to carry on the selection. The PAB members were presented with different varieties of wrist-worn devices. With assistance from caregivers and researchers when needed, they were asked to rate the various features and to order them by personal preference. The device names were not disclosed for the sake of simplicity and to avoid bias. Thus, the researchers were not bound to select the specific devices presented in the meeting, but rather have extracted guidelines and preferences to select from the enormous pool of

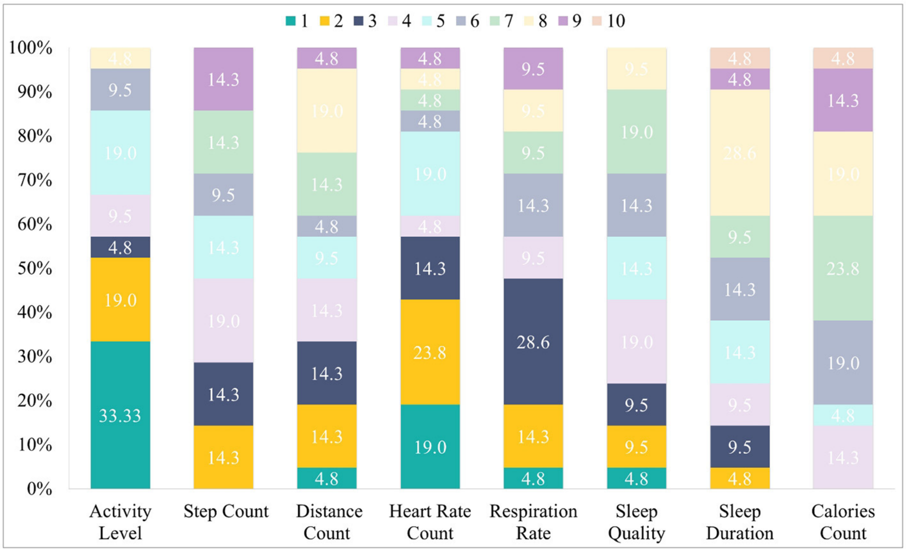

FIGURE 8 | Preferred order of Metrics: percentage of members of the PAB that placed the metric in each place from 1 to 10 (most to least preferred).

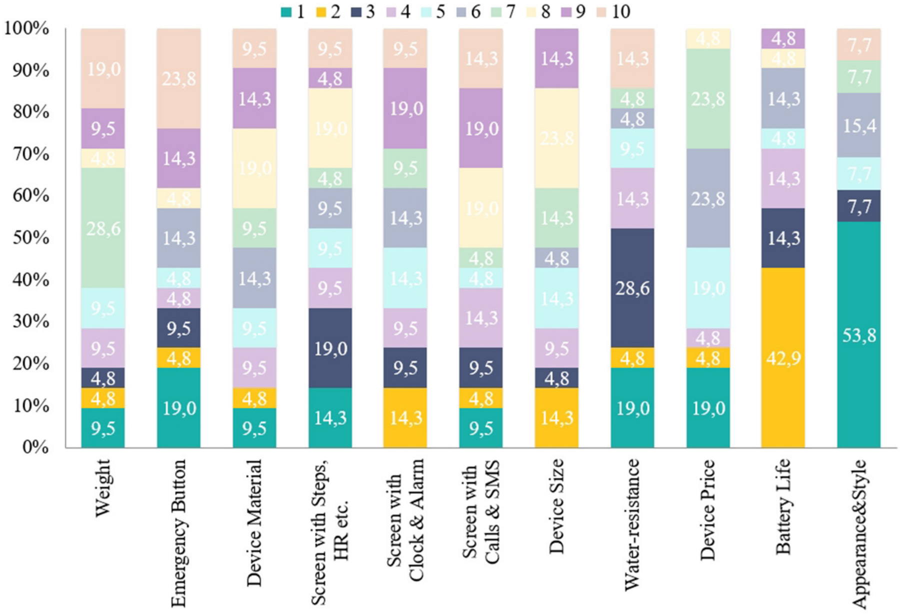

FIGURE 9 | Preferred order of features: percentage of PAB members who placed each feature in each place from 1 to 10 (most to least preferred).

ever-changing devices in the market and literature. Exploring users' rating of wearable solutions helps to understand users' requirements and preferences for e-health services and provide suggestions for e-health system construction. The present PI activity aimed to explore the main factors affecting wearable sensors and particular features and application characteristics acceptable to people with dementia and their caregivers while exploring their preferences. The feedback provides insightful design implications for e-health developers, clinicians and service providers, and several key findings can be derived from this work. From their feedback, activity level, HR, and respiratory rate as well as practical elements such as appearance, battery life, and the device being waterproof were all relevant aspects to consider. The latter, seemed particularly relevant in the case of dementia due to cognitive impairments and possible stigmatization (in the case of appearance).

To the best of our knowledge, this is one of the first PI activities having explored the perceptions, priorities, and

TABLE 2 | Open Questions and Feedback about potential benefits and concerns raised from people with dementia and caregivers.

Benefits	Concerns
People with dementia	
• I'd be interested in knowing what information is being collected • Great to know certain information/details about my health • Monitors heart rate and blood pressure • Beneficial to understand your sleep patterns, sleep quality or sleep duration • Makes your life considerably easier • Gives information about time, date, and alarm • The person should be able to receive SMS/texts • It should be simple and cute • Waterproof • Speak the messages and text to speak • GPS tracker and alarm SOS • "Locate/ Find your device" function if the person does not remember where the device is • Locate each other (e.g., I know where my wife is, and she knows where I am) • It should enable people to feel safe when they are on their own • Help me to find my way home • Map whilst cycling or being outside	• It could be intimidating (e.g., the camera) • Worried about maintaining human contact (don't want this to be replaced by devices) • The person may forget to charge the devices, misplace it or lose it • The person may forget how to use the device • The person may feel anxious if the device does not work, stops working, or the person has difficulties to make it work—ideally, someone should be able to access the device remotely and fix it for the person. • The device should be quite robust/solid • Soft material, not make the person sweaty • Color which the person likes • Compatible with other Apps that the person likes/uses • Adapted to native language of the user • Would it work in very cold weather (−32° in the winter in some countries)? • Rechargeable Battery • Can you charge it whilst wearing it? • How long does it take to charge? • Battery life • Device's guarantee?
Caregivers	
• Helpful to know that the person is being monitored • Peace of mind—Reduces worries • Gives people independence • Enables people to live alone • It may help to save money (e.g., linked to delayed institutionalization) • Believe to be beneficial after some time	• Having to be a bit knowledgeable to it • Too expensive • Would not want to be observed (myself)

concerns of people with dementia and their caregivers from different countries regarding remote monitoring solutions and wearable sensors. In accordance with previous studies (Wang et al., 2011; Deng et al., 2014; Liu and Yang, 2014; Peek et al., 2014; Calvillo et al., 2015; Khosravi and Ghapanchi, 2015; Yusif et al., 2016; Hoque and Sorwar, 2017; Alshahrani et al., 2019), PAB members underlined the potential of using the technology for daily monitoring particular aspects such as Heart and Respiratory Rate as well as Sleep quality and daily activity while they stated that they would like to receive certain information—report about the health status and metrics which is consistent with (Steggell et al., 2011; Liu et al., 2016; Klemets et al., 2019). However, none of the proposed features presented was clearly rejected but rated lower compared to the others (e.g., distance count, calories). Feedback from the PAB showed that signaling emergencies (emergency button) was rated highly (as the most preferable feature by the 19% of the participants) and indicated in open questions that they would find it beneficial. Concerns were raised surrounding the topic of battery life, since it was prioritized as the second most important metric. This result is in alignment with previous studies which support that from technical perspective, short battery life was one of the main issue for technology adoption by older people (Chen et al., 2012; Sun and Rau, 2015; Jamal et al., 2016). The wearables in this study range from 1- to 7-day battery life, depending on their heavy or light use of sensors and their purely research-oriented to more lifestyle-oriented purpose. Currently wearables are reaching close to 14-day battery life and prototypes of no-charge self-powered wearables, e.g., using thermoelectric energy to convert body heat to electricity, are emerging. According to the findings, such future developments would highly facilitate assisted living research and practice.

Several PAB members expressed also some critical concerns with regard to privacy issues of handling data from caregivers and clinicians, which is in line with (Claes et al., 2013, 2015; Peek et al., 2014). Similarly to other studies, financial costs have been identified as a major concern of people with dementia and their caregivers regarding wearable sensors and remote monitoring technologies (Chen et al., 2012; Xue et al., 2012; Claes et al., 2015; Sun and Rau, 2015). This is in line with the present paper's findings, in which the caregivers explicitly indicated that they would be reluctant to pay high costs for such devices by themselves. Moreover, it was highlighted also that the water-resistance is of high importance since the people with dementia may not be able to remember to remove it before taking a bath or washing their hands. Also, feedback suggested that some people with dementia may be more willing to accept technology that supports them in their daily functioning, in addition to assessing it. For example many referred to GPS and in particular, to a feature which would help them to track the route back home as very important, This indicated that they would value a digital device which would be useful for the researchers but also to them (e.g., to manage finding their way home and dealing with orientation problems, which is a common problem in people with dementia). Also, the caregivers believed that one of the core benefits from using such technology would be the delay in institutionalization since they would feel safer to monitor their relatives with dementia. Also, our PI activity revealed that personalization, appearance, degree of usefulness, and ease of use would be factors contributing to acceptance of technology, a finding compatible with previous research (Wu and Wang, 2005; Wu et al., 2007; Tung et al., 2008).

According to the recent systematic reviews exploring the factors influencing the adoption of the technology by older people, among the top common barriers in the adoption of technology by older people is the familiarity and access, need for assistance, trust, privacy implications, design, reduced dexterity, precision, and physical issues (e.g., hearing loss), the cost of the device, forgetting how to operate technology, false alarms and how to turn them off, obtrusiveness, low ease of use, potential negative effect on health, loss of control over technology and stigmatization, functionality and suitability for daily use, perception of no need, fear of dependence, limited training tailored to older learners, feeling of embarrassment, autonomy, loss of dignity, and social inclusion (Fischer et al., 2014; Peek et al., 2014; Claes et al., 2015; Khosravi and Ghapanchi, 2015; Sun and Rau, 2015; Liu et al., 2016; Yusif et al., 2016; Zhao et al., 2018; Alshahrani et al., 2019). Similar to the aforementioned studies, the present PI activity revealed that the appearance and style of the remote monitoring technology is of high importance to them. Moreover, based on existing studies, the benefits of using technology include safety, perceived usefulness, independence, and reduced "burden" on family caregivers, perceived need, monitoring their health status, social influence, influence of family and friends and professional caregivers (Peek et al., 2014). However, the strong, positive acceptance in the present PI activity indicates that PAB members might be willing to adopt wearable monitoring technology. Moreover, the participants considered one device (Bracelet 1) as being the optimal solution, highlighting as main features its screen showing daily feedback, its battery lasting for days and its affordable cost (less than EUR 150). These findings are vital since understanding factors of technology acceptance plays a pivotal key role to device selection for trials and research and, later on, the successful adoption of solutions and services based on technology (Wilkowska and Ziefle, 2009).

CONCLUSION

The present PI activity indicated that PAB participants were in general willing to accept and incorporate remote monitoring technologies based on wearable devices into their daily lives. Furthermore, various concerns and requirements related to the use, battery life, features to be extracted, functioning and financing of the monitoring devices have to be considered, since they might hinder acceptance of the technology. To the best of our knowledge, no prior PI activities have investigated different perspectives among several people in dementia and pre-dementia stages as well as caregivers across different countries in Europe. Moreover, it has been conducted through face-to-face contact and not by telephone interviews, where time length is a critical limitation. In addition, the PAB had the opportunity to explore the particular features of each device hands-on, to interact with them and have their features and metrics explained to maximize their potential to understanding them and their potential benefits and pitfalls. A systematic way for the PAB to provide feedback in a straightforward and measurable manner was devised using cards, to rate and order features and devices by preference. By considering their feedback, future research design and clinical practice, researchers, technology developers as well as policy makers, and professional caregivers can promote the acceptance and implementation of remote monitoring in the care of people with dementia. As the PI activity was conducted in the framework of the RADAR-AD research project, its valuable insights were already used to support important decisions related to its ongoing developments and mainly the choice of devices to be used in prospective European remote monitoring cohort study with research participants from pre-dementia to dementia stages. A positive impact on the recruitment, retention and wellbeing of the RADAR-AD research participants is expected, demonstrating the importance of PI in dementia research.

DATA AVAILABILITY STATEMENT

The data that support the findings of this PI activity are available on request from the corresponding author, TS. The data are not publicly available since they contain information that could compromise the privacy of PI activity participants.

ETHICS STATEMENT

Written informed consent was obtained from the relevant individuals for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

TS, IL, AD, DG, and JG: conceptualization, validation, and investigation. TS and IL: methodology, formal analysis, writing – original draft preparation, and visualization. TS, SN, and IK: software. CH, MT, and IK: resources. TS, IL, NM, and EP: data curation. AD, DG, JG, NM, EP, and SN: writing – review and editing. JG, NM, EP, CH, MT, SN, and IK: supervision. TS, JG, NM, EP, CH, MT, SN, and IK: project administration. TS, JG, NM, EP, CH, MT, and IK: funding acquisition. All authors have read and agreed to the published version of the manuscript.

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Conflict of Interest: EP was employed by company Alfasigma Schweiz AG. NM is an employee of Janssen Research and Development, LLC and holds equity.

The remaining 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.

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Can Exergames Be Improved to Better Enhance Behavioral Adaptability in Older Adults? An Ecological Dynamics Perspective

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Finding effective training solutions to attenuate the alterations of behavior and cognition in the growing number of older adults is an important challenge for Science and Society. By offering 3D computer-simulated environments to combine perceptual-motor and cognitive exercise, exergames are promising in this respect. However, a careful analysis of meta-analytic reviews suggests that they failed to be more effective than conventional motor-cognitive training. We analyzed the reasons for this situation, and we proposed new directions to design new, conceptually grounded, exergames. Consistent with the evolutionary neuroscience approach, we contend that new solutions should better combine high level of metabolic activity with (neuro)muscular, physical, perceptual-motor, and cognitive stimulations. According to the Ecological Dynamics rationale, we assume that new exergames should act at the agent–environment scale to allow individuals to explore, discover, and adapt to immersive and informationally rich environments that should include cognitively challenging tasks, while being representative of daily living situations.

Keywords: exergames, cognition, brain, behavioral adaptability, ecological dynamics, complex systems

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STRIVING FOR HEALTHY ACTIVE AGING: A SCIENTIFIC AND PUBLIC HEALTH CHALLENGE

With the increase in life expectancy, the number of older adults suffering from declines in brain, cognitive, physical, and perceptual-motor functions also increases. Thus, an important challenge for cognitive and behavioral science is to identify the most attractive and effective solutions for attenuating the deleterious effects of aging on the brain–mind–body system (BMBS). By combining physical and cognitive exercises thanks to virtual environments and game scenarios, exergames are promising in this respect and constitute a growing market exploited by the video games and fitness industries to penetrate the field of geriatrics and rehabilitation. Introduced by the big players of the video games industry, exergames are considered as innovative solutions to improve brain functions and cognitive performance. This hypothesis remains, however, to be unequivocally demonstrated in older adults. In this *prospective paper*, on the basis of available reviews and meta-analyses, we address this issue. Our conclusion is that, until now, exergames did not keep their promises, in particular in comparison with conventional cognitive-motor training. We contend that, beyond the heterogeneity and methodological weakness of exergames studies, a more fundamental reason is that most commercial products are implicitly based on the theoretical commitments of the classic cognitive science, which considers dual-task training as the gold standard for targeting brain plasticity and cognitive functioning (Wollesen and Voelcker-Rehage, 2014; Gallou-Guyot et al., 2020; Wollesen et al., 2020). This has two important consequences. On the one hand, exergames do not fully exploit the functional relationships between perceptual-motor, physical, and cognitive domains resulting from our evolutionary history (Raichlen and Alexander, 2017). On the other hand, they do not take advantage of the resources offered by virtual reality to improve adaptive perceptual-motor behaviors, through (inter)active exploration of immersive environments. To remedy this situation, we suggest some avenues, grounded on the theoretical frameworks of evolutionary neuroscience and ecological dynamics that could inspire the design of Ecological-Exergames (E-EG).

EXERCISE AND COGNITION: FROM SEPARATE TO COMBINED TRAINING

For a long time, cognitive training was considered the only way to improve brain functions and cognitive performance and make older adults smarter and more able to learn faster and better (Simons et al., 2016). However, although positive training effects were observed in some studies [e.g. (Green and Bavelier, 2003, 2006; Anguera et al., 2013)], inconsistent results were also frequently reported [for meta-analyses, see (Lampit et al., 2014; Toril et al., 2014)], which has led to vivid controversies [for an overview (Simons et al., 2016)]. Progressively, they died down, thanks to the studies that have identified the effective specifications of cognitively demanding digital environments, which make video games effective to stimulate brain and cognition [for details, see (Bediou et al., 2018; Dale et al., 2020)].

In this context, the meta-analysis conducted by Colcombe and Kramer (2003) has considerably renewed the view of the relationships between exercise and cognition by showing that physical activity may also improve neuroplasticity and cognitive functioning. Then, subsequent studies contributed to elucidate the mechanisms underlying the benefits of endurance training and muscular resistance training on brain and cognitive functioning [for overviews (Voelcker-Rehage and Niemann, 2013; Herold et al., 2019; Netz, 2019)]. More recently, it has been demonstrated that complex motor skills training also improved brain plasticity and cognitive functioning [e.g. (Voelcker-Rehage et al., 2010, 2011; Niemann et al., 2014; Netz, 2019)]. For instance, available data suggested that the effects of aerobic training were magnified when aerobic effort was supported by complex motor skills [e.g. (Pesce, 2012; Diamond and Ling, 2016, 2019)]. In addition, physical-cognitive training (Fissler et al., 2013; Bamidis et al., 2015) and motor-cognitive training (Gallou-Guyot et al., 2020; Gavelin et al., 2020) were found to be more effective than separate training to improve cognitive functions [but see (Zhu et al., 2016)], for a different conclusion]. In view of these findings, exergames are expected to be more effective than conventional training (i.e., interventions supervised by a coach and not assisted by technologies) to improve behavior and cognition in older adults (Stanmore et al., 2017; Martin-Niedecken and Mekler, 2018). However, this optimistic hypothesis needs to be confirmed, in particular with respect to conventional motor-cognitive training and physical-cognitive training. This issue is addressed in the following sections.

ARE EXERGAMES EFFECTIVE FOR ENHANCING BRAIN PLASTICITY AND COGNITION?

Although encouraging results were observed in several studies [e.g. (Anderson-Hanley et al., 2012; Maillot et al., 2012; Barcelos et al., 2015; Eggenberger et al., 2015; Schättin et al., 2016; Ballesteros et al., 2018)], controversial findings have also been reported as exergames were found to be effective [e.g. (Stanmore et al., 2017)], ineffective (Ordnung et al., 2017; Sala et al., 2019), or unclear (Stojan and Voelcker-Rehage, 2019), in comparison with conventional interventions. Several reasons may explain these inconsistencies. The first reason lies on the low methodological quality and the great heterogeneity of the available studies, which is reported by most reviews and meta-analyses reported (Stojan and Voelcker-Rehage, 2019; Gallou-Guyot et al., 2020; Gavelin et al., 2020). A second reason is that most studies were carried out with off-the-shelf products, which (i) lacked proper theoretical founding concepts, (ii) disregarded basic learning and training principles provided by Movement and Sport Sciences (Caserman et al., 2020) and, (iii) were neither suited for research purposes nor adapted to the specific psychological, physical, and cognitive characteristics of older adults [e.g. (Ordnung et al., 2017)]. A third reason is that the contents of digital environments and game scenarios provided by the different products were scarcely analyzed in the literature [for a noticeable exception, see (Fronza et al., 2019)], though research on action video games has demonstrated that they significantly affect the level of cognitive demands (Bediou et al., 2018; Dale et al., 2020) and that they could have more weight in the observed benefits on cognition than the physical components (Maillot et al., 2012). Thus, whether the virtual environments of the current commercial exergames (more or less) heavily load cognitive processes remains unknown. Similarly, whether the movements requested by gameplays were effectively performed by the players was never analyzed in the different studies [for a noticeable exception, see (Anders et al., 2020)]. In addition, in most studies interested in the effects of exergaming on cognition, changes in cardio-respiratory fitness and muscle strength were not analyzed. However, this should be a prerequisite for the analysis of cognitive modifications, which are presumably mediated, at least in part, by the improvement of aerobic capacities and muscle strength. Inconsistent findings have been reported in this respect in the literature. In their meta-analysis, Peng et al. (2011) concluded that exergames facilitate light-to-moderate physical activity [see (Maillot et al., 2012) for confirming evidence], but they also mentioned that participants were often below the moderate level. However, it might depend on the type of used exergame. In support of this hypothesis, using a biking exergame, Moholt et al. (2017) showed that Exergaming can be an innovative way of high-intensity training. With respect to muscle strength, although Monteiro-Junior et al. (2016) argued that, due to weight-bearing exercises, exergames might lead to effects comparable to those observed during muscular resistance training, this hypothesis was challenged by DeVries et al. (2020), who showed reported low muscular activation in balance games. A fourth reason is that, while a wide range of exergames was used to support training interventions across the different studies, their potential differences in effectiveness were scarcely assessed in the literature. This was also the case for lab-customized exergames [e.g. (Ben-Sadoun et al., 2016; Anderson-Hanley et al., 2017; Wall et al., 2018)], whose effects were never systematically compared with those of commercial products or of conventional training [for a noticeable exception, see (Willaert et al., 2020)]. Thus, the conclusions reported in most reviews on exergames were generally based on the assumption that the different exergames were all comparable in their effectiveness, which was certainly wrong.

In summary, studies on exergames predominantly aimed at describing their benefits on cognition and behavior [scarcely on brain functions (Stojan and Voelcker-Rehage, 2019)] by comparing them to a control group of more or less active individuals [e.g. (Maillot et al., 2012; Karssemeijer et al., 2019; Adcock et al., 2020)]. Few studies aimed at determining whether their benefits were larger than those of physical or cognitive training [e.g. (Martin-Niedecken and Schättin, 2020)]. On the other hand, whether exergames are equally or more effective than conventional motor-cognitive training has been scarcely addressed until now and available findings are inconsistent in this respect [e.g. see (Eggenberger et al., 2015; Htut et al., 2018) versus (Bacha et al., 2018; Schättin et al., 2018)]. A plausible reason is that the differences between the mechanisms at work in conventional motor-cognitive training and exergaming are still unclear. Monteiro-Junior et al. (2016) argued that these mechanisms could be, at least in part, similar. Specifically, neuroplasticity (i.e., neurogenesis, synaptogenesis, and angiogenesis) could be facilitated by the stimulation of neurotrophic factors (e.g. BDNF) resulting from light to moderate aerobic physical activity, while guidance effects might result from interactions with 3D virtual environments, which are hypothesized to increase the activation of the brain areas that are related to involved cognitive functions. With respect to cognitive content of commercial exergames, several authors considered that they allow delivering motor-cognitive dual-task training (MCDT) [e.g. (Wollesen and Voelcker-Rehage, 2014; Monteiro-Junior et al., 2016; Anders et al., 2018; Gallou-Guyot et al., 2020; Gavelin et al., 2020; Wollesen et al., 2020)] since additional challenges, in the form of extra tasks, such as counting, matching objects, or avoiding obstacles, are often used to add cognitive training to the physical exercise (Anders et al., 2018). These elements create dual task situations [i.e., *Thinking while moving* situations, (Herold et al., 2018)], in which the player needs to focus on two or more things simultaneously. Strikingly, few studies investigated the effects of exergames on dual-task performance [for noticeable exceptions, see (Schättin et al., 2016; Peng et al., 2020)] but, recently, Gallou-Guyot et al. (2020) compared (indirectly) conventional MCDT training and exergaming. They did not observe any superiority of the latter over the former, though some studies suggested the opposite [e.g. (Eggenberger et al., 2015)]. In addition, they reported that most of the tested exergames weakly improved physical performance, suggesting that cognitive-motor dual-task training delivered through exergames moderately loaded metabolic capacities [e.g. (Larsen et al., 2013; Anderson-Hanley et al., 2017; Levin et al., 2017; Martin-Niedecken and Mekler, 2018; Taylor et al., 2018), but see Peng et al., 2011; Maillot et al., 2012], for a different conclusion]. Consequently, one can conclude that, in most cases, exergames did not fully exploit the synergy between facilitation and guidance effects, which is considered a basic condition for observing strong benefits on brain structures and cognitive functions, when aerobic and cognitive exercise are associated (Fabel et al., 2009; Fissler et al., 2013; Raichlen and Alexander, 2017). In summary, the available literature did not demonstrate unequivocally the superiority of exergames over the other forms of training (see **Table 1**). These findings suggest that new exergames should be designed to improve their effectiveness relative to conventional motor-cognitive training. In the following, we propose some avenues in this respect.

HOW CAN EFFECTIVENESS OF EXERGAMES BE IMPROVED?

According to the above considerations, new exergames should be designed to allow better combining high level of metabolic (aerobic) activity with (neuro)muscular, perceptual-motor, and cognitive stimulations, to provide the whole BMBS the multiple and synergically combined inputs that are necessary for its plastic adaptation. This hypothesis is consistent with the Adaptive Capacity Model (ACM) developed by Raichlen and Alexander (2017) in the context of the evolutionary neuroscience approach. However, a limitation of the ACM is that it endorses the mainstream approach of cognitive (neuro)science, without deeply considering the potential of virtual environments to elicit other mechanisms, at the scale of the performer–environment relationship, which underlie the way individuals perceive, explore, navigate, and, finally, act upon their surroundings in dynamic environments (Raja and Calvo, 2017). This hypothesis is consistent with the framework of ecological dynamics (ED), which may help to formalize these mechanisms and provide guidelines for designing new products.

THE ECOLOGICAL DYNAMICS APPROACH

Ecological dynamics focuses on the whole BMBS, considered as a complex dynamical system (Kelso, 1995; Seifert et al., 2015) that is embedded and informationally coupled to the

TABLE 1 | Summary table of the main findings of the literature for (i) cognitive training alone, (ii) physical/motor training alone, (iii) combined motor-cognitive and physical-cognitive training, and (iv) simultaneous, dual-task training.

Cognitive training	Conventional physical and motor training	Combined training	Dual task training
** Cognitive training is hypothesized to improve neuroplasticity and brain functioning as a result of exercises that make significant demands on specific cognitive resources. ** Appropriate, controlled, process-based intervention designs, cognitive training may lead to small or moderate gains relative to control groups, for information processing speed, visual attention, working memory, visuo-spatial abilities, and executive functions. ** With regard to transfer to other untrained tasks, cognitive multi-tasking training seems more effective, presumably since it corresponds to cognitive demands that are closer to real-life situations than those proposed in most classic cognitive training studies. ** Whether and under what conditions cognitive training and video games are effective to improve cognitive performance and favor transfer to everyday life situations remains unclear and controversial.	** Two categories of training are commonly divided into two categories: physical training (i.e., endurance and muscular resistance) and motor training, that is, the practice of complex motor skills (balance control, multi-limb coordination, mobility. . .). ** Endurance training mainly affects executive functions supported by the frontal and prefrontal cortex. ** Muscular resistance training improves neuro-muscular control and has a positive impact on brain plasticity, especially in the frontal lobe, which is accompanied by improvements in executive functions, in short- and long-term memories, or attention. ** All these effects are mediated by increases in neurotrophic factors, which presumably reflects the common denominator between endurance training and muscular resistance training. ** Combining aerobic and strength training leads to a greater benefit than aerobic exercise alone. ** Complex motor skill training relies on cognitive control than the highly automatic movements that are currently used in aerobic or muscular resistance training.	** Physical-cognitive and motor-cognitive training denote two forms of association between physical and cognitive exercise. ** It is well established that (i) combined training is more effective than separate training and (ii) sequential training is more effective than simultaneous training. Whether physical-motor training is more effective than motor-cognitive training is still unknown. ** Combined training also triggers general effects depending on the physical/motor components that are integrated into the training. Whether enhancement of physical and motor capacities is a pre-requisite to observe larger effects of combined training is controversial and remains to be confirmed.	** Dual-task training is hypothesized to accustom the CNS to the sharing of cognitive/attentional resources between multiple tasks. ** Most studies investigated whether healthy older adults benefit from training interventions in DT situations, with the need of balance control while standing or walking. ** The most promising approach to reach motor benefits under dual-task conditions seems to be a general dual-task intervention program, in particular under variable priority conditions. Indeed, the majority of standing and walking studies reported positive effects on standing or walking performance under dual-task conditions.

References are mentioned in the text.

continuously evolving environment (Chiel and Beer, 1997). Thus, agent–environment relationship is considered the appropriate level of analysis of adaptation mechanisms. In the BMBS, the perceptual, cognitive, cardiovascular, respiratory, and motor subsystems are deeply intertwined by virtue of mutual couplings, which give rise to stable and flexible behavioral (motor) patterns that are shaped by the coalition of organismic, task, and environmental constraints (Newell, 1985; Bingham et al., 1991; Chiel and Beer, 1997). These flexible patterns make the BMBS able to adapt to the dynamic environment.

In this perspective, perception and action cannot be understood one without the other. On the perceptual side, it is assumed that information is directly available and can be picked up by individuals to attune action (Gibson, 1979). Thus, the agent would perceive affordances, i.e., action opportunities (e.g. reaching, grasping, sitting, walking, jumping, etc.) provided to the agent by the substances, surfaces, objects, and other living creatures that surround it (i.e., the environment) (Fajen et al., 2008). That means that the environment is perceived in terms of properties scaled to the performer's motor abilities, and action, considered as an expression of cognition, is the behavioral realization of an affordance. Thus, behavioral dynamics emerge from the continuous exploration of the perceptual-motor workspace that links the performer's perception of task constraints to the opportunities for action, given the state of the agent–environment system at each moment in time (Pacheco et al., 2019).

The idea that perception and cognition are mutually embedded and embodied in action leads to consider cognition as a virtual supervisor, distributed over the brain, mind, body, and environment, whose function is twofold. On the one hand, cognition modulates functional interactions between the different components of the BMBS, thereby allowing to shape the emerging behavioral patterns [e.g. (Zanone and Kelso, 1992; Monno et al., 2002; Taylor et al., 2018; Temprado et al., 2020)]. On the other hand, cognition supports the attunement of behavior to the perceptual-motor workspace by supervising how the individual *does something somewhere* (Araujo, 2009), that is, how it attains a functional relationship with the world by virtue of changes in information-movement coupling [e.g. (Davids et al., 2015)].

In this context, behavioral adaptability is the primary criterion for assessing individual functional states and training benefits.

It can be directly or indirectly assessed through dynamical markers (Sleimen-Malkoun et al., 2014), as, for instance, directly through (i) the repertoire of behavioral patterns (Sleimen-Malkoun et al., 2013, 2014; Temprado et al., 2020) and/or of execution strategies [e.g. (Poletti et al., 2016)] that are available and effectively used by the performer; and (ii) the dynamics of switching between behavioral patterns and strategies that are observed when task constraints are increased [e.g. (Kelso, 1984; Temprado et al., 2020)]. Moreover, adaptability can also be indirectly assessed through the complex structure of the non-linear fluctuations of the output of the system under consideration [e.g. (Lipsitz, 2002; Vaillancourt and Newell, 2002)]. It has been suggested that complexity markers can be used to assess the training benefits of behavioral adaptability [e.g. (Manor and Lipsitz, 2013; Wayne et al., 2013)], but to our knowledge, this approach has not been yet applied to the study of the consequences of cognitive-motor training with exergames.

DESIGNING NEW EXERGAMES: AN ECOLOGICAL DYNAMICS PERSPECTIVE

Two main assumptions should guide the design of exergames inspired by the ecological dynamics framework (hereafter E-Exergames). First of all, the agent–environment relationship is the appropriate level at which E-Exergames must act to transform behavior and cognition. Secondly, to develop the capacity to produce adaptive behaviors, E-Exergames should allow older adults to refine or enlarge their behavioral repertoire through repeated stimulation of the synergistic relationships between cardiovascular, muscular, perceptual-motor, and cognitive subsystems, thanks to performing complex motor tasks in immersive environments. In sum, E-Exergames should be designed to allow the players learning by *exploring*, *discovering*, and *adapting* to dynamic environments (Rudd et al., 2020), while producing moderate to high level of cardiovascular effort and muscular force (Wall et al., 2018).

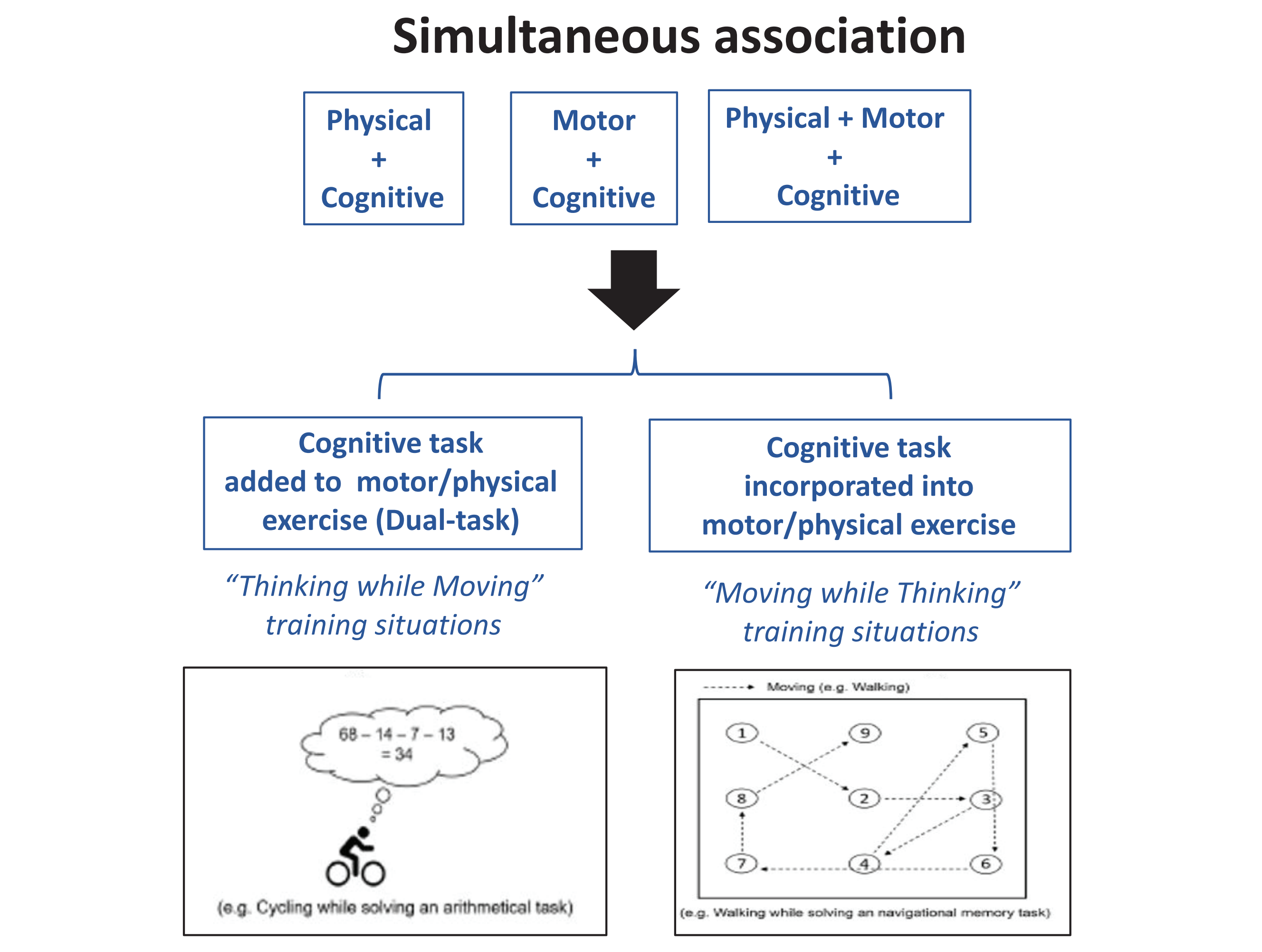

FIGURE 1 | *Thinking while Moving* and *Moving while Thinking* training situations, which are hypothesized to be two different kinds training conditions. In the former, the cognitive task is simply added to the motor/physical task, while in the latter, cognition is "incorporated" into motor tasks, making them more closely related to real daily life situations [modified from Herold et al. (2018)].

To achieve these general objectives, E-Exergames should confront older adults with novel, challenging, immersive, and interactive 3D environments to facilitate the transfer of training benefits to daily living tasks. This issue is crucial and might lead to a superiority of E-Exergames over classic commercial products. Specifically, game scenarios provided by virtual environments should simulate natural activities, in emotionally salient contexts, to afford goal-oriented, exploratory motor behaviors (e.g. spatial navigation, catching, hitting, aiming, interception of mobile objects, aperture crossing, jumping, coordinating multi-limb, or controlling dynamic balance). In addition, training situations should facilitate the detection of action possibilities, to make quick and accurate decisions under time pressure, in a context of rapidly changing visual scenes [e.g. (Bediou et al., 2018; Dale et al., 2020)]. In this aim, virtual environments should enhance affordances (walkability, reachability, graspability, throwability, etc.) and allow manipulating task constraints, to afford different action possibilities and lead the exer-players to either exploit the existing patterns of their repertoire or insert new (learned) patterns (Zanone and Kelso, 1992). These guidelines are consistent with the *Moving while thinking* training situations, which have been recently hypothesized to be optimal training conditions since, in these situations, cognition is "incorporated" into motor tasks, making them more closely related to real daily life situations (Herold et al., 2018; see **Figure 1**).

To be more effective than commercial products, E-Exergames should combine the principles of effective cardiovascular and muscular training [e.g. (Niemann et al., 2014; Wall et al., 2018; Herold et al., 2019)], with those of perceptual and motor learning proposed by movement and training sciences [e.g. (Papegaaij and Steenbrink, 2017; Stone et al., 2019)]. In this aim, game scenarios should also be adapted to allow *task simplification*, *progressive increase in tasks difficulty*, *manipulation of information*, *modulation of constraints*, *variable conditions of practice*, and *feedback of information* about successful behaviors and goal achievements (Vaillancourt and Newell, 2002; Hristovski and Araujo, 2009; Rudd et al., 2020). Task simplification aims at making the tasks easier to achieve, while keeping present all the components of the perceptual-motor behavior (perception, decision-making, and movement patterns). Then, difficulty of the tasks must be progressively increased over the training program, in order to keep the players in the optimal flow zone. Information manipulation allows enhancing the perceptual saliency of existing affordances that invite specific functional actions needed to reach intended task goals (Raja and Calvo, 2017). It can be achieved by making some aspects of the environment more salient, while blocking others (Raja and Calvo, 2017) and/or by including additional cues, thanks to Augmented Reality (AR). In this aim, the most important information to be picked up must be identified to be subsequently used to direct the attentional focus in order to facilitate affordance perception and learning (Wulf, 2013; Becker and Fairbrother, 2019). Manipulation of constraints related to tasks, individual, or environment (Newell, 1985) allows providing variables conditions that force the exer-player to explore and discover the optimal solution (Rudd et al., 2020). Indeed, variable conditions of practice allow the exer-player to explore the perceptual-motor workspace without imposing movement solutions, until the behavioral patterns become stable and reproductible (Pacheco et al., 2019). Information feedback provided to the players will be helpful in this respect, allowing them to either reinforce their behavioral responses or explore new solutions.

Though prominently acting at the agent–environment level, E-Exergames will target cognition through the "explore–discover–adapt" process, which requires a cognitive supervision and, specifically, the involvement of executive functions, through intention and attention (Kramer and Erickson, 2007). In this context, Augmented Reality included in E-Exergames may allow educating intention (through instructions, rules, etc.) and the direction of attentional focus to the more useful variables (through the salience of some features), which, in turn, influences exploration of the environment and the detection of affordances. E-Exergames will also contribute to stimulate brain plasticity and self-repairs of the altered functional components of the BMBS, thanks to the dissipation of flows of energy and information generated by exploratory motor behavior produced at moderate-to high-intensity levels of cardiovascular effort (Kramer and Erickson, 2007; Reuter-Lorenz and Park, 2014; Raichlen and Alexander, 2017). Based on these mechanisms, extensive practice of E-Exergames could contribute to restore age-related loss of complexity of the whole brain–mind–body–behavior system that is currently associated with behavioral adaptability (Vaillancourt and Newell, 2002; Manor et al., 2010).

CONCLUSION AND PERSPECTIVES

During the last two decades, a number of studies aimed to assess the effects of exergaming on behavior and cognition. However, due to its great heterogeneity and methodological weaknesses, poorly informative or inconsistent findings piled up across studies, which precluded researchers to firmly conclude its superiority over conventional training.

In the present paper, we proposed new directions to design (hopefully more effective) E-Exergames, which should be based on two main pillars: on the one hand, exploiting the functional relationships between perceptual-motor, physical, and cognitive domains resulting from our evolutionary history, and on the other hand, acting at the agent–environment scale to allow individuals *to explore* the dynamic perceptual-motor workspace offered by each game situation and *to discover* and *select* appropriate actions in order *to adapt* to complex environments. In addition, to improve engagement and enjoyment, they should to create a positive flow experience for the players (Martin-Niedecken and Mekler, 2018). Then, E-Exergames would be both attractive, to encourage further meaningful engagement in active live habits, and effective to develop a wide range of complex and flexible perceptual-motor skills (Rudd et al., 2020).

To verify the hypotheses developed in the present paper, further studies are necessary, in particular to determine whether and under which conditions they are more effective, attractive, and acceptable than currently available commercial products and conventional training interventions.

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.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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frontiers in Aging Neuroscience

STUDY PROTOCOL
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Changes in Metabolic Activity and Gait Function by Dual-Task Cognitive Game-Based Treadmill System in Parkinson's Disease: Protocol of a Randomized Controlled Trial

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Balance and gait impairments, and consequently, mobility restrictions and falls are common in Parkinson's disease (PD). Various cognitive deficits are also common in PD and are associated with increased fall risk. These mobility and cognitive deficits are limiting factors in a person's health, ability to perform activities of daily living, and overall quality of life. Community ambulation involves many dual-task (DT) conditions that require processing of several cognitive tasks while managing or reacting to sudden or unexpected balance challenges. DT training programs that can simultaneously target balance, gait, visuomotor, and cognitive functions are important to consider in rehabilitation and promotion of healthy active lives. In the proposed multi-center, randomized controlled trial (RCT), novel behavioral positron emission tomography (PET) brain imaging methods are used to evaluate the molecular basis and neural underpinnings of: (a) the decline of mobility function in PD, specifically, balance, gait, visuomotor, and cognitive function, and (b) the effects of an engaging, game-based DT treadmill walking program on mobility and cognitive functions. Both the interactive cognitive game tasks and treadmill walking require continuous visual attention, and share spatial processing functions, notably to minimize any balance disturbance or gait deviation/stumble. The ability to "walk and talk" normally includes activation of specific regions of the prefrontal cortex (PFC) and the basal ganglia (site of degeneration in PD). The PET imaging analysis and comparison with healthy age-matched controls will allow us to identify areas of abnormal, reduced activity levels, as well as areas of excessive activity (increased attentional resources) during DT-walking. We will then be able to identify areas of brain plasticity associated with improvements in mobility functions (balance, gait, and cognition) after intervention. We expect the gait-cognitive training effect to involve re-organization of PFC activity among other, yet to be identified brain regions. The DT mobility-training platform and behavioral PET brain imaging methods are directly applicable to other diseases that affect gait and cognition, e.g., cognitive vascular impairment, Alzheimer's disease, as well as in aging.

Keywords: Parkinson's disease, dual-task, randomized controlled trial, positron emission tomography, magnetic resonance imaging

INTRODUCTION

Disruption of frontostriatal circuits in Parkinson's disease (PD) have been shown to be associated with gait impairments (Rochester et al., 2004; Rosenberg-Katz et al., 2015) and deficits in executive cognitive functions (Kudlicka et al., 2011; Olchik et al., 2017). It is now well established that gait and cognition are closely linked (Plotnik et al., 2011; Kelly et al., 2012; Callisaya et al., 2016). For example, community ambulation requires walking while also performing a variety of executive cognitive functions, such as navigating busy environments, managing complex terrains, searching for and tracking various visual targets, information processing of what is being seen, reading, etc. Unfortunately, both mobility skills and cognition are often affected in PD (Mak et al., 2014; Paul et al., 2014; Schneider et al., 2015).

The dual-task (DT) paradigm has been used in a number of studies to assess the magnitude of DT interference of cognitive load on gait function and vice versa in PD (Rochester et al., 2014; Heinzel et al., 2016; Penko et al., 2018). DT testing is considered representative of real-life situations, and provides better insight into functional capacity. The concept of motor automaticity has an important implication in the pathophysiology of PD related to mobility limitations and increased fall risk (Wu et al., 2015; Gilat et al., 2017). One model of executive cognitive functions presents the supervisory attentional system, which distinguishes between processing of non-routine, attentionally demanding activities vs. routine, automated tasks (Dirnberger and Jahanshahi, 2013). The role of the sensorimotor striatum has been equated with that of routine tasks, such as locomotion, that are usually performed automatically (Gilat et al., 2017). The increased attentional and information processing demands of DT-walking are presumed to reduce the already limited locomotor control of PD patients (Kang et al., 2005; Wu and Hallett, 2008), and this may result in greater gait variability/instability and a higher risk of falls.

Emerging evidence suggests that the decline in mobility function due to a combination of motor and cognitive impairment can be improved by DT training (Gregory et al., 2017). For example, virtual environments viewed during treadmill walking provides a task-orientated approach to DT-walking training (Mirelman et al., 2016). Maximizing participation is also a main goal of any exercise program. Long-term exercise programs are often fraught with low compliance and adherence, so maintaining motivation is thus central to long-term functional success of a therapy program. A promising methodology is to combine exercise with computer games, making training a more engaging and enjoyable experience (Barry et al., 2014). Digital media in the form of computer games can also challenge and improve many different aspects of executive cognitive function (Strenziok et al., 2014; Bonnechère et al., 2020). Many common and modern computer games are readily available in which processing speed, cognitive inhibition, task switching, working memory, and problem-solving are main components of interactive game play.

There is a need to develop and validate a low-cost platform that combines walking and executive cognitive activities. For this purpose, our research group has developed and validated an engaging cognitive game-based treadmill platform (GTP) for DT training, which includes an automated assessment subsystem (Nankar et al., 2017; Szturm et al., 2017; Ahmadi et al., 2019; Mahana et al., 2021). The GTP provides an integrated approach to address the decline in balance, gait, visuomotor, and executive cognitive functions. The GTP consists of: (a) a standard treadmill instrumented with a pressure mapping system to record center-of-foot pressure during walking, (b) an interactive computer game subsystem for DT; and (c) an automated monitoring application and analysis methods to quantify both gait and cognitive outcome measures (electronic records) while DT-walking.

At present, understanding of the neural underpinnings of DT-walking and training effects in PD is limited due to methodological limitations in neuroimaging (Monchi et al., 2004; Holtzer et al., 2014; Maidan et al., 2016). While diffusion tensor imaging (DTI) suggests that reduced white matter integrity—in pathways such as the forceps minor, corpus callosum, uncinate fasciculus, and cingulum—is associated with decreased gait stability and can indicate an increased risk of falling (Ghanavati et al., 2018; Snir et al., 2019), most neuroimaging data are limited to correlational analyses that take place in the absence of a walking task, or are limited in terms of spatial extent, such as functional near infrared spectroscopy (fNIRS). Some fNIRS investigations of walking have revealed that in healthy, able-bodied adults, prefrontal cortex (PFC) is bilaterally active and remains active during DT-walking as compared to single-task walking, whereas activation of the frontal lobe during DT-walking is impaired in persons with PD (Maidan et al., 2016). Recent functional magnetic resonance imaging (fMRI) studies have shown similar lack of PFC engagement during an executive function task (i.e., Wisconsin Card Sorting Task) in PD patients (Monchi et al., 2001; Nagano-Saito et al., 2014). It was suggested that basal ganglia degeneration affecting the striatum would result in less PFC activation during set-shifting in PD patients compared to the age-matched controls (Monchi et al., 2001).

Studies using resting fluorodeoxyglucose (FDG) positron emission tomography (PET) imaging have identified altered metabolic patterns in PFC and motor planning regions in PD that are associated with various gait abnormalities (and executive cognitive dysfunction (Fasano et al., 2015; Olchik et al., 2017). A few studies have examined FDG-PET in which the FDG uptake period involves either treadmill walking or overground walking (Shimada et al., 2013; Hinton et al., 2019; Mitchell et al., 2019a,b). FDG-PET imaging provides the unique opportunity to study functional imaging during interactions with different environments, in particular, during walking, because participants do not need to be constrained during the FDG uptake period. For example, PET imaging studies have been able to demonstrate a decline in sensorimotor cortical processing in middle-age during walking and obstacle negotiation (Mitchell et al., 2019b), and in PD patients with freezing of gait (Mitchell et al., 2019a). However, how DT-walking changes brain metabolism in PD has not been investigated. In this study, we will investigate behavioral analyses of gait and cognitive function, in addition to FDG-PET to assess a 10-week DT-walking training intervention, compared to treadmill walking only.

Although it is not possible to directly observe changes in brain function during a DT-walking task using MRI, this methodology can still provide important information regarding changes in brain structure and function at rest that can result following DT-walking training. Thus, in addition to the task-based PET imaging, pilot DTI and resting state data will be acquired—i.e., measuring brain function in the absence of an overt task—using both resting state fMRI (RS-fMRI) and pseudo continuous arterial spin labeling (pCASL). Although not much research has directly compared the relationship between gait impairment and functional connectivity—i.e., how different brain regions' activity correlates over time—data suggest that PD patients with postural instability and gait difficulty have reduced functional connectivity in the cerebellum and putamen, compared to healthy controls (Chen et al., 2015; Ma et al., 2017; Tessitore et al., 2019). Furthermore, postural instability negatively correlates with functional connectivity in the putamen (Chen et al., 2015). Finally, using support vector machine-based [SVM, using an iterative single data algorithm (ISDA)] scores, our previous work shows that PD patients have similar metabolic and perfusion patterns (i.e., SVM-ISDA scores) as those with Alzheimer's disease—importantly, these SVM-ISDA scores may be useful for monitoring disease progression and treatment response, and will be piloted in this study as a result (Katako et al., 2018).

MATERIAL AND EQUIPMENT

DT Equipment

Both single-task (treadmill walking only) and DT conditions will use a standard treadmill instrumented with a pressure mapping system to measure center-of-foot pressure (Vista Medical Ltd., Winnipeg, MB, Canada). An interactive computer game system for DT will also be used, including a computer monitor for visual display (placed at the front of the treadmill), and a pool of 30 commercial games available from www.bigfishgames.com for the DT training program (see **Supplementary Table 1** for a list and description of the games). Additionally, a miniature, wireless plug-n-play inertial-based computer mouse (IB-mouse; Therapy Mouse Mobility Research, AZ, United States) will be secured to a plastic headband and will allow interaction with the videogame system *via* head pointing movements (head rotation) to control the motion of any game sprite/paddle.

Neuroimaging Equipment

Positron emission tomography images will be acquired using a Siemens Biograph mCT PET/CT scanner (Siemens Healthineers, Knoxville, TN, United States). Participants will be administered 185 MBq of [^{18}F] FDG. For participants recruited in Winnipeg, MRI images will be acquired on a 3-Tesla Siemens/IMRIS MAGNETOM Verio MRI scanner (Erlangen, Germany), using a 12-channel head and neck coil. Participants recruited in Toronto will be scanned using a 3-Tesla, GE Discovery MR750 scanner.

METHODS

Objectives

The aim of the proposed study is twofold. Behavioral analysis of gait and cognitive function together with PET and MRI brain imaging methods will be used to evaluate the molecular basis and neural underpinnings of (1) the decline of mobility function in PD, and (2) the effects of an engaging, cognitive game-based DT-walking program on mobility functions.

The first objective is to determine if the metabolic brain activity during single and DT treadmill walking is different in PD as compared to able-bodied age-matched controls. It is hypothesized that there will be significant changes in brain metabolic activity of several cortical and subcortical regions of the PD patients relative to able-bodied controls. This will be the case for both single and DT-walking conditions.

The second objective is to conduct a multi-centered, single-blind, randomized, two-arm, and parallel group-controlled trial and examine the effects of a 10-week DT treadmill training program: on (a) gate and cognitive function tested under single and DT conditions, (b) the pattern of metabolic brain activity quantified with single and DT-walking uptake periods, and (c) structural and functional changes (at rest) occurring prior to and after DT-walking training.

Participants

52 patients with PD [26 from Winnipeg, MB, Canada (site 1) and 26 from Toronto, ON, Canada (site 2)], and 15 age-matched healthy, able-bodied control subjects (site 1) will be recruited in a 2-year time period. The criteria used for recruitment of the patients will include; (a) diagnosis of PD according to United Kingdom brain bank criteria (Hughes et al., 1992), (b) stage II-III of PD according to the Hoehn and Yahr scale (Bhidayasiri and Tarsy, 2012), (c) age 50–75 years, (d) adequate vision to see required images on a standard computer monitor, (e) able to score 26 or greater on the Montréal cognitive assessment scale [MoCA (Marinus et al., 2011)], (f) on stable medications for the past 3 months, and (g) able to walk overground for 2 min without an aid or cane. The exclusion criteria for participation will include the following: (a) diagnosis of any psychiatric comorbidity or history of any other neurological disease other than PD, (b) any other medical condition limiting participant ability to walk on the treadmill,

and (c) neuroimaging contraindications (i.e., claustrophobia, severe dyskinesia, diabetes, non-compatible metal implants, etc.). Healthy able-bodied adults with the same inclusion/exclusion criteria listed above except for diagnosis of PD will be recruited.

All responders to calls for participation will undergo a screening assessment. Ethics approval has been obtained from the institutional Human Research Ethics Boards. All volunteer participants will be asked to read and sign the informed consent form. The Clinical trial has been registered at ClinicalTrials.gov, identifier: NCT04415775.

Successfully screened PD participants will be randomized to the experimental intervention (XG) or an active control arm (CG). A computerized block randomization procedure will be implemented by an independent statistician. Randomization will be stratified by stage of the disease (Hoehn and Yahr stage II and III). To ensure similar representation of men and women, randomization will also be stratified by sex. Randomization will be achieved by having participants choose an opaque sealed envelope, each containing a group assignment.

Test Procedures and Protocols

Intervention Protocol

The experimental timeline is visualized in **Figure 1**. All PD participants will undergo a 10-week exercise program, three times per week. Each therapy session will involve: (a) 10-min warm-up of balance exercises while standing on a sponge or balance disk, and (b) treadmill-walking of 3- to 5-min intervals and with 1-min rest periods for a total duration of 35 min. The type of compliant surface used, and the treadmill speed will be adjusted so that participants will not require the use of the handrails or any other body support. As with the gait assessments participants will be fitted with a body harness connected to a LiteGait support structure.

Participants in the CG group will complete 10 weeks of a "single-task" exercise program including videogames only (i.e., for 10 min while sitting) and walking-only on the treadmill—these tasks are conducted independently, one at a time. Participants in the XG will perform various cognitive computer games during the warm up period on the compliant surface and during all treadmill walking intervals. The computer games will be played using the head mounted IB-mouse as described above. Many inexpensive and easily accessible common and modern games exist which are visually rich, fun, and engaging. They include a variety of tasks that require; (i) visual search and tracking of multiple targets, (ii) speed accuracy requirements, (iii) presence of distracters, (iv) matching tasks, and (v) working memory. Note that the games that will be used during behavioral and PET assessments and those used in the XG exercise program are different.

As in most physical therapy programs, the specifics of DT training are customized for each patient, and the program gradually becomes more challenging as a patient's performance improves. In the first DT training meeting, 6–10 games will be selected for each participant for their 10-week training session. They will be selected according to the domains of executive function, and also the personal preferences of the participant. Each game has hundreds of difficulty levels and as each level is successfully completed then the game automatically advances to the next difficulty level. Some games are less difficult than others, i.e., starting difficulty level can be easy, moderate, or hard. Thus, different games can be chosen to progress the difficulty level of the mental activities, i.e., speed of play, precision level, movement amplitudes, and distractions. Physical demands (i.e., type, thickness, and density of the compliant surface and the treadmill speed) will be progressed as tolerated. Participants in the CG group will be asked to play the computer video games using the IB-mouse while sitting for 10 min prior to treadmill walking. This will allow the CG group to have adequate practice using head rotation to control the IB-mouse which is used for assessment of DT performance.

Behavioral Testing

Behavioral testing includes motor and gait assessment and neuropsychological testing (described below). Behavioral testing will occur prior to intervention at baseline, immediately following intervention, and at a 6-month follow-up (see **Figure 1**). Gait measurements will be conducted throughout the duration of the experiment to track participant progress; however, it is important to note that these gait variables are in addition to those gathered under the more stringent assessment sessions. Additionally, physical activity tracking will take place continuously and will be acquired for 12 months following treatment.

Motor and Gait Assessment

Behavioral assessment of each PD participant will be conducted on three occasions, before and after a 10-week exercise program, and at a 6-month follow-up time period. Healthy control participants will be assessed at time 1 only. PD participants will initially be assessed with the Part-III (motor) section of the Movement Disorder Society—Unified Parkinson Disease Rating Scale [MDS-UPDRS (Goetz et al., 2008)]. Assessment of gait function under single-task (walk only) and DT conditions will be conducted on a treadmill, instrumented with a pressure mapping system. Treadmill walking is used to obtain 40–60 consecutive steps and at a constant speed [see Bhatt (2018) and Szturm et al. (2017) for a detailed description of data recording, analysis, and test-retest reliability]. Participants will be instructed to walk on the treadmill at their preferred gait speed without hand support for four 1-min intervals (one single-task walking only, one VMT, and two VCG trials, described below). The center-of-pressure of foot displacement in the mediolateral (ML) and anteroposterior (AP) directions will be collected at 100 Hz.

A custom computer application with the following two assessment modules will be used for the DT test conditions: (a) a visuomotor tracking (VMT) task and (b) a visuospatial cognitive game (VCG) task. **Figure 2** illustrates the gaming set-up for the VMT and VCG tasks. As described previously (Nankar et al., 2017; Szturm et al., 2017; Ahmadi et al., 2019; Mahana et al., 2021), an IB-mouse will be used to control and interact with the cognitive assessment games. The VMT task used in the present study requires real-time, on-line visual feedback of the relative positions of two objects. The VCG task requires visual search to locate target objects and cognitive inhibition to avoid distractors.

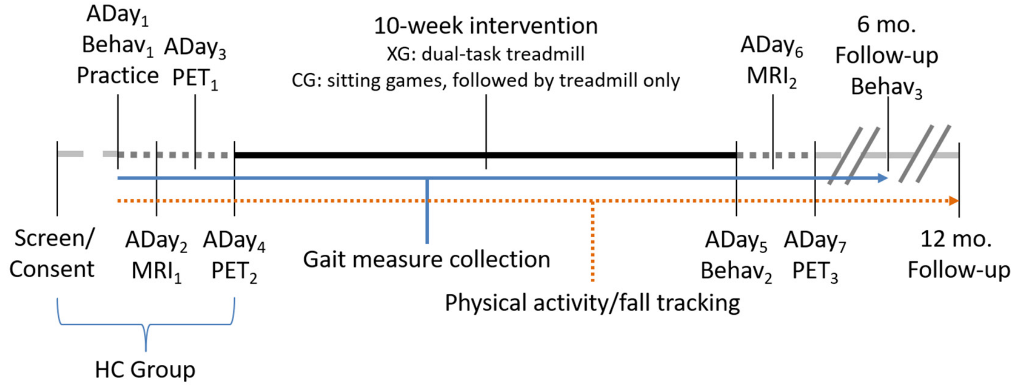

FIGURE 1 | Experimental timeline. Assessment days (ADay) indicate order of assessments. PET scans on $ADay_3$ and $ADay_4$ will be counterbalanced between a single-task treadmill walking only task and a DT treadmill walking and cognitive game condition. A final DT PET scan will be acquired following intervention ($ADay_7$). MRI scans will be collected pre- ($ADay_2$) and post-intervention ($ADay_6$). Behavioral testing (Behav; including motor measures and neuropsychological testing) will occur on three occasions: prior to intervention ($ADay_1$), following intervention ($ADay_5$), and again after a 6-month follow-up. Fall-history and physical activity tracking will be acquired throughout, until 12-months post-intervention. Measures of gait will be acquired throughout the program, including during behavioral assessment days, at each training session, and on PET assessment days. The experimental (XG) and control arm (CG) groups will complete the entire timeline, while healthy controls (HC) will complete up until $ADay_4$.

The VMT and VCG tasks require precision head-pointing movement. Many real-life tasks involve head movements to track and locate various objects, and for information processing of what are being seen. The increased visuospatial processing necessary to maintain walking rhythm and to correct for any drifting on the treadmill would compete for resources required to perform the VMT and VCG tasks, and vice versa.

A treadmill was chosen for the DT gait and cognitive functions for the following reasons. First, treadmill walking was chosen to overcome the confounding effect of gait speed. The treadmill allows the speed to be kept constant between walking conditions (single-task and DT), and over repeated measures (pre- and post-intervention time periods). This is of particular importance to standardize the uptake period of the PET imaging analysis at the three test periods. Most DT gait studies are performed overground, and all overground studies report a significant decrease in gait speed during the DT-walking condition, as compared to walk-only trials (Stegemöller et al., 2014; Raffegeau et al., 2019). Therefore, during overground DT-walking trials, there is a planned strategy to reduce the physical demands or threat to balance. Besides gait speed, many DT gait studies examine how cognitive demands affect gait rhythm and stability [i.e., recording spatiotemporal gait variables or analysis of trunk linear acceleration (Ijmker and Lamoth, 2012; Montero-Odasso et al., 2012; Asai et al., 2013; Martinez-Martin et al., 2013; Nankar et al., 2017; Ahmadi et al., 2019)]. However, gait speed is a confounding variable, as spatiotemporal gait variables and trunk acceleration are sensitive to changes in gait speed (Frenkel-Toledo et al., 2005; Jordan et al., 2007; Kang and Dingwell, 2008; Keene et al., 2016; Cole et al., 2017). Most overground DT-walking studies use an instrumented walkway, which records only 4–6 consecutive steps. It has been shown that using a continuous walking protocol, instead of short intermittent walks, and collecting more than 30 consecutive steps improved reliability, in particular for measures of gait variability and during DT-walking trials (Bruijn et al., 2009; Hollman et al., 2010; Galna et al., 2013). In addition, there is a limited choice of executive cognitive tasks that can be assessed during the short time period to walk a few meters. For example, cognitive tasks used during overground walking include walking while talking, recall of names/words, serial subtraction, or auditory Stroop (Stegemöller et al., 2014; Gregory et al., 2017; Ghanavati et al., 2018; Raffegeau et al., 2019; Snir et al., 2019). The present study extends these assessments to include visuomotor and visuospatial cognitive tasks assessed over a 1-min time period. Tracking visual objects and processing of what is being seen are important cognitive functions to consider in the analysis of DT interference on mobility (Nagamatsu et al., 2009; Logan et al., 2010). Cortical areas devoted to visual spatial ability such as the frontal and parietal lobes may be particularly susceptible to the neurodegenerative process of PD (Battisto et al., 2018; Lally et al., 2020). Following the principle of neural overlap (Crockett et al., 2017), DT interference should be greatest when the cognitive and motor tasks engage the same neural circuits and processing resources, e.g., visual-spatial processing. Walking endurance will be evaluated with a 6-min walk test [6MWT (Combs et al., 2014)]. Overground walking speed will also be evaluated over 25 m in a straight corridor.

Neuropsychological Tests

Parkinson's disease has been associated with cognitive impairment across a range of domains, including aspects of cognitive flexibility, inhibitory control, sustained attention, and working memory (Owen et al., 1993; Uekermann et al., 2003; Kudlicka et al., 2011; Weintraub et al., 2018). The Cambridge Neuropsychological Test Automated Battery (CANTAB) for PD will be used for assessment of cognitive function. These will include; (a) Paired Associates Learning, (b) Pattern Recognition Memory, (c) One Touch Stockings of Cambridge, (d) Spatial Working Memory, and (e) Match to Sample Visual Search. Health-related quality of life will be assessed with the PD

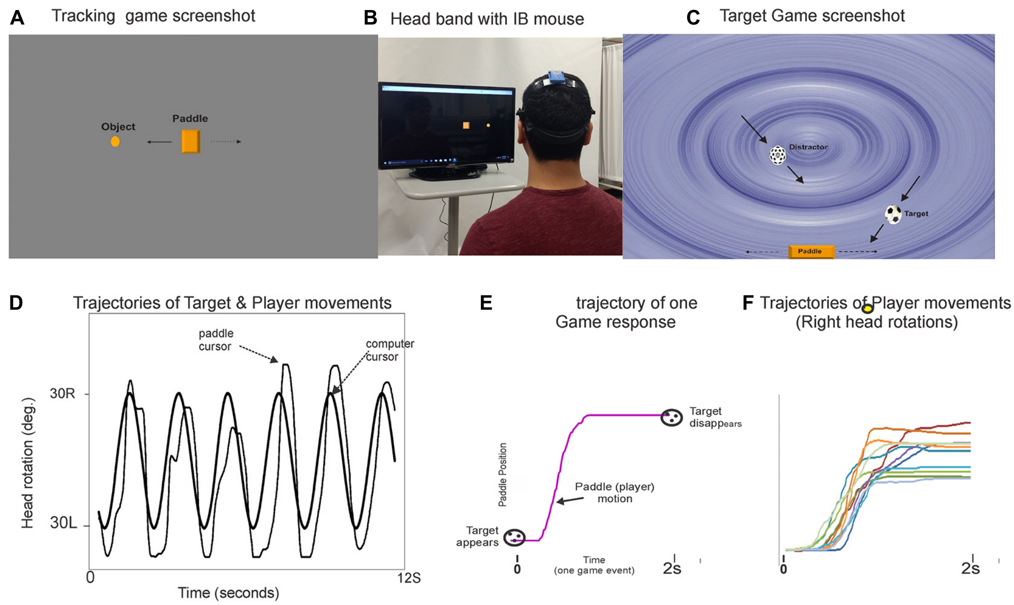

FIGURE 2 | Illustration of the DT gaming set-up and snapshots of the visuomotor tracking (VMT, panel **A**) and visuospatial cognitive games (VCG, panel **C**). Panel **(B)** shows a participant wearing a plastic headband with inertial motion mouse. The goal of the VMT game is to track and overlap the game paddle (rectangle object) with a moving circle object (computer controlled). The goal of the VCG is to move the game paddle, catch target objects (soccer ball), and avoid distractors (dotted sphere). Panel **(D)** plot shows typical movement trajectory of a healthy young adult playing the game. Panel **(E)** presents a single game movement trajectory (game paddle coordinates) of one game event from target appearance (time zero) to target disappearance (time 2 s). All segmented game movement trajectories of one game session are sorted and grouped by direction. Panel **(F)** presents overlay plots of the segmented and sorted game movement trajectories for a 60 s game trial. Presented are the game movement trajectories for rightward head rotations. Details on how to quantitate behavioral output measures have been published elsewhere (Nankar et al., 2017; Szturm et al., 2017; Ahmadi et al., 2019).

Questionnaire (Damiano et al., 1999). This neuropsychological data will be collected prior to participation commencement, at the end of the 10-week intervention, and at a 6-month follow-up, in the same session as the other behavioral assessments.

Fall rate will be recorded for a period of 1-year after completion of the exercise program. Falls rates will be considered a secondary outcome, due to concerns about the reliability and validity of self-report falls diary data. A fall will be defined as an unexpected event in which the participant comes to rest on the ground, or the floor (Mirelman et al., 2016). Several options will be used for the recording of fall events and to maximize the accuracy of reporting. Participants will receive fall calendars, either a paper version, a web-based calendar, or a smartphone application. Information logged in the online or smartphone-based calendars will automatically be uploaded to a database. Participants will be provided pre-addressed envelopes, and will be instructed to mail the paper version once every month. If a fall is recorded, the participant will be contacted by their treating therapist and asked when and how the fall occurred and whether there was any injury or need for medical treatment.

Physical Activity Tracking

In the second week of the exercise, program participants will be given a Fitbit watch (Ionic) to track physical activity levels during waking hours (Liang et al., 2018; Tedesco et al., 2019; Fuller et al., 2020). This model records steps taken, GPS and heart rate. Participants will be shown how to use the watch and how to access and transfer the stored data. Recorded activity data from the watch will be transferred to the therapist once a week during a treatment session. Over a 10-week time period this will provide ample practice on how to use the Fitbit watch and how to access and transfer its recorded activity data. Following the 10-week exercise program, the participants will be shown how to transfer their activity data to the research team. They will be instructed to do this once a week. Participants will be sent an e-mail or text message to remind them to do so.

Walks of more than 1 min will be determined by data showing continuous steps and where there are concurrent and adequate changes in GPS and increased heart rate. For each walking bout exceeding 1 min, the walking distance will be determined using the GPS data. The main physical activity outcome measures will be the total monthly walking duration and walking distance. Walking speed will also be computed for each walking bout over 1 min, and a monthly average obtained. Following the exercise program, all participants will be contacted by phone once a month to remind them of the use of the physical activity tracker.

Image Acquisition

PET Data

All subjects will undergo two pre-intervention [^{18}F] FDG-PET scans after fasting for at least 6 h before scanning. A head CT scan will be acquired for attenuation correction purposes. Static images (10 min) will be acquired starting 40 min after injection. During the FDG uptake period, participants will perform in different sessions, on different assessment days; (a) treadmill walking only (test session 1) and (b) DT treadmill walking (test session 2; see **Figure 1**). The order of the walk-only and DT-walking sessions will be counterbalanced. The single and DT treadmill walking will be done for 28 min each. This will involve seven 3-min walk intervals with 1-min rest periods (standing). Walking speed and duration will be carefully controlled, and repeated for each test session (i.e., single and DT conditions, pre- and post- intervention). Seven different standardized cognitive games will be selected for the seven DT-walking intervals. These will include; (a) five 3-min VC games with different difficulty levels (i.e., increasing game speed, adding distractors, and changing path of target motions), and (b) two 3-min VMT games, one played using horizontal head rotations and one with vertical head rotations. The PD patients will repeat the DT-walking PET imaging protocol after completion of the 10-week exercise program.

MRI Data

All participants will undergo an MRI session before the intervention, Data collected will include a structural, T_1-weighted anatomical image, a T_2*-weighted resting state fMRI scan, pCASL, and DTI data. Following the intervention, all PD participants will undergo a second MRI session, including the same scans as those acquired before intervention.

First, structural T_1-weighted (T1w) MR images will be acquired, using a 12-channel head and neck coil. T1w data will be acquired using an MP-RAGE sequence with TR/TE/TI = 2300/3.02/900 ms, 240 slices, flip angle = 9, FOV = 256 mm × 256 mm, 1.0 mm^3 (isotropic) resolution. This T1w data will provide the anatomical data over which the PET, RS-fMRI, pCASL, and DTI will be overlaid. Although MRI data cannot be used to directly investigate neural changes occurring during DT-walking, this technology will provide valuable information regarding how brain function and structure may change before and after DT-training in PD participants.

RS-fMRI data (T_2*-weighted) will be collected using a gradient-echo, echo planar imaging (GE-EPI) sequence with the following parameters: TR/TE = 2000/28 ms, 240 slices, flip angle = 77, FOV = 220 mm × 220 mm^2, 3.4 mm × 3.4 mm × 4.0 mm resolution. The parameters for the resting state pCASL data are as follows: TR/TE = 4000/12, 20 slices, flip angle = 90, FOV = 240 mm × 240 mm^2, 3.8 mm × 3.8 mm × 5.0 mm resolution, inter-slice space = 1 mm, labeling time = 2.0 s, post label delay time = 1.2 s, bandwidth = 3 kHZ/pixel. For each participant, 45 label/control image pairs will be acquired. DTI data will be acquired using a single-shot spin echo, echo planar imaging sequence with the following parameters: 35 directions (b = 700 s/mm^2), TR/TE = 10413/70.8 ms, FOV = 240 mm × 240 mm × 163 mm, 65 transverse slices, 2.5 mm^3 (isotropic) resolution.

Data Analysis

Details of the analysis procedures used to quantify the following spatio-temporal gait variables, and the VMT and VCG performance measures have been published elsewhere (Nankar et al., 2017; Szturm et al., 2017; Ahmadi et al., 2019). In brief, the following spatio-temporal gait variables were computed from the center-of-pressure of foot displacement time series recordings; (a) step length (SL), the distance between two successive heel contacts in the AP direction, and (b) swing time (SW) time, the time between toe-off and heel contact of each leg. The average SL and SW were then determined for each 1-min walk trial. Variability measures quantify the inter-stride fluctuations in SL and SW around the mean value and will be report it as coefficient of variance, COV-SL and COV-SW. The location of all heel contacts during each 1-min walk trial were also determined in both AP and ML directions. The dispersion of heel contact locations will be computed as the COV, and reported as AP-drift and ML-drift.

Figure 2 illustrates the VMT and VCG game tasks and plots of game movement responses. The following outcome measures for the VMT task include: (a) total residual error (TRE), determined by computing the difference between the trajectories of the target and head cursor motions, (b) amplitude variability (AV), a measure of movement consistency determined as the coefficient of variation of the mean right-to-left and left-to-right tracking movements for 20 cycles (i.e., a 45 s. trial). The following performance measures for the VCG will be quantified: (a) success rate (SR), (b) response time (RT), and (c) movement variance (MV).

Statistical Analyses

Our sample size was calculated based on our previous work involving PET imaging in PD in which participants were randomized into either gene therapy or sham-surgery groups, and assessed at 6 months follow-up (Ko et al., 2014a). With anticipated ρ2 = 0.673 [20% more than what is expected for placebo effect-related pattern's explanation of clinical benefits induced by sham surgery over 6-months (Ko et al., 2014a)], G*Power (version 3.1.9.2; RRID:SCR_013726) estimates the minimal sample size to be 12 (effect size f2 = 2.060). With maximally anticipated drop-out rate of 10% (e.g., motion artifacts, patient's voluntary withdrawal, etc.); we require 13 subjects per group/site.

MATLAB (The Math Works Inc., Natick, MA, United States version 2010a) will be used to compute the outcome measures. Normality of the data will be assessed using the Shapiro-Wilks test. Sphericity will be assessed using Mauchly's test. For normally distributed data sets, a mixed-model ANOVA will be used to examine the effects of time (pre– and post-intervention), group (XG and CG) and interaction of time*group of all behavioral outcome measures (gait, cognitive, neuropsychological, fall rates, physical activity levels, and health-related quality of life). Note the time factor for fall rates, physical activity outcome measures, and health-related quality of life will include the 6-month and 12-month follow-up time periods. Non-normally distributed data will be assessed using the Wilcoxon-Signed rank test to determine differences between pre- and post-intervention. The significance level will be set at $p < 0.05$, and statistical analysis will be conducted using SPSS (v.22; SPSS Science, Chicago, IL, United States).

For the neuroimaging data, Aim 1 will use PET data to compare levels of metabolic activity by region between; (a) single-walk only and DT-walk trials, and (b) PD and able-bodied age-matched controls. Aim 2 will use PET and MRI (RS-fMRI, pCASL, and DTI) data to investigate neural changes (whole-brain and ROIs) between pre- and post-intervention. See **Table 1** for the ROIs to be used in the PET and RS-fMRI data for Aims 1 and 2. Paired sample *t*-tests will be conducted for these different neuroimaging modalities, with age and gender included as regressors of no interest. Additional correlational analyses are planned to investigate the relationship between changes in neural activity and behavioral metrics such as cognitive task performance and gait measures.

Imaging Analyses

Preprocessing

Neuroimaging data will be converted from dicom to NIfTI format using the dicm2nii converter, and will then be preprocessed using different software toolboxes, largely based in SPM12 ([1] RRID:SCR_007037), in MATLAB® (2017b; The MathWorks Inc., Natick, MA, United States). The RS-fMRI data will be preprocessed and analyzed using the functional connectivity toolbox (CONN;[2] RRID:SCR_009550). The pCASL data will be preprocessed and analyzed in ASL Perfusion MRI data processing toolbox ([3]RRID:SCR_005997). Functional data will undergo motion correction, coregistration with the structural (T1w) image, segmentation/spatial normalization, and spatial smoothing (8 mm full-width at half maximum Gaussian kernel). Segmentation/spatial normalization for T1w data will use DARTEL registration to the MNI152 template, using the CAT12 toolbox ([4]RRID:SCR_019184). During the segmentation, white matter, gray matter and cerebrospinal fluid will be isolated; WM will be masked out from the functional analyses. Normalized images will be resliced to 1.5 mm (isotropic). The resulting deformation field will be applied to the functional images.

FDG-PET Analysis

For FDG-PET data, an in-house whole-brain mask will be used as the explicit mask. PET images will be proportionally scaled to each image's global values for statistical analysis. For both walk only and DT-walking conditions FDG-PET, ordinal trend/canonical variate analysis [OrT/CVA (Habeck et al., 2005)] will be applied to characterize the normal DT-walking-related brain metabolic pattern (NDWP), by comparing FDG-PET of single-walking vs. DT-walking in the healthy controls. First, the OrT transforms the preprocessed image data to increase the salience of ordinal trend effects, allowing the proceeding principal component analysis (PCA) to identify principal components with targeted expression (i.e., a consistent increase of pattern expression at the individual subject level), while also controlling for the salience of untargeted expression (Habeck et al., 2005). The principal components that result from the OrT can either be used individually, or can be linearly combined, allowing the expression of a given metabolic pattern to be quantified in each scan. Similarly, the PD-specific DT-walking-related brain metabolic pattern (PDWP) will be produced (i.e., DT-walking vs. single-walking in PD patients at pre-intervention). Additionally, we will examine if there is a different metabolic pattern, specific to the 10-week treatment-induced clinical benefits in PD by OrT/CVA (post- vs. pre-intervention during DT-walking). The topographical rating scale of the proposed FDG-PET patterns (i.e., NDWP, PDWP, and longitudinal pattern) will be computed in each FDG-PET image. Furthermore, behavioral scores (such as gait and cognitive performance) will be correlated with changes in metabolic patterns from pre- to post-intervention. The topography of the resulting spatial patterns will be compared using similarity test correcting for auto-correlation (Ko et al., 2014b).

RS-fMRI Analyses

RS-fMRI will undergo two types of analyses in the CONN toolbox: (1) ROI-to-ROI analyses (using the ROIs listed in **Table 1**), and (2) a whole-brain independent component analysis (ICA). For the ROI analyses, region-to-region connectivity (z-matrix) will be extracted using the 210 V Maximum Probability Map parcellation method (Glasser et al., 2016). The z-matrix will be sorted and undirected adjacency matrices will be defined with varying cost (1–50%). For example, at 25% cost threshold, the top 25% of the z-values will be set to 1 and the rest set to 0, excluding the diagonal elements. Global graph theory metrics (e.g., characteristic path length, clustering coefficient, smallworldness, global efficiency and mean local efficiency) will be compared between groups (Watts and Strogatz, 1998; Humphries and Gurney, 2008; Rubinov and Sporns, 2010). Degree centrality (DC) refers to the number of regions that are functionally connected to a region—this is an appropriate connectivity metric for the dlPFC in PD as this region is important in top-down cognitive control. Betweenness centrality (BC) refers to the number of times a region (i.e., node) is along a shortest path between region-pairs and thus is a suitable connectivity metric to assess convergent neuroanatomical structure, such as the caudate nucleus (Alexander et al., 1986). Both DC and BC will be computed at a regional level. Recently, we demonstrated that DC of the left dlPFC correlates with inhibition control performance in normal healthy individuals (unpublished pilot data) while the BC level of the caudate correlates with cognitive performance in non-demented PD patients (Wright et al., 2020).

For the whole-brain analyses, data will be run through an ICA in CONN, which separates the RS-fMRI data into components, with the signal of these components being maximally independent from each other (Calhoun et al., 2009). The components separated using ICA tend to separate into groups, comprising highly replicable resting state networks: regions whose activity is correlated over time, in the absence of a task. Several resting state networks of interest will be investigated in pre- vs. post-intervention, including the central executive, sensorimotor, visual, default mode, and cerebellar networks, as these networks are related conceptually to the motor and cognitive deficits observed in PD and many have been shown to

[1]https://www.fil.ion.ucl.ac.uk/spm/software/spm

[2]http://nitrc.org/projects/conn

[3]https://www.cfn.upenn.edu/~zewang/ASLtbx.php

[4]http://www.neuro.uni-jena.de/cat/

TABLE 1 | Regions of interest for the PET and fMRI ROI analyses.

Amygdala, L	Dorsolateral PFC, L	Inferior Temporal, R	Mesial Temporal, L	Orbital frontal, R	Thalamus, R
Amygdala, R	Dorsolateral PFC, R	Insula, L	Mesial Temporal, R	Putamen, L	Uncus, L
Anterior Cingulate, L	Frontal pole, L	Insula, R	Midbrain	Putamen, R	Uncus, R
Anterior Cingulate, R	Frontal pole, R	Lateral Temporal, L	Middle Temporal, L	Substantia nigra	Ventral Striatum, L
Subgenual cingulate (BA 25)	Hippocampus, L	Lateral Temporal, R	Middle Temporal, R	Superior Temporal, L	Ventral Striatum, R
Caudate, L	Hippocampus, R	Medial PFC, L	Occipital	Superior Temporal, R	Ventrolateral PFC, L
Caudate, R	Inferior Temporal, L	Medial PFC, R	Orbital frontal, L	Thalamus, L	Ventrolateral PFC, R

L, left; R, right; PFC, prefrontal cortex.

be altered in PD in the past (de Schipper et al., 2018; Wolters et al., 2019; Dong et al., 2020; Schneider et al., 2020).

pCASL Analysis

For the pCASL images, the preprocessed cerebral blood flow (CBF) images will be assessed using SVM-ISDA, which will be used to train a classifier that separates patients into PD patients with normal cognition, and those with mild cognitive impairment. The pCASL data will be analyzed by Machine-based Alzheimer's disease Designation (MAD) to compute Alzheimer's-like pattern expression scores (Katako et al., 2018). High scores in metabolic/perfusion patterns indicate similarity with Alzheimer's patients—we have previously shown that PD dementia patients show similar brain metabolic patterns and that perfusion imaging may replace FDG-PET imaging when MAD is applied (Katako et al., 2018). Our recent work suggests the utility of using SVM-ISDA-based scores for monitoring disease progression in repeated measures designs. Changes in these scores will be used to assess the neural correlates of the treatment response.

DTI Analysis

Diffusion tensor imaging data will be preprocessed using SPM12 and the artifact correction in diffusion MRI toolbox (ACID;[5] RRID:SCR_010470)) and after coregistration of each participant's diffusion weighted data with their T1w image, data will undergo eddy current and motion correction, before fitting the diffusion tensor, using an ordinary least squares algorithm. CAT12 will be used for segmentation and skull stripping of the b0 map. Fiber tracking, fractional anisotropy (FA), axial diffusivity (AD), radial diffusivity (RD), and mean diffusivity (MD) map creation will be done using the ACID toolbox. ROIs [e.g., forceps minor, corpus callosum, uncinate fasciculus, and cingulum (Ghanavati et al., 2018; Snir et al., 2019)] will be investigated.

ANTICIPATED AND PRELIMINARY RESULTS

The anticipated results of this study can be broken down by objective. First, in comparing if and how metabolic brain activity differs during single and DT-walking in PD patients, compared to able-bodied controls, we will likely observe increased activation of sensorimotor and cerebellar brain regions and decreased activation in the PFC of the PD patients. We hypothesize that these changes in brain activation patterns will be associated with decreased gait and cognitive performance measures and the magnitude of DT effects. Second, we hypothesize that both training programs will result in significant improvements in gate and cognitive function with medium to large effect sizes, and that the DT training program will result in significantly greater improvements in the XG compared to CG, also with medium to large effect sizes. It is hypothesized that the DT treadmill-training program will result in specific and significant changes of the DT gait-related abnormal brain metabolic pattern observed in Objective 1.

Our behavioral and PET hypotheses are supported by a recent feasibility study that we completed in which 15 PD patients (Hoehn and Yahr stages II-III) participated in a 10-week DT-treadmill gait training program using the VMT and VCG as described in the "Methods" section above (Mahana et al., 2021). Significant improvements in the majority of gait variables (average and COV of SL and SW) with medium to large effect sizes were observed following the intervention. This was the case for both walk-only and DT-walking assessments. There were also significant improvements in VMT and VCG outcome measures post-intervention with medium to large effect sizes. This was the case when tested while sitting and while treadmill walking. In addition, a qualitative analysis of the participant's experiences revealed that the program was challenging and required a high degree of mental processing. The majority of participants reported that the games were engaging and they appreciated the variety of games used for the DT training. Also, to note 3 of the 15 participants did not like playing the games.

In a recent pilot study, we tested the feasibility of imaging the DT-walking-related changes in brain glucose metabolism in patients with PD (Szturm et al., 2020). Fifteen patients with PD (stage II and III) were scanned with FDG-PET. Ten patients were rested during the FDG uptake period and five patients performed DT treadmill walking for 28 min. All

[5]http://www.diffusiontools.com/

five PD patients receiving the DT-walking protocol showed a consistent DT interference of gait measures (average and COV) and of all VMT and VCG performance measures. Glucose metabolism was significantly increased in several brain regions of the patients who performed the DT treadmill walking as compared to those who rested during the uptake period. These regions include primary visual/sensorimotor areas, thalamus, superior colliculus, and cerebellum. When individual results were analyzed, patients in the earlier stage of PD (Hoehn and Yahr stage II) showed increased FDG uptake in the PFC regions during DT treadmill walking as compared to resting levels. More progressed PD patients (Hoehn and Yahr stage III) did not show any notable increase in PFC activity during DT treadmill walking. It should be also noted that patients with mild cognitive impairment (MCI) also show suppressed PFC activity during walking (Holtzer and Izzetoglu, 2020).

In regards to the pilot MRI data, we expect significant neural changes across modalities. Due to the importance of the dorsolateral PFC for both cognition and gait, we expect both PD groups to have reduced functional connectivity between this region and other basal structures compared to able-bodied controls using RS-fMRI data (Monchi et al., 2004; Nagano-Saito et al., 2014). We expect that following intervention, the XG group will have increased functional connectivity between these regions compared to the CG group, and that this functional connectivity will correlate with PD stage. Similarly, in the whole-brain RS-fMRI analysis, we hypothesize that pre-intervention, both PD groups will have altered functional connectivity within central executive, sensorimotor, visual, default mode, and cerebellar resting state networks compared to healthy controls (de Schipper et al., 2018; Wolters et al., 2019; Dong et al., 2020; Schneider et al., 2020), but that PD groups will not differ from each other. Post-intervention, we hypothesize that functional connectivity within these networks will differ between XG and CG PD groups. For the pilot pCASL data, we hypothesize that SVM-ISDA scores will not differ between PD groups at baseline, but will differ from able-bodied controls. Following intervention, we hypothesize that scores for both XG and CG groups will be reduced, with a larger effect observed for the XG group, indicating a larger treatment response. Although the DTI data are largely pilot data in nature, based on previous research indicating that reduced white matter integrity in forceps minor, corpus callosum, uncinate fasciculus, and cingulum is associated with reduced gait stability and may be associated with an increased risk of falling (Ghanavati et al., 2018; Snir et al., 2019), we hypothesize that the same relationship will hold in our sample. While it is thus far unclear whether structural changes in DTI can be observed in our population following 10-weeks of intervention, we expect that increased white matter integrity at post-intervention will be associated with improved gait stability and reduced number of falls at the 6-month follow-up.

DISCUSSION

An integrated approach to treatment with embedded assessment of balance, gait, visuomotor, and cognition has the potential to impact both the prevention and rehabilitation of mobility limitations, and in cognitive function. Improved mobility functioning in PD directly translates to improved community ambulation, as well as increased physical activity and social participation. These benefits are known to have a significant preventative and disease-modifying impact.

New telerehabilitation technologies will likely improve clinical outcomes by making therapy more available, more motivating, and more specific and effective. While one of the pitfalls of the present study includes possible patient attrition, previous pilot-testing work showed high retention of participants, partly due to the engaging nature and low-level of adverse events related to the intervention (Mahana et al., 2021). The computerized DT platform presented in this study broadens the type of standardized visuomotor and executive cognitive activities for use for DT balance-gait training that has previously been reported. A comprehensive analysis of spatial and temporal features of steady state gait has a greater validity to measure gait performance (rhythm, pacing, and stability) as compared to gait speed alone. The use of interactive digital media provides a flexible method to produce a wide range of executive cognitive activities while performing complex motor behaviors such as walking. The types and amount of cognitive stimulation participants engage in during intervention needs to be objectively measured, and this will help clarify the potential added benefit of activities beyond physical exercise alone. Quantification of cognitive-motor interactions has the potential to be a valid non-invasive biomarker for early detection of balance-mobility limitations and cognitive decline in the early stage of disease, and with aging, although these results will not be generalizable to later stages of PD. Although participant motion is a potential pitfall for the neuroimaging data, only early-stage PD patients with controlled tremor will be recruited. Outcomes of this research will provide new insights into brain plasticity mechanisms and will accelerate further optimization and commercialization of multi-modal mobility-cognitive training applications along with accompanying smart electronic monitoring tools.

The computer game-based treadmill platform and embedded automated electronic monitoring tools were designed to transition from physiotherapy clinics to community fitness/wellness centers, as well as assisted-living complexes. Improved and cost-effective methods of screening and fall risk assessment in the community, linked with highly-effective interventions and eHealth tools, will allow more individuals with PD to have access to, and the support of, personalized, scientifically motivated rehabilitation, no matter where they are located. In addition, the availability of electronic outcome measures and, ultimately, the creation of a web-based portal, will help optimize the platform and strengthen accountability.

While the focus of the present proposal is on the study of brain-behavior relationships and neuroplasticity mechanisms in PD, our DT mobility-training platform and behavioral PET and MRI brain imaging methods are directly applicable to other diseases that affect gait and cognition (e.g., cognitive vascular impairment, Alzheimer's disease, and aging).

ETHICS STATEMENT

This study has received ethical approval from the University of Manitoba's Biomedical Research Ethics Board and this clinical trial has been registered at ClinicalTrials.gov, identifier: NCT04415775.

AUTHOR CONTRIBUTIONS

TS, TK, and JK: conceptualization and writing – original draft. TS, TK, BM, AG, DH, JM, AS, and JK: writing – review and editing. TS, AS, and JK: funding acquisition. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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A Large-Scale Open Motion Dataset (KFall) and Benchmark Algorithms for Detecting Pre-impact Fall of the Elderly Using Wearable Inertial Sensors

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Research on pre-impact fall detection with wearable inertial sensors (detecting fall accidents prior to body-ground impacts) has grown rapidly in the past decade due to its great potential for developing an on-demand fall-related injury prevention system. However, most researchers use their own datasets to develop fall detection algorithms and rarely make these datasets publicly available, which poses a challenge to fairly evaluate the performance of different algorithms on a common basis. Even though some open datasets have been established recently, most of them are impractical for pre-impact fall detection due to the lack of temporal labels for fall time and limited types of motions. In order to overcome these limitations, in this study, we proposed and publicly provided a large-scale motion dataset called "KFall," which was developed from 32 Korean participants while wearing an inertial sensor on the low back and performing 21 types of activities of daily living and 15 types of simulated falls. In addition, ready-to-use temporal labels of the fall time based on synchronized motion videos were published along with the dataset. Those enhancements make KFall the first public dataset suitable for pre-impact fall detection, not just for post-fall detection. Importantly, we have also developed three different types of latest algorithms (threshold based, support-vector machine, and deep learning), using the KFall dataset for pre-impact fall detection so that researchers and practitioners can flexibly choose the corresponding algorithm. Deep learning algorithm achieved both high overall accuracy and balanced sensitivity (99.32%) and specificity (99.01%) for pre-impact fall detection. Support vector machine also demonstrated a good performance with a sensitivity of 99.77% and specificity of 94.87%. However, the threshold-based algorithm showed relatively poor results, especially the specificity (83.43%) was much lower than the sensitivity (95.50%). The performance of these algorithms could be regarded as a benchmark for further development of better algorithms with this new dataset. This large-scale motion dataset and benchmark algorithms could provide researchers and practitioners with valuable data and references to develop new technologies and strategies for pre-impact fall detection and proactive injury prevention for the elderly.

Keywords: pre-impact fall, fall detection, public dataset, wearable sensor, algorithm development

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INTRODUCTION

The safety and health of old people have increasingly drawn attention due to accelerated global population aging. Falling is a serious problem faced by our society as 28–35% of the population aged 65 or older suffer at least one fall per year (Organization et al., 2008), and 20–30% of fall accidents lead to mild to severe injuries or even death (Lord et al., 2007). In order to mitigate the serious consequences of falls, multiple studies have been conducted to develop fall detection systems.

Based on the types of sensors being used, fall detection systems can be divided into context-aware systems and wearable systems. Context-aware systems mainly rely on ambient sensors, such as radar and floor sensors as well as vision-based devices (Igual et al., 2013). One fundamental disadvantage of such systems is that they are restricted to indoor use, so they cannot detect the fall anywhere and anytime. In fact, up to 50% of the falls happen outside home premises (Lord et al., 2007). Over the past decade, wearable inertial sensor-based fall detection systems have gained tremendous popularity among researchers because they offer high portability (no space constraints), accurate motion sensing, and low cost (Micucci et al., 2017). Therefore, this study particularly focuses on wearable inertial sensors. Generally, there are two main directions for the development of wearable inertial sensor-based fall detection systems. The majority of existing studies focus on post-fall detection, which is designed to rapidly detect fall events and initiate medical alarms timely to reduce the frequency and severity of long lies (Aziz et al., 2017). However, this approach has an inherent drawback, that is, it cannot prevent fall-induced injuries since fall impacts have already occurred. Another branch of studies targets pre-impact fall detection, which aims to detect the fall during the falling period but before body-ground impact. Therefore, it could activate on-demand fall protection systems, such as wearable airbags, to prevent injuries caused by the fall impact (Hu and Qu, 2016). This method provides a more fundamental solution for the elderly for fall injury prevention. However, it is also more challenging than post-fall detection because the sensor signal of body-ground impact moment, which includes most differentiated information (usually with peak acceleration and angular velocity), cannot be seen by algorithms.

In recent years, researchers have begun to shift their focus from post-fall detection to pre-impact fall detection and shed some light on this topic. Jung et al. (2020) developed a threshold-based algorithm, which combined multiple thresholds (magnitude of acceleration, magnitude of angular velocity, and vertical angle) based on inertial sensors for pre-impact fall detection and achieved 100% sensitivity and 97.54% specificity with an average lead time of 280 ms. This algorithm was developed based on their own simulated dataset with six types of falls and 14 types of activities of daily living (ADLs) by 30 young subjects. Another research conducted by Kim et al. (2019) applied seven machine learning algorithms and two deep learning algorithms to detect pre-impact fall, using accelerometers, and most of the models achieved ≥98% sensitivity and specificity. Similarly, those algorithms were based on their own dataset with 10 types of falls and 14 types of ADLs by 12 subjects. Quite recently, one group of researchers has proposed a multisource CNN ensemble framework for pre-impact fall detection based on the data from four pressure sensors, one acceleration sensor, and one gyro sensor (Wang et al., 2020). Ten subjects participated in their experiment, and each subject performed four types of falls and five types of ADLs. This deep learning architecture also reached high accuracy of 99.30%, with an average lead time of 350 ms. Even though the reported results were impressive, earlier studies only showed good performances of the developed algorithms on their relatively small datasets (small number of human subjects and limited types of motions), and they rarely made those datasets publicly available. This poses a challenge to fairly evaluate the performance of different algorithms on a common basis and their generalizability to different datasets. A few preliminary studies showed that algorithms based on a specific database with good performance had poor external validity on other databases (Sabatini et al., 2015; Jung et al., 2020). For instance, when Jung et al. (2020) applied their thresholds to the SisFall dataset (Sucerquia et al., 2017), both sensitivity and specificity dropped considerably by 4 and 7%, respectively. Similarly, Bourke et al. (2008) proposed an algorithm, using the vertical velocity of the trunk as the threshold and achieved 100% sensitivity and specificity on a dataset, which was built from five subjects with four types of falls and six types of ADLs. However, the same threshold with optimized value only yielded 80% sensitivity on a comparatively larger dataset with five types of falls and seven types of ADLs acquired from 25 subjects (Sabatini et al., 2015). The lack of public datasets also makes it hard to objectively compare newly developed algorithms (Noury et al., 2008). This situation thus hinders the technology advancement for pre-impact fall detection, which is expected to protect the elderly from fall injuries in a proactive way.

Some public fall databases, such as SisFall, tFall, MobiFall, and FallAllD, have been established recently. However, they are only appropriate for post-fall detection rather than pre-impact fall detection. The details will be discussed in the next section. To overcome the aforementioned limitations, in this study, we proposed and publicly provided a large-scale motion dataset called KFall. This dataset is expected to be the first public dataset suitable for pre-impact fall detection, not just for post-fall detection. We also developed three benchmark algorithms, using this new dataset, which allows researchers to fairly compare their new algorithms for pre-impact fall detection. This large-scale motion dataset and benchmark algorithms could provide researchers and practitioners with valuable data and reference to develop new technologies and strategies for pre-impact fall detection and injury prevention for the elderly.

RELATED PUBLIC FALL DATASETS

As mentioned in the introduction, due to the limitations of context-aware systems, the review of public fall datasets emphasized on wearable inertial sensors and was carried out through five major electronic databases (Scopus, ScienceDirect, IEEE Explorer, Web of Science, and Google Scholar). Two basic inclusion criteria were utilized for refining the search results:

(1) datasets should be fully open to the public and published in English; (2) there should be at least 10 subjects in the datasets. In addition, a recent review paper, which performed a comprehensive analysis of public datasets for wearable fall detection systems, was also referred (Casilari et al., 2017a). The same group of authors has reviewed public datasets again very recently and applied CNN to those datasets for fall detection (Casilari et al., 2020). Cross-check was implemented to prevent missing any important references for this study. In the end, our search yielded 16 representative datasets (**Table 1**).

As illustrated in **Table 1**, no dataset provides temporal labels for the fall time, which annotates the fall onset moment (when a fall begins) and the fall impact moment (when the body hits the ground) in the sensor data sequence. Lack of temporal labels for the fall time will not influence the development of algorithms for post-fall detection, since sensor data in the fall impact moment has very distinguishable patterns, which are usually with a peak value of acceleration and angular velocity. However, for pre-impact fall detection, it is important to detect the fall during the body descending period but before the moment of body-ground impact. Because of this, the algorithm for pre-impact fall detection should learn to recognize the difference of sensor data between the non-falling period and the falling period based on the known dataset. Therefore, the falling period of the sensor data, which starts from the fall onset moment and ends at the fall impact moment, should be labeled out. Unlike the fall impact moment, without temporal labels or synchronized video clips published together with motion datasets, it is almost impossible to determine the fall onset moment merely by referring to the sensor data since there is no significant signal change from preceding normal activities to the start of falls. Even though the UP-Fall dataset, the CMDFALL dataset, and the TST Fall dataset also released synchronized video references, they were at a low frequency of 18 Hz, 20 Hz, and 30 Hz, respectively. Since the entire duration of common falls is very short, with an average interval of 746 ms (Tao and Yun, 2017), such low frequency would introduce high errors when labeling the fall onset and impact moments.

Another common drawback of publicly available datasets is that most of them include limited types of falls and ADLs (≤10, e.g., DLR, tFall, MobiFall, Cogent Labs, TST Fall, MobiAct, UMAFall, UniMiB SHAR, IMUFD, CMDFALL, CGU-BES, DU-MD, and UP-Fall) to represent complex real-life scenarios. The number of human subjects used to build the dataset is also relatively small (≤20, e.g., DLR, tFall, TST Fall, Ericiyes University, UMAFall, IMUFD, CGU-BES, DU-MD, UP-Fall, and FallAllD). In addition, we also noticed that orientation data, which represent rich information of human motion (Incel, 2015), were frequently missing among the published datasets except MobiFall and MobiAct.

KFALL DATASET CONSTRUCTION

We set four main requirements when designing the KFall dataset in order to complement the deficiencies of existing public datasets. (1) High-frequency synchronized video clips should be captured for labeling the fall time of sensor data; (2) the dataset should include various types of falls and ADLs with a sufficient number of subjects; (3) sensor orientation measurement should also be provided, which allows more flexibility to the interested researchers when designing their algorithms; and (4) the sampling frequency and measurement range of the inertial sensor should be sufficient (Saleh et al., 2021).

Data Acquisition System and Experimental Setup

In order to record the sensor data together with the synchronized high-frequency video clips, a custom data acquisition system was designed. This system can be easily replicated since all the components are available from the market at affordable prices. A nine-axis inertial sensor (LPMS-B2, LP-RESEARCH Inc., Tokyo, Japan), which includes a three-axis accelerometer (±16 G), a three-axis gyroscope (±2,000°/s), and a three-axis magnetometer (±16 G), was used for collecting motion data. Orientation measurement (Euler angle: roll, pitch, and yaw) provided by the manufacturer is the integration of angular velocity and further modified, using an extended Kalman filter by combining the information from the accelerometer and the magnetometer (Petersen, 2020). The sensor was configured at a frequency of 100 Hz, which was consistent with many studies for pre-impact fall detection (Zhao et al., 2012; Wu et al., 2019). The sensor data were transmitted through Bluetooth Dongle, which was connected to Raspberry Pi 4 (4 GB) as the host PC. As for synchronous video capture, a Raspberry Pi HQ camera mounted with 6-mm 3MP Wide Angle Lens, was used at the maximum FPS of 90. Data acquisition of this research was implemented on a self-developed GUI program, running in Raspberry Pi 4 in which data synchronization between the sensor and the camera was handled by the multiprocessing technique in the Python language.

The inertial sensor was attached to the low back of each subject (see **Figure 1A**), which was used by many researchers for fall detection (Kwolek and Kepski, 2014; Özdemir, 2016). In order to capture in-depth information of human motion, which is critical to judge the fall onset moment, the camera was set in the front side of the main experiment area rather than directly ahead of it. The whole experimental setup is shown in **Figure 1B**.

Participants and Experimental Protocol

This dataset was generated from 32 young Korean males (age: 24.9 ± 3.7 years; height: 174.0 ± 6.3 cm; weight: 69.3 ± 9.5 kg). All of them were healthy and independent, and none of them reported a recent history of musculoskeletal disorder, which could affect their mobility. Every participant signed informed consent for the experimental protocol, which was approved by KAIST Institutional Review Board (IRB No: KH2020-068).

The experimental tasks in our dataset were majorly formulated from the existing public datasets (Casilari et al., 2017a). Since the SisFall dataset has the largest type of falls and ADLs and motions in other datasets were usually a subset of it, the majority of motions in our dataset were directly adopted from SisFall. All types of falls and ADLs in the SisFall dataset were chosen based on a large-scale survey among 15 independent elderly people and 17 retirement homes. For

TABLE 1 | Wearable inertial sensor-based public datasets for fall detection.

Public dataset	Types of ADLs/falls	Subjects No.	Sensor data type	Temporal labels for the fall time
DLR Frank et al. (2010)	15/1	19	§A, G, M	No
tFall Medrano et al. (2014)	Not typified/8	10	A	No
MobiFall Vavoulas et al. (2014)	9/4	24	A, G, O	No
Cogent labs Ojetola et al. (2015)	8/6	42	A, G	No
TST fall Gasparrini et al. (2015)	4/4	11	A	No
MobiAct Vavoulas et al. (2016)	9/4	57	A, G, O	No
Erciyes University Özdemir (2016)	16/20	14	§A, G, M	No
UMAFall Casilari et al. (2017b)	8/3	17	§A, G, M	No
SisFall Sucerquia et al. (2017)	19/15	38	A, G	No
UniMiB SHAR Micucci et al. (2017)	9/8	30	A	No
IMUFD Aziz et al. (2017)	8/7	10	§A, G, M	No
CMDFALL Tran et al. (2018)	12/8	50	A	No
CGU-BES Wang et al. (2018)	8/4	15	A, G	No
DU-MD Saha et al. (2018)	8/2	10	A	No
UP-Fall Martínez-Villaseñor et al. (2019)	6/5	17	A, G	No
FallAllD Saleh et al. (2021)	*44/35	15	§A, G, M, B	No
KFall (Our dataset)	21/15	32	A, G, O	Yes

A, accelerometer; G, gyroscope; O, orientation measurement; M, magnetometer; B, barometer.
§Complex sensor fusion algorithm should be further applied to obtain the orientation measurement.
**For the same type of a fall, the authors considered all possible directions (left, right, forward, backward) under two conditions (with and without recovery); 12 ADLs were hand motions, and they separated one cyclic ADL into two, such as sit down and stand up.*

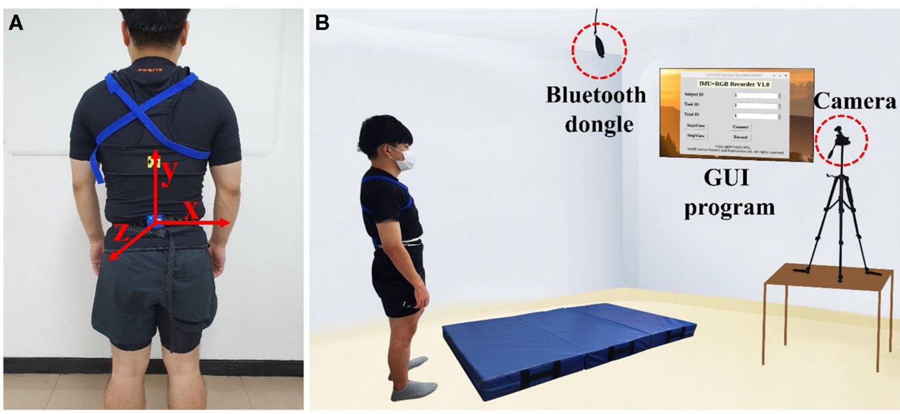

FIGURE 1 | (A) Inertial sensor location and 3D coordinate system; **(B)** experimental setup.

the ADLs, SisFall covers from simple daily movements (such as walking, sit to stand) to high-dynamic activities (jogging, jumping) and even near-fall scenarios (such as stumbling during walking, collapsing to a chair). As for the falls, we can divide them into three categories based on preceding activities: a fall from walking (such as caused by a slip, a trip), a fall from sitting (such as caused by fainting, trying to get up), and a fall from standing (such as trying to sit down). All the fall activities in the SisFall dataset include preceding ADLs, which are closer to the real-world falls. Another reason for choosing SisFall as our major reference is that it also provides instruction videos of each ADL and falls so that we can easily reproduce those motions.

Aside from the activities adopted from SisFall, we further added four common static activities, including sitting on a chair, sitting on a sofa, standing, and lying. Those static motions could be used as calibration postures for some fall detection algorithms (Yu et al., 2017). Considering the practical use of this dataset for the elderly population in Korea, two frequently observed ADLs in daily life of older Korean were also newly introduced. They are sitting to the ground and getting up (usually happened in restaurants), and sitting to a sofa with inclining to the back support and getting up (usually happened at home). For these reasons and the data from the Korean participants, we named our dataset as KFall. All fall activities in the KFall dataset are the same as the SisFall. While for several specific ADLs included

TABLE 2 | Experimental tasks of 21 types of ADLs and 15 types of falls.

Task ID	Activity	Trials
D01	Stand for 30 s	1
D02	Stand, slowly bendthe back with or without bending at knees, tie shoe lace, and get up	5
D03	Pick up an object from the floor	5
D04	Gently jump (try to reach an object)	5
D05	Stand, sit to the ground, wait a moment, and get up with normal speed	5
D06	Walk normally with turn (4 m)	5
D07	Walk quickly with turn (4 m)	5
D08	Jog normally with turn (4 m)	5
D09	Jog quickly with turn (4 m)	5
D10	Stumble while walking	5
D11	Sit on a chair for 30 s	1
D12	Sit on the sofa (back is inclined to the support) for 30 s	1
D13	Sit down to a chair normally, and get up from a chair normally	5
D14	Sit down to a chair quickly, and get up from a chair quickly	5
D15	Sit a moment, trying to get up, and collapse into a chair	5
D16	Stand, sit on the sofa (back is inclined to the support), and get up normally	5
D17	Lie on the bed for 30 s	1
D18	Sit a moment, lie down to the bed normally, and get up normally	5
D19	Sit a moment, lie down to the bed quickly, and get up quickly	5
D20	Walk upstairs and downstairs normally (five steps)	5
D21	Walk upstairs and downstairs quickly (five steps)	5
F01	Forward fall when trying to sit down	5
F02	Backward fall when trying to sit down	5
F03	Lateral fall when trying to sit down	5
F04	Forward fall when trying to get up	5
F05	Lateral fall when trying to get up	5
F06	Forward fall while sitting, caused by fainting	5
F07	Lateral fall while sitting, caused by fainting	5
F08	Backward fall while sitting, caused by fainting	5
F09	Vertical (forward) fall while walking caused by fainting	5
F10	Fall while walking, use of hands to dampen fall, caused by fainting	5
F11	Forward fall while walking caused by a trip	5
F12	Forward fall while jogging caused by a trip	5
F13	Forward fall while walking caused by a slip	5
F14	Lateral fall while walking caused by a slip	5
F15	Backward fall while walking caused by a slip	5

in SisFall, we made some modifications to avoid duplication or make them more natural. For the two motions, which are sitting in a low height chair and getting up slowly or quickly, we used the motion of sitting to the ground and getting up with normal speed (D05) to replace them since they have similar motion patterns. Likewise, with regard to two motions which are standing, slowly bending with or without bending knees and getting up, tying shoelaces (D02) with or without bending at knees, and getting up are the substitutes. We also removed two ADLs considered in the SisFall dataset. One is to rotate the body when lying in a bed since it usually occurs during sleep. Another one is to get into and out of a car due to the facility constraint. Finally, 21 types of ADLs and 15 types of simulated falls were included in the KFall dataset (**Table 2**). Except for the static tasks (D01, D11, D12, and D17), which required only one trial, all other tasks were designed for five trials. During the experiment, for the ADLs, the subjects were instructed to perform them based on their daily habits to make those motions as natural as possible. While for the fall activities, since the young subjects usually do not have fall experience, instruction videos from the SisFall and on-site demos by experimenters were provided if necessary. To ensure the subject safety, all the fall activities were performed on a 15-cm-thick mattress. After the experiment, incomplete data caused by Bluetooth signal disconnections or synchronization errors were removed. Finally, KFall contains a total of 5,075 motion files, including 2,729 ADL motions and 2,346 fall motions.

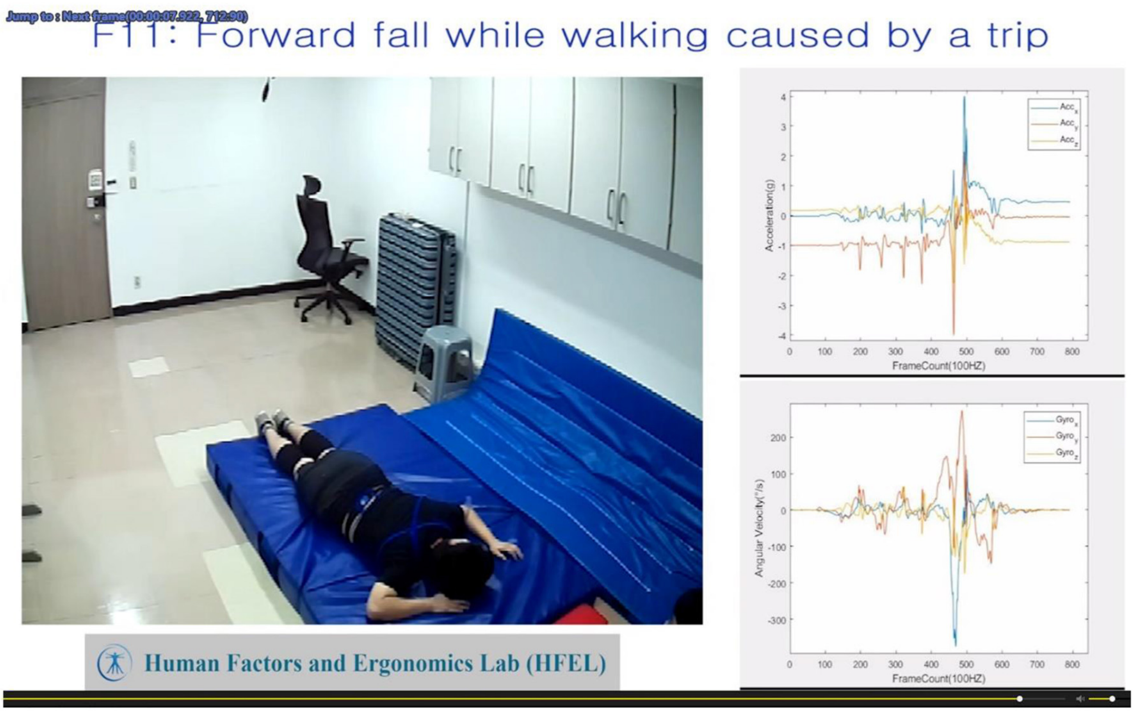

FIGURE 2 | Integrated motion video for the fall time labeling. Left: synchronized fall motion video from the camera; right: sensor data video converted from readings of the inertial sensor (acceleration and angular velocity).

Data Labeling for Fall Time

Since the existing public fall datasets lack synchronized video references on fall activities, it is very difficult to reliably label the fall onset moment solely based on the sensor data for pre-impact detection. On the other hand, because naked eyes cannot recognize subtle motions in the graphics, only referring to the video will also introduce large errors in the labeling process. Therefore, we propose a new method that combines information from both sensor and video data to reduce the labeling error. We firstly converted the sensor data in a csv format into a video format (avi, 100 Hz) and further integrated with a fall motion video (90 Hz) from a Raspberry HQ camera as a whole video, which was played at 90 Hz (see **Figure 2**). The video from the sensor data and the camera maintained the same frequency as the original data format to avoid time distortion. Secondly, based on the integrated video, we played synchronized fall motion and sensor data video frame by frame to accurately label the fall onset and fall impact moments.

The fall impact moment can be easily determined since body-ground impact and an acceleration peak are obvious in the integrated video. Whereas, for the fall onset moment, there is a less obvious motion pattern, and it is hard to define it quantitatively. For this reason, we have introduced a semiautomatic method for labeling the fall onset moment after a comprehensive review of the integrated fall videos (see **Figure 3**). Since the fall is preceded by dynamic movements (e.g., walking, getting up, and sitting down), the y-axis of acceleration is usually considered as a sensitive axis. This is because the acceleration on the y-axis shows the most obvious pattern during falling. Falls usually have significant motion changes in the gravity direction, which can be detected by the y-axis acceleration. However, for the falls caused by fainting during sitting, they are less dynamic and usually without obvious acceleration change at the beginning of falling. Therefore, the y-axis of acceleration could not be regarded as the sensitive axis. In such cases, the x-axis or z-axis of the angular velocity can be considered as the sensitive axis because there are more significant changes during rotational movements along the sagittal plane (a forward/backward fall) or the frontal plane (a lateral fall). Those body motion changes during different fall activities (Bourke et al., 2010) reflect local peaks in sensor signals along the sensitive axis. Based on the synchronized fall motion video, we can quickly move the cursor along the timeline to the rough period of the fall onset. Then we evaluated local peaks in the corresponding period of the sensor data video one by one. Those local peaks could be regarded as potential candidates of the fall onset moment. Choosing the local peak among the candidates involves some subjective judgments of the evaluator. Since the proposed semiautomatic labeling method achieved a high degree of consistency in labeling the fall onset moments between the two independent evaluators in the pilot test, the KFall dataset was labeled by an experienced evaluator for time efficiency. One representative case of labeling is illustrated in **Figure 4**, which is a forward fall during walking caused by a slip. Based on the fall onset and the fall impact moments, the fall event

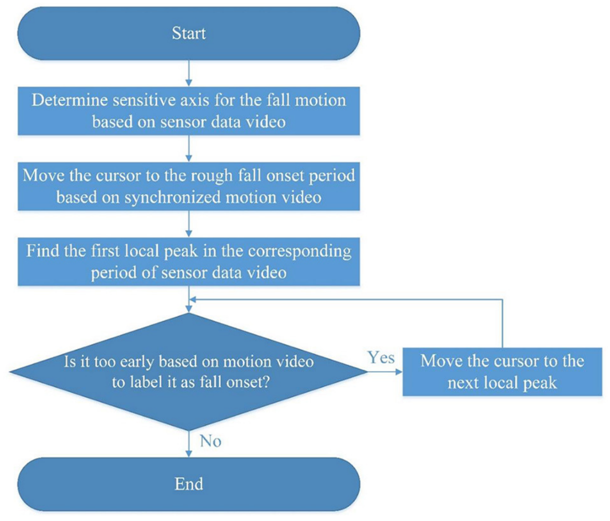

FIGURE 3 | A flowchart for labeling the fall onset moment in sensor data.

could be further divided into three phases: pre-fall, falling, and post-fall phases. Since our major focus is to detect the fall before body-ground impact (a pre-impact fall), the post-fall phase is not considered for the following algorithm development.

All the sensor data, labels of fall trials, and demo videos are publicly available from the Google site: https://sites.google.com/view/kfalldataset. The detailed data organization is summarized in **Figure 5**. For each motion file (csv), it contains 11 columns, which are TimeStamp(s), FrameCounter, acceleration (unit: g), angular velocity (unit: °/s), and Euler angle (°) along three axes. Each label file (xlsx) includes temporal labels for the fall time of all the fall trials from each subject, and it has six columns: task code (task ID), description, trial ID, fall onset frame, and fall impact frame in the sensor data. All the demo videos can be accessed from the attached links.

BENCHMARK ALGORITHMS FOR PRE-IMPACT FALL DETECTION

Based on our newly developed motion dataset KFall, we further developed and tested three different types of algorithms for pre-impact fall detection. Those algorithms cover three major distinct categories in the literature: (i) threshold-based (ii) conventional machine learning, and (iii) deep learning algorithms.

For the threshold-based algorithm, four thresholds (magnitude of acceleration, pitch angle, roll angle, and vertical velocity) were considered to detect a pre-impact fall based on recent publications (Jung et al., 2020; Kim et al., 2020). The magnitude of the acceleration is the L-2 norm of acceleration readings from three axes. Pitch and roll angles are defined as the rotations around the X-axis and Z-axis of the sensor. As for the vertical velocity, it is calculated by integrating the vertical acceleration, which is obtained by the Euler angle transformation of the three-axis acceleration data (Lee et al., 2014). The optimal threshold values were determined by the grid search method. Finally, the threshold values of the magnitude of acceleration (ACC_M), pitch angle, roll angle, and vertical velocity (VV) were set to 0.8 g, 25°, 25°, and 0.3 m/s, respectively. **Figure 6** shows the flowchart of the threshold-based algorithm for detecting pre-impact falls.

For the conventional machine learning algorithm, support vector machine (SVM) was applied in this study since it usually achieved better performance in similar tasks (Aziz et al., 2017; Qiu et al., 2018). A comprehensive set of motion features, which encompassed acceleration, angular velocity, and orientation-based information in both temporal and frequency domains, was selected (Incel, 2015). The magnitude of acceleration and angular velocity of each sliding window, with the width of 50 frames (0.5 s) were utilized for extracting features from the acceleration and angular velocity data (Aziz et al., 2014). Basic features include mean, variance, and root mean square (RMS). More advanced ones are listed as follows: (1) zero-crossing rate (ZCR): the number of samples, which is over the mean of the window; (2) absolute difference (ABSDIFF): the sum of the absolute difference between each sample and the mean of the window divided by the number of samples; (3) First 5-FFT coefficients: the first five of the fast Fourier transform (FFT) coefficients; (4) spectral energy (SE): the sum of the squared FFT coefficients divided by the number of samples. With respect to the orientation-based features, they were calculated from the pitch, roll, and yaw angles. Likewise, mean, standard deviation, RMS, ZCR, ABSDIFF, and SE were derived from those angles. Finally, a total of 40 features were generated and further normalized as the input for the machine learning model.

For the deep learning algorithm, a novel hybrid architecture, integrating both convolution and long short-term memory (ConvLSTM, **Figure 7**) was adopted from our latest publication (Yu et al., 2020). The model consists of three sequential convolutional blocks followed by two long short-term memory (LSTM) cells with dropout operations and one fully connection layer with softmax activation. Each convolutional block contains operations of convolution, batch normalization, relu, and max pooling. The preceding convolutional layers were designed as automatic feature extractors to provide abstract representations of the sensor raw data in the feature maps. Those high-level features with short-term dependencies were further processed by the recurrent layers, which could capture the long-term temporal relationship of the motion data. Nine-dimensional sensor raw data (three-axis acceleration, three-axis angular velocity, and three Euler angles), with a window size of 50 frames (0.5 s), were the input of the ConvLSTM model.

Following the general guideline, 80% of data (26 subjects) were randomly chosen as a training set, and the rest 20% of data (six subjects) were treated for testing purposes. Sensitivity, specificity, and lead time were calculated to evaluate the performance of three different algorithms. Lead time was defined as the time interval between the fall detection moment (when a fall was detected by the algorithm) and the fall impact moment. Sufficient lead time is an important practical application requirement for algorithms to be deployed to on-demand fall protection systems (such as wearable airbags). Algorithm sensitivity and specificity

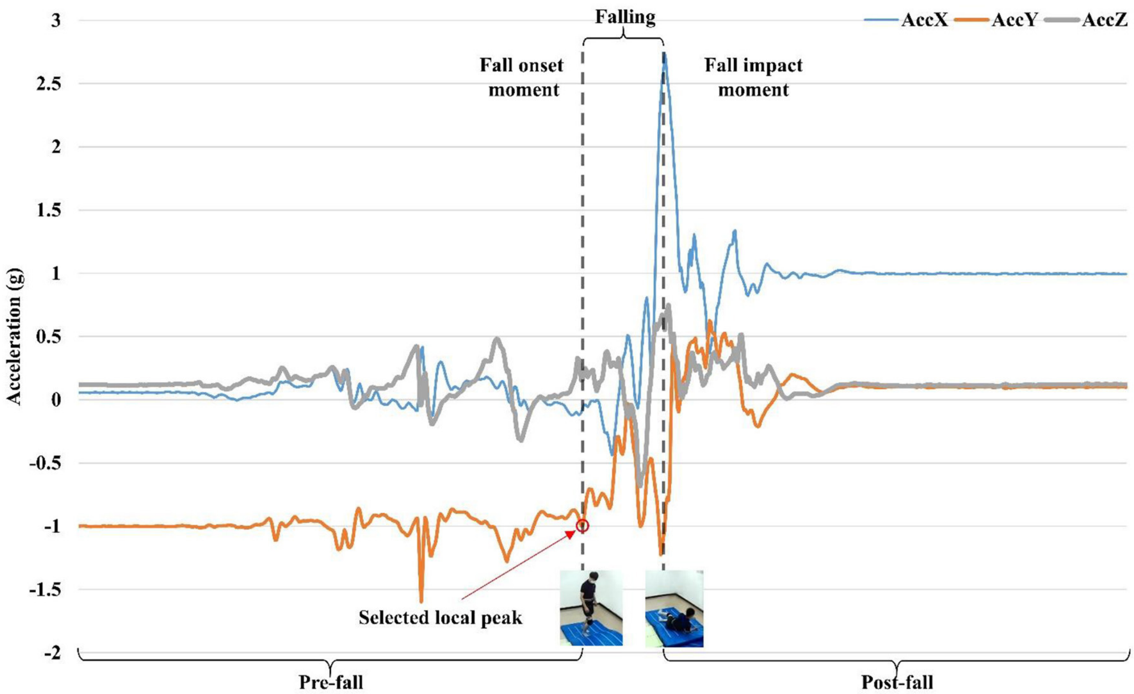

FIGURE 4 | Illustration of fall time labeling during a fall event based on the integrated motion video.

Demo videos of KFall

Task Code	Task ID	Description	Demo video link
D01	01	Stand for 30 seconds	https://drive.google.com/file/d/1VC9YeNUX5iWngpu-S94x4Fuk9oLpkiVO/view?usp=sharing
D02	02	Stand, slowly bend the back with or without bending at knees, tie shoe lace, and get up	https://drive.google.com/file/d/1V3S83c_-9jJPd1_f3Uz5k4TUf7CZ9MDi/view?usp=sharing
		…	
F13	32	Forward fall while walking caused by a slip	https://drive.google.com/file/d/1mi7AOI8SCsS3RDzKLPdZolQ6OGkcwU9y/view?usp=sharing
F14	33	Lateral fall while walking caused by a slip	https://drive.google.com/file/d/1_nk53ib3jqrhzYRo2t-a-IMkNM2Un57B/view?usp=sharing
F15	34	Backward fall while walking caused by a slip	https://drive.google.com/file/d/1oiGrWt3tcqjnZqX7yoLUynP-YCv7-XCh/view?usp=sharing

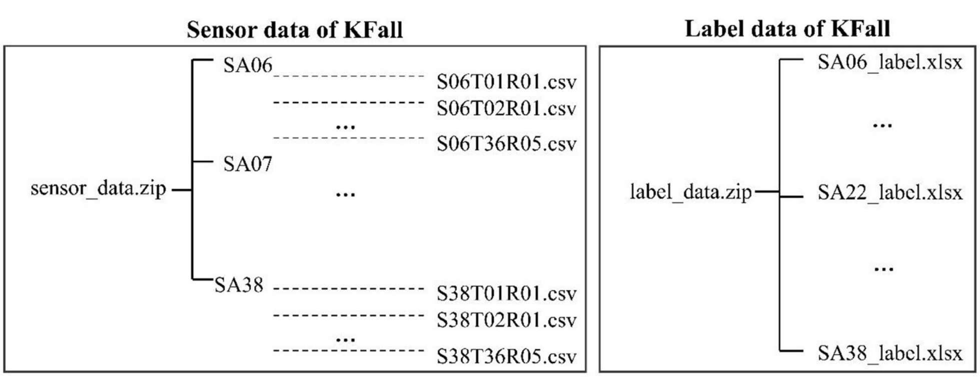

FIGURE 5 | Organization of the KFall dataset provided in the website.

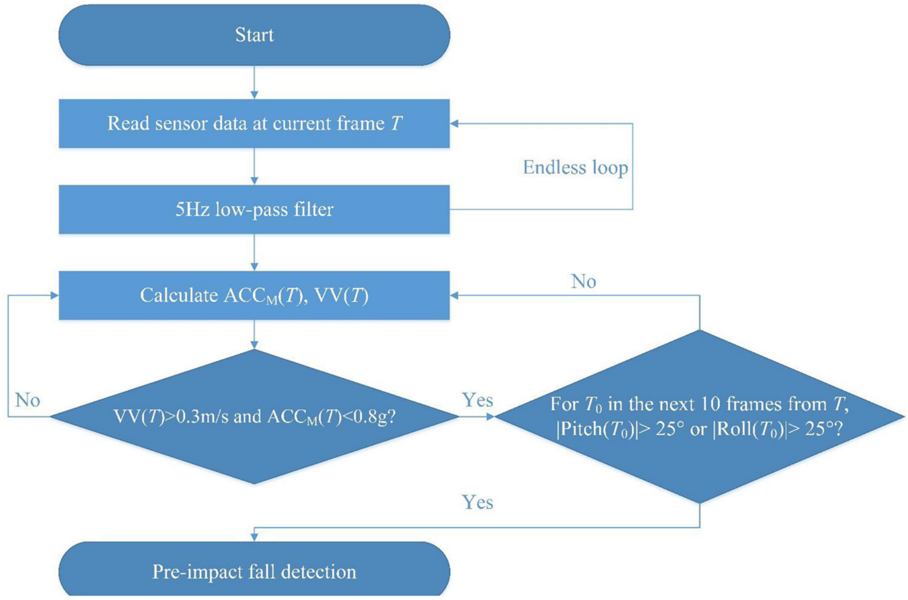

FIGURE 6 | A flowchart of the threshold-based algorithm for pre-impact fall detection.

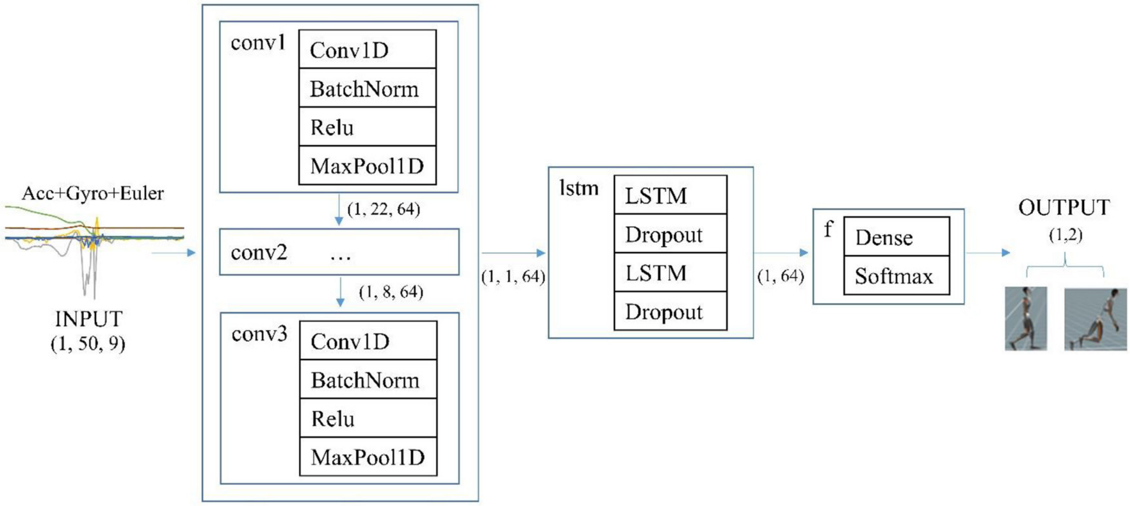

FIGURE 7 | The architecture of the deep learning model (ConvLSTM).

were calculated by equations 1 and 2, respectively.

$$\textbf{Senvitivity} = \frac{\textbf{TP}}{\textbf{TP} + \textbf{FN}} \quad (1)$$

$$\textbf{Specificity} = \frac{\textbf{TN}}{\textbf{TN} + \textbf{FP}} \quad (2)$$

where TP (true positive) is the number of fall files detected as falls; FN (false negative) is the number of fall files detected as ADLs; TN (true negative) is the number of ADL files detected as ADLs; FP (false positive) is the number of ADL files detected as falls.

Table 3 shows the overall performance of three different algorithms on the testing set, which contains 444 fall files and 507 ADL files. In terms of accuracy-related measures, conventional machine learning algorithm (SVM) and deep learning algorithm (ConvLSTM) outperformed the threshold-based algorithm. Particularly, ConvLSTM achieved both high overall accuracy and balanced sensitivity (99.32%) and specificity (99.01%). SVM also had a good performance with sensitivity of 99.77% and specificity of 94.87%. However, the threshold-based algorithm showed relatively poor results, especially the specificity (83.43%) was much lower than the sensitivity (95.50%). With respect to lead time, ConvSLTM obtained the best performance with an average lead time of 403 ± 163 ms, which was slightly longer than SVM (385 ± 159 ms) but much longer than the threshold-based algorithm (333 ± 160 ms).

ALGORITHM VALIDATION ON REAL-WORLD FALL DATASET (FARSEEING)

In order to further evaluate the feasibility of applying trained algorithms based on our simulated fall dataset of young volunteers to detect real-world falls in the elderly, the FARSEEING dataset, currently, the largest real fall repository (Klenk et al., 2016; Chen et al., 2017), was used in this study. A total of 22 records of real-world falls are available upon request. Each fall file contains 1,200 s of data, including data signals of ADLs and falling. In this study, 15 falls were selected because they were collected from the sensors with the same location and data acquisition frequency as our KFall. Those 15 falls were collected from eight older adults (two males, six females; age: 66.9 ± 6.5 years; height: 162.2 ± 9.3 cm; weight: 74.2 ± 10.3 kg). Since half of fall samples lack angular velocity data and they all lack orientation data, in order to fully utilize this dataset, only acceleration data were used. The best model (ConvLSTM) among three benchmark algorithms was selected for the validation purposes. Without changing the network structure, it was retrained only based on the acceleration data from KFall. Since the FARSEEING dataset does not have a video reference, the fall onset moment is defined as 1 s prior to the fall impact moment as in other studies (Shi et al., 2012; Chen et al., 2017). The data before the fall onset moment were segmented as an ADL file, and the data between the fall onset moment and the fall impact moment were segmented as a fall file, resulting in 15 ADL files and 15 fall files. The data after the fall impact moment were not considered for pre-impact fall detection as we did in the KFall. The same window size of 50 frames (0.5 s) was also applied. The performance of ConvLSTM on the FARSEEING dataset is summarized in **Table 4**. The results showed that the ConvLSTM model achieved a sensitivity of 93.33% (= 14/15), a specificity of 73.33% (= 11/15), and an averaged lead time of 411 ms.

DISCUSSION

Pre-impact fall detection based on wearable inertial sensors is still a research problem to be solved. Most of papers only published algorithms, using their own datasets but rarely made them publicly accessible, which hinders the development of pre-impact fall detection and proactive injury prevention. So far, there is no open fall dataset suitable for pre-impact fall detection; therefore, we newly established the KFall dataset and made it publicly available for the first time. This motion dataset was developed from the 32 Korean participants while performing 21 types of ADLs and 15 types of falls. This dataset covers almost all typical daily activities and falls, and it is expected to provide researchers and practitioners with a common foundation to develop new algorithms and technologies on pre-impact fall detection and proactive injury prevention.

Compared with the existing public fall datasets (Casilari et al., 2017a; Saleh et al., 2021) in the literature, the biggest advantage of the KFall dataset is that it is constructed with the synchronized video reference and motion sensor data. This enables accurate temporal labels for the fall time and allows the dataset to be further used for pre-impact fall detection, not just post-fall detection. We also proposed a new and semiautomatic method for reliably labeling the fall onset moment by checking local peaks of the sensor data through the integrated motion and sensor data video (**Figures 2, 3**). Even though this method still involves some subjective judgments from human evaluators, the induced variations should be minimal because the video is at a high frame rate (90 Hz). Musci et al. (2020) conducted an interesting study for pre-impact fall detection based on the SisFall dataset. Due to the lack of video references in the SisFall dataset, the authors and their colleagues formed an expert panel to label the fall time only based on the sensor data pattern. This approach is very difficult to implement and tends to be less accurate, especially for some falls with very short intervals, such as a backward fall when trying to sit down. In order to maintain the privacy of the participants, the synchronized videos are not open to the public, whereas ready-to-use labels of each fall trial (a fall onset frame and a fall impact frame) are published together with the KFall dataset. Another strength of this dataset is that it contains a comparable number of motion types and human subjects as the three most comprehensive datasets (SisFall, Erciyes University, and FallAllD) in the literature (**Table 1**). It covers different physical levels of ADLs from low-activity behaviors to high-dynamics and even near-fall scenarios, and also covers from less-intensive falls (such as caused by fainting) to very dynamic falls (such as caused by a slip or a trip). This dataset is closer to the complex real-world scenarios, so it is more valuable for research and development in the field of pre-impact fall detection and proactive injury prevention.

In addition, three different types of algorithms for pre-impact fall detection were implemented based on this comprehensive motion dataset. All of them were adopted from the state-of-the-art algorithms published recently (Jung et al., 2020; Kim et al., 2020; Yu et al., 2020, 2021) and thus were representative to be the benchmarks. It was expected that the threshold-based algorithm showed poorer performance compared with machine learning algorithms (SVM and ConvLSTM) since the number of motion features considered for the threshold-based algorithm was much less than the other two algorithms. It is usually infeasible to include many thresholds for threshold-based algorithms, which would dramatically increase the searching space and introduce undermined results (e.g., one fall, which satisfies some thresholds, could be against other thresholds). With respect to machine learning algorithms, ConvLSTM had a more balanced sensitivity and specificity (99.32 and 99.01%) than SVM (99.77 and 94.87%). Compared with hand-crafted features used in SVM, the automatic features generated by well-designed deep learning neural networks had more distinguishing power of ADLs and falls (Wang et al., 2019). As for the lead time, it is a critical performance indicator for practical applications,

TABLE 3 | Overall performance of three benchmark algorithms on the testing set.

Algorithm	FN	FP	Sensitivity (%)	Specificity (%)	Lead time (ms)
Threshold	20/444	84/507	95.50	83.43	333 ± 160
SVM	1/444	26/507	99.77	94.87	385 ± 159
ConvLSTM	3/444	5/507	99.32	99.01	403 ± 163

FN, false alarm; FP, false positive.

TABLE 4 | Validation performance of ConvLSTM on the FARSEEING real-world fall dataset.

Algorithm	FN	FP	Sensitivity (%)	Specificity (%)	Lead time (ms)
ConvLSTM	1/15	4/15	93.33	73.33	411 ± 317

FN, false alarm; FP, false positive.

such as on-demand airbags for fall injury prevention. In such a wearable system, a short lead time may fail to prevent fall-induced injuries since it is too short to fully inflate the airbag before the body-ground impact. In this work, both ConvLSTM (403 ± 163 ms) and SVM (385 ± 159 ms) showed a much longer lead time than the threshold-based algorithm (333 ± 160 ms), considering the very short duration of falling (∼746 ms as reported earlier). This fact also indicates that the features used in ConvLSTM and SVM are more comprehensive and robust to distinguish falls at the beginning stage of falling from ADLs. Readers should be aware that, in this study, only accuracy measures (sensitivity and specificity) and lead time were considered to evaluate the benchmark algorithms. Other practical issues, such as the computational resource and battery capacity in wearable embedded devices, should be explored in the future to have a more comprehensive evaluation of the algorithms (Torti et al., 2018).

It is worth discussing the sampling frequency and location of the sensor used in our KFall dataset. Since KFall is designed for pre-impact fall detection and proactive injury prevention rather than post-fall detection, only part of the fall data can be seen by the pre-impact fall detection algorithms. Considering the short period of falling (average 746 ms, Tao and Yun, 2017) and the buffer time required for the full activation of fall protection devices, such as inflatable airbags, low-frequency sensor data may not provide sufficient motion information and fine details for accurate classification, especially for machine and deep learning algorithms, because they extract features from sliding windows of multiple frames. In a recent review paper on pre-impact fall detection (Hu and Qu, 2016), only three out of 13 studies set the sensor sampling frequency below 100 Hz, and all of these studies applied threshold-based algorithms. Threshold-based algorithms are less sensitive to the sampling frequency since their working principle is usually based on a single frame of data, not multiple frames. Even for post-fall detection, Saleh et al. (2021) found that the detection accuracy was always improved by increasing the sensor sampling frequency from 20 to 40 Hz in three different sensor locations. In this study, KFall with a sensor sampling frequency of 100 Hz achieved promising accuracy and lead time in three benchmark algorithms, which also provides some flexibility for interested readers to evaluate the performance of different algorithms if downsampling is required. Regarding the sensor location, low back was chosen for the KFall dataset due to two main reasons. First, low back has been validated as one of the best sensor positions for fall detection (Ntanasis et al., 2016; Özdemir, 2016), and many studies on pre-impact fall detection have also achieved good accuracy from this position (Shan and Yuan, 2010; Jung et al., 2020). This is understandable since the low back position is close to the center of mass of the human body. Therefore, the motion data collected from this location could represent human motion well. The second reason is related to practical applications of preventing fall-related injuries. Since a hip fracture is one of the most serious fall-related injuries, it can reduce mobility and even cause death (Lord et al., 2007; Jung et al., 2020); the sensor in this location can be easily embedded into a belt-shaped airbag for protecting the hip in real time (Shi et al., 2009; Tamura et al., 2009; Ahn et al., 2018).

There is still an ongoing debate about the effectiveness of applying algorithms trained on simulated fall datasets of the young volunteers to real-world fall detections in the elderly. Klenk et al. (2011) observed that, compared with simulated falls, real-world falls have considerably larger changes in acceleration during the falling phase. While other researchers reported similar features in acceleration signals between two types of falls, they also found that some fall phases detected from simulated falls were not detectable from real falls (Kangas et al., 2012). Bagala et al. (2012) evaluated 13 published threshold-based algorithms on an acceleration dataset with 29 real-world falls. Their results showed the average sensitivity and specificity were 57 and 83%, respectively, which were much worse than the results of detecting simulated falls. On the contrary, another group of researchers trained the SVM algorithm based on their simulated fall dataset and further tested the model on the FARSEEING real-world fall dataset (Chen et al., 2017); they achieved both high sensitivity and specificity (>95%) in detecting real-world falls. The potential reason for this conflicting result may be that the features extracted from windows in machine learning algorithms have more distinguishing power than the features extracted from discrete frames in threshold-based algorithms. However, both studies only focused on post-fall detection because they did not investigate whether the fall was detected before the body hit the ground. In this study, we also used the FARSEEING real-world fall dataset to externally validate the best trained ConvLSTM model from our simulated fall dataset (KFall) for pre-impact fall detection. The results showed high sensitivity since 14 out of the 15 real-world falls were successfully detected before body-ground impact (**Table 4**). However, the specificity dropped sharply compared to the performance in the simulated fall dataset, which could be understandable since only acceleration data were used to train the model due to the lack of angular velocity and orientation data in FARSEEING dataset. Our validation results demonstrated a certain potential of using the simulated dataset for real-world pre-impact fall detection. For better validation, a larger real-world fall dataset with more comprehensive motion signals (including acceleration, angular velocity, and orientation) is needed.

There are some limitations related to our current KFall dataset. First, the current KFall only contains simulated falls from young male adults due to safety concerns and practical convenience. Caution is thus needed to directly apply KFall dataset into real-world applications. Second, the current KFall dataset does not include normal ADLs from older subjects due to some practical limitations from the COVID-19 pandemic. We will further expand our KFall dataset by recruiting older and female subjects as well as evaluate false alarm rates of benchmark algorithms on the target population in the future.

CONCLUSION

In this paper, we proposed and publicly provided a comprehensive motion dataset called "KFall" for pre-impact fall detection. This new dataset was developed from 32 Korean participants while performing 21 types of ADLs and 15 types of falls. The motion data contain acceleration, angular velocity, and Euler angle, which are collected from a nine-axis inertial sensor attached at the low back of each participant. Compared with the existing public datasets, the advantages of the KFall dataset are 3-fold. First of all, it covers almost all typical ADLs and falls, thus getting closer to the complex real-world scenarios. Secondly but more importantly, the KFall dataset is constructed together with a synchronized video camera at a high frame rate of 90 Hz, which makes it the first public dataset for pre-impact fall detection, not just for post-fall detection. In this process, we further introduced a practical and semiautomatic method to label the fall onset moment by integrating information from the sensor and video data. Thirdly, we also developed three different types of state-of-the-art algorithms (threshold based, a support-vector machine, and deep learning), using the KFall dataset for pre-impact fall detection. Performance of these algorithms could be regarded as benchmarks for further developing better algorithms with this new dataset. This large-scale motion dataset and benchmark algorithms could provide researchers and practitioners valuable data and references to develop new technologies and strategies for pre-impact fall detection and proactive injury prevention for the elderly.

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 in the article/supplementary material.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by KAIST Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SX conceptualized the study, obtained the funding, and reviewed the edited manuscript. XY developed the data acquisition software, developed the benchmark algorithms, and wrote the original draft. XY and JJ conducted the experiment. All authors contributed to the article and approved the submitted version.

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Efficacy of a Novel Exoskeletal Robot for Locomotor Rehabilitation in Stroke Patients: A Multi-center, Non-inferiority, Randomized Controlled Trial

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Objective: To investigate the efficacy and safety of a novel lower-limb exoskeletal robot, BEAR-H1 (Shenzhen Milebot Robot Technology), in the locomotor function of subacute stroke patients.

Methods: The present study was approved by the ethical committee of the First Affiliated Hospital of Nanjing Medical University (No. 2019-MD-43), and registration was recorded on the Chinese Clinical Trial Registry with a unique identifier: ChiCTR2100044475. A total of 130 patients within 6 months of stroke were randomly divided into two groups: the robot group and the control group. The control group received routine training for walking, while in the robot group, BEAR-H1 lower-limb exoskeletal robot was used for locomotor training. Both groups received two sessions daily, 5 days a week for 4 weeks consecutively. Each session lasted 30 min. Before treatment, after treatment for 2 weeks, and 4 weeks, the patients were assessed based on the 6-minute walking test (6MWT), functional ambulation scale (FAC), Fugl-Meyer assessment lower-limb subscale (FMA-LE), and Vicon gait analysis.

Results: After a 4-week intervention, the results of 6MWT, FMA-LE, FAC, cadence, and gait cycle in the two groups significantly improved ($P < 0.05$), but there was no significant difference between the two groups ($P > 0.05$). The ratio of stance phase to that of swing phase, swing phase symmetry ratio (SPSR), and step length symmetry ratio (SLSR) was not significantly improved after 4 weeks of training in both the groups. Further analyses revealed that the robot group exhibited potential benefits, as the point estimates of 6MWT and △6MWT (post-pre) at 4 weeks were higher than those in the control group. Additionally, within-group comparison showed that patients in the robot group had a significant improvement in 6MWT earlier than their counterparts in the control group.

Conclusions: The rehabilitation robot in this study could improve the locomotor function of stroke patients; however, its effect was no better than conventional locomotor training.

Keywords: lower-limb exoskeletal rehabilitation robot, stroke, locomotor training, locomotor function, rehabilitation

INTRODUCTION

Stroke is the leading cause of long-term disability in adults (GBD 2019 Diseases and Injuries Collaborators, 2020; Virani et al., 2020). With an aging population and advances in emergency care, the prevalence of stroke is increasing annually, leading to significant medical and social burdens (Wang et al., 2017). Previous studies show that up to 90% of stroke patients live with some form of dysfunction, among which locomotor impairment is highly prevalent (Gresham et al., 1975; Mayor, 2015). Asymmetric gait pattern, lower-limb spasticity on the hemiplegic side, as well as compromised ability of single stance and weight shift are observed in most stroke patients, thereby limiting their locomotor function (Lam and Luttmann, 2009). Although with early surgical/pharmaceutical interventions and rehabilitation therapies, 65–85% of the patients manage to walk independently within 6 months post-stroke; however, impaired gait and cardiopulmonary endurance continue to limit the daily ambulation for stroke patients (Shankaranarayana et al., 2021).

Conventional rehabilitation therapies for post-stroke locomotor training are performed manually by multiple therapists. This is labor-consuming, inefficient, and expensive. Besides, the therapeutic effects are subject to the personal skills of therapists and hence homogeneous and standardized therapies are not available for the patients. Additionally, for patients with lower-limb spasticity, at least two therapists are required to complete a training session. Thus, the training doses for individual patients are limited. Previous studies show that stroke registries in mainland China offered approximately 1.43 million physical therapy sessions in 2017; meanwhile, 5.5 million patients are diagnosed with stroke annually and hence there is a large unmet demand for physical therapy (Wang et al., 2019). To bridge this gap in rehabilitation therapies and ensure training doses for stroke survivors, the development and validation of intelligent rehabilitation robots in clinical settings are of great importance.

In recent years, studies recommending the use of exoskeletons in gait training for stroke patients are emerging (Tefertiller et al., 2011; Mehrholz and Pohl, 2012; Pennycott et al., 2012). Parallelly, clinical trials also show the therapeutic benefits of exoskeletons in balance and locomotion (Yeung et al., 2018; Kim et al., 2019; Ii et al., 2020; Moucheboeuf et al., 2020). For example, The ReWalk (ReWalk Robotics, Israel) provides targeted assistance of both paretic ankle plantarflexion and dorsiflexion in overground walking for patients with stroke (Awad et al., 2020). Likewise, gait performance in patients with chronic stroke using Ekso (Ekso Bionics, USA; Calabrò et al., 2018) and HAL (Hybrid Assistive Limb, Japan) is higher as compared to conventional training (Watanabe et al., 2017); gait speed and step length improve significantly (Yoshikawa et al., 2017). Additionally, researchers are using soft wearable robots for transmitting mechanical power generated by off-board or body-worn actuators to the paretic ankle, which can overcome deficits in forward propulsion on the hemiplegic side, thereby improving gait symmetry and reducing the metabolic cost (Awad et al., 2017). However, these soft wearable robots are still in an early stage of development, and validation clinical trials are few. However, only a few studies report the effectiveness of domestically made exoskeletons in China. Thus, the present study aimed at investigating the effectiveness of a domestically made robotic exoskeleton, BEAR-H1, in locomotor rehabilitation in post-stroke cases.

MATERIALS AND METHODS

Ethical Approval and Patient Recruitment

The present study was approved by the ethical committee of the First Affiliated Hospital of Nanjing Medical University (No. 2019-MD-43). Registration was recorded on the Chinese Clinical Trial Registry with a unique identifier: ChiCTR2100044475. All the subjects signed the consent form. Participants were recruited from March 2019 to June 2020 in five rehabilitation centers: the First Affiliated Hospital of Nanjing Medical University, Zhujiang Hospital affiliated to Southern Medical University, Shenzhen Second People's Hospital, Guangdong Work Injury Rehabilitation Hospital, and Shanghai Sunshine Rehabilitation Center. Patient eligibility criteria were as follows: (1) 18–75 years of age; (2) weight ≤85 kg, height: 1.55–1.90 m; (3) stable vital signs; (4) confirmed diagnosis of a first-ever hemiplegic stroke with duration ranging from 2 weeks to 6 months; (5) upper-limb strength enough to hold parallel bars; (6) impaired gait stability and speed; (7) acceptable range of motion in the hip and knee joints; (8) ankles could be placed in neutral position passively; and (9) cognitive function sufficient for understanding and participating rehabilitation training. Patients with any of the following criteria were excluded: (1) significantly restricted range of joint motion for walking; (2) unhealed fractures or severe osteoporosis; (3) skin injuries or infection in lower limb area; (4) unstable angina, severe arrhythmia, or other heart diseases; (5) severe chronic obstructive pulmonary disease; (6) untreated deep vein thrombosis; (7) pregnancy or lactation period; (8) poor compliance to the study; (9) other contraindications for locomotor training; and (10) ongoing involvement in other clinical trials.

Description of the Proposed Exoskeleton Robot

The BEAR-H1 (Shenzhen Milebot Robot Technology, **Figure 1**) was driven by brushless direct current motors to achieve assisted hip flexion/extension, knee flexion/extension, and plantar flexion/ dorsiflexion. It was also equipped with highly accurate sensors, anthropomorphic joints, controllers, and a software system. The software system recognized the patient's

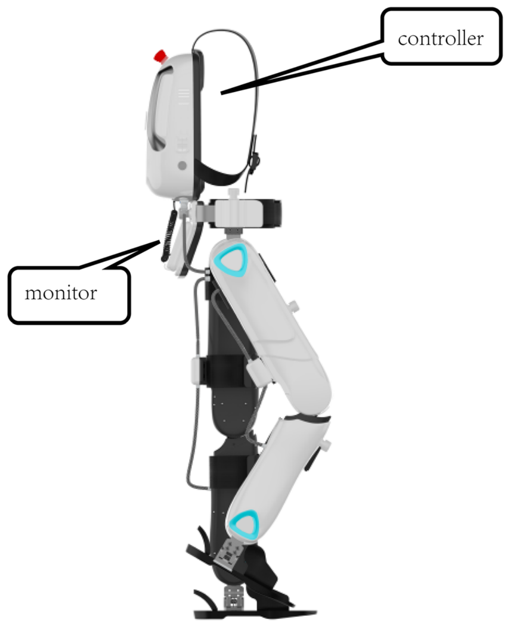

FIGURE 1 | The overall structure of BEAR-H1. The exoskeleton provides assistance with an impedance controller, where the assistance is bassed on the deviation of the joint to the reference trajectory. It is equipped with a gait monitoring and evaluation system, which enables physical therapists to monitor the patient's motion on the screen in real-time.

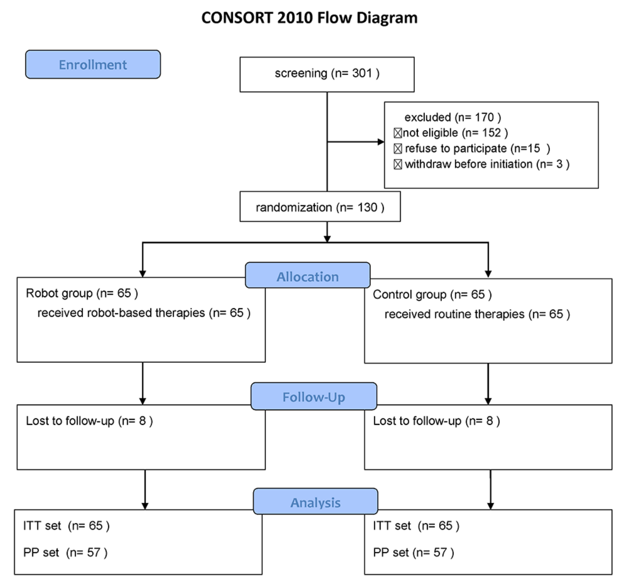

FIGURE 2 | Consort flow diagram of the study.

gait through intelligent algorithms based on the collected angle trajectory, human-computer interaction torque, plantar pressure, and other information of the lower limb joints (hip, knee, ankle). The joint configuration of BEAR-H1 was approximately consistent with the human lower limb joints. It had three active degrees of freedom (DOFs) and a passive DOF in each leg. The three DOFs were rotations along the hip joint, knee joint, and ankle joint in the sagittal plane, separately. The adduction and abduction of the hip joint was the passive DOF.

The BEAR-H1 had a training mode and an intelligent mode. For the training mode, stride frequency could be changed within 3% of the set gait cycle frequency. For the intelligent mode, stride frequency could be adjusted in real-time to achieve synchronization of human-robot interaction. The assistance was provided based on the assist-as-need concept. Specifically, reference trajectories of each joint were generated after the human-robot synchronization was achieved. The exoskeleton provided assistance with an impedance controller, where the assistance was based on the deviation of the joint to the reference trajectory. It was equipped with a gait monitoring and evaluation system, which enabled physical therapists to monitor the patient's motion on the screen in real-time.

Study Design, Treatment Protocol, and Evaluation

This study was a multi-center, non-inferiority, randomized controlled trial to investigate the effectiveness of a novel exoskeleton robot. Participants were randomized into an intervention group and a control group in 1:1 ratio. Randomization was done using an online system[1]. Subjects in the robot group were given robot-assisted locomotor training using the BEAR-H1 exoskeleton robot, while patients in the control group received routine walk training with assistance from therapists. Both groups received two sessions daily, 5 days a week for 4 weeks consecutively. Each session lasted 30 min.

Relevant indicators were evaluated before the treatment; after 2 weeks of treatment and 4 weeks' treatment. The evaluations were as follows: 6-min walk test (6MWT; Agarwala and Salzman, 2020); Fugl-Meyer assessment lower-limb subscale (FAM-LE; Gladstone et al., 2002); Functional ambulation category (FAC) evaluation (Park and An, 2016); Vicon gait analysis (the time ratio of the single stance to the swing period on the affected side, cadence, and gait cycle). Gait symmetry was measured using the swing phase symmetry ratio (SPSR) and step length symmetry ratio (SLSR); these were calculated with ratios of gait metrics on both paretic and non-paretic sides (Guzik et al., 2017; Rozanski et al., 2020). Both indicators for gait symmetry were no less than one with the larger number in the numerator (Guzik et al., 2017). Both SPSR and SLSR were further categorized as improved and not improved; changes from baseline larger than minimal detectable change (MDC) were considered as improved and those less than MDC were not improved. The MDC was 0.26 for SPSR and 0.19 for SLSR (Lewek and Randall, 2011). Gait analysis data was collected only before treatment and after 4 weeks of treatment, while all other evaluations were done before treatment, after 2 weeks' treatment, and 4 weeks' treatment. The primary outcome is the improvement of 6-min walk test after 4 weeks' treatment as opposed to baseline.

Sample Size Calculation

The standard deviation (SD) for the 6-min walking test was set at 15 meters and the non-inferior cut-off was −8 m, based on a

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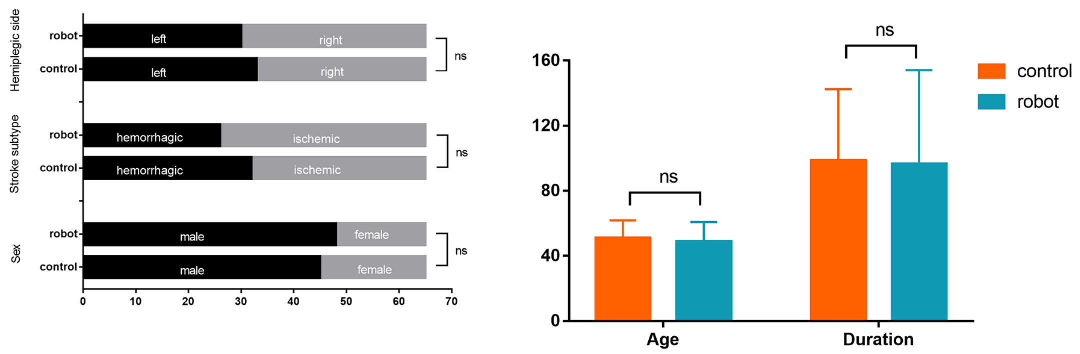

FIGURE 3 | Baseline characteristics of the enrolled subjects. Left panel: categorical data; Right panel: continuous data. Error bars indicate the standard deviation. ns: not significant.

previous study (Duncan et al., 2003). With α at 0.025, 1-β at 0.8, and a 10% drop-out rate, the minimal sample size was 128 cases using the following formula:

$$n_T = n_C = \frac{2(Z_{1-\alpha} + Z_{1-\beta})^2 \sigma^2}{(|\mu_T - \mu_C| - \Delta)^2}$$

n_T: required sample size in the treatment (robot) group;
n_C: required sample size in the control group;
μ_T: mean of the primary outcome in the robot group;
μ_C: mean of the primary outcome in the control group;
σ: standard deviation; Δ: non-inferiority cut-off

Statistical Analyses

Mean and SD were used for continuous data, while median and interquartile intervals were used for ordinal data. The process of patient selection, the actual number of cases in each center, the number of excluded cases, and the number of drop-out cases were recorded, and the intent-to-treat (ITT) along with Per-protocol (PP) sets were defined. For the ITT set, the values of the previous evaluations were used for the missing data so as to avoid overestimation of the treatment effect. T-tests were used for normal distribution; otherwise, the rank-sum test was used. Likewise, the Wilcoxon rank-sum test was used for ordinal data comparison. Between-group comparisons for each follow-up point were performed using Analysis of Variance (ANOVA) for normal distribution; else, Kruskal–Wallis tests were used. $P < 0.05$ was considered statistically significant.

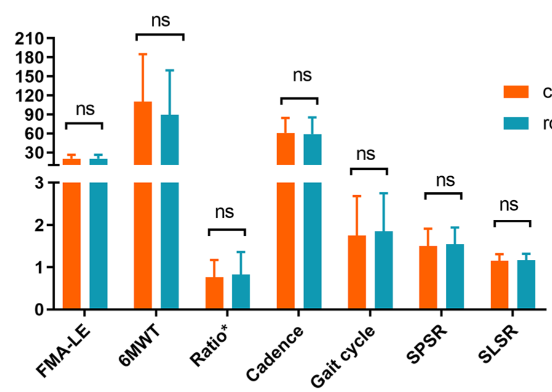

FIGURE 4 | Baseline assessment of the subjects. *Ratio: single stance time vs. swing phase on the affected side. SPSR, swing phase symmetry ratio; SLSR, step length symmetry ratio. Error bar indicates the SD. ns: not significant.

RESULTS

A total of 130 stroke patients who satisfied the above-mentioned criteria were selected from the centers from March 2019 to June 2020. Patients were randomly divided into the robot and the control groups, with 65 patients in each group. Sixteen patients could not be followed up for personal reasons; a total of 114 patients completed the trial. The enrollment status of patients in each center is shown in **Supplementary Table 1**, and the overall patient enrollment process is presented in **Figure 2**.

There were no significant differences in gender, age, duration of disease, stroke subtype, and hemiplegic side across the two groups of stroke patients ($P > 0.05$; **Figure 3**). Likewise, no statistically significant differences across the two groups were observed in FMA-LE, 6MWT, the ratio of single stance to the swing phase on the affected side, cadence, and gait cycle at baseline (**Figure 4**). Indicators on gait symmetry, including SPSR

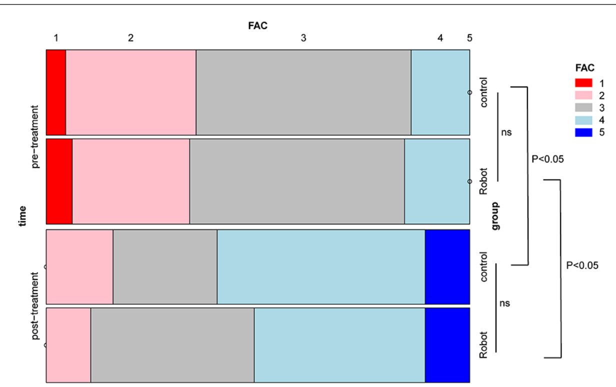

FIGURE 5 | A mosaic plot showing the differences in functional ambulation scale (FAC) scores within the group and between groups. ns: not significant.

and SLSR, also showed no statistically significant differences across different groups at baseline (**Figure 4**). Most of the baseline FAC scores of the two groups were distributed at 2–3, and there was no significant difference between groups based on the Wilcoxon rank-sum test (**Figure 5**). After 4 weeks of treatment, patients in both groups had considerable improvements in FAC score; however, no statistically significant difference was observed between groups.

As shown in **Table 1**, the FMA-LE, 6MWT, and cadence of the two groups of patients significantly improved after 4 weeks of treatment as compared to the baseline ($P < 0.05$). Additionally, the gait cycle was also significantly shortened ($P < 0.05$). There was no significant difference in the ratio of the duration of single stance to the swing phase within the group. No inter-group statistical differences were found in the aforementioned indicators. According to the predetermined non-inferiority plan, the null hypothesis was that the 6MWT of the robot group would be smaller than that in the control group, and the difference would exceed 8 m. As shown in **Table 1**, the point estimate of 6MWT in the robot group was greater than that in the control group, and thus, the null hypothesis was rejected. The changes in the 6MWT between groups were analyzed further. The results indicated that there were no statistical differences in both the PP and the ITT sets ($P > 0.05$). However, the boxplot showed that the mean increase in the 6-min walking distance of patients in the robot group was greater than that of the control group after 4 weeks of treatment (**Figure 6**). This indicated the potential benefits of robot-based training using the proposed exoskeleton.

Assuming that cases lost due to follow-ups were missing at random, we adopted the PP set to analyze the changes in the continuous variables at multiple time points and the differences between the groups; 6MWT and FMA-LE were analyzed. As shown in **Figure 4**, there was no statistically significant difference in 6MWT between groups before treatment (t1), after 2 weeks of treatment (t2), and after 4 weeks of treatment (t3; $P > 0.05$). Further analysis of the differences at multiple time points within the group showed that after 2 weeks of routine therapy, there was no significant improvement in 6MWT, while the 2-week robotic therapy was effective statistically ($P < 0.05$). After 4 weeks of treatment, the 6MWT of the two groups of patients was significantly improved as compared to the baseline. However, when compared with 2 weeks' treatment, there was no significant improvement ($P > 0.05$; **Figure 7**). Likewise, there was no significant difference in FMA-LE between the groups at the three time points ($P > 0.05$). Further, the two groups of patients showed significant improvement in FMA-LE after 2 weeks of treatment, and this improvement was maintained at 4 weeks; however, there was no significant gain for the additional 2 weeks of treatment (**Figure 7**).

Analyses of gait symmetry are presented in **Table 2**. Our findings showed that intra-group differences were not significant on SPSR or SLSR, suggesting no benefits on gait symmetry using either the proposed robot or therapies in the control group for locomotor training within 4 weeks. Between-group differences on gait symmetry indicators were not significant either with the Wilcoxon test or Chi-squared test. However, the proportions of patients showing improvements in gait symmetry in the robot group were higher than that in the control group (SPSR: 35% vs. 30%; SLSR: 16% vs. 12%, respectively).

TABLE 1 | Assessment after 4 weeks of treatment on the subjects ($\bar{x} \pm$ s).

	N	FMA_LE	6MWT	Ratio	Cadence (/min)	Gait cycle (s)
Control	57	23.82 ± 6.7[a]	160.37 ± 101.17[a]	0.75 ± 0.24	73.81 ± 27.25[a]	1.47 ± 0.86[a]
Robot	57	24.44 ± 5.29[a]	150.43 ± 100.77[a]	0.76 ± 0.29	72.17 ± 24.59[a]	1.46 ± 0.8[a]

Ratio: single stance time vs. swing phase on the affected side; a: significantly improved compared to baseline within group, P < 0.05.

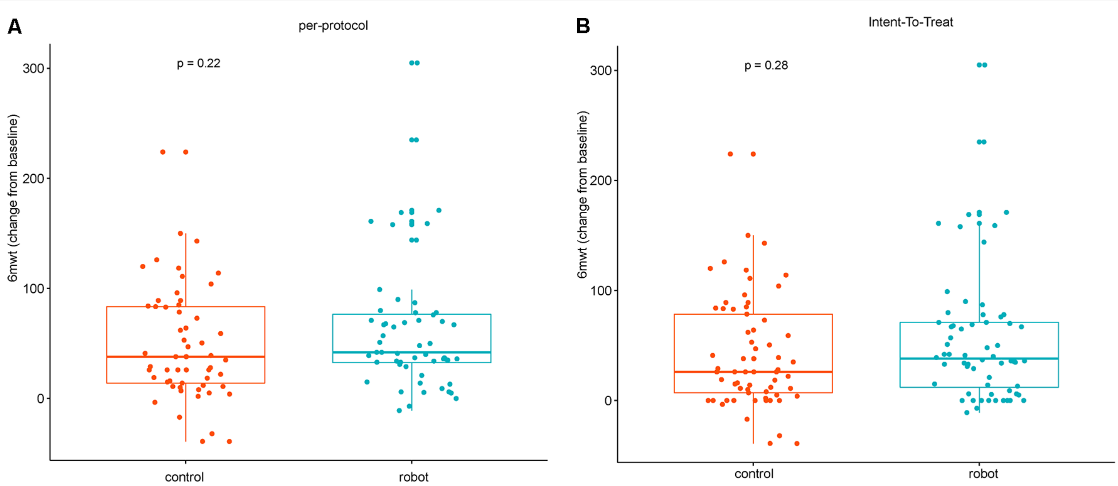

FIGURE 6 | Box plots of the changes in the 6-min walk test (6MWT) between groups after 4 weeks of treatment. **(A)** Per-protocol analysis. **(B)** Intent-to-treat analysis.

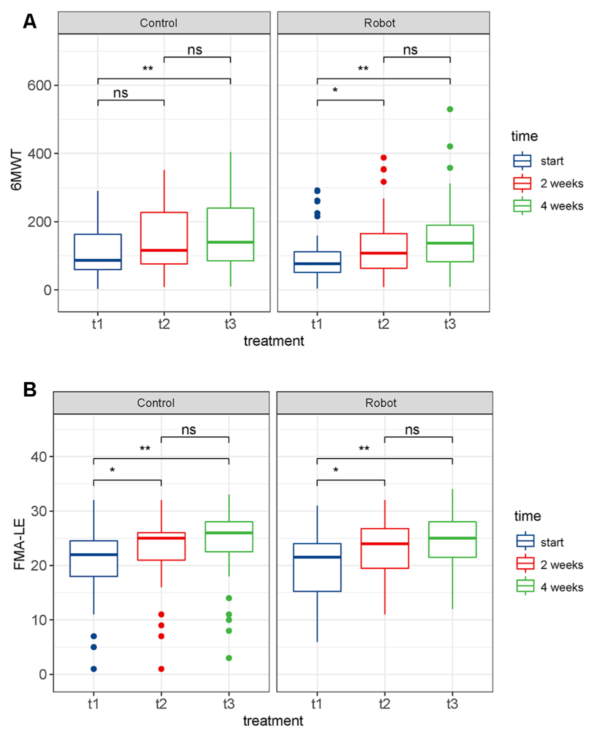

FIGURE 7 | Box plots of the differences in the outcomes at multiple time points. **(A)** 6-min walk test (6MWT). **(B)** Fugl-Meyer assessment lower-limb subscale (FMA-LE). ns: not significant, *$p < 0.05$, **$p < 0.01$; t1: before treatment, t2: after 2 weeks of treatment, t3: after 4 weeks of treatment.

DISCUSSION

In recent years, the exoskeleton robot has been used for locomotor rehabilitation. Its multidisciplinary natures contribute to effective functional compensation or training for individuals with impairments in upper or lower limbs (Pons, 2010; Molteni et al., 2018). In locomotor training, lower-limb exoskeleton robots provide support for patients with insufficient strength to facilitate normal gait (Díaz et al., 2011; Zhong et al., 2020b), offer opportunities for functional recovery with personalized locomotor training programs (Zhang et al., 2017; Shi et al., 2019; Zhong et al., 2020a), and reduce the physical burden of therapists (Díaz et al., 2011). Additionally, exoskeleton-based rehabilitation therapies can objectively and continuously monitor the performance and progress of patients (Louie and Eng, 2016). Even with these merits, clinical validation for most lower-limb exoskeleton robots remain a challenge. The aim of the present study was to validate the effectiveness of an over-ground exoskeleton robot, BEAR-H1. The results of this study showed that the proposed exoskeleton robot effectively improved the patient's locomotion, lower-limb motor function, and gait parameters. Its effect was equivalent to routine rehabilitation therapies ($P > 0.05$). Further analysis of the 6MWT showed that patients receiving robotic therapy showed higher improvement than with conventional therapies. Specifically, the point estimates of 6MWT at 4 weeks and its changes from baseline in the robot group were greater than that in the control group. In addition, the robot-assisted rehabilitation therapy showed early statistically significant improvement in 6MWT. Consistent with a previous study (Patterson et al., 2015), analysis of gait symmetry revealed no significant improvement on SPSR or SLSR in both groups. Neither was a between-group difference detected on either SPSR or SLSR, indicating no additional benefits of locomotor training using the proposed robot on gait symmetry. However, the proportion of improved individuals for both symmetry indicators in the robot group were higher than that in the control group.

The effectiveness of the exoskeleton robot could be attributed to the following mechanisms: first, bodyweight support of the robot led to increased walking stability and training efficiency of stroke patients (Chua et al., 2020; Pignolo et al., 2020); second, exoskeleton robots provided repetitive, highly intensive, and standardized training with greater continuity and consistency, which contributed to enhanced efficacy (Smith and Thompson, 2008; Langhorne et al., 2011). Additionally, exoskeleton robots promoted blood circulation in the lower limbs and improved cardiopulmonary function, which is in line with a previous clinical trial (Chang et al., 2012). A previous study shows that the 2-week Lokomat robot-assisted training can increase the maximum oxygen uptake (VO2 Max) of stroke patients by up to 12.8%, and also significantly improve the muscle strength of the lower extremities (Chang et al., 2012).

Notably, the patients enrolled in this study were stroke patients in the subacute phase, and the duration of the disease was approximately 3 months. The therapeutic effect may partly be due to natural recovery. With the design of randomized controlled trials, which effectively balanced the natural recovery between groups, the differences in treatment effect between groups could be explained by intervention factors. Previous studies show that the walking function of patients with chronic stroke improves after robot-assisted training (Molteni et al., 2017), suggesting that the effects of robot-assisted locomotor training are independent of spontaneous recovery. Reports

TABLE 2 | Gait symmetry indicators after 4 weeks of treatment on the subjects.

Indicator	Group	*N*	Mean (SD)	Wilcox P	Not improved	Improved*	χ^2	χ^2 *P*
SPSR	Control	57	1.4 (0.38)	0.58	40 (70%)	17 (30%)	0.16	0.69
	Robot	57	1.46 (0.36)		37 (65%)	20 (35%)		
SLSR	Control	57	1.1 (0.12)	0.94	50 (88%)	7 (12%)	0.07	0.79
	Robot	57	1.12 (0.13)		48 (84%)	9 (16%)		

*SPSR, swing phase symmetry ratio; SLSR, step length symmetry ratio; *if the change of specific indicator was larger than minimal detectable change (MDC), then it was considered Improved; otherwise, it was regarded as Not improved.*

suggest that a 4-week robot-assisted locomotor training decreases the lower-limb spasticity and promotes the functional recovery of stroke patients (Cho et al., 2015). Since most of the stroke patients enrolled in this study had mild spasticity (Modified Ashworth Scale: 0–1), there was limited scope for further improvement and no statistically significant differences were observed within the group. Future research on the effects of robot-assisted locomotor training on patients' lower-limb spasticity should focus on quantifying the degree of lower-limb spasticity using objective indicators. Similarly, robotic therapies to improve gait symmetry in stroke patients warrant further investigation.

The findings of the present study suggested that the proposed lower-limb exoskeleton robot could assist stroke patients in locomotor training with efficacy equivalent to that of conventional therapies. Although the 6MWT of the robot group patients showed a better improvement than conventional treatment, the difference was not statistically significant. Taken together, the advantages of robot-assisted therapy, including a standardized training environment, adaptive support, and sufficient training intensity and doses, the lower limb rehabilitation robot may have implications as a powerful technique for clinical rehabilitation.

CONCLUSION

Locomotor training using the proposed exoskeleton robot improved locomotion and lower-limb motor function of stroke patients. However, its effect was equivalent to conventional training. The purpose of introducing robotic therapy in rehabilitation practice is not to replace therapists, but to provide the patients with more choices of safe and effective therapies. The effects of exoskeleton robots in stroke rehabilitation need more investigation.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the ethical committee of the first affiliated hospital of Nanjing Medical University (No. 2019-MD-43). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YL, TF, QQ, and JW contributed to study design, patient recruitment, and data collection. HQ analyzed the data, wrote the initial draft, and organized the revision with the support of YL. LZ, XW, and JLo contributed to patient recruitment and coordination. JY and GC contributed to the design of the robotic device. GH, YW, and JLi contributed to study design, study supervision, and final approval of the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2021.706569/full#supplementary-material.

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Conflict of Interest: JY and GC were employed by company Shenzhen MileBot Robotics Co., Ltd.

The remaining 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.

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ORIGINAL RESEARCH
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Personalized Motor-Cognitive Exergame Training in Chronic Stroke Patients—A Feasibility Study

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Purpose: Exergame training may be beneficial for improving long-term outcome in stroke patients. Personalized training prescription applying progression rules, is missing. We adapted a theory-based taxonomy for a rehabilitation approach using user-centered exergames. The aims were primarily to investigate the feasibility of this rehabilitation approach, and secondarily to evaluate its performance of personalizing training progression, as well as explore the effects on secondary outcomes.

Methods: Chronic stroke patients ($\geq$ 18 years) were included, who were able to walk 10 meters and stand for 3 min. The rehabilitation approach was administered twice per week for 8 weeks. As primary outcome, feasibility was evaluated by comparing achieved rates of inclusion, adherence, compliance, attrition, motivation, and satisfaction to pre-defined thresholds for acceptance. Secondary outcomes were (1) perceived motor and cognitive task difficulty throughout the intervention; (2) measures collected during baseline and post-measurements—a gait analysis, the Timed-up-and-go test (TUG), several cognitive tests assessing attentional, executive, and visuospatial functions.

Results: Thirteen patients [median: 68.0 (IQR: 49.5–73.5) years, median: 34.5 (IQR: 12.25–90.75) months post-stroke] were included, of whom ten completed the study. Rates for inclusion (57%), adherence (95%), compliance (99%), motivation (77%), and satisfaction (74%) were acceptable, however, the attrition rate was high (23%). The perceived motor and cognitive task difficulty predominantly moved below the targeted range. We found a significant change in the TUG ($p = 0.05$, $r = 0.46$) and medium-to-large effect sizes ($p > 0.05$) for swing time of the affected leg, the asymmetry index, time needed for the Trail-making test (TMT) A and accuracy for the TMT B and the Mental Rotation Test (MRT; $0.26 \leq r \leq 0.46$).

Discussion: The intervention was feasible with minor modifications necessary, which warrants a larger trial investigating the effects of the rehabilitation approach following the adapted taxonomy on mobility, gait and cognitive functions. Two main limitations of the rehabilitation approach were; (1) the taxonomy decoupled motor and cognitive

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progression, which may be improper as motor and cognitive learning is coupled; (2) separate subjective ratings were used to guide the progression. Future studies should develop an instrument to objectively assess motor-cognitive task difficulty for monitoring the progression of an exergame-based training.

Keywords: stroke, mobility, training, cognition, gaming, virtual reality, rehabilitation, feasibility

INTRODUCTION

Stroke is a dominant global health burden and a major cause of long-term disability in adults (Feigin et al., 2016; Katan and Luft, 2018; Benjamin et al., 2019; Johnson et al., 2019). It can cause motor and cognitive impairments, depending on the involved brain region (Sun et al., 2014; Ursin et al., 2019). Despite carefully considered rehabilitation programs in the months following a stroke, full recovery is achieved only in a small proportion of stroke survivors (Gadidi et al., 2011). The majority of them, however, seem to reach a recovery plateau 6 months after stroke, which is typically at a lower functional level than before the stroke (Gadidi et al., 2011; McKevitt et al., 2011; Bernhardt et al., 2017). Intensive rehabilitation programs are then often terminated, leaving patients with residual impairments (Page et al., 2004; McKevitt et al., 2011). This can manifest by reduced mobility, gait functioning and cognitive ability, which limits stroke survivors in their independence and reduces quality of life (Mayo et al., 2002, 2009; De Wit et al., 2017). A further problem in chronic stroke survivors is physical deconditioning (Smith et al., 2012; Lennon et al., 2021), which increases the risk for secondary cerebrovascular diseases (Boulanger et al., 2018; Johnson et al., 2019; Lennon et al., 2021).

With intensive and continued rehabilitation, it is possible for chronic stroke patients to further regain and manage their impaired mobility, gait and cognitive functions (Ferrarello et al., 2011; Teasell et al., 2012; Lund et al., 2018; Cicerone et al., 2019). For continued rehabilitation interventions, physical exercise and cognitive training are recommended (Ferrarello et al., 2011; Gallanagh et al., 2011; Cumming et al., 2013). Different physical exercise regimes such as cardiorespiratory training, strength training, and neuromuscular training have improved mobility and gait in chronic stroke patients (Barak et al., 2016; Saunders et al., 2020). Moreover, physical activity has been found to improve cognitive functioning in chronic stroke (Oberlin et al., 2017). For cognitive rehabilitation, paper-and-pencil tasks and computerized cognitive training have been shown to beneficially affect specific cognitive abilities (e.g., working memory, attention and processing speed) (Yoo et al., 2015; Wentink et al., 2016; Cicerone et al., 2019). However, these programs often fail to show meaningful transfer effects to other cognitive domains or to daily-life tasks (Tiozzo et al., 2015; van de Ven et al., 2017). Recently, evidence has been emerging that approaches which combine motor and cognitive training, beneficially affect mobility, gait and cognitive functioning in older adults and neurological populations (Fritz et al., 2015; Levin et al., 2017; Stanmore et al., 2017; Mura et al., 2018). Such training approaches may, therefore, add to the possibilities to improve mobility, gait and cognitive outcome in chronic stroke (An et al., 2014; Tiozzo et al., 2015; Lee et al., 2017; Bo et al., 2019).

So-called Exergames are promising for simultaneous training of motor and cognitive functions (Herold et al., 2018). Exergames are active video games designed for a purpose beyond play (Michael and Chen, 2005; Rego et al., 2010), which require the trainee to perform whole-body movements (in contrast to finger movements in console gaming) to play the game and simultaneously challenge cognitive abilities (Herold et al., 2018). Their game-based character and the use of virtual reality (VR) can increase patients' motivation, therapy engagement and training intensity (Burdea, 2002; Shin et al., 2015; Swanson and Whittinghill, 2015; Johnson et al., 2016; Matallaoui et al., 2017; Zeng et al., 2017; Felipe et al., 2019; Lee et al., 2019). Exergames and VR methods in general were found to be feasible, safe and enjoyable in stroke patients, leading to higher adherence rates in rehabilitation interventions and may, thereby, promote improvements in functional outcome in the chronic stage after stroke (Iruthayarajah et al., 2017; Faria et al., 2018; Mura et al., 2018; Lee et al., 2019).

Personalization is important for rehabilitation programs, as it optimizes results and improves long-term adherence to the programs (Billinger et al., 2014). Exergames may be a powerful tool to personalize rehabilitation interventions, as they allow personalized therapy prescription according to the "FITT-VP" principles, including Frequency, Intensity, Time, Type, total Volume and Progression (Ruud et al., 2016; Medicine ACo et al., 2017). Nevertheless, a gap in current knowledge are schedules that enable such personalized therapy prescription for exergames, especially regarding personalized progression (Borghese et al., 2013). First steps to address this gap have been done using 'Gentile's taxonomy of motor learning' as a template for creating a personalized rehabilitation program using exergames (Borghese et al., 2013; Wüest et al., 2014) (more detailed information on this can be found in section "Adaption of Gentile's Taxonomy"). "Gentile's taxonomy of motor learning" is a systematic classification categorizing motor skills and movement according to two general dimensions of actions (Gentile, 1987; Laguna, 2008). So far, however, applications of this taxonomy were restricted to tailored progression and variability of motor tasks. As exergames are integrated motor-cognitive trainings and also cognitive training should be carefully and personally prescribed (Herold et al., 2018; Cicerone et al., 2019), it can be hypothesized that additionally considering cognitive tasks for the personalized progression may add further benefits in the long-term rehabilitation of chronic stroke patients. We, therefore, adapted "Gentile's taxonomy of motor learning" by adding a third cognitive dimension using customized and purpose-centered exergames.

The primary aim of this study was to examine the feasibility of this adapted taxonomy for use in the rehabilitation of mobility, gait, and cognitive functions in chronic stroke patients. We assumed that application of the adapted taxonomy would result in acceptable inclusion, adherence, compliance and attrition rates and that motivation and satisfaction with the training would be and stay high throughout the intervention period. As secondary aims, we (1) assessed whether applying the adapted taxonomy would ensure personalized perceived task difficulty throughout the intervention; and (2) wanted to gain first insight into possible effects of the rehabilitation approach on mobility, gait and cognitive functions in chronic stroke patients.

MATERIALS AND METHODS

Study Design and Procedures

This study was a feasibility trial. The recruitment was facilitated by a physiotherapy center and a senior home in the Canton Zürich (Switzerland). Instructed physiotherapists and care staff pre-screened the patients and older adults at the study sites on having suffered a stroke and interest in a study participation and if so, made contact to the researchers. Participants were then screened on all eligibility criteria face-to-face or by phone call (see section "Participants and Sample Size Considerations" for a more detailed description) by trained movement scientists of the study team. If meeting all criteria, participants were informed about the study procedures, benefits, and risks and subsequently, if willing to participate, signed informed consent and underwent baseline measurements. Depending on their baseline time for the timed-up-and-go test, participants were assigned either to a basic or to an advanced training group. Participants who completed the test in more than 10 s were assigned to the basic group, while participants who needed 10 s or less were assigned to the advanced group (Bohannon, 2006). The intervention lasted 8 weeks and sessions were performed twice per week for 15–45 min. All sessions were performed on separate days of the week and in case possible, with at least one resting day between sessions (e.g., always on Monday and Wednesday). The session duration was progressed over time, adding 3 min of intervention after every week. The basic group started with 15 min of training in the first week and ended with 36 min in the last week, while the advanced group went from 24 to 45 min. This meets the lower border of recommendations for exergame and VR interventions in stroke patients and healthy older adults (Lee et al., 2019; Stojan and Voelcker-Rehage, 2019). As motor learning and cognitive functions were the target of the intervention, the intensity of the trainings was monitored by perceived task difficulty and guided by the adapted taxonomy (see section Adaptation of Gentile's Taxonomy). The study procedures are summarized in the Study Flowchart (**Figure 1**). This study was approved by the Ethical Committee of the ETH Zürich (approval nr. 2019-N-180).

Participants and Sample Size Considerations

Participants had suffered a stroke at least 6 months ago, and were adult ($\geq$ 18 years), able to walk ten meters as well as stand for 3 min without assistance and German speaking. Participants were excluded if they suffered from a neglect, a hemi-anopsia, other neurological diseases or other progressive and uncontrolled diseases. Additionally, as this study was conducted during the COVID-19 pandemic, further eligibility criteria regarding high risk for a serious course of disease had to be complied with (acute, rapidly progressing or terminal illnesses, chronic respiratory disease, therapy or status weakening the immune system, cancer, adipositas, BMI $\geq$ 40). A sample size of 12 or more participants was targeted as for pilot and feasibility trials, at least 12 participants are recommended (Julious, 2005; Moore et al., 2011).

Exergame Device

The Dividat SENSO (Dividat AG, Schindellegi, Switzerland) exergame device, which consists of a pressure-sensitive plate and screen, was used. Trainees perform body weight shifts and step-based movements on the plate, which are used to control the cognitively demanding video games presented on the screen in front of them (**Figure 2A**). The plate is divided into five sub-plates, under which twenty sensors are placed to detect information on center of pressure position and movement timing (**Figure 2B**). This information is used by the system to provide real-time feedback to the gamer's performance. Visual and auditory feedback is given by the games on the screen, while the sub-plates vibrate to additionally give tactile feedback and pronounce the visual and auditory feedbacks. This enables the participant to interact with the video games. A selection of games is available, each of which is specified and graded for different motor and cognitive functions. The plate is equipped with a handrail on three sides to ensure safety of the participant and prevent falls (**Figure 2A**).

Adaptation of Gentile's Taxonomy

The rehabilitation approach was based on 'Gentile's taxonomy of motor learning' (Gentile, 1987; Laguna, 2008), which is a skill progression platform structured along two dimensions with four sub-dimensions each: environmental context (stationary vs. in-motion scheme and inter-trial variability vs. no inter-trial variability) and action function (body stability vs. body transport each with and without object manipulation), resulting in 16 motor skill categories (Laguna, 2008). This two-dimensional structure can easily be adapted to training using virtual environments. For patients with low skill levels an environment can be designed with low action task constraints and no distracting features in the virtual environment. When a game under these initial conditions is performed well, the environment, the action function, or both can be manipulated and made more complex. This enables stepwise progression through the framework. Used this way Gentile's taxonomy provides an "ecologically valid" practical and daily-life relevant way of motor learning. Due to the properties of the exergame device, the sub-dimensions "stationary vs. in-motion" as well as

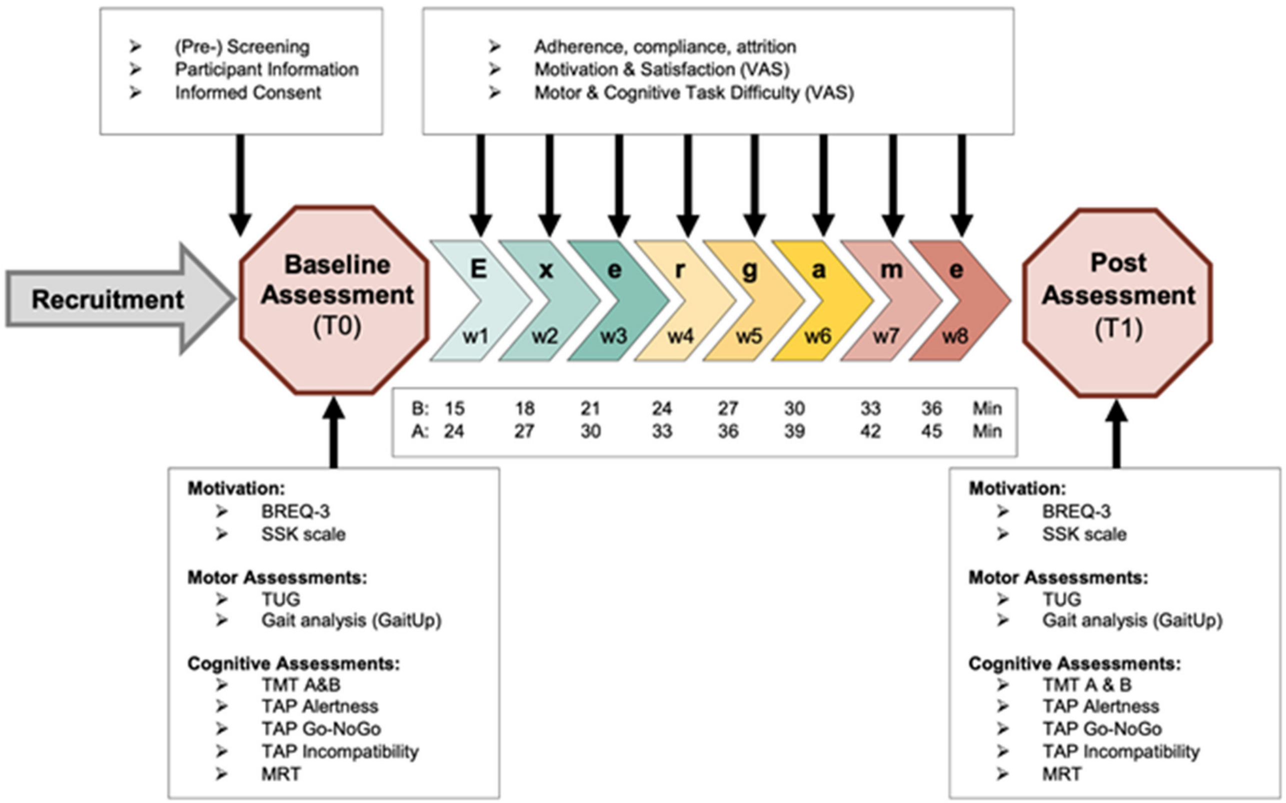

FIGURE 1 | Study flowchart, shows all study procedures and intervention details. B, basic training group; A, Advanced training group; Min, minutes of training in the respective week; VAS, visual analog scale; BREQ-3, Behavioral Regulation in Exercise Questionnaire; SSK, Sport- and Movement-specific Self-Concordance scale; TUG, Timed-up-and-go test; TMT, Trail making test; TAP, Test of attentional performance; MRT, mental rotation test.

FIGURE 2 | (A) A participant training on the Dividat SENSO (Dividat AG, Schindellegi, Switzerland). **(B)** Top view of the pressure-sensitive plate of the Dividat SENSO, showing the position of the sensors.

"without object manipulation vs. with object manipulation" were not distinguished within the adapted taxonomy for this study.

The adaption was performed in two steps. (1) We added one sub-dimension to both axes (environment, action) to provide variability in levels and to fully exploit the variety in possible motor and cognitive tasks of the Dividat SENSO. This defined three sub-dimensions for the environmental context (no inter-trial variability, partial inter-trial variability, inter-trial variability) and three sub-dimensions for the action function context (body stability, partial body transport, body transport). For the latter, we defined the three sub-dimensions as follows (see also **Table 1**); (1) body stability contained tasks during which the center of pressure (COP) moved within stable limits of stability; (2) in partial body transport, the COP moved within

TABLE 1 | Adapted taxonomy with 9 motor skill categories (after step 1 of the adaptation).

	Action function		
Environmental context	**Body stability**	**Partial body transport**	**Body transport**
No inter-trial variability	1A Body-weight shifting, small steps with handrail Fixed stimuli sequence, fixed interval between stimuli	1B Small and wide steps without handrail, Squats, Lunges Fixed stimuli sequence, fixed interval between stimuli	1C Step Touches, Walking, Dribbling, Jumps, Airex Fixed stimuli sequence, fixed interval between stimuli
Partial inter-trial variability	2A Body-weight shifting, small steps with handrail Random stimuli sequence, fixed interval between stimuli	2B Small & wide steps without handrail, Squats, Lunges Random stimuli sequence, fixed interval between stimuli	2C Step Touches, Walking, Dribbling, Jumps, Airex Random stimuli sequence, fixed interval between stimuli
Inter-trial variability	3A Body-weight shifting, small steps with handrail Random stimuli sequence, adaptive interval between stimuli	3B Small & wide steps without handrail, Squats, Lunges Random stimuli sequence, adaptive interval between stimuli	3C Step Touches, Walking, Dribbling, Jumps, Airex Random stimuli sequence, fixed interval between stimuli

moderately changing limits of stability; and (3) in body transport, the COP moved within constantly and rapidly changing limits of stability. This resulted in nine motor skill categories with different levels regarding "body stability vs. body transport" and "no inter-trial variability vs. inter-trial variability" (**Table 1**). (2) For adding a cognitive dimension, we further sub-divided each of these motor skill categories into four sub-categories; one for each of four different cognitive domains, which are targeted with the available games (attention, executive, memory, and visuo-spatial functions). Finally, the adapted taxonomy consisted of 36 skill sub-categories, which offered different motor skill levels in combination with different cognitive challenges (**Figure 3A**). Due to limited possibilities to adapt all games to all skill categories and a lack of games targeting the domain memory, some of these 36 skill sub-categories remained empty for this study (**Figure 3A**).

To comply with the training principles of personalized intensity and progression [FITT-VP principles for training prescription (Ruud et al., 2016; American College of Sports et al., 2018)], we developed progression rules guided by subjective ratings of the "perceived task difficulty" (Bratfisch, 1972; Paas et al., 2003; Sweller et al., 2011), rated on a visual analog scale (VAS) from 0 ("very very easy") to 9 ("very very difficult") after each training session (**Figure 3B**) by the participants. These ratings were used to propose the next training session. Based on the "Cognitive Load Theory," we targeted a task difficulty ranging from "neither easy nor difficult" to "difficult" (Sweller, 2011). Therefore, a rating within this range resulted in no progression, meaning no shift of the "position square" (compare section Intervention/Personalized Exergame Training) before the next training. Was the rating lower than the target range, either a soft progression (**Figure 3B**, yellow range) or a hard progression (**Figure 3B**, red range) was administered, increasing the level by moving to the right and to the bottom of the table, respectively. A soft progression moved the "position square" one sub-category and a hard progression moved it two sub-categories. In case of a rating higher than the target range, the soft or hard progression was administered in opposite direction, decreasing the level of difficulty. The location of the cognitive rating guided the progression on the y-axis of the taxonomy, while the motor rating was used to guide the progression on the x-axis (see example **Figure 3B**).

Intervention/Personalized Exergame Training

A "position square" defined both motor skill difficulty levels and cognitive content of each training session (see **Figure 3A**, e.g., red square). Each training session consisted of a 3-min warm-up, a main part (9–39 min depending on group assignment and time point in the intervention) and a 3-min cool-down. Both, the warm-up and cool-down games were chosen from the top-left sub-category within the "position square," as this contained the games with the lowest motor and cognitive levels according to the taxonomy. The warm-up and cool-down games should provide a motivating start and a feeling of success at the end of the session, respectively. The main part of the training was composed of games from the remaining three sub-categories, which lasted between 60 and 180 s each. The games were arranged so that sufficient variability was provided and that the perceived task difficulty increased after the warm-up, reached a peak in the last third of the main part and then decreased again toward the cool-down. Participants could take breaks or end the training session at all times, if the sessions were too long, if they were overcharged with the tasks or if they felt they did not intend to continue. All training sessions were supervised one-to-one by trained movement scientists of the study team and took place face-to-face in the physiotherapy center and senior home.

Measures

All data collection including primary and secondary outcomes was performed by trained movement scientists of the study team and took place face-to-face in the physiotherapy center and senior home. As primary outcome, the feasibility data were collected during the screening process and the training

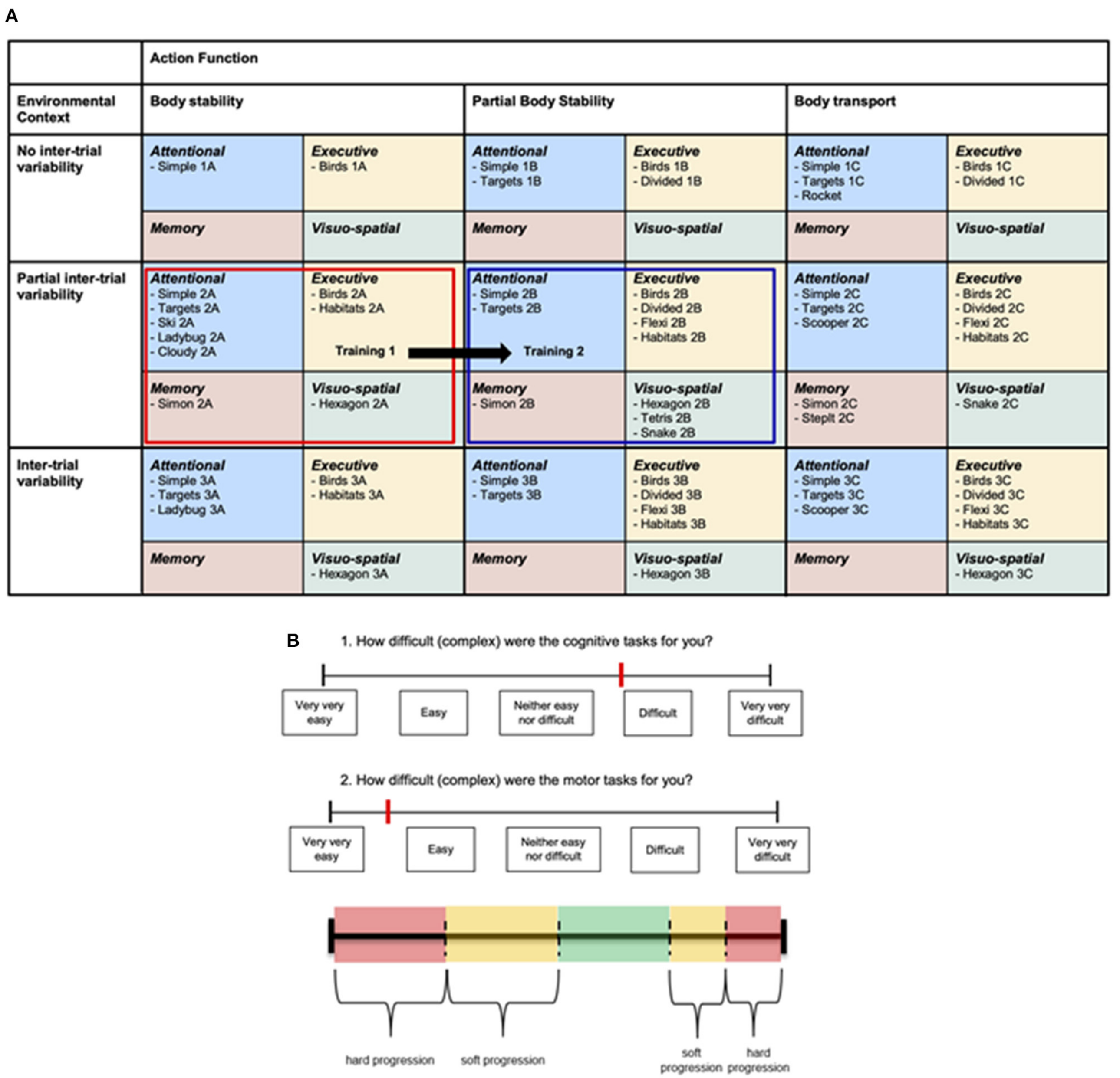

FIGURE 3 | (A) The final adapted taxonomy and two "position squares" of a first and second training. **(B)** Visual analog scale, which were used to rate perceived motor and cognitive task difficulty after each training session, and the scale indicating the ranges for no (green), soft (yellow), and hard (red) progression. Two possible rating locations are indicated (red lines), which would lead to the shift of the red "position square" of the first training to the green "position square" for the second training in **(A)**.

sessions (see **Table 3**). Regarding adherence, sixteen training sessions were planned for all participants. In case a session had to be canceled, it was replaced if possible, which could lead to a moderate extension of the 8 weeks intervention period. To determine compliance, completed training time was divided by the total planned training time, which was defined by the group assignment (basic or advanced) and the time point in the intervention (see section Study Design and Procedures). As participants could end training sessions earlier, completed training time could be lower than planned training time. To assess motivation and satisfaction with the trainings, participants rated their motivation and satisfaction on visual analog scales ranging from 0, "Not all motivated/satisfied" to 10, "Totally motivated/satisfied" collected after each training session (**Supplementary Material 1**).

To further explore the performance of the taxonomy and progression rules, the secondary outcomes included the VAS ratings of the perceived motor and cognitive task difficulty and the individual trajectories through the taxonomy of the participants. Further secondary outcomes were motor and cognitive assessments conducted during the baseline and post-measurements to gain a first insight into possible training effects. Two movement scientists were present during each measurement session, one of them performing the assessments and the other one securing the participant during upright activities to prevent falls. A gait analysis was conducted using Physilog® sensors (Gait up Sàrl, Lausanne, Switzerland), which have been shown to deliver valid and reproducible results for spatiotemporal gait analysis in stroke patients (Lefeber et al., 2019). The assessment followed the protocol for the *"Figure-of-8 Walk Test"* (F8W) by Hess et al. (2010), which is feasible and meaningful in stroke patients (Wong et al., 2013). Participants completed one F8W according to the protocol, while time was measured with a stopwatch. Then, the Physilog® sensors were switched on and the participants walked five F8Ws in a row to measure spatiotemporal gait parameters during straight and curved steady state walking. This procedure (1x F8W; 5x F8W) was repeated three times to capture at least fifty gait cycles, which is recommended for a reliable assessment of spatio-temporal gait parameters (Konig et al., 2014). From the output of the Physilog® gait analysis, values on "time needed for one F8W," gait speed, asymmetry index (based on stride time), stride length variability, stride time variability, double support time, swing time, and swing width were collected. A Timed-up-and-go test (TUG) was conducted to measure functional mobility, following methods described previously (Ng and Hui-Chan, 2005)[1]. The participants performed the test three times, and the scores were then averaged. The TUG has been shown to be feasible, reliable and valid in stroke patients (Ng and Hui-Chan, 2005).

Cognitive outcomes included the Trail-making-test A and B [TMT A & B (Reitan and Skills, 1958; Bowie and Harvey, 2006)], the Mental-rotation-test [MRT, "Shepard and Metzler paradigm" (Shepard and Metzler, 1971)] and three sub-tests of the Test of Attentional Performance [TAP (Zimmermann and Fimm, 1992)], namely (i) Alertness test, (ii) Go-NoGo test and (iii) Incompatibility test. The TMT A and B are sub-tests to assess the general information-processing speed and executive functions, particularly mental flexibility, respectively. The TMT was found to be a valid and reliable test of these functions (Reitan and Skills, 1958; Wagner et al., 2011). The MRT is a measure of visuo-spatial skills, particularly the ability for mental rotation (Shepard and Metzler, 1971). The TMT and the MRT were conducted using a computer with PEBL software (Mueller and Piper, 2014). The TAP allows an appropriate and differentiated diagnosis of attentional deficits and the used sub-tests provide data on the simple reaction time, selective attention and inhibition as well as the reaction to an incompatible stimulus (Zimmermann and Fimm, 1992). The subtests of the TAP have been widely used in various populations including stroke survivors (Starovasnik Zagavec et al., 2015; Spaccavento et al., 2019).

Motivation for physical activity was assessed at baseline and post measurements to observe the influence of the exergame training on general motivation for being active. Participants answered the Behavioral Regulation in Exercise Questionnaire [BREQ-3, German version of the BREQ-2 (Mullan et al., 1997; Markland and Tobin, 2004)] and the Sport- and Movement-specific Self-concordance scale [SSK (Fuchs et al., 2005)]. Both assess the degree of self-determination in terms of exercise behavior. However, while the BREQ-3 covers motivational aspects for physical activity in general, the SSK is directed into the future and, therefore, provides information about the future intention toward physical activity. The analysis of the BREQ-3 and the SSK scale leads to scores for different sub-types of motivation, which can be used to evaluate the degree of self-determination participants have toward physical activity. Intrinsic, integrated and identified motivation represent different forms of self-determined motives for physical activity, while introjected and external motivation are linked to less self-determined motives (Markland and Tobin, 2004; Fuchs et al., 2005; Chemolli and Gagne, 2014). The BREQ-3 additionally investigates amotivation, which can be used to explain low ratings in other motivational domains (Markland and Tobin, 2004). For the SSK scale, the SSK index was additionally calculated, which is a summary score integrating all motivation subtypes. A higher SSK index stands for higher self-determination in physical activity and vice versa (Fuchs et al., 2005).

Feasibility Analysis

The feasibility of the rehabilitation approach was determined using a pre-defined feasibility protocol including six parameters with thresholds (see **Supplementary Material 2**). The feasibility criteria were defined to detect problems with the recruitment process (inclusion rate), the intervention itself (attrition and satisfaction rates), the frequency and time applied (adherence, compliance and attrition rates), as well as the personalized progression (adherence, compliance, motivation and satisfaction rates). Thresholds for the feasibility criteria were based on guidelines for inclusion (≥50%), adherence (≥80%), compliance (≥80%), and attrition (≤15%) (Nyman and Victor, 2011) and established from results from comparable studies for motivation (≥60%) and satisfaction (≥60%) (Bernardoni et al., 2019; Spildooren et al., 2019; van Beek et al., 2019). The feasibility protocol contained instructions on how to interpret the results in all possible scenarios according to the different feasibility outcomes as well as on how to continue with the rehabilitation approach in a subsequent study (Thabane et al., 2010).

Analysis of Secondary Outcomes

The evaluation of the perceived motor and cognitive task difficulty and the individual trajectories was performed to discover reasons why the rehabilitation approach did or did not achieve personalized progression of task difficulty. Therefore, the VAS ratings of perceived motor and cognitive task difficulty were averaged for each session and compared to a pre-defined target range of perceived task difficulty (Sweller, 2011). This and the exploration of the individual trajectories of each participant should give in-depth insight in the development of the perceived task difficulty and reveal over- and undercharging of the participants. The data of the remaining secondary outcomes

[1]Timed-up-and-go test. Available online at: https://www.physio-pedia.com/Timed_Up_and_Go_Test_(TUG).

were reported and analyzed non-parametrically (Field, 2013), therefore descriptive data were reported and represented as median and interquartile range. Within-subject changes from baseline to post measurements were analyzed with the Wilcoxon signed-rank test. Median differences with interquartile range, the test statistics T, p-values and effect sizes were provided for each outcome. As recommended for pilot feasibility trials the main emphasis of our trial was placed on feasibility and not on statistical significance (Thabane et al., 2010). Thus, due to the exploratory nature of the analysis for the secondary outcomes in this study, no correction for multiple comparisons was performed (Rothman, 1990; Bender and Lange, 2001; Althouse, 2016). Consequently, p-values must be interpreted with caution. The level of statistical significance was set to $p < 0.05$. Effect sizes were interpreted to be small ($r < 0.30$), medium ($0.30 \leq r < 0.5$) and large ($r \geq 0.50$) (Fritz et al., 2012). All statistical analyzes were performed using SPSS Statistics (version 26 for windows; IBM, Chicago, IL, USA).

RESULTS

Participants Overview

Twenty-three possible participants were screened in March 2020 and from September to October 2020 of whom 13 were included (**Figure 4**). After having started recruiting, the study had to be postponed between April and August 2020 because of a national shutdown due to the COVID19 pandemic. The most common reason for non-inclusion was the inability of the participants to come to the study centers for the training sessions (**Figure 4**). Additionally, one screened patient had suffered a transient ischemic attack and was therefore excluded. Twelve participants of the included participants were recruited from the physiotherapy center and one participant lived in the senior home. This entailed that the majority (12 out of 13) of the participants received regular physical therapy (1 or 2 sessions of 30–60 min) beyond the training sessions of this study. Of the 13 initially included participants, 10 completed post-measurements while three dropped out of the study earlier. The reasons for the dropouts were the following; one participant wanted to stop the study participation due to fear of COVID19 infection at the study center; one participant suffered a severe flu (adverse event unrelated to the intervention) and was absent for several weeks, which made a continuation of the training impossible; one participant experienced an uncomfortable worsening of their head tremor after the first two trainings (adverse event related to the intervention), which forced them to stop the intervention. The participant flow is shown in **Figure 4** and baseline characteristics are presented in **Table 2**.

Feasibility

We found acceptable rates of inclusion (57%), adherence (95%), compliance (99%), motivation (77%), and satisfaction (74%), of which the highest was the compliance rate with almost full completion of planned training time (**Table 3**). The attrition rate (23%), however, was higher than the pre-study defined threshold set for acceptance. Mean motivation and satisfaction were rated "rather high" to "high" over the whole course of the intervention (**Figure 5**).

Secondary Outcomes

The mean perceived motor and cognitive task difficulty were rated from "rather easy" to "rather difficult" throughout the intervention period (**Figure 6**). The mean motor demand was generally rated higher than the mean cognitive demand. Participants moved in the taxonomy in individual ways (**Figure 7** shows two example trajectories).

The parameters of the gait analysis remained similar from pre- to post-measurements and no meaningful changes were observed with predominantly small effect sizes (**Table 4**). The swing time of the affected leg showed a medium effect size ($p = 0.21$, $r = 0.32$) and the asymmetry index a small-to-medium effect size ($p = 0.29$, $r = 0.26$). The TUG improved significantly from pre- to post-measurements with a medium-to-large effect size ($p = 0.05$, $r = 0.46$, **Table 4**). None of the cognitive assessments showed changes from pre- to post-measurements, however, medium effect sizes were found for improvements in time needed for TMT A ($p = 0.11$, $r = 0.35$), in accuracy in the TMT B ($p = 0.18$, $r = 0.30$) and accuracy in the MRT ($p = 0.15$, $r = 0.33$, **Table 5**). Additionally, medium to large effect sizes were found for increased reaction times in the TAP incompatibility test for both, compatible ($p = 0.12$, $r = 0.46$) and incompatible ($p = 0.25$, $r = 0.33$) stimuli (**Table 5**). One participant was not able to perform the TMT with the computer mouse and therefore, the paper-and-pencil version was administered as an alternative. Differences in the number of participants who were included in the analyzes of the different assessments were caused by several reasons; (1) technical problems with the Physilog® sensors during one measurement (spatio-temporal gait analysis, **Table 4**); (2) inability of one participant to perform the motor assessments at the post measurements due to a temporary worsening of the physical condition (TUG and gait analysis, **Table 4**); and (3) inability of four participants to perform the cognitive tests with both hands (TAP Incompatibility, MRT, **Table 5**).

According to the BREQ-3, the intrinsic motivation for general physical activity of the participants decreased over the course of the intervention with a trend toward significance and a medium effect size, while the other types of motivation for physical activity were maintained (**Table 6**). The SSK showed a significant decrease in identified motivation for physical activity with a medium to large effect size and a non-significant decrease in external motivation with a medium effect size. The SSK index did not change (**Table 6**).

DISCUSSION

This study investigated the feasibility of a rehabilitation approach using exergames and following an adapted skill-progression taxonomy in chronic stroke patients. Furthermore, possible effects of the rehabilitation approach on mobility, gait, cognitive functions, and motivation for physical activity in chronic stroke patients were explored. We found that the rehabilitation approach was feasible in terms of inclusion, adherence, compliance, motivation and satisfaction, and that,

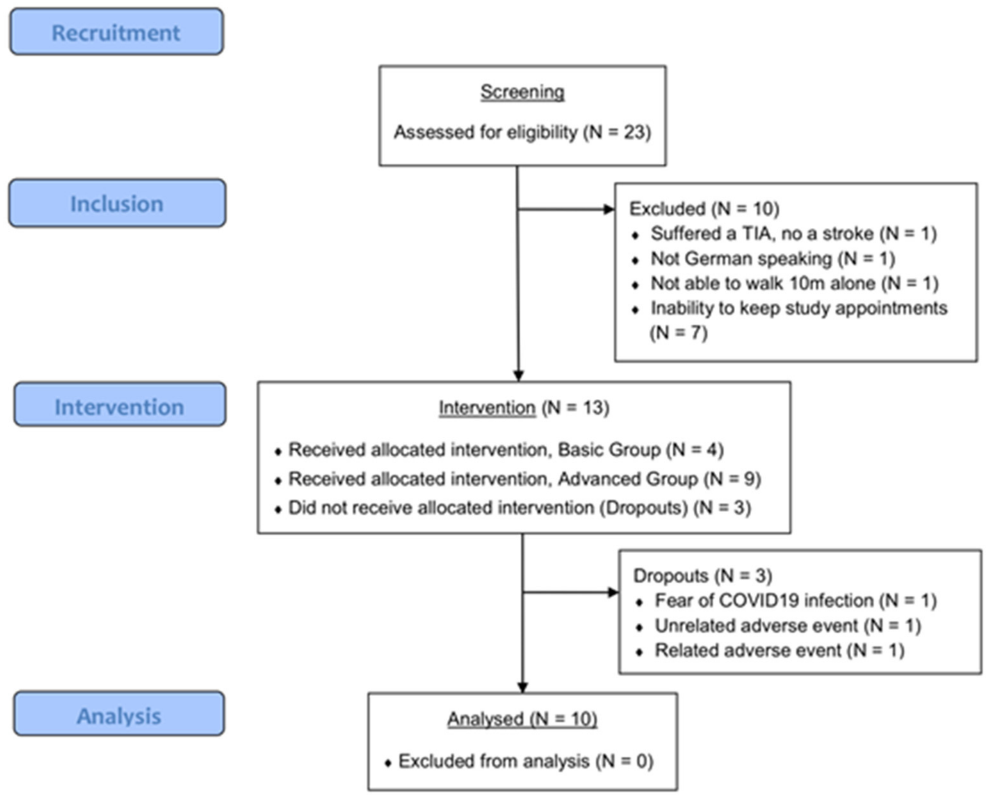

FIGURE 4 | CONSORT diagram of the participant flow.

TABLE 2 | Baseline characteristics.

	Median	IQR	Range	*N*	%
Age [years]	68.0	(49.5, 73.5)	34–79		
Gender [women/men]				5/8	38.5/61.5
Time post-stroke [months]	34.5	(12.25, 90.75)	6–179		
Impaired body side * [right/left]				4/9	30.8/69.2
FAC [ranging 0-5, 2/4/5]	5	(5, 5)	2–5	1/1/11	7.7/7.7/84.6
TUG [s, >10s/≤ 10s]	8.24	(6.78, 11.90)	7.50–29.03	4/9	30.8/69.2
Walking aids [none/one cane]				12/1	92.3/7.7
Education [years]	12.0	(12.0, 17.5)	9 - 20		
School level [Secondary, higher]				3/10	23.1/76.9
TMT A [s]	32.20	(28.26, 37.92)	23.54–85.26		
TMT B [s]	51.58	(38.90, 76.77)	24.08–289.90		

IQR, Interquartile Range; N, number of participants; %, percentage of participants.
**For two participants the impaired body side was unclear; therefore the body side with greater stride length variability was assumed to be the impaired body side.*

however, the attrition rate exceeded the pre-defined threshold. Each participant moved on an individual path through the taxonomy, however, the VAS ratings of perceived motor and cognitive task difficulty moved below the targeted range. This and the high adherence, compliance, motivation and satisfaction rates indicate that the adapted taxonomy enabled personalized progression, which, however, still has potential for improvement in achieving optimal task difficulty. A significant improvement was found for the TUG test, while none of the other motor and cognitive outcomes showed changes. However, medium to large effect sizes were found for improvements in the swing time on the affected side, the time needed for the TMT A and the accuracy in the TMT B as well as in the MRT. No changes in the degree of self-determination was observed for general physical activity in the BREQ-3 and future intention toward physical activity in the SSK scale.

TABLE 3 | Feasibility results.

Feasibility criteria	Threshold (%)	Data	Results	Outcome (%)	Criteria met
Inclusion rate	≥ 50[a]	Screened participants [#] Included participants [#]	23 13	57	Yes
Adherence rate	≥ 80[a]	Total offered training sessions [#] Total attended training sessions [#]	189 165	95	Yes
Compliance rate	≥ 80[a]	Total offered training time [min] Total attended training time [min]	4,974 4,915	99	Yes
Attrition rate	≤ 15[a]	Included participants [#] Dropouts [#]	13 3	23	No
Motivation rate	≥ 60[b,c,d]	Mean VAS rating over all sessions Maximal VAS rating	7.67 10.0	77	Yes
Satisfaction rate	≥ 60 [b,c,d]	Mean VAS rating over all sessions Maximal VAS rating	7.44 10.0	74	Yes

[a]*Nyman and Victor (2011).*
[b,c,d]*Thresholds established based on results from comparable studies (Bernardoni et al., 2019; Spildooren et al., 2019; van Beek et al., 2019).*

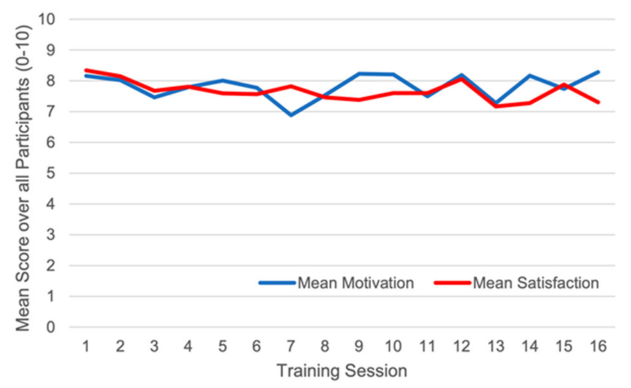

FIGURE 5 | Mean motivation and satisfaction ratings over all participants.

Primary Outcome—Feasibility

The inclusion, adherence and compliance rates as well as mean motivation and mean satisfaction during the trainings all reached or exceeded the thresholds set for feasibility (see **Table 3**, **Figure 5**), while the attrition rate was higher than the targeted threshold (see **Table 3**). This is in line with the results from other studies investigating exergame interventions in stroke patients and healthy older adults, where a similar recruitment process was implemented (Rozental-Iluz et al., 2016) and comparable adherence and compliance rates were observed (Anderson-Hanley et al., 2012; Schoene et al., 2013; Rebsamen et al., 2019; Burdea et al., 2020). Moreover, our results are in line with results in stroke and other neurological patients, where exergames and VR methods were found to be feasible for rehabilitation purposes and increased the motivation and satisfaction with rehabilitation interventions (Lange et al., 2010; Hamari, 2014; Cheok et al., 2015; Matallaoui et al., 2017; Dietlein et al., 2018; Mura et al., 2018; Garcia-Agundez et al., 2019; Wiley et al., 2020). The high attrition rate, however, indicates a problem with the exergame intervention itself. Other studies with exergame interventions reported lower attrition rates compared to this study (Fritz et al., 2013; Schattin et al., 2016). A possible reason therefore may be that this study took place during the time of the COVID-19 pandemic. This may have influenced the feasibility outcomes—in particular the inclusion and attrition rate—of this study as people were advised to shield and participants as well as investigators may have experienced limited allowance and emotional safety for contacts (Sloan et al., 2021). This is supported by the finding that one dropout was caused by the fear of getting infected with the Corona virus at the study center (see section Participants Overview). Moreover, several screened patients refused to participate, as they feared of an infection on the way or at the study center. However, the pandemic situation does not explain all dropouts, as one of them was caused by a training-related adverse event (see section Participants Overview). Exergames are generally reported to be safe (Cheok et al., 2015; Givon et al., 2016; Mura et al., 2018; Norouzi-Gheidari et al., 2019), which implies that this adverse event may be a rare case. Particularly, the participant concerned suffered an uncomfortable intensification of a pre-existing head tremor, possibly caused by the challenging simultaneous motor and cognitive actions required for the training. Therefore, the intervention could not be continued, however, it did not cause the head tremor but rather intensified the pre-existing condition. Nevertheless, such an adverse event should be prevented in a future study and how this may be done, is discussed below (section Future Directions).

Secondary Outcomes—Strengths, and Limitations of the Adapted Taxonomy

A strength of the rehabilitation approach was the careful adaption of the taxonomy based on theoretical reasoning, that consistently applied principles of motor learning (Gentile, 2000). The personalization of the progression was a further strength, however, as can be concluded from the mean ratings of perceived task difficulty predominantly moving below the targeted range, the adapted taxonomy did not achieve optimal task difficulty

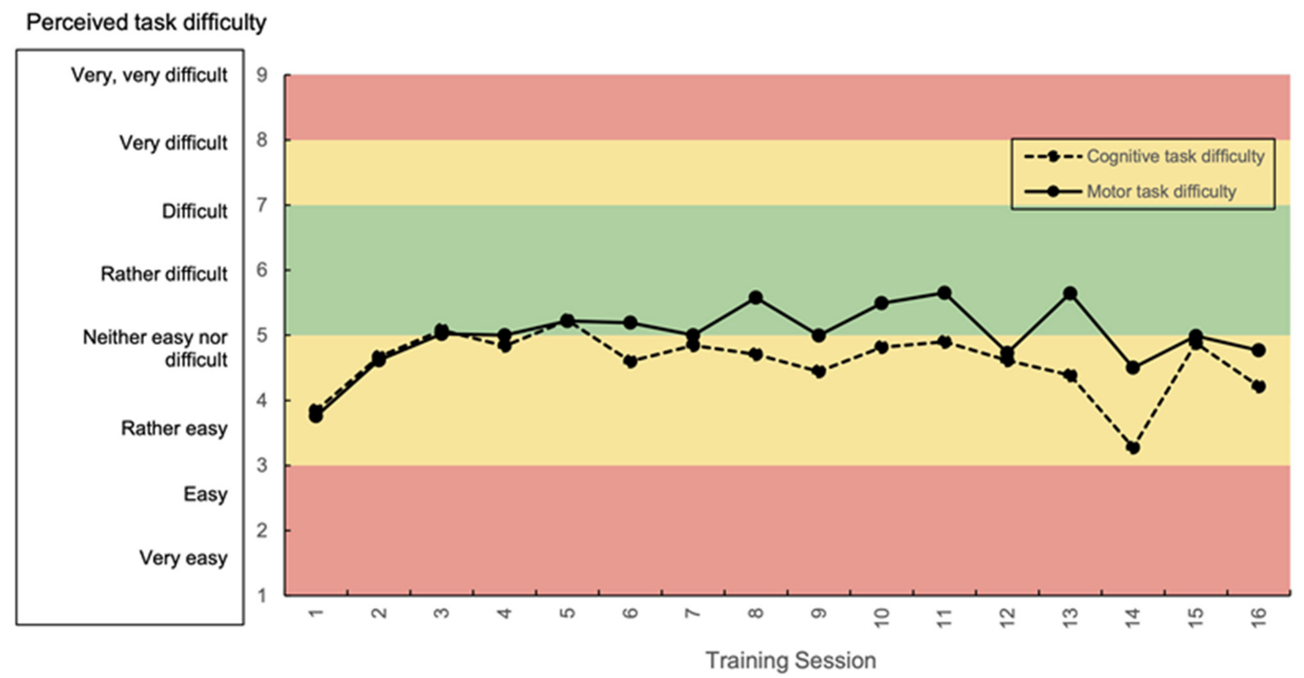

FIGURE 6 | Mean ratings for perceived motor and cognitive task difficulty over all participants. Green area: targeted range of perceived task difficulty.

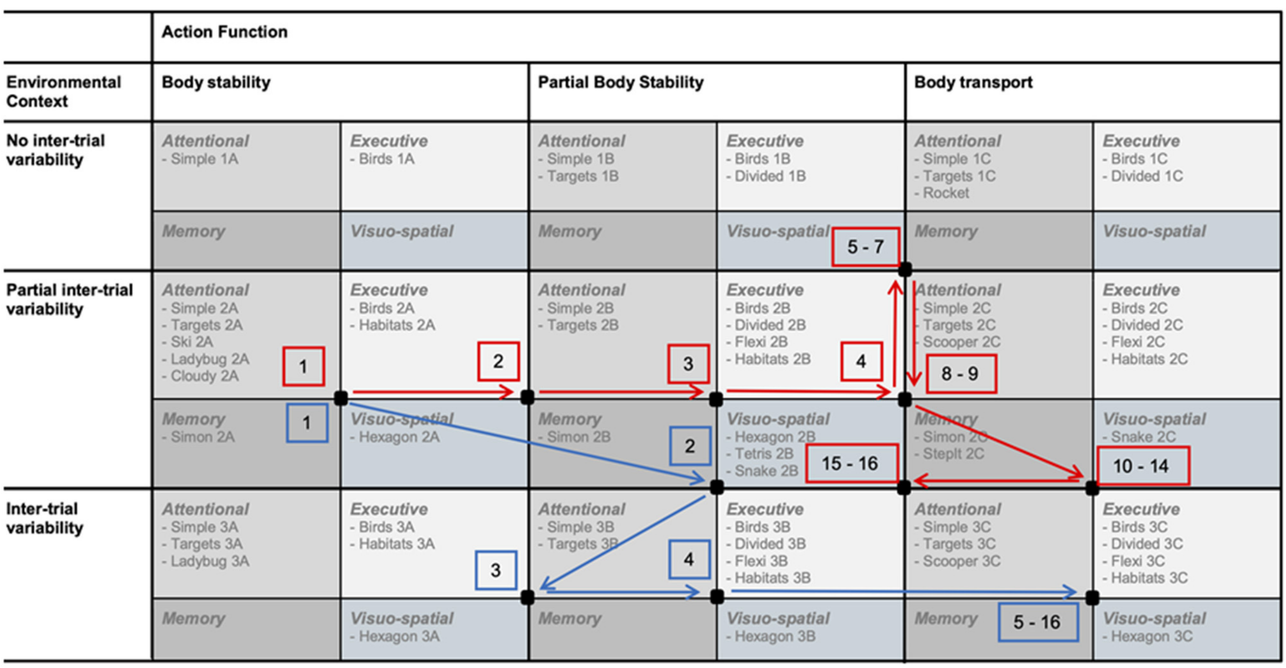

FIGURE 7 | Trajectories of two participants (red, blue) showing their "path" through the taxonomy from the first to the sixteenth training session. Black dots represent the center of the respective "position squares".

TABLE 4 | Results secondary motor outcomes.

Motor outcomes	N	T0	T1	Difference T1–T0	95% CI	T	Asymptotic significance	Effect size
F8W mean [s]	9	9.79 (7.96, 12.81)	9.35 (8.16, 11.90)	−0.12 (−1.69, 1.32)	[−1.67, 1.27]	20.00	0.77	0.07
Gait speed [m/s]	8	0.80 (0.62, 1.13)	0.75 (0.52, 0.94)	0.01 (−0.17, 0.04)	[−0.31, 0.13]	17.00	0.89	0.04
Asymmetry index [%]	8	1.09 (1.02, 1.22)	1.11 (1.03, 1.24)	−0.01 (−0.04, 0.00)	[−0.11, 0.09]	10.50	0.29	0.26
Stride length var aff [%]	8	20.81 (15.86, 26.77)	19.23 (14.34, 24.11)	−1.89 (−5.66, 4.48)	[−7.90, 4.05]	14.00	0.58	0.14
Stride length var unaff [%]	8	21.16 (15.53, 25.04)	21.68 (16.70, 26.57)	1.95 (−5.09, 6.01)	[−4.89, 6.80]	20.00	0.78	0.07
Stride time var aff [%]	8	6.67 (5.02, 10.29)	4.46 (3.42, 9.85)	−0.88 (−5.27, 2.61)	[−4.52, 2.20]	14.00	0.58	0.14
Stride time var unaff [%]	8	6.84 (4.74, 9.21)	6.45 (3.78, 10.12)	0.44 (−1.83, 2.54)	[−2.26, 2.38]	21.00	0.67	0.11
Double support time [%]	8	27.45 (25.03, 32.81)	31.01 (26.06, 34.16)	0.09 (−1.10, 3.04)	[−2.18, 5.14]	22.00	0.58	0.14
Swing time aff [%]	8	37.20 (36.99, 40.04)	36.83 (34.81, 40.04)	−0.37 (−1.67, 0.06)	[−1.57, 0.16]	9.00	0.21	0.32
Swing time unaff [%]	8	34.42 (30.62, 37.83)	34.01 (29.15, 36.14)	0.16 (−1.56, 1.56)	[−3.89, 2.36]	19.00	0.89	0.04
Swing width aff [cm]	8	7.58 (4.05, 9.39)	5.82 (4.87, 9.21)	−0.17 (−2.27, 2.07)	[−1.91, 1.69]	16.00	0.78	0.07
Swing width unaff [cm]	8	3.73 (0.71, 7.53)	4.20 (1.64, 5.39)	0.35 (−1.89, 1.17)	[−2.15, 1.69]	16.00	0.78	0.07
TUG mean [s]	9	8.24 (6.78, 11.90)	7.23 (6.16, 9.27)	−1.01 (−1.67, 0.57)	[−2.17, −0.08]	6.00	**0.05**	0.46

N, number of participants included in test; T0, Baseline, T1, Post-Measurements, CI, confidence interval; T, test statistic of Wilcoxon signed rank test; var, variability, aff, affected; unaff, unaffected.
Values displayed in median (interquartile range); [s] seconds, [m/s] meters per second, [m] meters; in bold, significant at $p < 0.05$.

TABLE 5 | Results secondary cognitive outcomes.

Cognitive outcomes	N	T0	T1	Difference T1–T0	95% CI	T	Asymptotic significance	Effect size
TMT								
TMT A time [s]	10	31.74 (27.43, 37.81)	30.16 (25.45, 31.66)	−3.67 (−5.44, 1.26)	[−5.07, 0.72]	12.00	0.11	0.35
TMT A accuracy	10	1.00 (0.99, 1.00)	0.96 (0.96, 1.00)	0.0 (0.96, 1.00)	[−0.65, 0.05]	5.00	0.50	0.15
TMT B time [s]	10	56.29 (40.81, 85.81)	59.61 (34.00, 69.28)	−7.44 (−29.08, 11.27)	[−36.08, 9.41]	18.00	0.33	0.21
TMT B accuracy	10	0.93 (0.90, 0.97)	0.90 (0.83, 0.97)	0.00 (0.00, 0.00)	[-0.34, 0.34]	6.00	0.18	0.30
TMT B:A ratio	10	1.92 (1.23, 2.67)	1.92 (1.44, 2.45)	0.03 (−0.90, 0.43)	[−0.66, 0.42]	24.00	0.72	0.08
TAP Alertness								
Mean RT w/o signal [ms]	10	299.0 (265.0, 387.5)	296.0 (260.8, 357.0)	15.0 (−42.0, 24.8)	[−30.68, 26.68]	25.00	0.80	0.06
Mean RT with signal [ms]	10	283.0 (267.8, 399.3)	269.0 (255.3, 346.5)	−10.0 (−26.3, 3.8)	[−46.84, 28.44]	14.00	0.31	0.23
TAP Go-NoGo								
Mean RT [ms]	10	498.5 (433.3, 542.5)	462.0 (398.3, 595.0)	−13.5 (−80.0, 56.3)	[-62.65, 54.45]	26.00	0.88	0.03
Errors	10	1.50 (1.00, 2.75)	2.00 (0.75, 2.25)	0.00 (−2.00, 1.00)	[−1.67, 0.87]	7.00	0.46	0.17
Omissions	10	0.00 (0.00, 1.00)	0.00 (0.00, 1.00)	0.00 (−0.25, 0.00)	[−0.76, 0.36]	1.50	0.41	0.18
TAP incompatibility								
Mean RT compatible [ms]	6	570.0 (509.0, 681.5)	603.0 (515.8, 785.0)	33.0 (6.8, 92.5)	[−25.83, 121.50]	18.00	0.12	0.46
Mean RT incompatible [ms]	6	721.5 (575.5, 807.3)	750.0 (575.3, 896.0)	35.0 (−10.0, 88.8)	[−15.06, 92.73]	16.00	0.25	0.33
Mistakes compatible	6	0.00 (0.00, 1.25)	0.00 (0.00, 1.00)	0.00 (−1.00, 0.25)	[−0.96, 0.62]	2.00	0.56	0.17
Mistakes incompatible	6	2.00 (0.00, 4.25)	1.50 (0.75, 3.00)	0.00 (−3.00, 1.75)	[−2.94, 2.60]	5.00	> 0.99	0.00
MRT								
Accuracy	9	0.58 (0.36, 0.61)	0.55 (0.46, 0.71)	0.13 (0.02, 0.19)	[−0.004, 0.18]	34.50	0.15	0.33
Mean RT of correct [ms]	9	1897.4 (1685.0, 2141.7)	1744.7 (1643.0, 1912.2)	−148.4 (−404.2, 154.8)	[−310.2, 46.6]	12.00	0.21	0.29

N, number of participants included in test; T0, Baseline; T1, Post-Measurements; CI, confidence interval; T, test statistic of Wilcoxon signed rank test; RT, reaction time; w/o, without.
Values displayed in median (interquartile range); [s] seconds, [ms] milliseconds.

throughout the intervention (**Figure 6**). Three limitations of the adapted taxonomy were identified. (1) The design of the taxonomy may have linked motor and cognitive progression in an improper way, as separate subjective ratings for motor and cognitive task difficulty and the separate progression on two axes rather decoupled motor and cognitive learning. This led to problems, particularly in patients who were cognitively rather fit and had motor impairments or, vice versa, struggled a lot with the cognitive tasks while being physically rather fit. We observed that in these cases, being unable to progress on one

TABLE 6 | Results secondary motivational outcomes.

Motivation outcomes	N	T0	T1	Difference T1–T0	95% CI	T	Asymptotic Significance	Effect size
BREQ-3								
Intrinsic motivation	10	12.50 (10.00, 15.25)	12.50 (9.25, 13.00)	−1.00 (−3.00, 0.00)	[−2.17, 0.17]	4.00	0.09	0.38
Integrated motivation	10	12.50 (10.50, 16.00)	12.50 (8.50, 15.25)	0.00 (−3.25, 1.00)	[−2.57, 0.77]	8.00	0.31	0.23
Identified motivation	10	12.50 (12.00, 15.25)	14.00 (13.00, 14.25)	0.00 (−2.00, 2.00)	[−1.91, 1.51]	28.00	0.96	0.01
Introjected motivation	10	9.50 (1.75, 11.25)	7.00 (3.50, 10.25)	−0.50 (−4.25, 2.50)	[−3.08, 2.28]	19.50	0.72	0.08
External motivation	10	0.50 (0.00, 3.25)	2.00 (0.75, 3.00)	0.00 (−1.50, 3.00)	[−1.79, 2.79]	20.00	0.78	0.06
Amotivation	10	0.00 (0.00, 0.00)	0.00 (0.00, 0.25)	0.00 (0.00, 0.25)	[−0.53, 1.73]	3.00	0.18	0.30
SSK-index	10	14.5 (10.25, 21.50)	19.0 (10.00, 21.50)	1.0 (−2.50, 6.50)	[−1.95, 5.75]	38.00	0.28	0.24
Intrinsic motivation	10	14.50 (12.50, 16.50)	14.50 (12.00, 16.25)	0.00 (−1.25, 1.25)	[−1.51, 1.31]	10.00	0.92	0.02
Identified motivation	10	18.00 (17.00, 18.00)	17.00 (15.50, 18.00)	−1.00 (−2.25, 0.00)	[−2.19, −0.01]	2.50	**0.05**	0.44
Introjected motivation	10	9.50 (7.75, 14.75)	9.50 (8.00, 10.50)	0.50 (−5.50, 2.25)	[−5.43, 2.23]	15.00	0.67	0.09
External motivation	10	5.50 (3.00, 7.75)	4.00 (3.00, 5.00)	−1.00 (−3.75, 1.00)	[−3.99, 0.59]	10.50	0.15	0.32

N, number of participants included in test; T0, Baseline; T1, Post-Measurements; CI, confidence interval; T, test statistic of Wilcoxon signed rank test.
Values displayed in median (interquartile range); in bold, significant at $p < 0.05$.

axis in the taxonomy, hindered progression on the other axis, which led to under-challenge of the stronger function. However, motor learning already contains a cognitive component, as it usually passes through three different stages, a cognitive phase, an associative phase, and an autonomous phase, in which the perception about motor and cognitive task difficulty will depend on the stage of learning an individual is in (Weaver, 2015). This would imply that it would be better to not decouple motor and cognitive components of motor-cognitive training and therefore, use one instrument for the determination of motor-cognitive task difficulty progression. However, currently there is no suitable instrument that can be recommended (Shishov et al., 2017). (2) Therefore, out of lack of a suitable alternative, subjective ratings of perceived motor and cognitive task difficulty were used to guide the progression in this study (Sweller, 2011). Subjective ratings bear the risk for over- or underestimation of the personal ability and performance. To prevent this, we used visual analog scales, as using a VAS has the advantage that the raters are not dependent on given options but can choose from a continuum to give their answer (Voutilainen et al., 2016). VAS may therefore result in greater responsiveness and be less vulnerable to bias from confounding factors (Pfennings et al., 1995; Voutilainen et al., 2016). Nevertheless, based on the obtained results of perceived task difficulty, we conclude that subjective ratings may not be the proper instrument to guide individualized progression in chronic stroke patients. Moreover, these subjective ratings may have been collected at the wrong time-point. Participants rated their perceived task difficulty at the very end of the session, after having completed the cool-down game. This time point was chosen to not interrupt the training session and therefore disturb the concentration and flow of the participants. Nevertheless, as this cool-down game was less difficult than the rest of the session (see section Intervention/Personalized Exergame Training), this may have influenced the ratings. The last game may have been most present in the thoughts of the participants when they rated their perceived task difficulty, which may have resulted in lower ratings than would have matched the actual perceived task difficulty during the main part. How therefore task difficulty should be progressed in a future trail is discussed below (section Future Directions). (3) Due to limited possibilities to adjust all games to all levels and a lack of games, which train memory functions, several skill sub-categories of the adapted taxonomy remained empty. This may have influenced the personalized progression, as in case an empty sub-category should have provided a game, this was substituted by a game from one of the surrounding sub-categories. As this was a feasibility study, this limitation was accepted, however, for a future study, it should be ensured that all sub-categories of the adapted taxonomy contain at least one game.

Secondary Outcomes-Motor, Cognitive, and Motivational Outcomes

The secondary aim of this study was to get insight into possible treatment effects of the rehabilitation approach in chronic stroke patients. Therefore, we explored changes from before to after the intervention and compared the meaningfulness of change values and confidence intervals to comparable literature (**Tables 4–6**).

The significant improvement in the TUG from pre- to post-measurements with a medium to large effect size is in line with other studies using exergames in chronic stroke patients, which found significant improvements in the TUG and comparable changes and confidence intervals to our results (Singh et al., 2013; Cheok et al., 2015). These changes in the TUG were significantly greater in groups with additional exergame training compared to the control groups receiving standard care, which corresponds with the conditions of this study (Cheok et al., 2015). We found a medium effect size for the non-significant decrease in swing time on the affected side, while no change and a very small effect size was observed for swing time on the unaffected side. A review on spatio-temporal gait parameters in chronic stroke patients found that the changes in swing time are more often observed on the paretic side compared to non-paretic side (Wonsetler and Bowden, 2017). Significant changes were generally greater compared to our findings. Swing time is an important gait parameter in stroke patients as it is associated with single limb support and postural stability (Chisholm et al., 2014). Furthermore, we found a small to medium effect size for the improvement in the asymmetry index, which is a parameter of special interest in chronic stroke patients (Patterson et al., 2008). A temporal asymmetry index between 0.9 and 1.1 is considered normative, while 1.1–1.5 indicates mild asymmetry and >1.5 severe asymmetry (Patterson et al., 2008). The median asymmetry index of the participants moved within the normative range closer to 1. Little is yet known about possible effects of exergame training on gait symmetry in stroke patients, however, high intensity exercise has been found to affect gait symmetry in stroke patients. A meta-analysis reported a trend toward significance (Luo et al., 2019) and our study seems to support this finding. The results of these motor outcomes seem a promising finding indicating that these chronic individuals still have room to improve their mobility and gait if adequate intervention content is provided. The TUG, swing time and the asymmetry index may serve as possible outcomes for a future study.

Among the cognitive outcomes, we found medium to large effect sizes for reduced time needed for the TMT A and accuracy in the TMT B and the MRT. These results are in line with two reviews, which found beneficial effects of exergames on cognitive functions including global cognition, executive functions and visuo-spatial perception in neurological patients and any population, respectively (Stanmore et al., 2017; Mura et al., 2018). In chronic stroke patients, highly significant improvements in time for TMT A and B were found after a dual-task training intervention (Park and Lee, 2019). This gives rise to the presumption that attentional processing speed and cognitive flexibility may be affected by motor-cognitive interventions in general and therefore may be recommendable outcomes for a future randomized controlled trial (RCT). Furthermore, we found moderate effect sizes for increased reaction times in the TAP Incompatibility. The TAP Incompatibility and the MRT, however, are intended to be completed with two hands, which more than half of the stroke patients included in this study were not able to do due to paretic arms. Therefore, some skipped the tests and a few used one hand to operate both buttons. This may have influenced the results, even though the procedures from the baseline measurements were repeated exactly in the post measurements to ensure comparability of the results between the two time points. Due to operational limitations for these tests, we do not recommend them for being used in a future RCT despite the promising effect sizes. To cover attentional performance on incompatible stimuli and mental rotation, other tests should be chosen, which do not require action of both hands.

In the BREQ-3, we found a trend toward significance and a medium effect size for a decrease in intrinsic motivation for general physical activity, while the other motivation sub-types and a motivation were maintained. In the SSK scale, identified motivation for future physical activity decreased significantly and showed a medium to large effect size, while the SSK index showed no change. These results are in line with a meta-analysis on the motivational effects of exergames, which found no difference between exergames and alternative instructional methods (Wouters et al., 2013). This stands in contrast to literature, which states that exergames are expected to increase self-determination of exercise (Lange et al., 2010; Matallaoui et al., 2017; Sailer et al., 2017) and have been found to be superior in improving intrinsic motivation compared to a non-gaming condition (Fitzgerald et al., 2010). It is argued that specific gaming elements such as points, badges and leader boards are important for raising self-determination for exercise (Sailer et al., 2017). Such gaming elements not being present or not being noticed enough by the trainees may be an explanation for lower self-determined motivation during exergame interventions (Sailer et al., 2017). This aspect may apply for the games used in this study, as several participants expressed the wish for more feedback during and after the games. These considerations suggest to further investigate self-determined motivation for exercise in future trials with exergames and to improve the choice and implementation of the motivational elements in exergames (Matallaoui et al., 2017).

Implications, Strengths, and Limitations of This Study

To our knowledge, this is one of the first studies to assess the feasibility of a rehabilitation approach using exergames and following a skill-progression taxonomy in chronic stroke patients. Therefore, this study contributes to the advancement of long-term care for stroke survivors, addressing motor and cognitive impairments. Progressing individually through the taxonomy based on current skills may be a motivating factor for the trainees that taps on the things they are currently able to do. In this scenario, the progression through the taxonomy may be based on patterns of recovery shared by similar patients. Future studies applying larger samples may be well-advised to also consider data mining approaches with the aim to uncover patterns of recovery (Marcano-Cedeño et al., 2013; Chu et al., 2020). Strengths of this study were the clear and pre-defined feasibility protocol, the rather long study duration for a feasibility study and the combination of motor and cognitive outcomes. Nevertheless, several limitations should be considered when reading this study. (1) As being a feasibility trial, this study was designed without a control group, with a total N and treatment duration sufficient to evaluate feasibility but not treatment effects. Therefore, the results in the secondary outcomes must be interpreted with caution and not generalized to other populations. Nevertheless, the derived data and effect sizes can be used for future sample size calculations. (2) The study sample was rather high functioning in mobility and cognitive assessments, highly educated and all but one participant attended regular physiotherapy (see baseline values, **Table 2**), which may have been a reason for the few changes observed in the secondary outcomes. As this was a feasibility study, the training principle "initial value" (Hoffman, 2002), which relates to the baseline performance of a trainee, was not considered as an inclusion criterion. Particularly, this did not hinder the primary outcome of this study—feasibility—to be evaluated. Nevertheless, for a future study, further eligibility criteria regarding "initial values" may be considered to increase the potential for detecting treatment effects (see section Future Directions). (3) Moreover, as participants in this study were recruited in a physiotherapy center and a senior home, the study team did not have contact to the participants' clinicians. Therefore, several diagnostic information, which is traditionally included in reports of studies conducted in a stroke population (e.g., ischemic/haemorrhagic stroke, affected territory) is missing in this report. This was considered acceptable as this study primarily investigated feasibility. In a future RCT, however, with the aim to investigate treatment effects, this information should be included (Kwakkel et al., 2017). (4) One participant was not able to perform the computer-based version of the TMT, as they were not proficient enough with a computer mouse (so that the test performance would probably have been limited by their speed to use the mouse and not by cognitive skills to accomplish the task). To prevent missing data, we administered a paper-and-pencil version of the test. This should, however, be prevented in a future trial, therefore careful considerations regarding the choice of the test version in the targeted study population and sample size should be undertaken. (5) Several assessments exhibited missing data, which were caused by reasons described above (section Secondary Outcomes). Several participants were not able to perform the cognitive tests, which required use of both hands. This should be prevented in a future study by choosing cognitive assessments, which can be completed with one hand. (6) A possible effect of the two study centers could not be investigated, as only one participant was finally recruited in the senior home and was therefore the only participant, who did not receive other therapy or attend therapeutical activities besides the study sessions.

Future Directions

As the rehabilitation approach was feasible with minor modifications and promising results were found for some outcomes, which are relevant for stroke rehabilitation, we recommend the conduction of a well-designed randomized-controlled trial to investigate the effects of the rehabilitation approach using exergames and following a skill-progression taxonomy in comparison to a control intervention. To achieve appropriate credible training effects in such a trial, an appropriate sample size should be achieved, and the intervention duration should be increased to at least 12 weeks (Lauenroth et al., 2016). To account for the training principle "initial value," further eligibility criteria regarding the motor and cognitive impairments of the participants may be considered (e.g., particularly participants with mild to moderate cognitive impairment may be included). To ensure the safety of the intervention, patients experiencing any problems during the use of VR or during challenging simultaneous motor and cognitive action should be excluded. To support this, a familiarization session with the training system for all interested participants may be helpful to foresee adverse reactions to the training. Moreover, before conducting a following study, the taxonomy should be revised. Specifically, we recommend expanding and refining the taxonomy to include a greater range of different motor and cognitive levels by adding more games, in particular for memory functions. Moreover, it may be recommendable to couple motor and cognitive progression more closely, e.g., by using a motor-cognitive parameter for guiding the progression instead of two separate outcomes for motor and cognitive task difficulty, respectively. To improve the progression rules, objective measures may be identified to monitor task difficulty during the training and replace the subjective ratings. Possible parameters therefore may be the reaction times to the stimuli in the games or the accuracy achieved in the cognitive tasks. Moreover, in future research, it may be preferable to combine external load measures with measures approximating internal load (Paas et al., 2003; Herold et al., 2020a). Conceivalbe solutions may be measuring eye activity such as cognitive pupillary response (Paas et al., 2003), galvanic skin response (Jaiswal et al., 2020) or functional near-infrared spectroscopy (fNIRS) (Herold et al., 2020b). Furthermore, the possibility to transfer the intervention into a tele-rehabilitation setting may be promising as stroke patients but also other neurological patients may generally be limited in their ability to reach study centers. Additionally, this would also improve the access to rehabilitation interventions during situations such as the COVID-19 pandemic or COVID-19 patients who are quarantined (Paneroni et al., 2021).

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 authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethical Committee of the ETH Zürich (approval no. 2019-N-180). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SH developed the taxonomy, the methodology and study protocol under the supervision of EB and RK. JH facilitated the recruitment process by providing contacts to the physiotherapy center in Zürich. SH performed data acquisition and analysis, the first interpretation of the data, the writing of the first version of the manuscript and manuscript revision. JH, EB, and RK were involved in in-depth interpretation of the data, revision of the scientific content and manuscript revision. The final manuscript was read and approved by all authors.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2021.730801/full#supplementary-material

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SYSTEMATIC REVIEW
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Towards Objective Quantification of Hand Tremors and Bradykinesia Using Contactless Sensors: A Systematic Review

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Assessing the progression of movement disorders such as Parkinson's Disease (PD) is key in adjusting therapeutic interventions. However, current methods are still based on subjective factors such as visual observation, resulting in significant inter-rater variability on clinical scales such as UPDRS. Recent studies show the potential of sensor-based methods to address this limitation. The goal of this systematic review is to provide an up-to-date analysis of contactless sensor-based methods to estimate hand dexterity UPDRS scores in PD patients. Two hundred and twenty-four abstracts were screened and nine articles selected for analysis. Evidence obtained in a cumulative cohort of $n = 187$ patients and 1,385 samples indicates that contactless sensors, particularly the Leap Motion Controller (LMC), can be used to assess UPDRS hand motor tasks 3.4, 3.5, 3.6, 3.15, and 3.17, although accuracy varies. Early evidence shows that sensor-based methods have clinical potential and might, after refinement, complement, or serve as a support to subjective assessment procedures. Given the nature of UPDRS assessment, future studies should observe whether LMC classification error falls within inter-rater variability for clinician-measured UPDRS scores to validate its clinical utility. Conversely, variables relevant to LMC classification such as power spectral densities or movement opening and closing speeds could set the basis for the design of more objective expert systems to assess hand dexterity in PD.

Keywords: bradykinesia, Parkinson's disease, UPDRS, leap motion, contactless

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1. INTRODUCTION

Parkinson's Disease (PD) is a movement disorder caused by the degeneration of the dopaminergic neurons of the *substantia nigra pars compacta*, a reduction of striatal dopamine, and is characterized by the potential presence of Lewy bodies (Jameson, 2018). PD requires constant monitoring to track progression and perform therapeutic adjustments. Monitoring is currently performed with questionnaires such as the Unified PD Rating Scale (UPDRS) (Goetz et al., 2008).

UPDRS rates different aspects of PD through visual observation of a series of tasks. These tasks are designed to monitor, among others, the most important symptoms of PD, also known as cardinal signs: resting tremors, asymmetry, bradykinesia, and a positive response to dopaminergic replacement therapy. In the case of hand dexterity, these tasks are related to bradykinesia and hand tremors, performing tasks such as finger tapping. UPDRS then rates these tasks on scales from zero (no symptoms) to four (patient is unable to perform the task), through visual observation.

While the criteria to identify zeroes and fours are mostly clear, intermediate scores are considerably more ambiguous, which irrevocably leads to sensibility and reliability problems (Patrick et al., 2001). UPDRS is commonly complemented with patient diaries, which, although helpful, can also be biased by the subjective view of the patient (Hauser et al., 2004). The fact that this ambiguity introduces variability in assessments is well-documented (Meara et al., 1999; Patrick et al., 2001). Furthermore, the relationship between PD and similar conditions also accompanied by hand tremor, such as Essential Tremor (ET), is still unclear (Jimenez-Jimenez et al., 2012).

A solution to minimize subjectivity is to introduce sensor-based measurements (Chaudhry et al., 2006), which provide a reproducible and objective assessment of hand tremor and bradykinesia. The Leap Motion Controller (LMC) has been proposed for this task (Garcia-Agundez et al., 2019). Capturing hand movements via contactless sensors has the potential to reduce ambiguity, providing neurologists with more objective assessments of hand dexterity that may lead to more accurate therapeutic adjustments. At the same time, variables that provide meaningful information for the estimation of UPDRS scores could be used to establish more objective assessment scales, allowing for a finer resolution in hand dexterity assessment and better adjusted pharmacologic therapies.

The goal of this article is to provide a systematic review of recent advances in hand dexterity assessment using contactless sensors in PD patients, in the domains of hand tremor and bradykinesia. This review aims to provide further insight into the feasibility and reliability of this paradigm, as well as suggesting best practice guidelines for both engineers and clinicians on how to proceed from this point.

2. METHODS

As a basis for this systematic review, we searched the databases Pubmed, ScienceDirect, IEEE Xplore, and Cochrane for articles matching the search query:

> *(Parkinson* `OR` *Tremor)* `AND` *(Leap Motion* `OR` *Contactless* `OR` *Infared* `OR` *Lidar)*

on March 31, 2021. This search yielded the following results:

- 28 matches in Pubmed
- 168 in ScienceDirect, including 10 duplicates
- 18 in IEEE Xplore, including 5 duplicates
- 3 in Cochrane, including 3 duplicates

The search was complemented by seven additional articles selected from the references of search matches, yielding 224 abstracts for screening. The abstracts of these matches were filtered according to the following criteria:

1. Research articles
2. Related to PD
3. Related to hand tremor or bradykinesia

This filtering reduced the abstracts to 47 full-text articles assessed for eligibility. These full-text articles were selected for analysis if they met the following *inclusion criteria*:

1. Articles presenting a method to measure hand tremor or bradykinesia using a contactless approach
2. In patients with PD
3. Aiming to link sensor data to clinical functional performance scores (MDS-UPDRS-III or similar)

Conversely, articles were excluded if they met at least one of the following *exclusion criteria*:

1. Articles not related to hand tremor or bradykinesia. Thirteen articles were excluded with this criterion.
2. Articles without participants (technical or otherwise conceptual papers). Seven further exclusions.
3. Articles aiming to test a novel rehabilitation tool or otherwise not linking sensor data to clinical functional performance scores. Nine further exclusions.
4. Articles not using contactless sensors. Three further exclusions.
5. Articles aiming to classify between PD patients and controls exclusively and not to assess symptom severity. Six further exclusions.

Finally resulting in $n=9$ articles for the qualitative and quantitative analysis (Khan et al., 2014; Butt et al., 2017, 2018; Lugo et al., 2017; Cakmak et al., 2018; Lee et al., 2019; Vivar et al., 2019; Williams et al., 2020a,b). Of the selected articles, six were first identified in the Pubmed search, one in ScienceDirect, and two were selected from the additional articles. This procedure was conducted in accordance with the PRISMA guidelines. A.G. was responsible for the selection and data collection process. The following data were sought from the articles: cohort data, procedure data (assessment method, sensor implementation), classification data, and classification accuracy. No studies are clinical trials and no bias assessment was conducted. The PRISMA flow diagram is included in **Figure 1**.

3. RESULTS

All identified articles use some form of video source, including hand detection and tracking. Six of the nine articles use the LMC (Butt et al., 2017, 2018; Lugo et al., 2017; Cakmak et al., 2018; Lee et al., 2019; Vivar et al., 2019), while three use other video sources (Khan et al., 2014; Williams et al., 2020a,b). Essentially, all studies follow the same structure: given a dataset of PD patients performing a certain MDS-UPDRS III task (e.g., finger tapping) rated by one or more neurologists and captured with a sensor, the resulting task score (or a linear regression model) is inferred using points of interest of the hand, defined by a series of features, with a classification method, as depicted in **Figure 2**.

The identified studies implement one or more of the following UPDRS specific tasks:

- Task 3.4, Finger Tapping: The patient taps the index finger on the thumb 10 times as quickly and as big as possible. Out of the nine identified studies, seven analyse this task (Khan et al.,

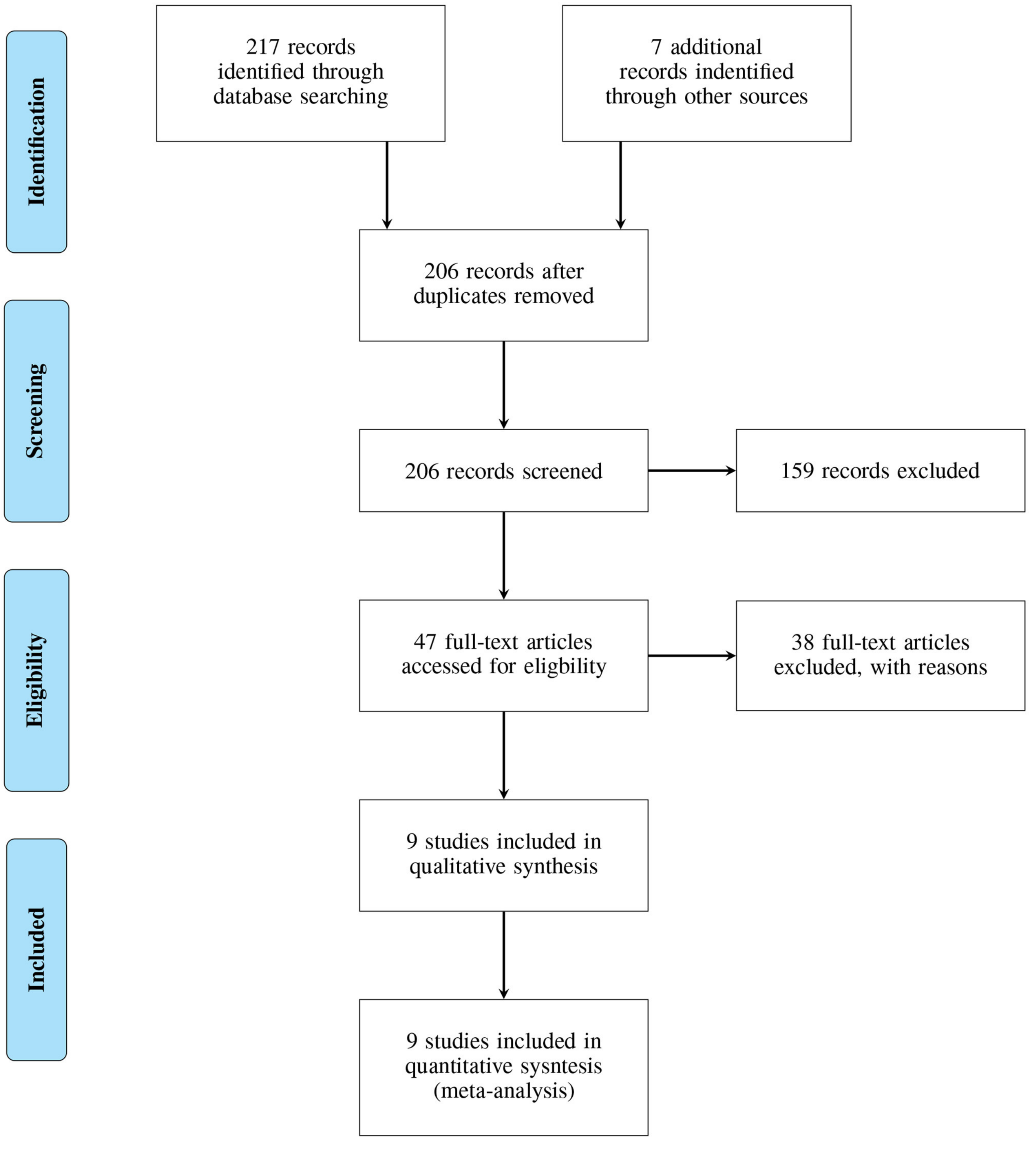

FIGURE 1 | PRISMA 2019 flow diagram.

2014; Butt et al., 2017, 2018; Cakmak et al., 2018; Lee et al., 2019; Williams et al., 2020a,b).

- Task 3.5, Hand Movements: The patient makes a tight fist, then opens the hand 10 times as fully and as quickly as possible. Out of the nine studies, three analyse this task (Butt et al., 2017, 2018; Lee et al., 2019).
- Task 3.6, Pronation-Supination: The patient extends the arm with the palm down, then runs the palm up and down

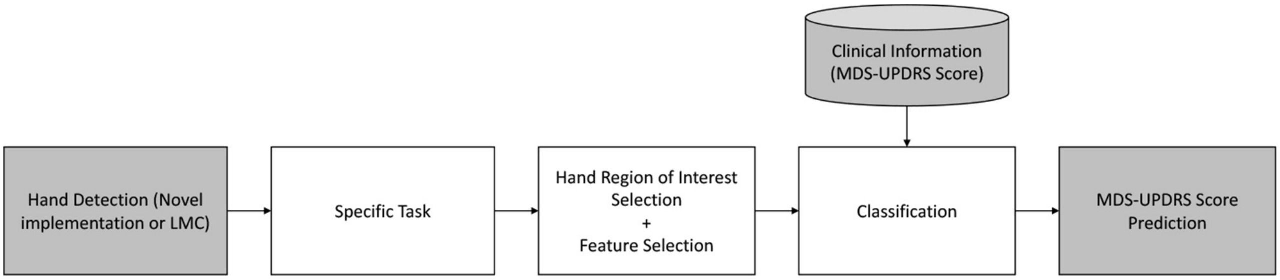

FIGURE 2 | Study design flow diagram.

TABLE 1 | Study tasks and signal of interest.

References	Finger tapping	Hand movements	Pronation-supination	Postural tremor	Kinetic tremor
Khan et al. (2014)	Index finger position				
Vivar et al. (2019)				Palm center × coordinate	Palm center × coordinate
Butt et al. (2017)	Thumb-index fingertip distance	Sum of all palm-fingertip distances	Palm roll angle	Fingertip velocity average	
Butt et al. (2018)	Thumb-index fingertip distance	Sum of all palm-fingertip distances	Palm roll angle	Fingertip velocity average	
Lee et al. (2019)	Thumb-index fingertip distance	Palm-phalanxes median cosine angle	Palm roll angle		
Cakmak et al. (2018)	Thumb-index fingertip distance				
Williams et al. (2020a)	Thumb-index fingertip distance				
Williams et al. (2020b)	Thumb-index fingertip distance				
Lugo et al. (2017)				Palm center coordinates	Palm center coordinates

alternately 10 times as fast and as fully as possible. The three same studies as above analyse this task (Butt et al., 2017, 2018; Lee et al., 2019).

- Task 3.15, Postural Tremor: The patient stretches the arm with the palms down. Tremor in this posture is observed for 10 s. Out of the nine studies, four analyse this task (Butt et al., 2017, 2018; Lugo et al., 2017; Vivar et al., 2019).
- Task 3.17, Kinetic Tremor: The patient performs at least three finger-to-nose maneuvers. Tremor in this movement is observed. Out of the nine studies, two analyse this task (Lugo et al., 2017; Vivar et al., 2019).

Table 1 summarizes the implemented tasks and signal of interest of each study. With the exception of task 3.5, the choice of hand region of interest for each task is consistent.

Table 2 presents the study devices, cohorts, total number, and type of samples, as well as the main study goals. The studies either aim to predict the UPDRS rating of a given sample (Khan et al., 2014; Lugo et al., 2017; Vivar et al., 2019; Williams et al., 2020a) or build a linear regression model relating variables extracted from the signals described in **Table 1** and UPDRS scores (Butt et al., 2017, 2018; Cakmak et al., 2018; Lee et al., 2019; Williams et al., 2020b). In this study, we refer to sample as an instance of either hand of a PD patient performing a UPDRS task. Cumulatively, the nine identified studies have a cohort of $n = 187$ patients and 1,385 samples.

In the following, we divide the qualitative analysis into two subsections. Section 3.1 compares the results of studies that aim to evaluate the scores of UPDRS tasks related to tremor, 3.15 (Postural Tremor) and/or 3.16 (Kinetic Tremor), while section 3.2 compares the results of studies that aim to evaluate bradykinesia with Tasks 3.4 (Finger Tapping), 3.5 (Hand Movements), and 3.6 (Pronation-Supination).

3.1. Tremor

Four studies aimed to assess hand tremor in PD using contactless sensors (Butt et al., 2017, 2018; Lugo et al., 2017; Vivar et al., 2019). All studies used the LMC and either the center of the palm (Lugo et al., 2017; Vivar et al., 2019) or changes in fingertip velocity (Butt et al., 2017, 2018). Butt et al. suggest the use of a 14 Hz lowpass filter, which should not affect the detection of Parkinsonian tremors. The studies also differed greatly in the choice of variables, as well as in the resulting accuracy, if classification was attempted.

Vivar et al. (2019) proposed the use of histogram-based variables, computing an addition and subtraction of data points within a sliding window of 449 samples that advances through

TABLE 2 | Study cohorts and goals.

References	Resolution	N	Sex M/F	Age range or Mean (SD)	Number of samples	Study goals
Khan et al. (2014)	Camera 352 × 288@25 Hz	13	8/5	50–75	387	Classify UPDRS scores in 0, 1, or 2
Vivar et al. (2019)	LMC@40 Hz	20	11/9	69 (14)	39	Classify UPDRS scores in 0, 1, or 2
Butt et al. (2017)	LMC@35 Hz	16	11/9	68 (7)	96	UPDRS Linear regression
Butt et al. (2018)	LMC@35 Hz	16	11/9	69 (9)	96	UPDRS Linear regression
Lee et al. (2019)	LMC@120 Hz	8	6/2	44-60	144	UPDRS Linear regression
Cakmak et al. (2018)	LMC@100 Hz	24	17/7	57 (9)	378	UPDRS Linear regression
Williams et al. (2020a)	Camera 1,920 × 1,080@60 Hz	20		67 (10)	40	Classify UPDRS scores in <=1 or >1
Williams et al. (2020b)	Camera 1,920 × 1,080@60 Hz	37	24/13	68 (10)	73	UPDRS Linear regression
Lugo et al. (2017)	LMC@40 Hz	33	21/12	65 (12)	132	Classify UPDRS scores in 0, 1, 2, or 3

TABLE 3 | Classification results for tremor.

References	Signal of Interest	Signal preprocessing	Variables	Results
Vivar et al. (2019)	Palm center × coordinate	None	Sum and difference of histograms	Bagged Tree classifier, 97% accuracy
Butt et al. (2017)	Fingertip velocity average	14 Hz Lowpass	8–12 Hz Power spectral density, signal strength	No significant correlations found
Butt et al. (2018)	Fingertip velocity average	14 Hz Lowpass	8–12 Hz Power spectral density, signal strength	$R = 0.59$ for signal strength
Lugo et al. (2017)	Palm center coordinates	15-frame windowing	Square Euclidean and Chi Square distance, Earth Mover's distance, Manhattan distance, Shannon entropy, Log energy enthropy	Unspecified classifier, 73.81% accuracy

the data. Standard features are then computed from these histograms, with contrast and homogeneity providing the best performance. This yielded the best performance in this task group, with an accuracy over 97% classifying scores of 0, 1, and 2.

Lugo et al. (2017) performed a similar study, using a significantly shorter windowing of 15 frames, as well as a different choice of variables. The resulting performance was worse at 74%, albeit the sample size was larger and a patient with a score of 3 on both hands was included.

Finally, Butt et al. (2017, 2018) did not aim to estimate UPDRS scores but rather find variables correlated with said scores. The first study found no correlations between the chosen variables (signal strength and power in the 8–12 Hz band). The second study used the same variables and identified a correlation of $R = 0.59$ with signal strength.

Table 3 summarizes the differences in these studies. Overall, data indicate that detecting resting tremor is feasible, but kinetic tremor is more difficult to identify.

3.2. Bradykinesia

Seven studies aimed to assess at least one UPDRS task related to bradykinesia using contactless sensors (Khan et al., 2014; Butt et al., 2017, 2018; Cakmak et al., 2018; Lee et al., 2019; Williams et al., 2020a,b). These studies used a mixture of LMC and video, and differed greatly in choice of signals and variables. As all of these studies implemented Task 3.4 (Finger Tapping) but only three included additional tasks (Butt et al., 2017, 2018; Lee et al., 2019). **Table 4** summarizes the results for all tasks. The following subsections offer a detailed analysis of each task.

3.2.1. Task 3.4 (Finger Tapping)

With the exception of Khan et al. (2014), all studies used the Euclidean distance between the tip of the index finger and the thumb as signal of interest. All studies are also reasonably consistent in the choice of variables: number of repetitions, amplitudes, variability of amplitude (particularly a decrease in amplitude with subsequent repetitions), speeds (generally considered as opening and closing speeds separately), accelerations, and frequency domain analysis. We can divide these seven studies into two groups: two that classify UPDRS scores (Khan et al., 2014; Williams et al., 2020a) and five that use linear regression instead (Butt et al., 2017, 2018; Cakmak et al., 2018; Lee et al., 2019; Williams et al., 2020b).

The two studies aiming at classification (Khan et al., 2014; Williams et al., 2020a) used video instead of a LMC. Interestingly, the resolution and frequency employed by Khan et al. (2014) is significantly lower, with a smaller number of participants but a significantly larger number of samples and a more complex classification task, as they aim to classify ternary scores of 0, 1, and 2 instead of classifying scores binarily as ≤ 1 vs. >1 (Williams et al., 2020a). Both obtained the best results when using support vector machines, with overall accuracies of 82% for Khan (Khan et al., 2014) and 84% for Williams (Williams et al., 2020a).

TABLE 4 | Classification results for bradykinesia.

Finger tapping	Signal preprocessing	Variables	Results
Khan et al. (2014)	Moving average filter, Standard deviation outlier removal	Average of the Cross-Correlation between normalized maxima and minima, total taps, tapping speed, tapping speed variation, differences between first and second half of the task, opening velocity, closing velocity, zero crossing rate, signal energy, facial movements	SVM classifier, 82% accuracy
Butt et al. (2017)	14 Hz Lowpass	Number of repetitions, speeds, variability of frequency and amplitude, power spectral density	Significant correlations for opening speed ($R = 0.515$) and closing speed ($R = 0.602$)
Butt et al. (2018)	14 Hz Lowpass	Number of repetitions, speeds, variability of frequency and amplitude, power spectral density	Significant Correlations for number of repetitions ($R = 0.728$), closing speed ($R = 0.804$) and opening speed ($R = 0.836$)
Lee et al. (2019)	120 Hz Linear interpolation	Amplitudes, frequencies, velocities and slopes	Significant correlations for velocity and frequency ($R = 0.45$), $R = 0.86$ combining all tasks
Cakmak et al. (2018)	None	Mean and standard deviation of speed, acceleration, frequency	root mean square error of 4.37 points (7.8%) for UPDRS-III and 2.12 points (10.7%) for bradykinesia
Williams et al. (2020a)	PCA	Power spectral density, frequency, peaks, ratio of maxima to minima, standard deviation of peaks	SVM classifier, 84% accuracy
Williams et al. (2020b)	Savitzky-Golay	Amplitude, speed, amplitude variability, power spectral density	Significant correlations for speed ($R = 0.56$), amplitude variability ($R = 0.61$) and rhythm regularity ($R = 0.50$), $R = 0.69$ using all variables
Hand movements	**Signal preprocessing**	**Variables**	**Hand movements results**
Butt et al. (2017)	14 Hz Lowpass	Number of repetitions, speeds, variability of frequency and amplitude, power spectral density	Significant correlations for variability of frequency ($R = 0.685$) and number of repetitions ($R = 0.630$)
Butt et al. (2018)	14 Hz Lowpass	Number of repetitions, speeds, variability of frequency and amplitude, power spectral density	Significant correlations for opening speed ($R = 0.647$), Variability of amplitude ($R = 0.647$), closing speed (= 0.639) and number of repetitions ($R = 0.539$)
Lee et al. (2019)	120 Hz Linear interpolation	Amplitudes, frequencies, velocities and slopes	Significant correlation for velocity ($R = 0.69$), $R = 0.86$ combining all tasks
Pronation-supination	**Signal preprocessing**	**Variables**	**Pronation-supination results**
Butt et al. (2017)	14 Hz Lowpass	Number of repetitions, speeds, variability of frequency and amplitude, power spectral density	Significant correlation for variability of amplitude ($R = 0.858$)
Butt et al. (2018)	14 Hz Lowpass	Number of repetitions, speeds, variability of frequency and amplitude, power spectral density	Significant correlation for variability of frequency ($R = 0.488$)
Lee et al. (2019)	120 Hz Linear interpolation	Amplitudes, frequencies, velocities and slopes	Significant correlation for amplitude ($R = 0.56$), $R = 0.86$ combining all tasks

The remaining five studies used linear regression (Butt et al., 2017, 2018; Cakmak et al., 2018; Lee et al., 2019; Williams et al., 2020b). Some, but not all studies report the correlation of each of the variables individually. Overall, correlated variables fall within the $[0.5, 0.6]$ range, with Butt et al. (2018) reporting significantly higher correlations for opening ($R = 0.836$) and closing ($R = 0.804$) speeds. **Table 5** provides a direct comparison of the correlations of these studies. Overall, data indicate that assessing UPDRS scores with video is feasible, and opening and closing speeds show good correlations with UPDRS scores.

3.2.2. Task 3.5 (Hand Movements)

Concerning Task 3.5 (Hand Movements), no classification has been implemented yet. Lee et al. (2019) explored the correlation of a 120 Hz linearly interpolated signal analyzed through amplitudes, frequencies, velocities, and slopes. The number of participants was small (eight), but a large number of samples was collected by measuring with and without deep brain stimulation. They employed the angle between the fingers and the palm as signal of interest. As they did not explore the regression coefficients on each task individually but rather build a global linear regression model, only the velocity of Task 3.5 is reported as showing a relevant correlation of $R = 0.69$.

Butt et al. (2017, 2018) also implemented this task in their two studies, using the Euclidean distance between palm and fingertips. Again employing a 14 Hz lowpass filter, they explored a very similar set of variables, using number of repetitions, speeds, the variability of frequency and amplitude, and power spectral density. They do report the individual correlation of each of the explored variables, showing significant correlations in

TABLE 5 | Correlation results for bradykinesia.

Finger tapping	Opening speeds	Closing speeds	Number of repetitions	Frequency	Amplitude
Butt et al. (2017)	−0.515	−0.602			
Butt et al. (2018)	−0.836	−0.804	−0.728	−0.006	−0.188
Lee et al. (2019)	0.45[a]	0.45[a]		0.45[a]	
Williams et al. (2020b)	−0.56[b]	−0.56[b]		−0.5	0.61

Hand movements	Opening speeds	Closing speeds	Number of repetitions	Frequency	Amplitude
Butt et al. (2017)			−0.63	−0.685	
Butt et al. (2018)	−0.647	−0.639	−0.539	0.313	−0.647
Lee et al. (2019)	0.69[b]	0.69[b]			

Pronation-supination	Opening speeds	Closing speeds	Number of repetitions	Frequency	Amplitude
Butt et al. (2017)					−0.858
Butt et al. (2018)	−0.009	−0.025	−0.257	−0.488	0.307
Lee et al. (2019)					0.56

Amplitude refers to amplitude or variations thereof. Frequency refers to frequency or variations thereof. [a]Combination of all elements. [b]No distinction between opening and closing speeds.

most variables. Interestingly, the correlations vary substantially between both studies.

Table 5 offers a comparison between the correlations of these three studies. Overall, data indicate good correlations for opening and closing speeds. No study has attempted to classify UPDRS scores so far.

3.2.3. Task 3.6 (Pronation-Supination)

The same three studies as in the previous subsection implemented Task 3.6, using the same variables as in the previous task but focusing on a different point of the hand, the roll angle of the palm. All three studies report worse results with Task 3.6, as summarized in **Table 5**. Overall, data only shows good correlations for amplitude and variability of amplitude. No study has attempted to classify UPDRS scores so far.

4. DISCUSSION

In this systematic review, we analyzed recent advances in sensor-based, UPDRS-inspired tremor and bradykinesia assessment in PD patients.

Concerning tremor, it seems that the coordinates of the palm center are a good predictor of UPDRS scores. Larger windows as well as statistical variables seem to be a better choice. Although the studies did not include patients with higher scores (three and four) classifying these should be easier as tremor is expected to be more severe. Although the limited number of studies does not yield definite conclusions, it would seem that classifying tremor UPDRS scores is nearly as accurate as classifying PD patients and healthy controls.

Figure 3 summarizes the number of samples, studies and sample-weighted correlations of all UPDRS bradykinesia tasks. The number of repetitions, opening and closing speeds, combined with changes in amplitude as the task progresses, seem to best characterize the rating in Task 3.4 (Finger Tapping). Implemented classification schemes in this scenario can already achieve excellent results, with accuracies over 80% when discriminating scores of 0, 1, and 2. As is the case with tremor, including higher scores would probably not decrease accuracy as these represent patients that are either almost (3) or fully (4) incapable of performing the task.

For Tasks 3.5 (Hand Movements) and 3.6 (Pronation-Supination) no full classification has been implemented yet. Early results seem to suggest that this task is more difficult to rate, as correlations between variables and neurologist ratings are somewhat lower, in the 0.5–0.6 range. A significant exception is variability of amplitude, which seemed to perform better in Butt et al. (2017).

In this study, we limited ourselves to contactless sensors because we believe the advantages of this approach are significant. However, contactless sensors cannot provide a comprehensive method to measure and quantify all motor symptoms of PD, since they cannot assess the stiffness and rigidity of the arms and legs. They are also more limited than electromyography, which provides richer information on muscular activity. On the positive side, they do not require any adjustment to the patient or any interaction other than the performance of the manual tasks, providing an ideal setup to monitor some of the motor symptoms of PD remotely as an addition, rather than a substitution, of more comprehensive PD assessment methods. Other contactless approaches, such as e.g., Lidar, remain to be explored. Finally, the LMC also presents the additional limitations of infrared sensors, such as measurement noise. Numerous authors indicate that the LMC is fallible depending on environmental light and dirt on the lens being present.

In spite of the limitations of this study, and considering the number of relevant studies is still small, available early evidence points to the LMC offering a feasible, objective alternative to

	Finger Tapping	Hand Movements	Pronation-Supination
Opening Speeds	409 (4)	240 (2)	96 (1)
Closing Speeds	409 (4)	240 (2)	96 (1)
Number of Repetitions	96 (1)	192 (2)	96 (1)
Frequency	313 (3)	192 (2)	96 (1)
Amplitude	169 (2)	96 (1)	336 (3)

	Finger Tapping	Hand Movements	Pronation-Supination
Opening Speeds	0.576	0.673	0.009
Closing Speeds	0.588	0.670	0.025
Number of Repetitions	0.728	0.585	0.257
Frequency	0.326	0.499	0.488
Amplitude	0.370	0.647	0.573

FIGURE 3 | Number of samples and (number of articles) using different variables and UPDRS bradykinesia tasks **(top)** and sample-weighted correlations **(bottom)**.

visual observation to capture and rate some features of hand motility in PD, as well as in other related diseases. Evidence shows that sensor-based methods have clinical potential and might, after refinement, complement, or even replace subjective assessment procedures, not only in patient care but as an additional outcome measure in the clinical trials of disease-modifying treatments. A significant advantage of a sensor-based approach is that a linear regression model could provide a much higher resolution than current UPDRS assessment. Apart from this advantage, a sensor-based assessment also shows potential to link objective tremor and bradykinesia assessment to dopaminergic replacement therapy (DRT) dosage directly. In this sense, a more accurately adjusted dose might help maximize the period in which DRT is effective as dosage needs to be subsequently increased and OFF periods become longer.

Nevertheless, a substantial number of additional studies in several domains are required. Future research should focus on including more than one clinician rating, as well as procedure standardization. Once pilot trials achieve UPDRS classification predictions that fall within the inter-rater range, designing expert systems that offer a much finer resolution of tremor and bradykinesia should become feasible.

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.

AUTHOR CONTRIBUTIONS

Both authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

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The Effect of Virtual Reality-Based Therapy on Improving Upper Limb Functions in Individuals With Stroke: A Randomized Control Trial

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Background: Stroke is a common cause of motor disability. The recovery of upper limb after stroke is poor, with few stroke survivors regaining some functional use of the affected upper limb. This is further complicated by the fact that the prolonged rehabilitation is accompanied by multiple challenges in using and identifying meaningful and motivated treatment tasks that may be adapted and graded to facilitate the rehabilitation program. Virtual reality-based therapy is one of the most innovative approaches in rehabilitation technology and virtual reality systems can provide enhanced feedback to promote motor learning in individuals with neurological or musculoskeletal diseases.

Purpose: This study investigated the effect of virtual reality-based therapy on improving upper limb functions in individuals with chronic stroke.

Methods: Forty Saudi individuals with chronic stroke (6–24 months following stroke incidence) and degree of spasticity ranged between 1, 1 + and 2 according to Modified Ashworth Scale were included in this study. Participants were randomly assigned into two groups, experimental and control, with the experimental group undertaking a conventional 1-h functional training program, followed by another hour of virtual reality-based therapy using Armeo Spring equipment and the control group received 2 h of a conventional functional training program. The treatment program was conducted three times per week for three successive months. The change in the scores of Action Research Arm Test (ARAT), Wolf Motor Function Test (WMFT), WMFT-Time (time required to complete the test) and Hand Grip Strength (HGS) were recorded at baseline and after completion of the treatment. Parametric (paired and unpaired *t*-tests) non-parametric (Wilcoxon and Mann–Whitney tests) statistical tests were used to identify the differences within and between groups (experimental group and control group) and evaluation times (pre- and immediately post-treatment).

Results: Both groups showed significant differences (all, $P < 0.05$) in all measured variables after 3 months of the treatment. Individuals with stoke in the experimental group had a better improvement in ARAT ($P < 0.01$), WMFT ($P < 0.01$) and WMFT-Time

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($P < 0.01$) scores after completion of the treatment compared to the control group. No significant difference in HGS scores was detected between groups after completion of the treatment ($P = 0.252$).

Conclusion: The use of combined treatment of virtual reality-based therapy and conventional functional training program is more effective for improving upper limb functions in individuals with chronic stroke than the use of the conventional program alone.

Keywords: virtual reality, exergames, physiotherapy, upper limb (UL), stroke

INTRODUCTION

Stroke is an acute event that primarily involves neurological damage leading to disability and mortality (Sabut et al., 2010; Sacco et al., 2013). Globally, it is the 2nd or 3rd most frequent cause of death as well as one of the main causes of acquired adult disability (Langhorne et al., 2011). In Saudi Arabia (SA), the incidence of stroke in adults is approximately 30–40 per 100,000 population annually (Qureshi, 2008; Alahmari and Paul, 2016), with an estimated 20,000 new strokes, 8,000 disabilities and 4,000 deaths (Al Khathaami et al., 2011). Multiple impairments are observed including weakness, fatigue, alterations in tone, sensory loss, cardiovascular deconditioning, uncoordinated responses, poor balance and difficulty in walking, which might impact on the ability to perform functional activities in those who experience a stoke (Guy et al., 2004; Langhorne et al., 2009).

Changes in the affected upper limb are often more pronounced than those in the affected lower limb (Wiklund and Uvebrant, 1991) and include functional limitations of the affected arm and slow uncoordinated motion of the hand (Brown and Walsh, 2000; Chin et al., 2020). There are also common changes such as the difficulty performing reaching tasks due to changes in the timing and coordination with abnormal postural adjustments (Hung et al., 2004; Steenbergen and Van Der Kamp, 2004) or inability to control grasping, finger-tip force and timing during manipulation of an object (Duff and Gordon, 2003; Gordon et al., 2003). Stroke patients often experience difficulties in participation in home, work, community life (Sköld et al., 2004) or difficulty performing daily living activities (ADL) such as feeding, dressing, and grooming due to a combination of physical, cognitive and perceptual problems (Mayo et al., 1999; Sköld et al., 2004).

The functional performance of the affected upper limb can be improved when stroke patients have sufficient opportunities to practice (Walker et al., 2000). There are different techniques/approaches that can be used in the management such as physiotherapy, occupational therapy, conductive education, splinting, casting pharmacotherapy and surgery or specific techniques such as neurodevelopmental therapy or constrained induced movement therapy (Sakzewski et al., 2009). However, there is no strong evidence of successful treatment with any of these techniques/approaches.

Virtual reality is the usage of interactive simulations created by computers to provide useful experiences for individuals by engaging and interacting within three-dimensional environments that are similar to objects and events of the real world (Sisto et al., 2002). The use of virtual reality for rehabilitation of stroke patients has been shown to be interactive and enjoyable, and may help to improve the motor control and function of upper limb with sufficient use (Holden et al., 2007; Kim et al., 2018). Using virtual reality in rehabilitation (known as virtual reality-based therapy) is one of the most innovative developments in rehabilitation technology, as virtual environments are a promising future approach in the rehabilitation and improvement of ADL after stroke. Virtual reality-based therapy has the potential to be used in a range of settings including patients' homes or nursing homes that allows additional practice outside formal rehabilitation sessions (Crosbie et al., 2007; Kim et al., 2020).

Few studies are available that have used virtual reality for rehabilitation in individuals with stroke and no study has investigated the use and effects of virtual reality-based therapy in Saudi individuals with stroke. Accordingly, further studies are required to prove the efficiency of virtual reality based training for improvement of the upper limb functions in patients with stroke in Saudi Arabia. Therefore, this study aimed to investigate the effect of virtual reality-based therapy on improving the functions of upper limb in comparison with the conventional functional training program in Saudi chronic stroke patients.

Few studies are available that have used virtual reality for rehabilitation in individuals with stroke and no study has investigated the use and effects of virtual reality-based therapy in Saudi individuals with stroke. In SA, stoke incidence is expected to increase and is becoming a critical problem and an important cause of mortality and morbidity and also impact on performing everyday activities in Saudi population. Therefore, treatments that can provide a quick and better improvement for upper limb functions in Saudi patients with stroke are necessary. Therefore, this study aimed to investigate the effect of virtual reality-based therapy on improving the functions of upper limb in comparison with the conventional functional training program in Saudi chronic stroke patients.

MATERIALS AND METHODS

Participants

A total of 62 chronic stroke patients were screened for inclusion in this study, with only 40 participants meeting the inclusion criteria. **Table 1** shows the characteristics of the included participants.

The inclusion criteria were adult participants aged 50–60 years with a confirmed diagnosis of chronic stroke (at least 6 months following the stroke incidence) secondary to ischemia or hemorrhage. The degree of spasticity of the affected upper limb ranged between 1, 1 + and 2 according to Modified Ashworth Scale (Rw and Smith, 1987; Sloan et al., 1992). All participants had the ability to extend the wrist at least 20° and the fingers for 10° from the full flexion, allowing participants to engage in performing functional activities. Also, they were cognitively able to understand and follow instructions and did not receive other treatments to improve the functions of affected upper limb except the treatment provided in this study.

Any participant with a cognitive reduction (<23 points based on Mini-Mental State Examination scale) was excluded (Pangman et al., 2000). Participants with fixed contractures and stiffness in upper limb joints (e.g., shoulder, elbow, wrist, and fingers joints), painful shoulder syndrome, and participants who had major rotational malalignments in the affected upper limb were also excluded from this study. Other exclusion criteria were participants with a cardiac pacemaker, visual, auditory, and perceptual diseases/impartments, uncontrolled seizures, those who received botulinum toxin (6 months before the beginning of the study) or muscle-tone control medication (3 months before the beginning of the study).

This study was approved by the Biomedical Ethics Committee, Umm Al-Qura University, Mecca, Saudi Arabia and conducted in the Physiotherapy Department of Umm Al-Qura University. The participants were recruited from the western region (Mecca and Jeddah cities) and provided written informed consent authorizing their participation. This study was registered in ClinicalTrials.gov (NCT04764994).

Study Design and Randomization

The study design was a two-armed randomized control trial. The randomization of the participants in both treatment groups (experimental and control) was performed using a computerized sequence generation. **Figure 1** shows the recruitment process and the flow of participants throughout the study.

Given the nature of the treatment in this study, it was not possible for therapists and participants to be blinded but both therapists and participants were blinded to the randomization process to ensure the maximum degree of credibility of the obtained results. The assessment of the stroke patients was performed by assessors who had not participated in the application of treatment and were blinded to the randomization process. The participants were allocated in two groups of twenty patients, experimental and control groups.

TABLE 1 | Participants' characteristics, number of affected dominant limb and spasticity degree.

	Control group (*n* = 20)	Experimental group (*n* = 20)
Participants' characteristics		
Age (years)	53.32 ± 5.13	54.46 ± 4.27
Sex (number; Male/Female)	15/5	16/4
Height (cm)	167.75 ± 5.69	168.62 ± 5.27
Weight (kg)	86.86 ± 4.47	87.41 ± 4.26
Dominant upper limb		
Number of affected dominant upper limb	17	16
Spasticity degree (Modified Ashworth Scale)		
1	5	2
1+	11	13
2	4	5

Assessment

Outcome measures were based on the following tests: (1) Action Research Arm Test, (2) Wolf Motor Function Test (WMFT), and (3) Hand Grip Strength (HGS). The change in the scores of these tests at baseline and after completion of the treatment were recorded. The assessment was performed by blinded assessors who did not engage in the treatment program and did not know which group each participant was in. The used outcome measures of this study can be linked to the "neuromusculoskeletal and movement-related functions" domain of "Body Functions and Structures" component of ICF classification (The International Classification of Functioning, Disability and Health).

Action Research Arm Test was used to assess the changes in limb functions including ability to handle objects with different size, weight, and shape. It is highly recommended as a clinical and research tool for assessing the changes in motor impairments of the upper limbs following stroke (Song, 2012; Carpinella et al., 2014; Nomikos et al., 2018; Dandekar and Ganvir, 2019; Spence et al., 2020). This test can be considered as an arm-specific measure of activity limitation and consists of nineteen items in four subscales: grasp, grip, pinch, and gross movements. Each item was scored on a four-level ordinal scale 0–3: cannot perform any part of the test (score = 0), performs partially (score = 1), takes a long time to complete the test (score = 2) and performs the test normally (score = 3). The total score ranged from 0 to 57, with a low score indicating no movements can be performed while the highest score indicates normal functional performance of upper limb (Lyle, 1981).

Wolf Motor Function Test is a tool with acceptable test-retest reliability to assess the motor ability of the upper limb in participants with stroke through timed and functional tasks (Morris et al., 2001; Nijland et al., 2010; Hodics et al., 2012). It consists of fifteen items, six items related to timed joint-segment movements tasks and nine items related to integrative functional movements tasks. The assessors tested the less affected upper limb first, followed by the most affected side. The fifteen timed items were rated on a 6-point scale (0–5): the participant is unable to use upper limb (score = 0), or the participant can use upper limb and its movement appears to be normal (score = 5). A maximum of 120 s was allocated to each item. The total score ranged from 0 to 75, with a lower score indicates lower functioning levels (Wolf et al., 2001). In addition, the time required to complete the test in seconds (WMFT-Time) was measured.

Hand Grip Dynamometer (BTE Technologies, Hanover, MD, United States) was used to assess the change in the strength

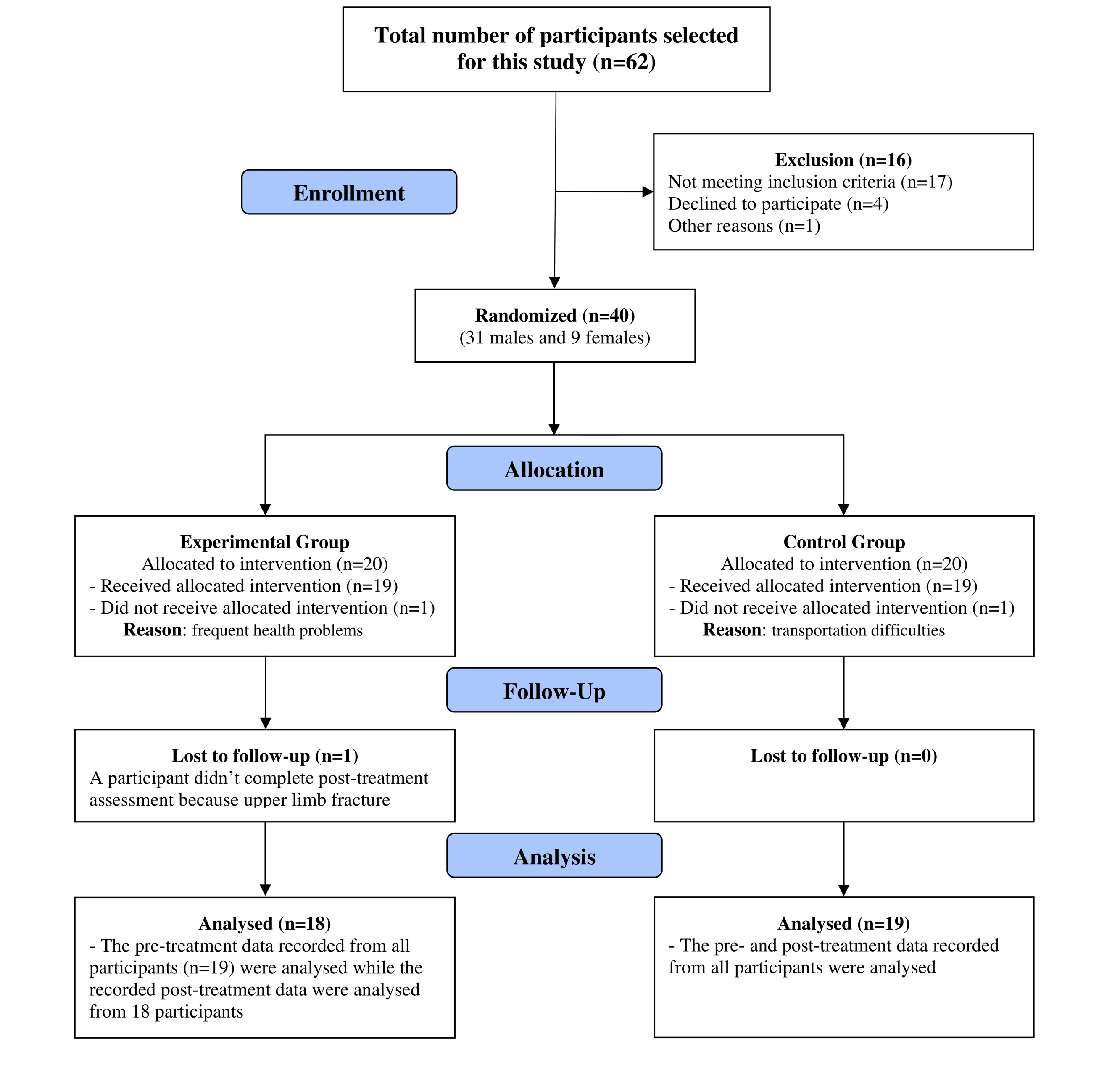

FIGURE 1 | Flow diagram of the study.

of the hand muscles of the affected upper limb (in pounds). The higher the score of the hand grip after completion of the treatment program compared to the baseline score, the better the improvement of hand functional abilities.

Treatment Protocol

The treatment was delivered face-to-face and provided individually in three sessions per week for 3 months for both experimental and control groups. Every treatment session lasted 2 h with a 15-min rest between the first and second hours.

Participants in the experimental group underwent a three-part treatment program. The first part involved muscle facilitation exercises, proprioceptive neuromuscular facilitation exercises, strengthening activities, stretching exercises and postural reactions exercises. The second part included arm-reaching tasks, arm-hand tasks, manipulative tasks (grasping and release activities) with the inclusion of the more affected upper limb in functional tasks of ADL. The first and second parts were applied for 1 h, followed by 15 min rest, then the third part was applied for 1 h. The third part included a virtual reality-based training program using Armeo Spring to simulate a range of upper limb tasks related to arm-reaching to target, reach and grasp (arm-hand activities) and manipulative tasks through using different games as appropriate. Armeo Spring

(MRF; Hocoma, Switzerland) is a functional device used for upper limb rehabilitation and can provide a specific therapy with augmented feedback. It facilitates intensive task-oriented upper limb therapy in neurological diseases and injuries such as stroke and traumatic brain injury. This device involves an adjustable arm support with augmented feedback and a large 3D workspace allowing to perform functional therapy exercises in a virtual reality environment.

The control group underwent a conventional functional training program (conventional physiotherapy program) for 2 h comprising two parts those provided to the experimental group but each part lasted for 1 h in the control group with 15 min rest in between.

The provided conventional functional training program in both groups focused on enhancement of the following functions and skills of the affected upper limb: (1) shoulder abduction and external rotation, (2) elbow extension, (3) forearm supination, (4) wrist radial deviation, and (5) thumb and fingers extension and abductions.

Power Analysis

To identify the required sample size, a preliminary power analysis was calculated. The power was set at 80%, alpha (α) was at 0.05 and the effect size was set at 0.5; considering two treatment groups and two different evaluation times. Subsequently, the power analysis revealed that the required sample size of this study was 40 participants.

Statistical Analysis

For parametric data, paired *t*-tests (paired samples) were used to compare the changes in WMFT-Time and HGS between pre- and immediately post-treatment within each group. Unpaired *t*-tests (independent samples) were used to compare between groups (experimental and control groups) at baseline and immediately after completion of the treatment. The results were expressed as mean ± standard deviation (SD). For non-parametric data, Wilcoxon tests were used to compare the changes in ARAT and WMFT between pre- and immediately post-treatment within each group. The Mann–Whitney test was used to compare between groups at baseline and immediately after completion of the treatment. The results were expressed as mean rank. SPSS (version 26) was used to analyze the data and P values less than 0.05 were considered significant.

RESULTS

There were significant differences (all, $P < 0.01$) in the mean scores of ARAT, WMFT, and WMFT-Time between pre- and post-treatment for each group (experimental and control groups) but no significant differences were detected between groups at baseline (**Table 2**). After completion of the treatment, significant differences were detected in favor of the experimental group in these tests (all, $P < 0.01$).

For HGS, there was a significant difference between pre- and post-treatment for each group (all, $P < 0.05$) but no differences were detected between groups at baseline and after the completion of treatment (**Table 2**).

TABLE 2 | Within- and between- group differences for upper-limb functional measures at baseline and immediately after 12 weeks of treatment.

Parameter	Control group	Experimental group	*P*-value
Action Research Arm Test			
Mean Rank–Pre	17.72	18.29	0.868
Mean Rank–Post	12.49	23.35	0.0034
P-value	0.0027	0.0011	–
Wolf Motor Function Test			
Mean Rank–Pre	18.47	17.50	0.778
Mean Rank–Post	11.83	24.35	0.0015
P-value	0.0031	0.0014	–
Wolf Motor Function Test–Time (in seconds)			
Mean ± SD–Pre	47.50 ± 4.77	47.94 ± 4.86	0.742
Mean ± SD–Post	41.39 ± 3.80	36.71 ± 4.19	0.0014
P-value	0.0017	0.0001	–
Hand Grip Strength (in pounds)			
Mean ± SD–Pre	10.72 ± 1.93	10.59 ± 2.06	0.844
Mean ± SD–Post	11.94 ± 2.18	12.88 ± 2.57	0.252
P-value	0.0183	0.0241	–

SD, standard deviation.

DISCUSSION

The present study aimed to investigate whether virtual reality-based therapy had a beneficial effect on improving the functions of upper limb in chronic stroke patients and compare its effect with that of the conventional physiotherapy program. The results revealed that virtual reality-based therapy combined (with conventional physiotherapy program) greatly improved upper limb functions in chronic stroke patients compared to the use of a conventional physiotherapy program alone.

The poor recovery of the affected upper limb after stroke can be explained by the phenomenon of learned non-use which can be easily developed after stroke and may lead to the development of secondary complications such as weakness or atrophy of the muscles, imbalance or tightness of the muscles, stiffness or deformity of upper limb joints, poor circulation to the upper limb and pain (Botte et al., 1988; Feys et al., 1998). These factors may cause reluctance to use the affected arm that might impede the recovery of motor functions. Therefore, any physical therapy programs to promote the utilization of the affected upper limb will certainly overcome this phenomena, allowing patients to use their upper limbs and accelerate functional recovery in stroke patients.

Therefore, the application of the conventional physiotherapy program in this study may explain the significant improvement that occurred in both groups after treatment. This training program encouraged the participants, providing them with the opportunity to use their affected upper limbs in different purposeful and meaningful activities, thereby augmenting the process of re-learning through facilitation of sensory-motor experience, controlling muscle contraction, coordination of neuromuscular activities, as well as improving the range of motion of joints in the affected upper limb.

In contrast to conventional face-to-face therapy, stroke survivors can be trained to practice virtual tasks independently which can increase the amount of time the patients spend in activities that may lead to better ADL outcomes (Kwakkel et al., 2004). The better results that were gained in the experimental group than in the control group might be attributed to the application of virtual reality-based therapy that allowed the participants in this group to perform motor activities in more enjoyable environments, manipulate items/objects virtually which motivated them to continue therapy.

The positive impact of the virtual reality-based therapy on improving motor functions has been supported in multiple previous studies as it can provide participants the capacity to practice movements independently in more challenging tasks and more motivating environments, stimulate patients to concentrate and exercise more control over the environment compared with real-life settings, as well as enable therapists to grade the task to the appropriate level of challenge and increase the intensity of training while providing augmented three-dimensional and direct sensorial feedback (Dobkin, 2004; Piron et al., 2005; Merians et al., 2006; Mihelj et al., 2012). It can also provide mechanical-assistance to the trained upper limb which partially relieves its weight enabling patients to use repetitive and active exertion of goal-directed movements with larger ROM and greater multi-joint coordination during the practice of complex motor tasks in an enriched learning environment (Beer et al., 2007; Timmermans et al., 2009). Furthermore, it can improve the ability of patients to address spatial and temporal accuracy necessary for the movement to meet environmental demands (Ada and Canning, 2005; Taveggia et al., 2016).

The significant effect of virtual reality-based therapy on improving motor performance in individuals with chronic stroke in the present study was in line with the findings of Merians et al. (2002); Kwakkel et al. (2008), Basteris et al. (2014), and Levac et al. (2019) who demonstrated that repetitive movements in real environments using robot-assisted arm rehabilitation and virtual reality therapy were effective in improving upper limb functions, positively enhancing the performance of ADL and better than those who trained with conventional treatment methods (Merians et al., 2002; Kwakkel et al., 2008; Basteris et al., 2014; Levac et al., 2019).

There are some limitations in this study that should be acknowledged. The first limitation is the difficulty to recruit more participants due to COVID-19 pandemic as some stoke patients that met inclusion criteria refused to participate in this study. The second limitation is due to not fully implementing the ICF classification. The third limitation is due to the demands placed on participants and their age as researchers did not apply measurements to examine other functional activities such as walking. The fourth limitation is that the long-term effect of virtual reality-based training for improving the functions of affected upper limb in stroke had not yet been established.

Future studies to consider different stroke stages (acute, subacute or chronic) and age groups, and to identify the ideal duration of treatment session and the optimal program length to obtain the maximum benefits from virtual reality-based treatment are recommended.

CONCLUSION

Combined treatment of virtual reality-based therapy and conventional physiotherapy program is more effective for improving upper limb functions in chronic stroke patients than the use of conventional physiotherapy program alone.

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.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by this study was approved by the Biomedical Ethics Committee (HAPO-02-K-012-2020-10-473), Umm Al-Qura University, Mecca, Saudi Arabia and conducted in the Physiotherapy Department of Umm Al-Qura University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

EE-K developed the study protocol and designed the study methods. EE-K, AE-F, and MG collected the data of the study. EE-K and AE-F performed the data and statistical analysis. EE-K, MA, AE-F, and MG cooperatively did the data presentation and interpretation. EE-K and MA drafted the manuscript. All authors read, revised, and approved the final version of the manuscript.

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Theoretical Rationale for Design of Tasks in a Virtual Reality-Based Exergame for Rehabilitation Purposes

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Virtual reality games are playing a greater role in rehabilitation settings. Previously, commercial games have dominated, but increasingly, bespoke games for specific rehabilitation contexts are emerging. Choice and design of tasks for VR-games are still not always clear, however; some games are designed to motivate and engage players, not necessarily with the facilitation of specific movements as a goal. Other games are designed specifically for the facilitation of specific movements. A theoretical background for the choice of tasks seems warranted. As an example, we use a game that was designed in our lab: VR Walk. Here, the player walks on a treadmill while wearing a head-mounted display showing a custom-made virtual environment. Tasks include walking on a glass bridge across a drop, obstacle avoidance, narrowing path, walking in virtual footsteps, memory, and selection tasks, and throwing and catching objects. Each task is designed according to research and theory from movement science, exercise science, and cognitive science. In this article, we discuss how for example walking across a glass bridge gives perceptual challenges that may be suitable for certain medical conditions, such as hearing loss, when perceptual abilities are strained to compensate for the hearing loss. In another example, walking in virtual footsteps may be seen as a motor and biomechanical constraint, where the double support phase and base of support can be manipulated, making the task beneficial for falls prevention. In a third example, memory and selection tasks may challenge individuals that have cognitive impairments. We posit that these theoretical considerations may be helpful for the choice of tasks and for the design of virtual reality games.

Keywords: exergaming, theoretical rationale, gait rehabilitation, motor, cognitive, virtual reality

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INTRODUCTION

Exergaming can broadly be defined as "A game that involves physical exercise and that integrates motion-tracking technology that enables interaction with the game and real-time feedback of user's performance" (Perez-Marcos, 2018). Over the last decades, there has been an increasing interest in using exergames for rehabilitation purposes, and systematic reviews show that exergaming may be beneficial for a variety of outcomes in different clinical populations (Mat Rosly et al., 2017; Page et al., 2017; Pacheco et al., 2020). Often, the ability to engage and motivate is pointed to as the main benefit of exergames: Players are caught up in solving the tasks of the game, and "forget" that they are moving. As such, it can be said that metabolic effects are the goal of the game. There is also great potential in designing games and tasks that are directed towards specific impairments, both physical or cognitive (de Bruin et al., 2010; Vogt et al., 2019). The content and characteristics of the games, therefore, seem important for facilitating specific domains that can be beneficial in rehabilitation. However, the theoretical rationale for tasks chosen in exergames is not always clear and declared (Anders et al., 2020).

In this non-empirical article, we aim to describe the practical approach for designing and developing an exergame that is played while treadmill walking, and discuss the theoretical rationale for choice and design of specific tasks. The game is meant to challenge motor and/or cognitive skills and is intended for rehabilitation purposes.

BACKGROUND

With an aging population, the burden on health care resources is expected to increase substantially (WHO, 2021). New digital technologies that can engage and motivate for movement and activity are emerging, with great potential for health care and rehabilitation services (McCaskey et al., 2018). Exergaming is one such technology that has been found to benefit cognitive functioning (Stanmore et al., 2017), enhance prefrontal brain activity (Eggenberger et al., 2016; Schättin et al., 2016), and improve physical and mental health (Xu et al., 2020). Patients are often seeking, or are being referred to rehabilitation for movement problems, such as poor balance and gait impairments. To train movement skills, rehabilitation professionals use physical equipment (obstacles, objects to grasp, etc.) and physical space. Virtual realities are, at least to some extent, less constrained by physical realities: Paths and patterns on the floor to navigate can be made virtually, and "objects" can be data animated and grasped using hand controllers. Tasks can be tailored to specific impairments: Virtual footprints can serve as cues for patients with Parkinson's disease and freezing gait (Gómez-Jordana et al., 2018), while the balance can be promoted using weight shifting tasks in persons with hemiparesis after stroke (Wüest et al., 2014). Fall prevention in older adults is an important issue in health care, and exercise is likely the most important all-round preventive measure that can be taken (Gillespie et al., 2012). Further, the most successful exercise programs to prevent falls are high-intensity balance exercises, meaning reducing the base of support, shifting of the center of mass, and little hand support (Sherrington et al., 2017). Mirelman and co-authors used a screen-based game that was played while walking on a treadmill in a randomized controlled trial of fall prevention and reduced the number of falls significantly compared to treadmill walking alone (Mirelman et al., 2016). The game involved stepping over and around obstacles (Mirelman et al., 2011), and thus involved narrowing the base of support and shifting of the center of mass. Importantly, the game involved both cognitive (navigation, planning) and motor processes (walking), which the authors argue are key to avoiding falls.

Exergames may be delivered through different platforms, such as desktop, CAVE, or head-mounted displays (HMD). One of the key differences between the platforms is the degree of immersiveness: While playing on a screen, the player is aware of her surroundings and the sensation of being in the game may be less pronounced than when wearing an HMD, which blocks out other visual (and auditory) stimuli. There are few studies comparing the platforms directly, but there is some research to suggest that memory performance within experimental tasks is enhanced in an immersive virtual environment compared to a non-immersive virtual environment (Ventura et al., 2019). More immersive platforms, therefore, show greater promise as a means of rehabilitation.

At our lab, the exergame VR Walk was developed in close collaboration between computer scientists and physiotherapists. The aim of the game is to improve balance and mobility for different clinical groups through engaging and motivating motor-cognitive training. As a guiding principle, we used training conditions based on Geurts and co-authors (Geurts et al., 1991), by adding difficulties to the basic task of walking:

Perceptual: Altering perceptual input (in this game, only visual).

Cognitive: Performing more than one task at the same time.

Motor: Increasing the dynamic complexity of a basic task, such as turning and throwing.

Mechanical: Changing and decreasing the base of support

An early version of VR Walk (the minimal viable product) has been tried on healthy adults, where we investigated how the different tasks changed gait regularity (Bovim et al., 2020), and the game is planned for use in projects with both children/adolescents and older adults.

MATERIALS AND METHODS

An iterative design approach is defined and used in this project, within an interprofession team including health (scientists and clinicians) and computer science (Still and Crane, 2016). Weekly user tests were arranged during planning and development phases, while validation and evaluation were performed over a longer time frame. The project was undertaken between 2018–2020. In overview, the project process can be presented in the following five phases;

1. Design and defining

    The initial aim was to design an HMD-based exergame that would challenge balance, and involve both motor and cognitive skills simultaneously. The idea for the game came from the first author (LPVB), who then pitched the project to the Department of Computer Science. Two students (LV&BBI) and two supervisors (HS&AG) from computer science were included in the project. From the outset, the aim was to make a game that could be played when walking on a treadmill, and this was a guiding principle for the rest of the design.

2. Prototyping

   A minimal viable product (MVP) was produced, following an iterative approach, including weekly proto-testing and adjusting and stage-based ease of use-testing. The MVP included a base of tasks, focusing on perceptual-, motor-, and mechanical constraints (Bovim et al., 2020). The MVP was then tested by investigating how gait parameters changed when executing the tasks of the game in a sample of healthy adults.
3. Validating

   The MVP was tested on 29 healthy, young adults (mean age 29 years old). Participants wore an accelerometer on their lower back to capture gait parameters (step length, cadence, walk ratio, and stride regularity in the anteroposterior, mediolateral, and vertical directions). As anticipated, gait patterns changed according to task: For example, regularity was low during the coin-catching task as the center of mass was shifted randomly to reach the coins, and regularity was high when participants used a more rigid movement pattern when balancing the ball. There was no increase in simulator sickness (Wüest et al., 2014). The validation phase was executed as a master thesis of Physiotherapy.
4. Evaluation

   Using the MVP as inspiration, an end-user panel of clinicians from the fields of physiotherapy, neurological rehabilitation, and psychiatry were included in a workshop focusing on potential tasks aiming towards their field of expertise as a part of a master thesis of Computer Sciences.
5. Design and development phase

   Based on the experiences from validation and evaluation, a new version of the game was developed, using a similar iterative approach as during prototyping, with some new tasks aimed at training motor-cognitive skills.

RESULTS

In 2020, the present version of VR Walk was finished. This is an HMD-based VR game designed for use on a treadmill. The game is set in an environment that resembles a Mediterranean area (**Figure 1**), and the main objective is to walk on a virtual path while avoiding obstacles and performing tasks of perceptual, cognitive, and motor characteristics (See "Tasks" section). A dynamic avatar of hand(s) and feet are included using hand controllers and HTC Tracker 2.0, replicating the user's real time movements of hands and feet. For all tasks except "Footsteps", only one hand controller is needed. Treadmill speed can be adjusted by either the player or therapist, with adjustment rates of 0.1 km/h. The game is only available using tethered VR, such as HTC Vive, Oculus Rift, etc.

Safety Measures

Several safety measures are embedded in the game. For the novel player, a virtual representation of the treadmill handrails is always visible for the player to grab on to when necessary. An experienced player may hide these for increased immersion. If the player is disoriented and heading towards one of the edges of the treadmill, a virtual grid-pattern appears, indicating the player to adjust the position. Treadmill handrails will also re-appear. The grid-pattern will disappear if the positioning is adjusted. If the player's position falls outside the defined area of the grid-pattern, the treadmill will automatically stop, and the player is requested to return to the "safe area" before the treadmill can be started again (**Figure 2**).

In addition to software features, external safety measures such as using a non-weight-bearing harness and close supervision are highly recommended, and each player is given thorough instructions (how to operate the hand controller(s), visual inspection of safety measures, etc.). New players also walk for a certain distance without any additional tasks, for familiarization with the virtual environment and treadmill walking.

Tasks

Based on the iterative design approach, six tasks with difficulty adjustments were developed (**Figure 3**);

1. *Full path*: The width of the path is equal to the treadmill width (100 cm).

   Increased difficulty: The width of the path is reduced by 30, 50, and 70 percent, or obstacles of large rocks can be placed on the path.
2. *Glass bridge*: A semi-transparent glass bridge simulated to appear approx. 200 m above the ground.

   Increased difficulty: Axe throwing at clusters of spheres that hang in the air, and "selective balls", where spheres that are shaped like skulls should be avoided, can be selected by the therapist.
3. *Coin collecting*: The player approaches coins that swirl in the air. The task is to catch the coins using the hand controller.

   Increased difficulty: Movement pattern and speed of coins can be adjusted from stillstand to extreme movement (2 m sideway and 1.5 m up/down), and "selective coins", where only gold coins are to be collected, can be selected by the therapist.
4. *Balance ball*: The player is holding a virtual disc in the hand with the hand controller. A virtual ball appears on the disc, and the player must balance the ball on the disc.

   Increased difficulty: The ball is on fire, and will melt the disc unless it is being bounced off the disc.
5. *Footsteps*: Virtual footsteps appear on the path, and the player is instructed to step on the footsteps. This task requires the player to wear foot trackers.

   Increased difficulty: The step length, step width, and between-step variability can be increased and decreased.
6. *Memorize*: A totem pole stationed by the path is to be memorized, and later physically puzzled in the correct order.

   Increased difficulty: Hight can be adjusted from 1–4 pieces, and the pieces may be individually painted in separate colors.

The player is given positive visual, audible, or/and haptic feedback on correctly performed tasks, and negative visual, audible, and haptic feedback when tasks are performed incorrectly. At the end of the game, a total score and subscores of each task are given.

FIGURE 1 | The virtual environment of VR Walk is set to a Mediterranian terrain.

User Interface

The main menu of VR Walk, with basic steps such as "start", "options" and "credits", is accessible both for the therapist *via* desktop and for the player directly in the HMDs. The desktop menu makes use of Unity's UI toolkit. Among other things, the toolkit includes buttons, sliders, toggles, and text fields, all of which can execute, and be accessed by, custom scripts. The therapist can use a standard mouse and keyboard. The menu accessible from the HMDs is placed in a world space position, and a laser pointer from the SteamVR plug-in is used to allow the player to interact with the UI elements.

In-game, the player can access a treadmill panel using said laser pointer. The treadmill panel is added to the visual representation of the treadmill's handrails and includes basic adjustments of speed and start/stop, live statistics of current speed, distance walked and distance remaining, and score of on-going tasks.

The desktop-based "therapist menu" includes the functions of "calibration" and "path builder".

Calibration

The calibration process takes full advantage of the precise positional data of the Lighthouse-tracked motion controllers. The controllers are placed on symmetrical markers on either side of the treadmill belt and the controller positions are registered (**Figure 4**). A vector is drawn between the two registered points. The cross product between this vector and a vector facing directly upwards in the virtual environment yields a new vector that is parallel to the treadmill band. This resulting vector is then reversed or left unchanged depending on the orientation and left/right assignment of the controllers.

Path Builder

The therapist can individualize paths using the Path builder (**Figure 5**). Here, all tasks can be added in chosen or random order. Further, each task can be defined using pre-defined settings of easy, medium, and hard, or in detail using added sliders. Detailed defined tasks can be saved for re-use later, as can full paths.

DISCUSSION

We have described an HMD-delivered exergame designed for treadmill walking. In this section, we discuss the elements of the game against relevant literature. First, we discuss some of the overall aspects of VR Walk, and then we discuss the specific tasks of the game.

VR Walk is situated in a life-like environment, with plants moving slightly in the breeze and mountains in the background, with realistic textures on the features of the game. The aim was to provide an attractive and soothing backdrop for the game and to add to the presence of the experience. Other games use more stylistic backgrounds, where the elements of the game are at the forefront (Giphart et al., 2007; Skjæret et al., 2015). It can be argued that realistic surroundings can be distracting, and that "cleaner" designs allow the player to focus on the tasks. It could also be argued that realistic environments would allow for greater transferability to real-life situations. This is

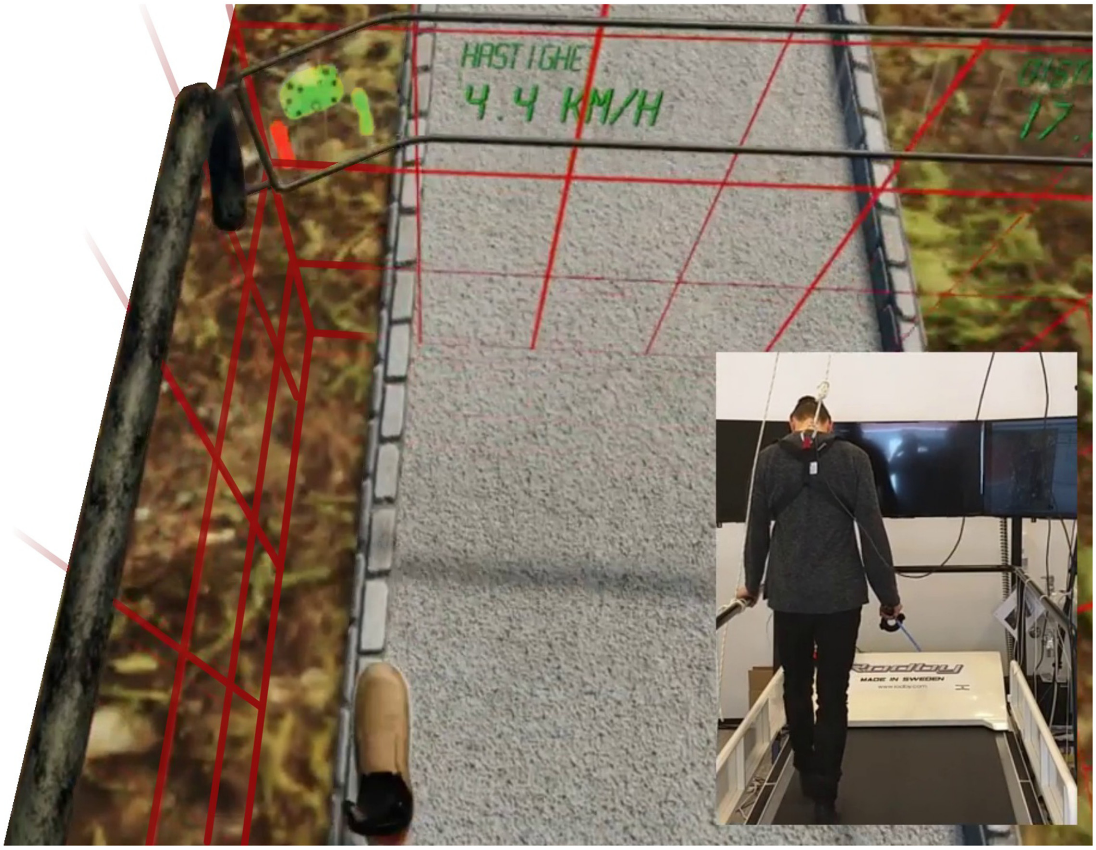

FIGURE 2 | When the player steps toward the limits of the game area, a grid is visualized. If the player steps past the game area, the grid turns red and the treadmill stops automatically. External safety measures such as harness and treadmill railing is recommended.

in line with principle no. 3 of Kleim and Jones' principles of neuroplasticity (Kleim and Jones, 2008), that the nature of the training experience dictates the nature of the plasticity. However, this is debatable regarding VR Walk, as it takes place in an environment that is specific to very few people. Busy streetscapes or suburban landscapes would likely be more relevant to the majority of players and should be considered in further updates.

When playing VR Walk, the player must walk. This is not entirely novel in exergaming contexts. Mirelman et al. (2016) and Shema-Shiratzky et al. (2019) have used exergaming during walking for both fall prevention purposes in older adults, and for cognitive and social functioning in adolescents with ADHD. The novelty of VR Walk is that the virtual environment is delivered through HMDs, making for a more immersive experience, and to our knowledge, very few games using natural walking (overground or treadmill) and HMDs exist. Although walking is often regarded as a relatively automated task, attention is still required, as evidenced by detriments in walking performance while doing an additional task simultaneously (Paul et al., 2005; Clark, 2015). Performing dual tasks, such as walking and exergaming can therefore be called "motor-cognitive training" (Mirelman et al., 2016; Herold et al., 2018). VR walk is a game that is designed for being played when walking, and as such should lend itself to gait rehabilitation purposes. However, it could also be argued that the game implicitly is a dual-task exercise, as all the tasks in the game are added to the task of walking. By this reasoning, the walking part can be seen as a tool for practicing complex tasks, which can be beneficial for many contexts, not just those where walking is involved.

On a general note, all the tasks of the game require anticipatory balance control, meaning that the players can adapt proactively and continuously to the tasks of the game. None of the tasks challenge reactive balance control, where the player would have to regain balance after unexpected perturbations (Winter, 1995). Reactive balance control has been found to be associated with falls in older stroke survivors (Mansfield et al., 2015). Virtual environment-based games offer the possibility for reactive balance control tasks in a safe environment: Objects could appear from different directions at random intervals, forcing the player to make quick avoidance movements. For further development of VR Walk, this option might be explored.

On a similar note, uncertainty is not a factor that has been explored in this exergame. Uncertainty is a much-used feature to increase engagement in games and can refer to for

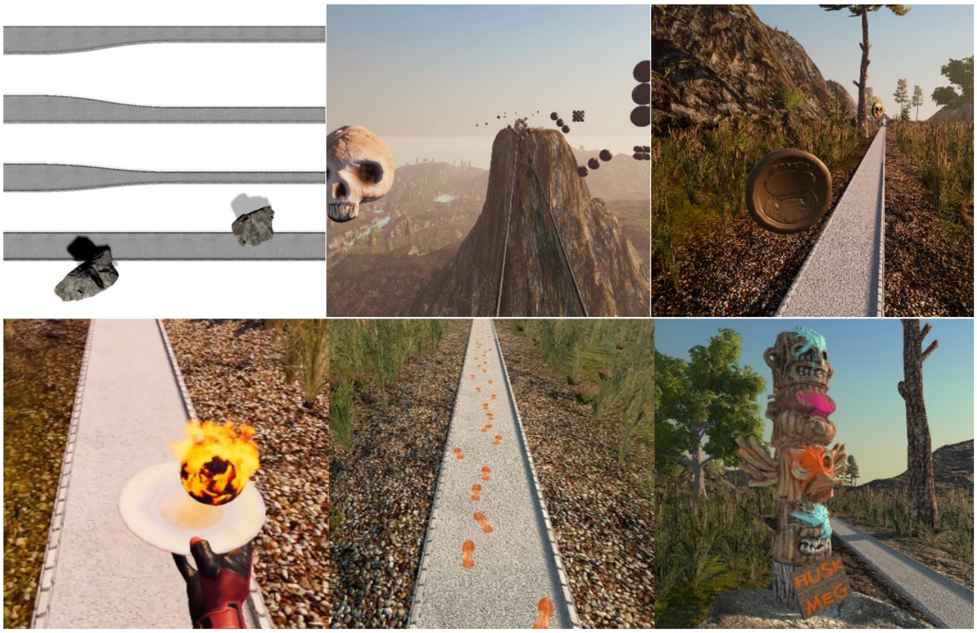

FIGURE 3 | The tasks of VR Walk (from upper left): Path adjustments. Glass bridge (with axe throwing). Coin collection. Balance ball. Footsteps. Memorize.

example unpredictability (uncertainty about what will happen next in the game element) or randomness (uncertainty about the order of what will happen in the game element; Li et al., 2020). Xu and co-authors showed that adding uncertainty in the game elements increased physical exertion in players (ibid). It could be argued that some of the tasks of VR Walk contain uncertainty, such as the flying-coins task, but uncertainty is not a feature that is systematically embedded in the game. Future versions of the game could use tasks that used for example unpredictability and randomness to a greater extent, and we are currently working on adding human figures that appear from the side or suddenly rise up to the environment. It should also be noted that the game is intended for clinical groups and older adults that may not have extensive gaming experience generally, and virtual reality experience specifically, and it may not be necessary to add many elements that increase exertion.

In the MVP of VR Walk, points were not awarded for the completion of the tasks, and there was very little possibility for progression of difficulty. We have not found studies that show whether player-engagement is enhanced by scoring and progression in rehabilitation, but intuitively, scoring systems and increasing difficulty are important for not getting bored. Studies of gamers show that certain features are important for video games to become engaging, such as challenges and appropriate feedback (Altamimi and Skinner, 2012). Although the context of rehabilitation is different than that of gaming for entertainment, at the core is still the ability of the game to engage and motivate users. We, therefore, view scoring, haptic feedback, and progression of difficulty as an important aspect of the game, both from a motivational point of view and for tracking of progression. Also, progression of difficulty is vital for individualizing the tasks.

FIGURE 4 | During calibration process, the hand controllers are physically placed on the treadmill as illustrated.

The Tasks and Their Rationale

In this section, we will discuss the specific tasks.

Players who are naive to the game or to immersive VR start with a familiarization walk without constraints or tasks. In data presented as conference proceedings, we found immediately increased gait variability when walking on a treadmill with HMD compared to walking without in adults. However, gait patterns returned to normal in a relatively short time, showing that healthy adults adapted well to walking with HMDs (Bovim et al., 2019).

Path Adjustment

In the first task, the path narrows down by 30, 50, and 70 percent. In mechanistic terms, balance is defined as keeping the line of gravity within the base of support (Pollock et al., 2000). During walking, the line of gravity routinely falls outside of the base of support when one foot is off the ground (Mansfield et al., 2015). By making the path narrower, the ability of wider step width is reduced, potentially making the base of support smaller also during double support. We have not found studies where the effect of narrow walking is studied alone or specifically with regards to reduction of fall risk or to improve balance. However, manipulation of the base of support is common in exercise programs focusing on for example fall prevention. In a systematic review, Sherrington et al. (2017) report that for fall prevention exercises to be successful, they need to be intensive and challenging. One of the features of challenging exercises was reported to be a small base of support. It could be argued that at 30 percent, the path is still 30 cm wide and that older adults tend to walk with step widths of approximately 10 cm or less (Hollman et al., 2011). Thus, there is potential for making this task even more challenging.

In experimental conditions, older adults perform worse at obstacle avoidance tasks than young adults (Galna et al., 2009; Chen et al., 2017), suggesting that this is a task that is relevant for rehabilitation settings (e.g., increasing balance or cognitive capacity). However, the nature of treadmill walking is to walk in one direction. We have included a condition where the player is to pass large rocks in the path, by stepping to the side, but it is our experience that players who have tried the game do not find this very difficult. It should be noted that Mirelman et al. (2016) used an obstacle negotiation task that involved stepping over virtual objects, which proved efficacious in preventing falls in older adults, and this is easier to integrate into a straight walking paradigm.

Glass Bridge

Crossing the glass bridge is different from the other tasks, as no other effort than walking is required. However, height exposure in virtual reality can be perceived as stressful as in physical reality (Simeonov et al., 2005), so walking can be seen as a challenge in itself. We have not found any studies on fall or balance outcomes after height exposure in virtual reality, but Peterson et al. (2018) have found that walking on a beam with virtual height exposure decreased dynamic balance and increased cognitive load in young adults, suggesting that this condition was challenging and could have a training effect. We found that gait regularity and walk ratio decreased when participants walked onto the glass bridge, i.e., they walked more unsteady and cautiously, but also that these gait characteristics returned to normal before walking off the bridge, suggesting that people adapt quickly (Bovim et al., 2020). For progression, players can throw an ax at objects that hang in the air. This necessitates players to look away from the drop and focus on the spheres, and as such, the height exposure feels less precarious and is really a different task more than a progression of difficulty. A better progression of the height exposure challenge would possibly be to start at lower heights and then gradually increase the height.

Coin Collecting

The coin-collecting task requires the player to touch flying and swirling coins with the hand-controller. This task is meant as a motor task, placing demands on eye-hand coordination (and is an added task to the task of walking). In the validating phase, the coin-catching task was the task that induced the most gait variability on the participant (Bovim et al., 2020). We suggest that due to the nature of the task, where coins come at different heights and at both sides of the player, and the player has to reach for the coins, the center of gravity is being continually shifted in the direction of the reaching arm, leading to larger stride-to-stride fluctuations than the other tasks. As such, the task has considerable biomechanical aspects. At high levels of difficulty, the coins follow largely unpredictable paths, adding some similarity to reactive balance control training. Further, it is possible to add a response-inhibition-task, where only golden coins should be touched, and gray skulls should be avoided. This is an additional effort that puts demand on executive function. Executive functioning is higher-order mental processing that allows us to concentrate, to self-regulate, and to adapt to new circumstances (Theill et al., 2011). Reduced executive functioning is associated with gait dysfunction and falls in older adults (Zhang et al., 2019), and is an important target for fall prevention strategies (Liu-Ambrose et al., 2013).

Balance Ball

The balance ball task is a manual task that involves keeping a ball on a disc that is held in the hand by the hand controller. Like the coin collecting task, this task imposes the need for cognitive resources and eye-hand coordination. However, while the coin-collection task requires the player to reach in different, random directions, the balance ball task requires the player to adopt a rigid and cautious gait pattern, as seen in the validation phase where gait regularity in the anteroposterior direction increased substantially from the coin-collection task (Bovim et al., 2020). We have not found earlier research about balance- or mobility-related benefits from training by walking with a rigid gait pattern, but suggest that practicing different gaits for different tasks and contexts is beneficial for an overall ability to adjust physical behaviors to different situations.

Footsteps

In the footsteps-task, virtual footprints appear on the ground in front of the player, and the player is rewarded points for hitting the footsteps with his own feet. Progression of difficulty can be achieved by altering step width, step length and by making the sequence of footsteps more variable. Foot placement accuracy is lower in older adults and is a relevant task for example fall prevention exercises (Hoogkamer et al., 2017). Gómez-Jordana and co-authors (Gómez-Jordana et al., 2018) used a similar approach for patients with Parkinson's disease, with the aim of improving gait performance by using the footprints as cues. In VR Walk, the difficulty is achieved by making gait patterns more challenging, in reality imposing

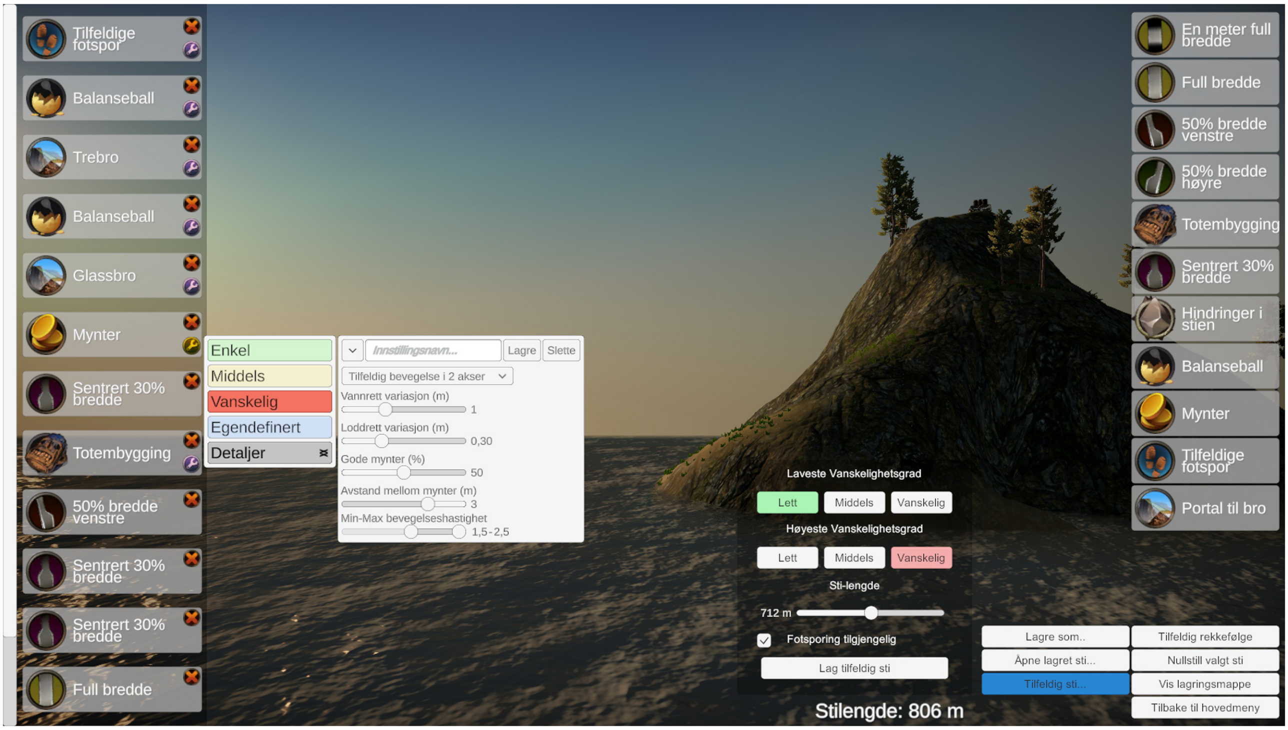

FIGURE 5 | The therapist/operator can access a detailed Path Builder and design individualized tasks and paths.

gait variability upon the player. This task forces the player to make rapid shifts of the center of mass, and there is a component of reactive balance control to this task. It should be noted that there are some issues with the accuracy of the HTC foot trackers, for example such as large offsets when tracking is lost (Niehorster et al., 2017). This could mean that the physical hits with the feet do not match the virtual footprints entirely. This emphasizes the importance of thorough calibration of the game space and sufficient tracking (base stations and lighting).

Memorize

VR Walk includes a memory task; when walking along the path, a sign appears saying "Remember me". The player then sees a totem pole with distinct heads on top of one another. Each head has a color. The heads then disappear, and after a 60 m walk (potentially including a separate task), the heads reappear, and the player has to stack them in the correct order, and give them a stroke of paint with a virtual paint brush with the correct color. The aim of this task is to challenge attentional capacity: The ability to walk and retain information in working memory at the same time. Dual task-exercising has been investigated in several studies, showing benefits on balance outcomes in multiple populations such as older adults and persons with neurological disorders (Fritz et al., 2015; Ghai et al., 2017; Martino Cinnera et al., 2021). The benefits are believed to arise from increased automatization of the motor task, and less need for executive resources (Clark, 2015; Fritz et al., 2015). The nature of the added task is important, and both semantic, arithmetic and manual tasks have been used in studies (Diamond, 2013; Leone et al., 2020). Nordin et al. (2010) showed that the cognitive-motor inference or dual task-cost of different added tasks (manual task, counting task, verbal task) had different impacts on gait parameters. In VR Walk, the additional task is to memorize two four shapes and three colors, and therefore relies more on processing and retaining visual information than the tasks in the aforementioned studies. Virtual environments are less bound by physical possibilities and allow for more diverse additional tasks than normal clinical settings, which in our opinion should be explored and refined further: For example, regarding this specific task in VR Walk, stacking and operating a paint brush add a manual aspect to the task. This could be considered a third task, which makes it quite complex. There is an argument that too high motor-cognitive interference may have negative effects in individuals with for example reduced cognitive capacity (Peterson et al., 2018). The inclusion of colors can therefore be removed for difficulty adjustment. Even less complex additional tasks could still be useful in later updates. In addition, the players are not given explicit instructions for prioritization, but the treadmill may give implicit prioritization; unless the player prioritizes walking, she will fall.

Limitations

In this article, we describe and discuss the rationale for the design and choice of tasks for VR Walk, without any data to substantiate the discussion. The MVP of the exergame has been tried on a convenience sample of healthy adults, with the aim of investigating how the tasks would affect gait. However, it is not clear how the exergame would be accepted in a clinical population, nor whether it would be efficacious in improving motor- or cognitive skills. Also, although the difficulty of the game can be adjusted, we do not have firm knowledge about how increased difficulty affects the player. For example, does a 30, 50, or 70 percent narrower path make users 30, 50, or 70 percent more unstable? Based on our observations of people who have tried the game, instability during this particular task appears to change in a non-linear way; a path that is 30 and 50 percent narrower seems well accepted, while 70 percent appears to induce changes in locomotion (less regular walking). This could suggest that 30 and 50 percent represent an attractor state and that 70 percent represent a (literally unstable) phase transition (Van Hooren et al., 2018). However, as we have no real-life data, this is conjecture. It also emphasizes that careful consideration should be put into how difficulty is progressed or regressed in the game, especially as the aim of the game is to provide tasks that can be specific to specific conditions.

Also, the overall design process is not grounded in a specific model, it is only inspired by the wide concept of the iterative design approach.

The target group for the game are individuals who need training or exercise for health purposes. While exergaming has been found well accepted among for example older adults (Nawaz et al., 2016), there may still be barriers for rehabilitation providers in providing technological services. Glegg et al. (2013) investigated the adoption of virtual reality for rehabilitation after traumatic brain injury among rehabilitation therapists, and found that the therapists were positive and had intentions to use the method, but scored lower on self-efficacy. In a scoping review, Glegg and Levac (2018) show that lack of knowledge and skills, and beliefs about capabilities and consequences were barriers to using virtual reality games in rehabilitation. This emphasizes an important clinical aspect of the game: That regardless of how well it may perform, the downstream uptake among rehabilitation professionals may be low. Clinicians may be hesitant due to the perceived lack of technical skills. Also, using the game has a practical and financial side; a treadmill is required, in addition to an adequate computer and a safety harness, as well as a room where the equipment will fit. Although not outlined in this article, the developers are focusing on how to implement the game into clinical practice, such as giving workshops and courses and identifying super-users who are motivated and preferably have experiences with exergaming. Hopefully, this can be helpful for more extended use of the game.

CONCLUSION AND CLINICAL IMPLEMENTATION

In this article, we have described the development of the exergame VR Walk, and discuss theoretical considerations behind the tasks in the game. On a general note, we believe that the game can offer engaging and motivating motor-cognitive training for balance and mobility, increasing fellow researchers' and clinicians' possibilities to reproduce and implement future relevant findings. Neither the effectiveness nor the efficacy of VR Walk has been tested in trials yet, but we intend to use the game in a feasibility study of balance exercises in older adults with hearing impairment[1], and we also plan to use it in a trial of children and adolescents with chronic disease. Further developments of the game are ongoing, using the design process that has been described.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

All authors contributed relatively equal to the development and execution of the project. LPVB and BBo contributed with theraputic knowledge and relevance, and manuscript. LV and BBl contributed mainly on the development on MVP and VR Walk, with HS and AG as supervisors and key persons of knowledge within the field of computer sciences. All authors contributed to the article and approved the submitted version.

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[1] https://clinicaltrials.gov/ct2/show/NCT04283279

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Experiences of Stroke Survivors and Clinicians With a Fully Immersive Virtual Reality Treadmill Exergame for Stroke Rehabilitation: A Qualitative Pilot Study

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Use of VR-games is considered a promising treatment approach in stroke rehabilitation. However, there is little knowledge on the use and expectations of patients and health professionals regarding the use of treadmill walking in a fully immersive virtual environment as a rehabilitation tool for gait training for stroke survivors. The objectives of the current study were to determine whether stroke survivors can use fully immersive VR utilizing modern HMDs while walking on a treadmill without adverse effects, and to investigate the experiences of stroke survivors and clinicians after testing with focus on acceptability and potential utilization in rehabilitation. A qualitative research design with semi-structured interviews was used to collect data. Five stroke survivors and five clinicians participated in the study and tested a custom-made VR-game on the treadmill before participating in individual semi-structured interview. Data were analyzed through thematic analysis. The analysis of the interview data identified two main categories: (1) *experiencing acceptability through safety and motivation,* and (2) *implementing fully immersive VR in rehabilitation.* Both stroke survivors' and clinicians enjoyed the treadmill-based VR-game and felt safe when using it. The stroke survivors experienced motivation for exercising and achievement by fulfilling tasks during the gaming session as the VR-game was engaging. The clinicians found additional motivation by competing in the game. Both groups saw a potential for use in gait rehabilitation after stroke, on the premise of individual adaptation to each patient's needs, and the technology being easy to use. The findings from this qualitative study suggest that a fully immersive treadmill-based VR-game is acceptable and potentially useful as part of gait rehabilitation after stroke, as it was positively received by both stroke survivors and clinicians working within stroke rehabilitation.

The participants reported that they experienced motivation in the game through safety, engagement and achievement. They also saw the potential of implementing such a setup in their own rehabilitation setting. Elements that enable safety and engaging experience are important to maintain when using a fully immersive VR-game in stroke rehabilitation.

Keywords: stroke, virtual reality, treadmill walking, rehabilitation, exergames

INTRODUCTION

Each year, 15 million people world-wide are affected by a stroke, making it the second most frequent cause of death (Ngandu et al., 2015) and the leading causes of disability in adults (Organization, 2003; Feigin et al., 2014). At the same time, there is a decline in stroke mortality due to better care and follow-up (Sarti et al., 2003), leading to an increase in stroke survivors that face impairments in physical, psychological and cognitive functions after the stroke (Engstad et al., 2012; Feigin et al., 2015). The incidence of stroke increases with age in both men and women, with ∼50% of all strokes occurring in people over the age of 75 and 30% over the age of 85 (Lui and Nguyen, 2018).

Loss of motor functions in part of the body is one of the most common impairments caused by stroke (Langhorne et al., 2011). In stroke survivors, regaining gait function is the most frequent self-stated rehabilitation goal (Bohannon et al., 1988; Maclean et al., 2000) and plays a vital role in regaining independence (Mant and Walker, 2011). Gait rehabilitation is typically performed as over ground walking or treadmill walking (Park et al., 2013). Treadmill walking is an attractive option as it allows for continuous walking of varying lengths in a safe and controlled environment. Moreover, working with repetitive tasks and adherence to training is essential to increase the amount of training to the levels necessary to regain function after a stroke (French et al., 2016). Likewise, getting immediate response and feedback on the performance is vital for the rehabilitation progress (Schmid et al., 2016).

Previous studies suggest that technology-based rehabilitation, such as serious games in virtual reality (VR), can be effective in rehabilitation after a stroke (Deutsch and Mirelman, 2007; Kim et al., 2011; Laver et al., 2017; Faria et al., 2018). VR is a computer-simulated environment imitating a physical presence in real or imagined worlds where one controls a visualization of one's body to perform different tasks (Howard, 2017). Here, one can improve both physical and cognitive function at the same time, as well as work with repetitive tasks and receive immediate feedback on activity performance. In the western world, VR and interactive video gaming have emerged as treatment approaches, and commercial gaming consoles are being adopted rapidly in clinical settings, also in stroke rehabilitation (Laver et al., 2017). Several studies have designed and tested VR-based systems for rehabilitation of individuals in the chronic phase post-stroke, but the focus has been mainly on upper extremity rehabilitation (Jang et al., 2005; Henderson et al., 2007). Although not as extensive as the upper extremity work, there have also been efforts to design and test VR systems to improve walking ability of people post-stroke (Jaffe et al., 2004; You et al., 2005; Fung et al., 2006; Mirelman et al., 2010), and VR-based intervention has been found to have advantage in improving balance training, gait speed and the quality of gait, compared to conventional interventions (Corbetta et al., 2015; Darekar et al., 2015).

In recent years, advances in technology have made it possible to provide a *fully immersive* VR-experience by using head-mounted displays (HMDs). This way, the wearer is visually and potentially audibly separated from the real environment (Waller and Hodgson, 2013). It has been suggested that HMD-based games are likely to increase the sense of presence, to be more engaging, and thereby have even greater potential for motor (re-)learning than less immersive forms of VR, such as desktop-based and cave automatic virtual environments (CAVE), (Guo et al., 2013). Particularly, the enriched environment and goal-oriented tasks with repetition that are possible in fully immersive VR stimulate the neuroplasticity of the injured brain in terms of interest and motivation which is important in rehabilitation after stroke (Levin, 2011). Immersive virtual reality extends the affordances of merely a screen, allowing the user to enter a different world surrounding them in three dimensions. This allows for interaction with elements while performing novel functions that might not be as easily achieved in traditional rehabilitation settings (Blascovich et al., 2002; Patel et al., 2006). However, evidence supporting the use of fully immersive VR in gait rehabilitation is largely lacking at the moment, as very few studies so far have focused on *fully immersive* VR for gait rehabilitation. Jaffe et al. (2004) designed a system using HMDs while walking at a self-selected speed on a treadmill secured with a harness. They found that virtual objects were just as effective as real objects in shaping the stepping characteristics of individuals with post-stroke hemiplegia. Likewise, Kim et al. (2017) found that both healthy older adults and people with Parkinson's disease were able to successfully use fully immersive VR during walking without adverse events. However, a fully immersive VR treadmill exergame can expose the individual to tasks beyond merely viewing a scene as in the study by Kim et al. (2017). A good example of this is the VR environment used by Winter et al. (2021) where players rebuild their companions world by walking on a treadmill. The technology can easily be used to create a multi-component environment where the player can perform more complicated tasks that focus on training specific functions while walking on a treadmill—although these could turn out to be too demanding and cause frustration or rejection (Laver et al., 2015). However, previous studies using VR for upper extremity training after stroke, found that both stroke patients and clinicians enjoyed using VR, valued the intensive and motivational character of VR training, and saw VR as an opportunity to participate in enjoyable activities bridging environmental or psychological barriers without serious adverse effects (Farrow and Reid, 2004; Lewis et al., 2011; Schmid et al., 2016). Also, Cortés-Pérez et al. (2020) found that immersive VR had higher effects on improving balance and reducing the risk of falls than conventional therapy in their study that aimed to assess whether an experimental protocol based on immersive VR therapy was valid for stroke rehabilitation. Clinicians also enjoy seeing patients' activity, engagement and motivation for activity (Schmid et al., 2016), which indicates that clinicians perceive VR as a complement to conventional methods for upper extremity rehabilitation after stroke as long as the training is guided by motor learning principles (Schmid et al., 2016). Also, walking on a treadmill using VR has been found feasible and acceptable by people suffering a stroke (Winter et al., 2021). These earlier studies provide promising indications that fully immersive VR on a treadmill may be applicable to rehabilitation after stroke. However, it has been emphasized that VR cannot replace the therapist's clinical reasoning or their social interaction with the patients (Schmid et al., 2016). If fully immersive VR is to be implemented widely as part of stroke rehabilitation, more knowledge is needed about the feasibility and acceptability of use by gaining insight from the experience of use from stroke survivors and health professionals working within rehabilitation. The current study explores stroke survivors' and clinicians' initial experiences of testing a fully immersive VR exergame on a treadmill for gait rehabilitation after stroke. Specifically, the objectives of this study were to determine whether stroke survivors found the fully immersive VR utilizing HMDs while walking on a treadmill acceptable without experiencing adverse effects, and to investigate the user experiences of stroke survivors and clinicians after testing with focus on potential utilization in rehabilitation after stroke.

MATERIALS AND METHODS

VR-Game

The game used in this study was a prototype of a treadmill-based Virtual Reality exergame developed by 3D-Motech called "*VR Mølle*" ("VR-Mill") [Unity, version 18.4], (**Figure 1**). The game uses a Virtual Reality headset (HTC Vive), an off-the-shelf treadmill (X-erfit 4,000 Pro Runner), and a 3D motion capture system (Qualisys AB, Gothenburg, Sweden).

The exergame is played by walking on a treadmill while performing cognitive exercises visualized in a VR headset. The player's movements are tracked by a 3D motion capture system through reflective markers attached to the feet. The player's feet are continuously displayed in the virtual world. The speed in the VR world is synchronized to the speed of the treadmill and can be adjusted during the game. The railing of the treadmill is visible in the game and can be used as support if needed. Moveable Lite Gait harness was installed to secure the player in case of a balance disturbance or fall.

The exergame consisted of six mini-games (**Figure 2**). The first two mini-games are introduction worlds to familiarize the user with walking on the treadmill while wearing the VR-equipment and setting the user-preferred treadmill speed for the exercise session (**Figures 2A,B**). The next three mini-games (**Figures 2C–E**) add different tasks where the user must aim at targets using head movements while walking. By completing these tasks, the user earns stars to be used for shooting at targets in the 6th and final mini-game (**Figure 2F**). The final mini-game was performed standing still and was not included as a part of the exercise in this experiment. The total walking distance was fixed at 620 m (100 m in each mini game, with 10 m walking before and after the entire game).

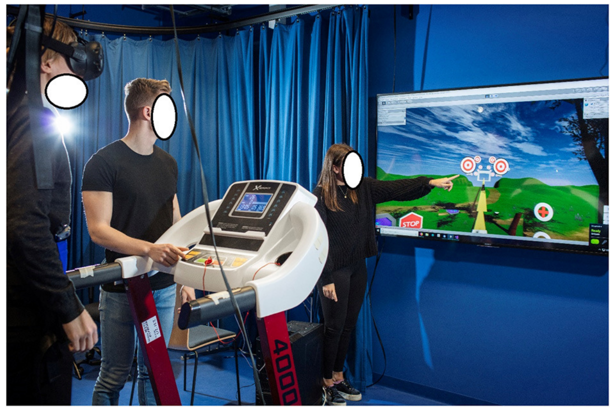

FIGURE 1 | VR-mill game setup. The player is wearing an HMD and a safety harness while walking on the treadmill. Clinicians or assistants can see a 2D image of the scene and the player's actions on the screen in front of the treadmill.

In the current study, the VR-game was played individually in a visualization and motion capture laboratory. A researcher, an assistant and a computer technician were present during the use of the VR-Mill. All participants played the six mini games on the VR-Mill once. As the game is set to each player's preferred gait speed, the playing time varies from person to person. Before gameplay, the treadmill system and exergame were demonstrated and explained to the participants. All participants were fitted with a safety harness (Lite Gait, USA) and the VR-headset, and the built-in safety features within the treadmill were demonstrated. These included user access to an emergency stop button and speed controls within the exergame (as illustrated in **Figure 2**). Virtual representations of the treadmill position gave the participants the possibility to locate and hold on to the treadmill handrails during the exergame.

Study Design

This was a qualitative interview study which instigated experiences with the VR-game among stroke survivors and clinicians working with stroke rehabilitation. Study participants performed the VR-game on the treadmill (as described above) before participating in a semi-structured interview at the venue of the VR-lab.

Recruitment

Two groups of individuals were recruited to the study. Stroke survivors were included in the study if the stroke had occurred more than 6 months before data collection, they were able to walk

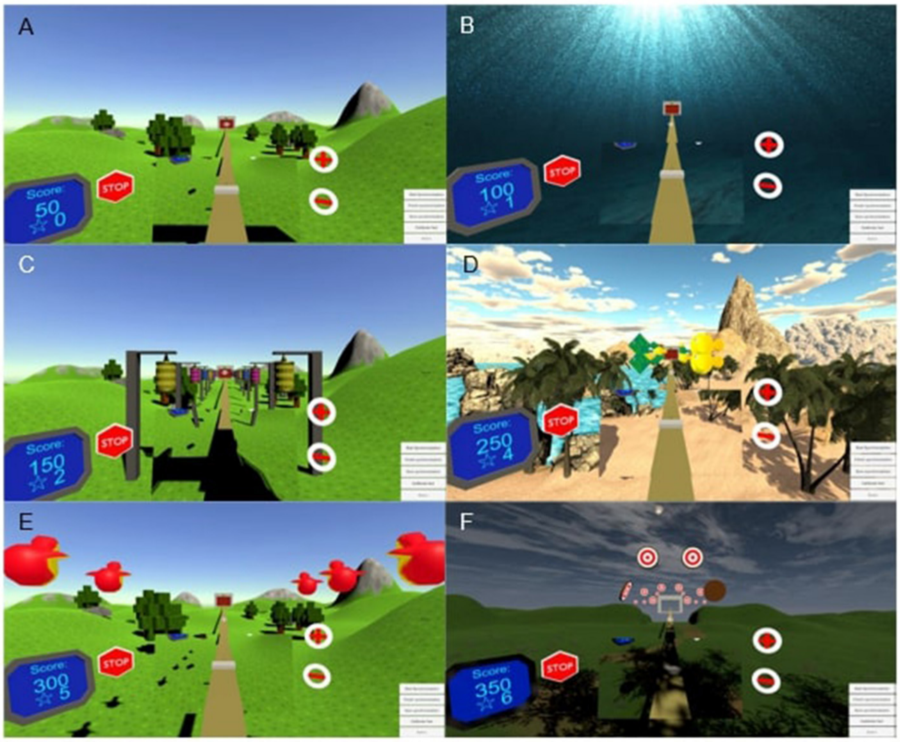

FIGURE 2 | (A–F) Screenshots from all six mini-games.

safely without a walking aid, could follow instructions, and had not been diagnosed with epilepsy, aphasia, or neglect. Clinicians who were included had to be employed in stroke rehabilitation at the time of data collection. All individuals were recruited through a rehabilitation center in Central Norway. Clinicians were invited to the study at their place of work, and the stroke survivors were contacted at the rehabilitation center during their stay or received a phone call from one of the employees at the center. Of the ten individuals who opted into the study, five clinicians and three of the stroke survivors received the information letter by mail and the two remaining stroke survivors received it directly from an employee at the rehabilitation center. Time and date for the try-out and the interview was planned individually with each participant. All study participants provided written consent prior to participating in the study.

Participants

Five stroke survivors and five clinicians participated in the study. Of the five participants that had suffered a stroke (mean age 59, range 40–75 years), two were women. Two stroke survivors had suffered an ischemic stroke, two a hemorrhagic stroke, and one had a combination of both types. Three had an affected right side where two had drop foot, and two had an affected left side. The five clinicians (mean age 42.8, range 36–48 years) consisted of four women and one man. Two were physiotherapists, two were occupational therapists, and the last was a speech therapist. Their work experience within stroke rehabilitation ranged from 2.5 to 20 years, with a mean of 8.4 years. None of the participants in the study had previous experience with VR-games, but all had experience from using a treadmill.

Data Collection and Analysis

Interviews were carried out in a separate room at the VR-lab during October 2018 to January 2019 by the first author (MEM). Each interview lasted from 18 to 43 min. Interviews were based on a semi-structured interview guide for each group of participants. Each interview guide was developed to investigate how participants experienced the use of the VR-Mill. Both interview guides focused on users' perspectives on safety, motivation, and potential adoption in their rehabilitation process. The development of each interview guide was based on theories on motivation (Deci and Ryan, 1985; Lillemyr, 2007). In addition, the clinicians' interview guide included questions on the potential for stroke rehabilitation and implementation (see **Table A1**). The first author (MEM) used the interview guide as a flexible framework for the structure of the interview. The interview guide had suggestions for follow-up questions if needed. All the interviews were audio-recorded and transcribed verbatim.

Data analysis was guided by reflexive thematic analysis which is described by Braun and Clarke (2020) as a flexible approach which could be used for experiential qualitative research. It allowed us to explore experiences of participants who were first time users of a treadmill VR-game designed for rehabilitation use, which meant that the experience was not part of their lifeworld but rather an experiment for the participants. Moreover, we chose reflexive thematic analysis since it is not resting upon one theoretical stand but allows the use of theory at several levels of the analysis (Braun and Clarke, 2020).

Reflexive thematic analysis includes a six-step process identifying prominent themes (Braun and Clarke, 2013). In the first step, the aim is to get an overview of, and get to know the data material (Braun and Clarke, 2013). The first author (MEM) read through all the transcribed interviews several times, marked paragraphs and took notes relevant for the following coding process. Three other authors (BV, MS, NS-M) read and took notes from a sample of the interviews and contributed to all stages of the analysis. One author (MS) has substantial competence, and all other authors some competence, in qualitative analysis, which has contributed to the validity of the results. The second step of the analysis is to generate initial codes. The transcribed interviews were read in detail and the material was coded. Codes were compared between interviews in order to get a sense of the whole, understand connections between the codes and to construct categories, main themes and sub themes (see **Table 1**). All authors participated in discussions about coding. In the next step, the aim was to systematize the data material under different themes (Braun and Clarke, 2013). During this step, we separated quotes from each of the two participant groups into two documents and examined for patterns across participants and variance between participants. To construct a theme, the codes had to have common traits and enlighten the theme from different perspectives. One example of codes for the theme *safety* was *safety harness, handrails, familiar equipment, no experience of dizziness, safe experience* (see **Table 1**). Step four, reviewing themes, consisted of refining the themes that was made in step three (Braun and Clarke, 2013). To do this, the first author made two mind maps to get an overview of all the themes. These were discussed by all authors to reach consensus on the valid constructions of each theme (see **Table 1**), and in defining and naming themes (Braun and Clarke, 2013). The initial codes "experiences with treadmill training," "safety harness," "handrails," "no experience of dizziness" and "safe experience" were grouped as the theme *safety*. The initial codes "fun game," "a feeling of being in the game," "new technology" and "collecting points" were grouped as the theme *motivation*. Initial codes concerning *implementing VR* were "cognitive function," "physical function," "goals for rehabilitation," "changes and improvement," and "when to use the VR-game in rehabilitation" (see **Table 1**). Subsequently, our analysis resulted in two main categories answering our objectives in the current study: (1) *experiencing acceptability through safety and motivation,* and (2) *implementing immersive VR in rehabilitation*. Category 1 consist of the subcategories "safety harness and handrails," "familiarity with the technology," "having fun" and "getting feedback." In category 2 the subcategories are "conditions relating to patient health," "training multiple functions simultaneously," "adaptation to individual users" and "organizational difficulties." The names of the subcategories are based on the initial codes in **Table 1**. In **Table 2** selected quotes from the data material are presented under each subcategory to exemplify the analytical findings (see **Table 2**).

TABLE 1 | Coding process of the reflexive thematic analysis.

Initial codes	Sub themes	Main themes
Safety harness Handrails No experience of dizziness Safe experience	Safety	Experiencing acceptability through safety and motivation
Fun game A feeling of being in the game New technology Collecting points	Motivation	
Cognitive function Physical function Goals for rehabilitation Changes and improvements When to use the VR-game in rehabilitation	Implementing VR	Implementing VR in rehabilitation

Ethics

The study was approved by the Norwegian Center for Research Data and the Regional Ethical Committee for Medical and Health Research Ethics and conducted in accordance with the Declaration of Helsinki. Informed written and verbal consent to participate were obtained from the participants. Participation was voluntary, and withdrawal was possible at any time without changes to ongoing or future rights to treatment. All information was processed without name or personal identification number, or any other information that was directly identifiable of participants. To preserve anonymity, identifiable places or situations related to the participants have not been provided in the article. Audio files were stored according to the ethical approval.

RESULTS

All participants completed the mini games without adverse events. The stroke survivors used a mean of 21.45 (range 18.11–31.39 min) min to complete the five-exercise mini-games, while the clinicians used a mean of 10.6 (range 9.5–15.33 min) min.

Experiencing Acceptability Through Safety and Motivation

Before the treadmill testing started, some of the stroke survivors had been concerned about whether they would be able to play the game, as they had seen younger people play games that looked too difficult for themselves. The participants' lack of experience with VR games led them to feeling unprepared for what they were about to do. However, after experiencing the VR-game, they expressed engagement and joy from participating. Receiving instructions prior to playing, and reminders about what was to come next while playing, contributed to mastering the game. No one experienced dizziness or motion sickness while playing, and the VR-headset did not hinder their movements.

TABLE 2 | Quotes to exemplify the analytical findings.

Categories	Subcategories	Quote number	Quotes	Anonymous identification
Experiencing acceptability through safety and motivation	Safety harness and handrails	*Quote 1*	*"... I was held up by the safety harness, then you didn't have to worry about falling down."*	Ron 75 years, person with stroke
	Familiarity with the technology	*Quote 2*	*"We use safety harness at [the rehabilitation center], so some of the equipment is familiar."*	Andy 37 years, clinician
	Having fun	*Quote 3*	*"That went by terribly fast when I think about the fact that I walked 620 meters. You hardly think about the walking. That was great, I thought it was fun."*	Miriam 64 years, person with stroke
		Quote 4	*"It's fun because it's new and different... You want to master those tasks, it's fun when you master it."*	*Robert 48 years, clinician*
	Getting feedback	*Quote 5*	*"It was fun collecting points and see that you could master the tasks in the game."*	Kate 53 years, person with stroke
Implementing immersive VR in rehabilitation	Conditions relating to patient health	*Quote 6*	*"There is a lot of cognitive training... need to pay attention to what's going on, the tempo and concentration and focus, a lot of those things get stimulated."*	Robert 48 years, clinician
	Training multiple functions simultaneously	*Quote 7*	*"... you need to use your head as early as possible, you know, concentrate. It's something entirely different than being at [the rehabilitation center], where they almost do your thinking for you, but, like the VR-game is something entirely different."*	Jim 48 years, person with stroke
		Quote 8	*"... choose different levels… you achieve one level, and maybe manage to get to the next level."*	Kate 53 years, person with stroke
	Adaptations to individual users	*Quote 9*	*"If I could increase or decrease the difficulty level… tailored to the person's skills, then it would be very useful."*	Andy 37 years, clinician
	Organizational difficulties	*Quote 10*	*"… if it takes too long to get the VR-game ready, the required effort exceeds the benefits … it's an important factor that the game doesn't glitch."*	Julia 41 years, clinician

Safety Harness and Handrails

The stroke survivors and the clinicians identified two common elements that contributed to the experience of safety: the harness and the handrails. When having these two elements, the stroke survivors felt safe and were not concerned about falling or injuring themselves (**Table 2**, quote 1). The clinicians also liked to know that they could hold on to the handrails whenever they wanted.

Familiarity With the Technology

A third element that contributed to safety for the stroke survivors was being familiar with using treadmills and having used treadmills in previous exercise and rehabilitation. The clinicians also focused on the control buttons visible in the VR-environment, which provided the possibility to stop playing when feeling uncomfortable. The opportunity to stop the game while playing could, according to the clinicians, lower the bar to try the game for persons that might feel unsure about this type of technology (**Table 2**, quote 2).

Having Fun

For the clinicians, the VR-game was perceived as new, exciting, and different from conventional rehabilitation, thereby holding the potential to motivate persons with stroke who are less motivated for traditional rehabilitation. They saw the game as motivating and fun to play, while at the same time having the potential to provide good quality exercise of gait function. For the stroke survivors, the VR-system provided a dynamic setting, and the mini games were fun to do while walking on the treadmill. Both the stroke survivors and the clinicians reported experiences of forgetting that they were walking on a treadmill or even forgetting themselves. For some of the stroke survivors, it was a surprise to learn that they had walked for a longer distance and longer duration than they had expected. This contributed to motivation and engagement (**Table 2**, quote 3).

Forgetting time and space was regarded as very positive by the clinicians as well, especially as it was experienced while exercising. Their stories contained feelings of being a part of the game and being in a different dimension. They described this as being in a state of flow, which they saw as a source of excitement, motivation, and joy for themselves as well as for their patients (**Table 2**, quote 4).

Getting Feedback

Visualization, such as lights that lit up when they hit the target, provided immediate feedback throughout the game. Some of the persons with stroke experienced the collection of points as a motivational factor. They also experienced immediate feedback as motivating, especially through the built-in reward system of collecting points. One of the stroke survivors could relate the last mini game to earlier experiences of shooting clay pigeons. Motivation increased even more when hitting the targets in the last mini game.

The competitive element of the game was motivating for the clinicians. They enjoyed competing with themselves (or others) to increase their scores. Clinicians expected that collecting points to use in the last mini game could motivate patients as future users of this game. An element that would motivate clinicians toward using this technology was the opportunity to measure progress during the rehabilitation process. The game's social aspect was also appreciated as it could lead to new conversations if users wished to share their experiences with friends and family (**Table 2**, quote 5).

Implementing Immersive VR in Rehabilitation

All participants in the study found the VR-game to be beneficial for implementation in rehabilitation services but highlighted the need to adapt specific play options to specific patients.

Conditions Relating to Patient Health

The stroke survivors felt good after completing the VR-game and thought that the game should be implemented in rehabilitation if cognitive and/or functional impairments were present. However, in their opinion, users would need a certain level of physical and cognitive functioning to master the game while walking. This was also pointed out by the clinicians. Abilities such as attention, concentration, memory, and the capability to plan what to do next were important, as one needs to pay attention to the tasks in the game while planning the next action. A possible obstacle of using the game system in the early stages of the rehabilitation process could be lack of concentration, dizziness, or wandering thoughts (**Table 2**, quote 6).

For the stroke survivors, challenges with concentration, attention, and memory while simultaneously walking was a new experience within rehabilitation exercises, and they found the VR-game to be an effective way to exercise.

Training Multiple Functions Simultaneously

Previous rehabilitation programs had typically targeted one element of physical or cognitive functioning at the time. During their own previous rehabilitation process, the clinicians had controlled the exercise and progress, but the VR-game allowed them independence, through challenging their concentration, attention and memory. The stroke survivors could see themselves using the game several times per week as part of their post-acute rehabilitation. They described the VR-game as different and exciting, which was important regarding variation and motivation during a rehabilitation process (**Table 2**, quote 7).

The stroke survivors gave feedback about possible changes and suggestions that could further improve the usefulness of the VR-game, such as training reaction time and adapting the difficulty level depending on the user's level of functioning. One suggestion was to avoid repetition with two similar worlds at the beginning of the game. Another suggestion was to implement more tasks in the mini games (depicted in **Figure 2**) to allow participants to reach additional difficulty levels (**Table 2**, quote 8).

Adaptation to Individual Users

Both the stroke survivors and clinicians indicated that it should be possible to tailor the game to each user to adapt to each player's individual level of functioning. Clinicians stated that they would have liked the opportunity to ensure that the exercise is in line with each rehabilitation program's goals and patients' goals. If the game could be adapted to different rehabilitation needs, the game would be relevant for even more patient groups and appropriate for a longer period of the rehabilitation stay. This could also justify a higher cost when implementing the game in a rehabilitation center. Furthermore, including tasks that resembled real-life tasks, such as stepping over objects, could also add relevance to the game. The clinicians thought this could increase balance training in the mini games (**Table 2**, quote 9).

Organizational Difficulties

Some of the clinicians described that having an VR-game like this at the rehabilitation center would be a dream, as they felt that VR-games like the one used in this study, could be useful for many of their patients, and could be combined with conventional rehabilitation. However, implementation would necessitate the possibility of adjustments and removing potential barriers to using the technology, such as experiencing problems with the system's technical components or using time to get the system ready. Clinicians did not want to risk wasting valuable time on dealing with technical issues that they could otherwise devote to their patients through conventional therapy (**Table 2**, quote 10).

DISCUSSION

This study explored acceptability and potential utilization of a fully immersive VR-game on a treadmill for gait rehabilitation after stroke through testing and interviews with stroke survivors and clinicians working in stroke rehabilitation. To the best of our knowledge, this is the first study to investigate both clinicians' and stroke survivors' perspectives regarding a fully immersive gait-specific VR-game. Analysis of the interviews identified two key categories of considerations for using VR-technology in stroke rehabilitation: experiencing acceptability through safety and motivation, as well as implementing immersive VR in rehabilitation. Both stroke survivors and clinicians enjoyed trying the VR-Mill game and felt safe when using it. The stroke survivors experienced motivation for exercise during the treadmill session as the VR-game was engaging, as well as experiencing achievement when fulfilling tasks during the game. The clinicians found additional motivation by competing in the game. Both groups saw a potential for use in gait rehabilitation after stroke, as long as the game could be adapted to each individual user and the technology would be easy to use.

Feeling safe during rehabilitation is of paramount importance for a person after stroke and needs to be addressed adequately (Laver et al., 2017). When using VR in neurological patients, visual or cognitive overload must always be avoided as this might act as a confounding factor (Lewis and Griffin, 1997). If being or feeling unsafe, the risk of falling and the fear of falling may significantly hamper the use and potential benefit of VR exercises. Despite the ample focus on the use of VR in stroke rehabilitation in recent years (e.g., De Rooij et al., 2016; Porras et al., 2018), there is sparse knowledge on the safety of using fully immersive VR games over a longer duration of time. Results in our study revealed that stroke survivors felt safe when walking on the VR-Mill for over 20 min and there were no adverse events nor any cases of motion sickness or dizziness. A safety harness, use of handrails and being familiar with walking on a treadmill were all highlighted as being important for feeling safe. The sense of control provided by the possibility to directly pause and stop the game was also mentioned as critical for feeling safe. Participants in the current study did not report any difficulties in understanding the tasks or comprehending the virtual world. This might be due to the game and virtual environment being specifically developed for this patient group to avoid confusion and misinterpretation while playing. Furthermore, the fact that the belt on the VR-Mill moved at the same speed as the virtual world may have prevented the motion sickness that is often experienced when there is a mismatch between visual and motor-sensory stimuli (Hettinger and Riccio, 1992). Similar results were found in a study from 2011, where older adults did not experience motion sickness or dizziness after using an HMD while walking on a treadmill (Parijat and Lockhart, 2011). Our findings are also in line with other research on motion sickness from using HMDs (Huygelier et al., 2019), although there might be some bias in our results, since the exposure time was relatively short, and increased exposure time increases the risk for experiencing motion sickness from HMD use (Duzmańska et al., 2018). The participants in this study did not report any difficulties in understanding the tasks or comprehending the virtual world. This might be due to the game and virtual environment being specifically developed for this patient group to avoid confusion, cyber sickness and misinterpretation while playing.

Motivation is seen as an important factor in adherence to the rehabilitation process as people with stroke have been found to be more likely to understand the nature and purpose of their rehabilitation when having high motivation (Maclean et al., 2000). In the present study, both clinicians and stroke survivors enjoyed playing the game, which is in line with previous research that confirms "fun experience" as a motivating effect of VR-based rehabilitation (Pallesen et al., 2018). Mastering the game, despite their lack of VR-experience, contributed highly to motivation for continuing the gameplay. While playing, the participants experienced a state of flow which was tightly connected to their enjoyment. Although previous studies have hypothesized that the sense of presence is stronger in an immersive environment than that in a non-immersive environment (Ventura et al., 2019), it is not clear whether reaching the flow zone is a consequence of the immersive nature of the exergame or if the immersive nature of the game has in any way impacted the state of flow. A controlled experiment where this is compared with the results from a non-immersive exergame is needed to understand this, which could be an interesting future study as we now have established the feasibility of such a setup. Another possible contributing factor is that the activities in the mini-games were goal-directed, which required concentration and appropriate cognitive and physical skills, which in turn made the tasks challenging yet attainable (Sweetser and Wyeth, 2005). It can be hypothesized from our study that an immersive approach that does not exceed the stroke survivors' skills, combined with the design of the mini-games (challenging activities with clear goals and immediate feedback that require skills and concentration) led participants into the flow zone. Using this type of technology is potentially very useful as part of stroke rehabilitation as it provides intensive, task-specific, multi-component training. The combination of VR and treadmill exercise can help to increase training volume and the courage and motivation to exercise for a more extended period (Sisto et al., 2002; Fung et al., 2006), which are essential to regain function after stroke. This was also seen as one of the main benefits of the system by the participants, especially the clinicians. The immediate feedback on performance was also considered encouraging and contributed to motivation, which was also shown in an earlier study by Kim et al. (2011). Furthermore, using fully immersive HMD-based VR on a treadmill provides new opportunities for visual independence from the support surface, which is highlighted as an important quality of adaptive behavior (Mulder et al., 2002). For example, in the three mini games C to E, the participants need to turn their heads and eye gaze in order to hit targets in the game. The headset was able to capture the head movements and only provided rewards when the head was turned properly, indicating that the players were able to take their eyes off their feet or support surface without becoming disoriented or falling down (Mulder et al., 2002).

Proper information on use and safety, as well as removing potential barriers related to using the technology itself, need to be addressed adequately to avoid frustration among clinicians and stroke survivors when implementing new technology into health services (Pallesen et al., 2018). The VR-Mill game in this study has a relatively complex setup, which could be an obstacle for its implementation into clinical rehabilitation services, as it is found that characteristics such as difficult set-up, discomfort, and lack of time and knowledge could hinder the use of technology (Levac and Miller, 2013; Nguyen et al., 2018). Furthermore, having individually tailored relevant tasks is vital. Tailoring tasks and adapting the challenge level is seen as a major potential for positive improvement (Levin et al., 2014; Shin et al., 2014). It is essential that the clinicians working within rehabilitation are aware of each patient's strengths and weaknesses (Schmid et al., 2016) and adapt the tasks and difficulty level in the game tasks to each specific rehabilitation goal in order to increase the motor (re)learning and improve the possibilities for a better rehabilitation outcome. One concrete suggestion that was raised in our study was to include balance training elements to increase the training of the lower limbs. As balance control is essential for optimal gait function (Winter, 1995), it would indeed be beneficial to add elements in the game that can be tailored to each individual to challenge postural control even more. Some participants also suggested adding some kind of social interaction in the game, which is considered a contributing factor to motivation and enjoyment (Sweetser and Wyeth, 2005). Finding ways to incorporate social interaction elements is therefore of interest for further development of VR technology.

This study is an initial step toward establishing fully immersive VR-games on a treadmill for gait rehabilitation after stroke. However, there are some limitations that need to be taken into account. First, the included study sample was small which could limit the interpretation of the results. However, this was the first time the VR-Mill was tried with stroke survivor and the provided information on experiences and motivation for further use in rehabilitation after stroke paves the way for testing on a broader scale and possible implementation of the system in a rehabilitation setting to assess effect on rehabilitation outcomes. Further, the study sample was constrained by availability and access to patients, and the participants were motivated and interested in testing such technology, which in turn could influence their feedback of the system toward being more positive. Additionally, the analytical approach with reflexive thematic analysis aims for validity through reflexive discussions of coding and construction of main themes. It could be a limitation to the validity of the results that we did not assess inter-coder reliability. Also, this study is merely based on subjective feedback from the participants and did not include standardized tools to measure acceptance. The fact that the results are linked merely to the first impression of using the system for a very limited amount of time might also be a limitation and an evaluation after sustained use would provide more robust indicators. However, as this was an explorative study where the aim was to gain a broader perspective of the possibilities of use in a rehabilitation setting more than just feedback on the system itself. Lastly, the experimental setting of the VR-Mill testing may have been a limitation compared to a study in a more real-life setting such as a rehabilitation clinic. Future studies should aim toward testing the technology in a larger prospective trial in real rehabilitation settings.

CONCLUSION

The current study provides valuable insights into the use of a fully immersive treadmill VR-game for gait rehabilitation after stroke. The game, VR-Mill, was positively received both by stroke survivors and clinicians working within stroke rehabilitation as they found the game to be both acceptable and potentially useful as part of gait rehabilitation after stroke. The results from the current study illustrate that a VR-game on a treadmill can be safe for the players as long as safety measures such as handrails and harnesses are available. Furthermore, using an immersive VR-game is motivating as the participants found it fun and enjoying as well as experiencing a feeling of flow when playing. As both clinicians and stroke survivors saw a high potential of implementing VR-games in clinical practice, future studies should aim to develop and improve the systems such that they can easily be implemented in clinical settings, where use of resources and feasibility can be further studied. In addition to ensure the safety of the players, future studies should also strive to add more quantitative measures of function like the number of steps taken or objects hit while walking on targets that can provide feedback to professionals in clinical settings to help guide rehabilitation. In addition, studies should strive toward gaining a better understanding of the relationship between immersion and motivation and include games that provides sustained motivation for use, preferably over a longer period of time.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because audio files and transcripts are not available for review because of the risk of participant identification. Requests to access the datasets should be directed to nina.skjaret.maroni@ntnu.no.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Regional Ethical Committee for Medical and Health Research Ethics, REC Central, Norway. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

EV, BV, and NS-M conceived the study. MM, BV, and NS-M formulated the research question and designed the qualitative study. MM and MS developed the interview guide and conducted the data analysis. MM and EV conducted the VR-Mill testing and drafted the manuscript. MM interviewed all study participants. All authors contributed to the manuscript text, edited, and approved the final manuscript.

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APPENDIX

TABLE A1 | Interview guides.

Interview guide for persons with stroke

1.	Could you please start by telling a little bit about yourself? (Age, occupation, your experiences in rehabilitation, earlier life)
2.	Could you tell me about how you experienced trying the VR-Mill? • Could you tell me why or why not you experienced it as safe to use? • Did you experience any form of dizziness or nausea while playing? • Have you ever used a treadmill earlier?
3.	Did you experience the game as meaningful or motivating to use? • Could you please say a bit more about what made the game motivating? • How did you experience the collecting of points during the game?
4.	Was there something lacking in the game that could have made the game more motivating or more fun to use? • Do you have any thoughts on how such games may contribute to motivation to do work outs in everyday life?
5.	What did you like and what did you not like about using the game?
6.	Would you like to use the VR-Mill one or several times more? • Why, why not?
7.	How did you experience the introduction to the VR-Mill ? • How challenging, how easy?
8.	What do you think about this form for training? • For gait function? • For balance?
9.	Could you tell me about your earlier experiences with computer gaming or Virtual Reality? • How did your previous experiences with such technology affect today's testing? Did it (not) affect you?
10.	In your opinion, for whom is this form of rehabilitation suitable (i.e., patients)? For other persons you know, or for other groups?
11.	Before we end the interview: would you like to add something to any of the questions, or are there any important subjects that we haven't touched upon yet? Thank you for your participation.

Interview guide for clinicians

1.	Could you please start by telling a little bit about yourself? (Occupation, work experience, age)
2.	How did you think it was to use the VR-Mill? • Did you experience it as safe? • As meaningful? • As motivating?
3.	How did you experience the introduction to how the VR-Mill works? • How challenging / how easy?
4.	In your opinion, in which way can the VR-Mill be used by persons with stroke with reduced gait function? • Should some features of the VR-Mill or game be changed? • Which elements are most important for the usability of the VR-Mill?
5.	What did you like and what did you not like about the gait training while using the VR-Mill? • Why?
6.	Why or why not would you recommend this training method to your patients?
7.	In which way could the VR-Mill be used at your workplace? • What are the potential positive effects of implementing it? • What are the potential negative effects of implementing it? • Do you see any barriers for implementing it at your workplace?
8.	To which groups of patients would you recommend this form of rehabilitation?
9.	Do you have any previous experiences with VR or computer gaming?
10.	Before we end the interview: would you like to add something to any of the questions, or are there any important subjects that we haven't touched upon yet? Thank you for your participation.

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The VITAAL Stepping Exergame Prototype for Older Adults With Major Neurocognitive Disorder: A Usability Study

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Purpose: This study investigates the usability of a stepping exergame in older adults with major neurocognitive disorder (MNCD) residing in a long-term care facility.

Materials and Methods: A mixed methods study was conducted. Participants played exergames for 30 min on one try-out session. During the exergames, the think aloud method was used, and field notes were taken by the facilitator. Following the exergames, participants completed the System Usability Scale (SUS) and a semi-structured in-depth interview about usability including their personal experiences. Audio files were transcribed and a thematic content analysis of the think aloud data, field notes and interviews were performed using NVivo 12.

Results: Twenty-two participants with MNCD were included [mean age = 84.3 ± 5.5 (70–95) years; 81.8% women; Short Physical Performance Battery score = 7.5 ± 3.2 (1–12), Montreal Cognitive Assessment score = 11.9 ± 4.4 (2–19)]. System usability was rated “ok to good” with a mean SUS score of 57.8 (*SD* = 12.3) with scores ranging from 37.5 to 90.0. Five main themes emerged from the thematic content analysis: (1) perceived user friendliness and acceptability of the exergames; (2) interactional experience; (3) motivational factors; (4) training modalities; and (5) risks. There were no adverse events nor dropouts.

Conclusion: Participants evaluated the usability of the exergames positively. The results indicate that the stepping exergame is usable in older adults with MNCD.

Keywords: active videogame, dementia, feasibility, motivation, physical activity, residential care, serious game

INTRODUCTION

The number of older adults with major neurocognitive disorder (MNCD) is increasing, primarily driven by population aging (Alzheimer's Disease International, 2019). MNCD is a clinical syndrome marked by cognitive decline, motor deficits and psychological and behavioral problems (LoGiudice and Watson, 2014). Older adults with MNCD often require added assistance with their activities of daily living (Arvanitakis et al., 2019) and this can ultimately lead to the displacement to a long-term care facility (Forbes et al., 2015). This is imposing a compelling burden on health care systems and has resulted in MNCD being considered a global public health priority (WHO, 2016). The burden of MNCD on health care systems is further compounded by a high risk of falling and associated injuries and disability (Sharma et al., 2018).

In order to reduce the risk of falling in older adults with MNCD residing in long-term care facilities, physical activity should be an important component of the multidisciplinary approach (Forbes et al., 2015; Vancampfort et al., 2020). There is compelling evidence that physical activity improves strength, endurance, balance, gait stability, gait speed, and overall wellbeing in older adults with MNCD (Forbes et al., 2015; Groot et al., 2016; Lam et al., 2018). Currently, clinical practice guidelines do not refer to combined cognitive and physical training programs (Laver et al., 2016; Shaji et al., 2018). This is surprising as not only a decline in physical functions is responsible for gait impairments and higher risks of falls, but also impaired cognitive performance including impairments in executive functioning (Holtzer et al., 2006; Yogev-Seligmann et al., 2008; de Bruin and Schmidt, 2010; Segev-Jacubovski et al., 2011; Mirelman et al., 2012). More recently, the prevalence of coexisting physical limitations and cognitive decline, described as motoric cognitive risk syndrome, has been estimated to be 10% in aging adults (Meiner et al., 2020). To slow down the cognitive and physical decline, and to prevent falls, combined motor-cognitive interventions which are adapted to the participants' individual needs might be useful (Pichierri et al., 2011; Bamidis et al., 2014; Eggenberger et al., 2015). A promising option for such a simultaneous cognitive-motor training is exergame training (de Bruin et al., 2010). Exergames are videogames that require movement in order to play the games (Stanmore et al., 2017). Previous studies have found that exergaming improves gait speed, mobility, balance, and cognitive functions, and reduces apathy and fear of falling in older adults with MNCD (Dietlein et al., 2018; Swinnen et al., 2020; Robert et al., 2021). Another advantage is that exergames are engaging and might overcome low adherence rates that are often reported in physical interventions for this population (Forbes et al., 2015; Ben-Sadoun et al., 2016).

Stepping exergame training is feasible and engaging in older adults with MNCD in long-term care facilities (Swinnen et al., 2020). Stepping exergames require participants to stand upright and perform steps, which directly addresses gait and balance (Kappen et al., 2018). Exergaming in an upright standing body position also enhances processing speed and attentional selectivity (Rosenbaum et al., 2017) and influences visual working memory performance (Dodwell et al., 2019). However, compared to seated cognitive games, exergames might impose a higher risk of falling than seated exergames. Currently, safe stepping exergame programs designed for older adults that are portable and affordable are still lacking. In order to fill this gap, an international research group developed a prototype of an individualized multicomponent stepping exergame training solution for geriatric rehabilitation (VITAAL, 2020). This project, entitled VITAAL, was launched in May 2018 and is funded by the European Commission as a part of the Active Assisted Living Program (AAL Association, 2020). The developed solution consists of two wearable sensors and a web-based interface that allows a direct follow-up and data processing by healthcare professionals. The system aims to provide evidence-based motor-cognitive training with high usability and easy setup in the clinic and at home.

However, in order to develop a user-friendly and acceptable training solution, end user involvement is required. Older adults with MNCD are often still able to communicate their opinions about what is important to them (Cahill and Diaz-Ponce, 2011). Researchers have previously recommended an end user participatory design with direct involvement of older adults with MNCD throughout the whole development process (Meiland et al., 2012). It has been highlighted that older adults with MNCD can contribute to establishing technological solutions that support them in the self-management of their symptoms and challenges in daily living, as well as contribute to the development by providing useful feedback, also in long-term care facilities (Span et al., 2013; Kort et al., 2019).

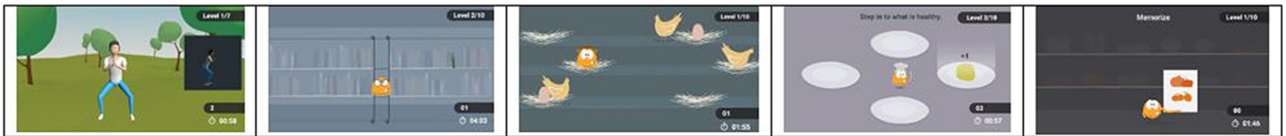
Therefore, the aim of this study is to investigate the usability of the VITAAL exergame prototype through a mixed methods design that combines observations, the think aloud approach, semi-structured interviews, and a system usability scale in institutionalized older adults with MNCD. The combination of both quantitative and qualitative data provides a full picture of the users' perspectives. A secondary aim is to investigate whether, and to what extent, the variance in the system usability score can be predicted by the variance in age, gender, cognitive functioning, and lower extremity functioning in institutionalized older adults with MNCD.

MATERIALS AND METHODS

A mixed methods design was used. The Consolidated criteria for reporting qualitative research (COREQ) framework was implemented (Tong et al., 2007). The trial was registered in ClinicalTrials.gov (Identifier: NCT04664920).

Participants and Procedure

Over a period of 1 month, all residents of long-term care facility de Wingerd in Leuven, Belgium, with MNCD were screened for inclusion. Possible causes of major neurocognitive disorder eligible for inclusion were vascular dementia, Alzheimer's disease, mixed dementia, Parkinson's disease, or Lewy body disease, as well as unspecified, as stated by the criteria of the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders



Outdoor	Library	Mommy chicken	Healthy food	Shopping list
Tai-Chi inspired strength training	Balance training	Inhibition control	Inhibition control	Short-term memory
Player imitates movements of an avatar instructor	Player avoids books from falling through multidirectional stepping	Player collects eggs while avoiding mommy chicken	Player points out healthy food and avoids unhealthy food	Player indicates whether the shown items correspond to the previously memorized shopping list

FIGURE 1 | Game description.

(DSM 5) (American Psychiatric Association, 2013). Diagnoses were made by the treating psychiatrist. Additional inclusion criteria were age ≥60 years; visual acuity with correction sufficient to work with a TV screen; a minimum stay of 2 weeks in the long-term care facility at the time of inclusion and being physically capable of doing stepping exercises. Subjects manifesting one or more of the following criteria were excluded from the study: any unstable health condition which, according to the American College of Sports Medicine Standards, might lead to unsafe participation (ACSM); and mobility impairments that didn't allow to play the exergame. All eligible participants played the exergame for 30 min on one try-out session. During the exergame performance, the think aloud method (Ratcliffe et al., 2019) was used, and field notes were taken by the observer. After the exergame performance, participants completed the System Usability Scale (Brooke, 1996) and a semi-structured in-depth interview concerning the usability of the device. To describe the population more in detail, participants completed the Montreal Cognitive Assessment (MoCA) (De Roeck et al., 2019) and the Short Physical Performance Battery (SPPB) (Guralnik et al., 2000; Fox et al., 2014) prior to the exergame. Their comorbidities, indoor mobility, fear of falling, and level of physical activity prior to participation were investigated. The protocol was approved by the Medical Ethics committee of UZ Leuven (registration: S63304/B322201941828). Written informed consent was obtained from the participants according to the Declaration of Helsinki. No compensation for participation was given.

VITAAL Exergame Prototype Session

Participants individually performed one single exergame session using the VITAAL prototype, which is an innovative, comprehensive system for geriatric rehabilitation and treatment in geriatric healthcare. The VITAAL solution implements personalized training programs based on interventions for mobility impairment, urinary incontinence, and cognitive impairment. The exergame mainly consists of three components: strength training, balance training, and cognitive training (VITAAL, 2020). For strength training, a combination of classical strength exercises and Tai Chi-inspired movements are included. Since Tai Chi is mainly performed in a semi-squat posture, a large load is placed on the muscles of the lower extremities. For balance training, step-based training is included, as the execution of rapid and well directed steps has been shown to be effective in preventing falls (Kattenstroth et al., 2013; Merom et al., 2013; Okubo et al., 2016). Both Tai Chi-inspired exercises and step-based exercises, combined with challenging game tasks, provide a holistic training requiring motor functions, cognition, and mental involvement (Gajewski and Falkenstein, 2016; Lim et al., 2019). Some cognitive training is already included in these training components as they represent simultaneous cognitive-motor interaction and require motor and cognitive functions. Specific attentional and executive functions are important for walking abilities and safe gait (Holtzer et al., 2006; Yogev-Seligmann et al., 2008; de Bruin and Schmidt, 2010; Segev-Jacubovski et al., 2011; Mirelman et al., 2012). Therefore, the VITAAL exergame explicitly targets these neuropsychological functions (selective attention, divided attention, inhibition/interference control, mental flexibility, working memory). See **Figure 1** for an overview of the different minigames and the focus of training per game. To maximize the benefits for participants, the exergame implements some basic general training principles: feedback, optimal load of task demands, progression of difficulty and high variability (Healy et al., 2014). The system set-up was developed to be easily applied with limited technical equipment and knowledge in long-term care facilities or in clinics. As a web-based exergame, it is designed to run anywhere if there is a Bluetooth and internet-enabled device connected with a screen (e.g., PC, laptop, tablet, etc.). The front-end is designed for large screens and is ideally visualized on a TV screen. The system is supported by a backend (main server supporting the whole service and data storage), a web portal (with information about interventions, sessions, results per session or over a specific period, etc.) and two wearable inertial sensors for measuring the stepping movements and game navigation. The web portal enables a follow-up of the personalized training intervention and provides relevant data in the rehabilitation process for researchers or healthcare providers. The two inertial sensors are placed on the shoes and are capable of sensing accelerations and angular rotations caused by movement. They communicate via Bluetooth with the software running on the web-enabled device. Participants played all the minigames that were available in this prototype, namely a minigame focusing on Tai Chi-inspired strength training (i.e., 'outdoor'), two minigames focusing on balance training (i.e., 'library' and 'mommy chicken'), a minigame focusing on inhibition control (i.e., 'healthy food'), and an minigame focusing on short-term memory (i.e., 'shopping list'). The design and development of these VITAAL minigames considered inputs from older adults, resulting from the investigation phase of the project (AAL Association, 2020), from the feedback obtained in a previous study (Guimarães et al., 2018), and from a multidisciplinary team, including movement scientists, clinicians and game designers. Movement scientists and clinicians agreed that an exergame mostly based on the execution of multidirectional steps would fit the needs of the target population the best. Users should also be able to perform multidirectional steps while responding to specific cognitive tasks, or contracting the pelvic floor muscles, which could largely improve the outcomes of the training. Considering that most daily life activities require simultaneous performance of physical and cognitive functions, combining physical and cognitive exercises in a single exergame solution could potentially boost the benefits of the exergames (Sauro, 2011). The design team on its turn aimed to motivate and engage the player by balancing challenge and fun as follows: (i) distributing types and number of exercises by several minigames with different scenes and goals to promote variety and avoid monotony, (ii) adapting the difficulty level of each game according to the individual in-game progression in order to prevent frustration and foster learnability (although this option is not yet available in the current prototype), and (iii) providing one single instruction and focus at a time to avoid an overwhelming experience (Sauro, 2011). The participants played the exergames autonomously and the facilitator (a physiotherapist) only intervened when help was required. An example of the system set-up is included in **Figure 2**.

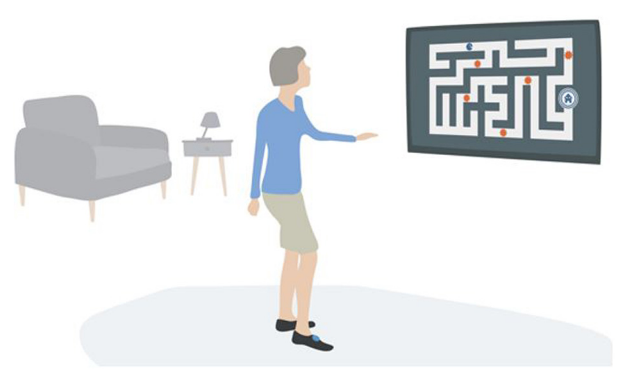


FIGURE 2 | System set-up.

System Usability Scale

After the exergame session, the System Usability Scale (SUS) was completed (Brooke, 1996). It is a commonly used scale for exergame evaluation and provides a global view of subjective usability of a product or a system. The SUS consists of ten questions/items which are scored on a 5-point Likert scale, ranging from 1 (strongly disagree) to 5 (strongly agree). In the SUS, five questions have a rather negative connotation and five have a positive connotation. The evaluation results in a total score, provided in a scale from 0 to 100. The score is calculated by subtracting one from the user responses for items with a positive connotation (items 1, 3, 5, 7, and 9) and by subtracting five from the user responses for items with a negative connotation (2, 4, 6, 8, and 10). This scales all values from 0 to 4, with 0 being the most negative and 4 the most positive response. The converted responses were multiplied by 2.5 to convert the scale from 0 to 100. SUS scores below 25 correspond to a worst imaginable system; scores from 25 to 39 correspond to worst imaginable to poor; scores from 39 to 52 correspond to ok; from 52 to 73 correspond to ok to good; scores from 73 to 85 correspond to good to excellent and from 85 to 100 corresponds to excellent to best imaginable (Sauro, 2011). The SUS is reliable and valid in non-clinical adults (Brooke, 1996; Tullis et al., 2008). Previous studies have reported internal reliability with Cronbach's alpha values between 0.79 and 0.97 (Finstad, 2010; Dianat et al., 2014). The convergent validity with other measures of perceived usability were acceptable. Regarding exergames, SUS provides information on whether older adults are confident playing the minigames, whether they desire to use the exergames frequently, and whether the exergames are easy to use for cognitive training and physical activity.

Think Aloud Method

Participants were encouraged to explain their views and experiences during exergaming through a think aloud approach (Ratcliffe et al., 2019). The think aloud approach is a common observational technique for eliciting insight into the users' thinking process while actively performing a task (Eccles and Arsal, 2017; Ratcliffe et al., 2019). Participants were encouraged to say everything that came to their mind while performing the exergame activities. Field notes were taken during and after exergaming performance to complement the information gained from the think aloud approach. The observer wrote down the user actions for each of the tasks, as well as all the problems that occurred. It has been previously demonstrated that the think aloud method is an appropriate method to engage older adults with MNCD as co-creators of solutions that accommodate to their needs (Kort et al., 2019).

Semi-Structured Interview Regarding the Participants' Exergame Experiences

A semi-structured interview was executed after the exergame to acquire the participants' experiences with the exergame. The interview focused on the qualitative evaluation of the user's gameplay experiences related to the body movements and the virtual game scenario. During the interview, no notes were taken in order to fully focus on the participants' verbal and non-verbal communication. The recorded interviews lasted between 3 and 11 min (mean 6 min). The interview guide is included in **Supplementary Material 1**. The interviewer was also the person that observed the exergame session. Therefore, the interviewer and participant were familiar with each other. Every interview was recorded and fully transcribed to a written form. Transcripts were not returned to participants for comment or correction. Guidelines for ethical and methodological issues in qualitative research in older adults with major neurocognitive disorder (Hellstrom et al., 2007; Beuscher and Grando, 2009) were applied. The interviewer had a respectful attitude, made eye contact when appropriate, used a calm voice, and avoided contradicting participants' statements or asking about details. The interviewer considered the communication challenges – such as word-finding difficulties, abstract reasoning, memory deficits, fluctuating awareness, attention, and concentration – by allowing sufficient response time, and gently redirecting the dialogue when needed.

Montreal Cognitive Assessment

Participants completed the Montreal Cognitive Assessment (MoCA) before the exergame try-out. The MoCA is a paper and pencil test that assesses memory, language, executive functions, visuospatial skills, attention, concentration, abstraction, calculation, and orientation. The scores range from 0 to 30, with higher scores indicating better cognitive functioning. The MoCA has good construct validity (r-values range from 0.46 to 0.75) (Freitas et al., 2012), inter-rater reliability (r = 0.97), test–retest reliability (r = 0.88) and internal consistency (Cronbach's α = 0.89) in older adults with MNCD (De Roeck et al., 2019).

Short Physical Performance Battery

Prior to the exergame try-out, the SPPB was administered. The SPPB assesses gait speed, balance, and lower limb strength (Guralnik et al., 1994; Fox et al., 2014). It is composed of three subtests; a standing balance test, a short 4-m walk at usual pace (Kim et al., 2016), and 5 chair rises. The maximal total score is 12 and higher total scores indicate a better lower extremity functioning. The reliability of the SPPB is high in older adults with MNCD, with intraclass correlation coefficient values ranging between 0.82 and 0.92 (Guralnik et al., 2000; Ostir et al., 2002; Olsen and Bergland, 2017). The SPPB is highly predictive for disability in older adults (Guralnik et al., 2000) and the internal consistency is acceptable (Cronbach's α = 0.76) (Guralnik et al., 1994).

Data Analysis

Continuous data were tested for normality using the Shapiro–Wilks test and found to be normally distributed. Descriptive statistics (means and standard deviations) were used to provide general information on the study outcomes. To aid management and analysis of the think aloud method, field notes and interviews, the NVivo 12 Microsoft software for qualitative data analysis (QSR International Pty Ltd., VIC, Australia) was used (McLafferty and Farley, 2006; Zamawe, 2015). Individual interviews, field notes and think-aloud data were transcribed in Microsoft Word format and afterward inserted into one project in NVivo 12. A thematic analysis of this project was performed through six consecutive steps (Braun and Clarke, 2006, 2014). The first step in the analysis consisted of repeatedly reading the transcripts and listening to the interview recordings to obtain further information from the tone of voices and pauses. Next, initial codes were created by open coding – the process of indexing or categorizing the text to establish a framework of related ideas. Subsequently, the residual data were examined through axial coding, which is relating codes to possible sub-codes to form a more precise and complete explanation. Codes with similar content were merged. The categories that remained were further interpreted and abstracted into the remaining themes. Although the observations and interview transcripts in NVivo 12 formed the primary data set, the SUS scores were investigated separately. After these steps, a composite description of the participants' perspectives on using the exergames was written, while using quotes to underpin the interpretation. A backward stepwise multivariable regression analysis was performed to evaluate independent variables (i.e., age, gender, MoCA and SPPB total score) explaining the variance in SUS. To test for multicollinearity, a variance inflation factor was computed for each independent variable in the model. Values above 3 were used to indicate a multicollinearity problem in the model. A priori, a two-sided level of significance was set at $P < 0.05$. Statistical analysis was performed using the statistical package SPSS version 28.0 (SPSS Inc., Chicago, IL, United States).

RESULTS

Participants

Thirty-three of the 147 residents in the long-term care facility were eligible. Main reasons for exclusion were limited comprehension due to an advanced stage of MNCD, the use of a wheelchair, or being bedridden. Eleven residents refused as they were not interested. Therefore, in total 22 participants were enrolled in the study. They had a mean age of 84.3 $\pm$ 5.5 (70–95) years, a SPPB score of 7.5 $\pm$ 3.2 (1–12), and a MoCA score of 11.9 $\pm$ 4.4 (2–19). 81.8% of the participants were female. **Table 1** gives an overview of the characteristics of the included participants. A more detailed description of the participants' individual characteristics is provided in **Table 2**. None of the participants suffered adverse events during or after the exergame session.

System Usability Scale

The mean rating given to the VITAAL exergame by participants was 57.8 (SD = 12.3) with total scores ranging from 37.5 to 90.0. The mean SUS score of 57.8 corresponds to a system that is considered ok to good (Sauro, 2011). The SUS scores per participant are provided in **Table 3**.

TABLE 1 | Characteristics of the included participants (n = 22).

Age, median	85 (70–95)
Women, n (%)	18 (81.8%)
Montreal Cognitive Assessment (0–30), mean ± standard deviation	11.9 ± 4.4 (2–19)
Diagnosis	
- Alzheimer's disease, *n* (%)	10 (45.5)
- Vascular dementia, *n* (%)	5 (22.7)
- Neurocognitive disorder not otherwise specified, *n* (%)	6 (27.3)
- Lewy body disease, *n* (%)	1 (4.5)
Comorbidities	
- Diabetes, *n* (%)	9 (40.9)
- Heart failure, *n* (%)	5 (22.7)
- Dizziness, *n* (%)	9 (40.9)
- Urinary incontinence, *n* (%)	9 (40.9)
- Mild back pain, *n* (%)	4 (18.2)
Indoor mobility	
- 4-wheeled walker, *n* (%)	4 (18.2)
- Single-point walking cane, *n* (%)	3 (13.6)
- No walking aid, *n* (%)	15 (68.2)
Fear of falling	
- Never, *n* (%)	12 (54.5)
- Sometimes, *n* (%)	3 (13.6)
- Regularly, *n* (%)	5 (22.7)
- Always, *n* (%)	2 (9.1)
Physical activity level before participation	
- No physical activities, *n* (%)	8 (36.3)
- One walking session per week, *n* (%)	7 (31.8)
- One to three walking sessions per week, *n* (%)	5 (22.7)
- More than three walking sessions per week, *n* (%)	2 (9.1)
- One gymnastics session per week, *n* (%)	1 (4.5)

TABLE 2 | Individual characteristics of the included participants.

Subject ID	Age	Gender	MoCA	Diagnosis	Mobility	SPPB
1	88	F	19	AD	No aid	1
2	87	F	4	AD	No aid	8
3	86	F	13	AD	No aid	7
4	87	F	2	AD	No aid	2
5	70	F	15	AD	No aid	12
6	80	F	7	NCD NOS	No aid	11
7	88	F	8	AD	Walker	2
8	83	F	14	VD	Cane	7
9	82	F	15	NCD NOS	Cane	7
10	80	M	11	LBD	No aid	8
11	85	F	8	AD	No aid	7
12	82	F	15	VD	No aid	11
13	95	M	17	NCD NOS	Walker	5
14	77	F	17	NCD NOS	No aid	9
15	89	F	7	VD	No aid	9
16	90	F	13	AD	Walker	4
17	84	F	12	AD	No aid	6
18	78	M	16	NCD NOS	No aid	11
19	85	F	14	VD	Walker	11
20	81	F	13	AD	No aid	11
21	92	M	12	VD	Cane	9
22	85	F	9	NCD NOS	No aid	6

AD, Alzheimer's disease; F, female; LBD, Lewy body disease; M, male; MoCA, Montreal Cognitive Assessment (total scores range from 0 to 30 with lower scores indicating more cognitive impairment); NCD NOS, Neurocognitive disorder not otherwise specified; SPPB, Short Physical Performance Battery (total scores range from 0 to 12 with lower scores indicating a higher risk and a score lower than 10 indicates one or more mobility limitations); VD, vascular dementia.

Thematic Analysis

The collective analysis of the interviews, the think aloud method and the field notes revealed five main themes which describe the experiences of the participants: (1) perceived user friendliness and acceptability of the exergames; (2) interactional experience; (3) motivational factors; (4) training; and (5) risks.

Perceived User Friendliness and Acceptability of the Exergames

Attitude Toward Using the Exergame Device

All participants liked the minigames and experienced enjoyment while playing them (n = 22, 100%). Ten participants stated that they would be interested in using the minigames in the future, next to traditional activities in the long-term care facility (45.5%).

I would like that because I feel that it's good for my lower vertebrae (P9).

Five participants were not sure about using the exergame device in the future (22.7%).

I would have to think about that... it's something peculiar, isn't it? (P17)

Six participants would not be interested in exergaming in the future (27.3%).

I prefer to go walking instead of exergaming (P3).

Ease of use and Understandability of the Instructions

Participants were all assisted by the facilitator with the setup of the system and the positioning of the sensors. They were not expected to do this independently. Participants experienced difficulties in navigating between different minigames. The minigames were depicted at the home screen and could be accessed by performing steps in the right direction. A representation of the home screen can be found in **Supplementary Material 2**. Participants needed verbal guidance to perform steps in different directions to access the various minigames from the home screen. They found it difficult to understand that they were supposed to perform stepping movements to access the minigames. In addition, they did not understand the minigame instructions and needed supplementary explanation from the facilitator. Verbal guidance was needed in all participants during game performance for assistance in navigating between the minigames and game explanation (n = 22, 100%). Three participants kept looking at their feet and had to be reminded to look up to the screen to see the game interface (13.6%). Four participants initially moved their hands to the screen (instead of using whole-body movements to interact with the game) because they did not understand that they needed to perform steps to play the minigame (18.2%). Nine participants were

TABLE 3 | System usability scale scores.

Participant ID	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Sum	Score
1	4	3	4	4	4	2	4	2	2	4	23	57.5
2	4	4	3	5	5	3	4	2	4	1	25	62.5
3	1	2	5	5	3	3	4	3	4	3	21	52.5
4	4	4	2	5	4	4	4	3	2	5	15	37.5
5	1	1	4	5	3	2	5	1	5	2	27	67.5
6	4	2	4	5	4	4	4	2	4	3	24	60
7	1	2	4	5	3	3	2	2	2	4	16	40
8	4	2	4	5	4	4	5	2	5	3	26	65
9	5	2	4	5	4	2	2	4	4	5	21	52.5
10	4	4	4	1	4	2	4	4	2	1	26	65
11	4	2	4	4	5	4	2	2	5	2	26	65
12	4	1	4	2	4	3	3	1	4	2	30	75
13	4	3	4	4	4	3	4	2	4	2	26	45
14	5	2	5	2	5	2	4	1	5	1	36	90
15	2	2	4	2	3	3	4	2	3	2	25	62.5
16	4	4	3	5	3	2	2	2	5	2	22	55
17	3	4	4	4	4	3	4	4	5	1	24	60
18	2	2	2	5	4	3	2	2	4	2	20	50
19	4	2	3	4	4	4	5	2	2	1	25	62.5
20	2	3	2	5	4	2	2	3	2	2	17	42.5
21	4	4	4	2	4	2	4	4	5	4	25	62.5
22	1	2	2	5	4	2	3	2	2	4	17	42.5

1: strongly disagree, 2: disagree, 3: neutral, 4: agree, 5: strongly agree, Q: SUS question
Questions:
(1) I think that I would like to use this system frequently.
(2) I found the system unnecessarily complex.
(3) I thought the system was easy to use.
(4) I think that I would need the support of a technical person to be able to use this system.
(5) I found the various functions in this system were well integrated.
(6) I thought there was too much inconsistency in this system.
(7) I would imagine that most people would learn to use this system very quickly.
(8) I found the system very cumbersome to use.
(9) I felt very confident using the system.
(10) I needed to learn a lot of things before I could get going with this system.

not able to play the minigame without constant verbal guidance (40.9%).

Sensor Application
Eight participants said that the sensors were user-friendly (36.4%). Some participants said that they forgot that they were even wearing sensors (*n* = 3, 13.6%).
The sensors didn't bother me, I wasn't even aware that they were attached to my feet (P5)
Two participants stated that they expected that they would not be able to apply the sensors to their feet themselves (9.1%).
I wouldn't be able to apply the sensors myself (P4).

Sensor Reactivity
One participant accidentally exited the minigames ten times, because the sensors often falsely perceived her steps as calf raises, which is also the movement required to go to the menu (4.5%). In five participants, the exergame did not respond to a good execution of the calf raises because of processing delays (22.7%). Two participants accidentally exited the game because their movements were perceived as movements required to exit the game (9.1%).
One participant performed her steps very slowly; when she placed her foot back in the center, this was perceived as an opposite direction sidestep by the device (4.5%). Often, the steps were not detected at all, or with a delay. In most participants, the sensors did not correctly process steps, so the facilitator had to assist by clicking the arrows on the keyboard to play the minigames and navigate through the minigames.

Technical Problems
Apart from the problems with the sensors, participants did not experience any technical problems with the exergame solution while playing.

Physical Limitations
Five participants were not able to perform the calf raises on both feet to exit the game or to go back to the menu without assistance of the facilitator (22.7%). Seven participants needed extra support from the facilitator, a walker, or a walking cane to play the minigames (13.6%).
The step backward was regarded as the most difficult step direction, because this action requires a good equilibrium.
It was also hard for participants with hearing difficulties to understand the game instructions given by the facilitator.

Mental Effort
For most participants, the minigames were cognitively more challenging than physically. Some had difficulties staying focused on the exergames.
Twelve participants said that exergaming was mentally exhausting (54.5%) and nine said that it was not (40.9%).
It was a bit mentally challenging because it was all new to me (P20)
It was necessary to keep your attention (P6).

Interactional Experience

Feedback
Participants enjoyed receiving feedback from the game (*n* = 17, 77.3%) and some even laughed out loud when positive feedback was given (*n* = 6, 27.3%).
Oh, it feeds your ego of course (P12)
It is encouraging (P19)
I realized that I was good at it due to the score (P14)
Sometimes participants were performing well but received negative feedback because their intended steps were not properly evaluated by the system (*n* = 22, 100%).

Multidirectional Steps
Some participants were not able to link the steps to the directions in the minigames (*n* = 5, 22.7%). For example, it was hard to link the backward step with downstairs in the library game. For several participants, it was difficult to navigate between the minigames, so the facilitator had to assist by pressing the arrows on the keyboard. Some participants had a hard time learning to just tap their feet and took a whole sidestep with both feet instead, causing the exergame device to react falsely (*n* = 9, 40.9%).

Avatar Interaction

Participants were able to associate themselves with their avatar. They enjoyed seeing their avatar and found it easy to imitate the avatar's movements. One participant even scratched her hair when her avatar did (4.5%). However, the home screen avatar "Vita" was recognized as a dog by one participant (4.5%). A picture of the avatar Vita can be found in **Supplementary Material 3**. The squatting avatar in the outdoor game especially was perceived as enjoyable and helpful. A picture of this avatar, which displays a full human body, can be found in **Figure 1**.

Motivational Factors

Exergame Motivation

Most of the participants found exergaming to be motivating (n = 19, 86.4%).

It motivated me because the exercises were easy to perform (P9)

It is very healthy, and you must know that I am very patient, but lately (due to COVID-19 restrictions) we are not allowed to do gymnastics anymore (P11)

I don't exercise enough, and you should exercise, exercise, exercise (P14)

However, four participants said that they were already active enough and did not need exergames to motivate them to be physically active (18.2%).

The exergame did not motivate me because everything hurts. I never really enjoy physical activity. I have done enough in my life already (P7).

Enjoyment and Positive Emotions

All participants experienced having fun and smiled while exergaming (100%). Some stated that they just liked being invited to go outside their living unit and enjoyed the distraction. Participants were enthusiastic about the exergames. Exergaming evoked memories and three participants spontaneously started talking about past experiences with physical activity (13.6%). Eight participants felt that they excelled in it (36.4%).

Engagement

Participants spontaneously started talking about healthy food while playing the healthy food game (n = 4, 18.2%). Seventeen participants experienced feeling "in" the game regularly (77.3%).

In the beginning, I had to listen carefully to understand the instructions, but afterwards I experienced it (P11).

Long-term Acceptability

Fourteen participants said that they expected that the exergames would still be nice, even after they would have played them several times (63.3%). Two of them argued that this would be the case, provided that the games would become more difficult over time.

I think it would be even more nice, because then you really know how it works and it's easier (P16)

I will become better at it and these are movements that you usually don't do; you never step backwards and it's actually very beneficial for your balance (P8).

Game Design: Sounds and Images

Participants liked the appearance of the minigames. They enjoyed the music that was played during the exergames and while navigating between the minigames. Two participants (9.1%) spontaneously started dancing to the exergame music.

Training Modalities

Exergame Intensity

Most of the participants stated that the minigames were of low intensity levels (n = 13, 59.1%). However, three participants said that performing the squats was particularly difficult and needed to rest in between (13.6%). Two participants said that the walk to the exergame room was already exhausting for them (9.1%).

I would prefer to do more high intense exercises (P14)

I was already fatigued and to perform this on top of that... It's particularly exhausting for my eyes (P7).

Training Duration

All participants said that the duration of the exergame session was good (n = 22, 100%).

Feeling Safe

Although all participants felt safe during exergaming (n = 22, 100%), four stated that they were extra careful not to fall (18.2%).

I am not afraid of falling, but I try to be careful not to fall (P22).

Risks

Fall Risk

The facilitator always individually guided the participant and there were no fall incidents. Two participants indicated that the floor on which they were standing was slippery (9.1%). This feeling was augmented because the sensors were attached to the feet with fabric straps that slid on the floor very easily.

Negative Emotions

Four participants felt confused because they didn't understand the instructions of the games (18.2%). One participant said that the games at first seemed to be childish.

It might seem childish at first, but it's not (P10).

Variables Explaining the Variance in the System Usability Scale Scores

None of the variables (i.e., age, gender, MoCA and SPPB total score) included in the backward stepwise multivariable regression analysis had a variance inflation factor of more than 3 and needed to be removed. Only the variance in the SPPB total score remained a significant predictor of the variance in the SUS score and explained 21.9% of the variance (unstandardized B coefficient = 1.80, standard error = 0.76, standardized β coefficient = 0.47, t = 2.37, P = 0.028; constant: unstandardized B coefficient = 44.5, standard error = 6.12, t = 7.26, $P < 0.001$).

DISCUSSION

The primary aim of this study was to evaluate the usability of the VITAAL stepping exergame prototype in residential older adults with MNCD. Overall, the mean SUS score given to the VITAAL exergame was 57.8, which corresponds to a system usability that is ok to good. The SUS scores also correspond to the observations of the facilitator and the content of the interviews. Five main themes emerged from the thematic content analysis: (1) perceived user friendliness and acceptability of the exergames; (2) interactional experience; (3) motivational factors; (4) training modalities; and (5) risks. There were no adverse events nor dropouts. We will discuss all the themes more in detail.

A first theme was the perceived user friendliness and acceptability. Overall, the VITAAL exergame prototype was well accepted by participants. Participants were always assisted by the facilitator with the setup of the exergame and the correct application of the sensors to the feet. However, some difficulties regarding user friendliness and acceptability were reported. For example, all participants experienced difficulties in understanding at least some of the game instructions. Additional verbal guidance from the facilitator was therefore needed in all participants. Nine participants (40.9%) were not able to play the game without constant verbal guidance of the facilitator. Some participants also needed extra physical support, their walker, or their walking cane during exergame performance (13.6%). From all these findings, the importance of prompts given by the facilitator when learning people with MNCD to use new technologies becomes evident. Previous research already demonstrated that verbal prompts (i.e., words used to provide instruction), gesture prompts (i.e., steps modeled using physical actions), and physical assistance (i.e., any physical intervention) are essential for people with MNCD when learning to use motion-based technologies such as exergames (Dove and Astell, 2019). Recently, a call was made to formulate guidelines for researchers, clinicians, care providers, and families on how to start implementing these new technologies in the rehabilitation of people with MNCD (Dove and Astell, 2017b). One should, however, be aware that difficulties regarding understanding the game instructions and game navigation in the current study might also be due to the fact that participants only had one try-out session. One session might not be sufficient to get familiarized with the instructions and execution of the exergames. Another aspect related to perceived user friendliness and acceptability was that the exergames were cognitively challenging for most participants. Twelve participants reported that exergaming was mentally exhausting (54.5%). It would be interesting to examine in the updated prototype how to adapt the game to the performance level and needs of the individual. This adaptation will likely also increase the usability. Our backward stepwise multivariable regression analysis demonstrated that in particular the variance in lower extremity functioning explained the variance in usability, with lower extremity functioning being associated with a lower perceived usability. It has been previously reported that in people with MNCD, the acceptance and user friendliness of an exergame device strongly depends on the task itself and the perceived competence (Vallejo et al., 2016). The current usability study therefore confirms previous findings that in order to create an exergame-based rehabilitation program, it is essential to consider the usability of the involved device, the persons' abilities and the motivations to play of the target population (Vallejo et al., 2016). For example, one in five participants were also not able to perform calf raises on both feet to exit the minigame or to go back to the menu without assistance of the facilitator. The final design should therefore consider these physical limitations, in particular for old-aged populations at risk for falling. In addition, participants were not able to navigate between the minigames because the sensors were not responding correctly to the calf raises (100%). When the sensors were not working well and the system falsely provided negative feedback, the facilitator tried to solve this by giving appropriate positive verbal feedback. A possible explanation might be that Bluetooth and Wi-Fi devices, such as a smartphone or a tablet from nearby staff in the long-term care facility, might have caused interference in the connection between the sensors and the software. Therefore, it is recommended to examine the difficulties with sensor reactivity and to solve them before using the prototype in a future trial. Despite these issues, the sensors were perceived as user-friendly (36.4%), and participants did not report experiencing any technical problems with the exergame while playing (100%). Nearly half of the participants also expressed a wish to continue exergaming in the future, supplementary to their traditional activities in the long-term care facility (45.5%).

A second theme was the interactional experience with the minigames, which was overall positive as well. Participants particularly liked the squatting avatar in the Tai Chi-inspired strength training game. Participants found it helpful to imitate the avatars' movements because they were able to associate themselves with their avatar. A reason for this might be that in this game, the avatar was displayed as a full human body. This contrasts with the avatar of the home screen and avatar in the other minigames, which was more abstract and did not resemble a human being. For application in our population, it might be recommended to adapt avatars to resemble a more human-like avatar. Concerning the audio-visual feedback, the VITAAL prototype exergame focused on positive feedback and this was greatly appreciated by the participants. They enjoyed receiving feedback (77.3%) and laughed out loud when positive feedback was given (27.3%). Positive feedback is commonly recommended in order to promote motor skill learning and neurorehabilitation of motor functions (Vassiliadis et al., 2021). Despite the positive interactional experience, some interactional issues were detected as well. For example, participants had difficulties learning to just tap their feet and took a whole sidestep with both feet instead, causing the exergame to react falsely (40.9%). Moreover, some participants initially pointed their fingers to the screen or tried to grab items displayed on the screen, instead of performing steps to control the minigames (18.2%). This was easily solved by extra verbal guidance of the facilitator. Related to the interaction experience, although the VITAAL exergame is conducive for single-player activities, future research should explore differences in interactional experience of the VITAAL exergame between individual and group settings. Previous studies in people with MNCD already demonstrated that using single-player exergame technology in a group setting fosters an encouraging and supportive environment which further contributes to the leisure experience. Using motion-based technology in a group setting creates opportunities for social interaction amongst group members and between the players and facilitators (Fenney and Lee, 2010; Dove and Astell, 2017a). The value of well-trained facilitators and the verbal and non-verbal communication between the facilitator and institutionalized players with MNCD has been discussed previously. Researchers underlined the importance of enjoyment, empathetic communication in both ways, the use of praise, and the development of social roles (Yamaguchi et al., 2011).

Third, with regards to the motivational factors, most of the participants found exergaming to be motivating (86.4%). All participants experienced enjoyment and fun while playing the exergames (100%). Our data confirm previous trials showing that exergames can be engaging and motivating in people with moderate cognitive impairments (Ben-Sadoun et al., 2015, 2016). This finding is important since drop-out is a major problem in physical activity programs for people with MNCD (Forbes et al., 2015) and experiencing enjoyment is a strong predictor for training adherence in exergame programs for old-age populations (Wiemeyer and Kliem, 2012). Most participants experienced feeling "in" the game regularly (77.3%). This feeling possibly reflects the experience of participants being in their "flow zone," a feeling of complete and energized focus in order to improve the enjoyment and learning experience (Robert et al., 2014). Participants in our study stated that the game design was engaging. They also enjoyed the music while playing the exergames and when they were navigating between the minigames. Two participants spontaneously started dancing to the exergame music (9.1%). The healthy food game that focused on inhibition control was preferred by all participants and some of them spontaneously started talking about healthy food while playing (18.2%). We believe that this reflects a proper choice of minigame themes and a possible relation of their game experience to daily life situations.

A fourth theme handled the training modalities. Most of the interviewees stated that they experienced the intensity of the exergames as low (59.1%). However, executing the squats in the Tai Chi-inspired strength training game was perceived as more intense, and some participants sat down on a chair during the breaks (13.6%). Since older adults with MNCD are less able to describe their perceived exertion validly due to impaired judgment, awareness, and insights as well as increased communication difficulties, it might be hypothesized that an automatic adaptation of the exergames to the individual needs and performance of the player will increase the usability of the VITAAL exergame even further. The duration of the exergame session was 30 min and this was unanimously perceived as good (100%). It should be considered, however, that once the exergame automatically adapts to the individual's needs and performance, the intensity level might increase. Consequently, 30 min might be too long for our sedentary population. In such a case, gradual progression of exergame play time should be warranted and the 30 min should be a target that should only be reached following a skilling-up phase (Rogan et al., 2012).

A fifth and final theme included the risks regarding the use of the VITAAL exergame. Although all participants felt safe during exergaming (100%), some explained that they were extra attentive not to fall (18.2%). The facilitator considered five participants as having a higher risk of falling, although this was not objectively represented (Shimada et al., 2011). The sensors were attached to the feet with fabric straps that slid on the floor very easily. Depending on the floor, this might increase the risk of falling during exergame performance. Therefore, in future exergame trials it is recommended that the facilitator is aware of the potential risk of falling and takes the necessary precautions. The VITAAL exergame occasionally evoked negative emotions such as confusion when the participants did not understand the instructions of the minigames (18.2%). Therefore, the facilitator assisted by explaining the game instructions in a friendly way. This also underscores the advantage of the one-on-one guidance during exergaming.

Some limitations of this study should be considered. First, the current study was limited to only one long-term care facility in Belgium, so the findings may have limited generalizability to other settings and countries. Second, only residents who were willing to participate, in other words, those who were more interested in technology and physical activity than the average person with MNCD, were included. This limits the generalizability to all older adults with MNCD. It has been previously stated that only a minority of long-term care residents with a MNCD are suitable for inclusion in an exergame training program. A factor that might influence acceptance of exergames is the level of cognitive functioning. More specifically, residents with more severe cognitive impairments were more likely to reject exergame training (Ulbrecht et al., 2012). A third limitation of the study was that more female (81.8%) than male (18.2%) participants were included. A reason for this might be that women are at greater risk for developing Alzheimer's disease (Podcasy and Epperson, 2016) and more women than men are living in long-term care facilities in Belgium (Vlaamse overheid Statistiek Vlaanderen, 2018). Fourth, the SUS has not been validated in older adults with MNCD yet (Gibson et al., 2016). Therefore, these results were interpreted in conjunction with the data from the observations and interviews. Fifth, although the think aloud method has previously been applied in research in older adults with MNCD (Ratcliffe et al., 2019), for most participants, talking out loud while exergaming was complex. This is in line with a preliminary usability study in older adults with MNCD stating that participants experienced difficulties in verbalizing and narrating their experiences, even when prompted and reminded to do so during completion of the tasks (Gibson et al., 2016). Sixth, the results may have been influenced by social desirability bias. This was considered during the interviews by for example actively asking about negative impressions. Finally, the views and opinions of the caregivers were not assessed. It would be of added value to actively involve caregivers and ask about their opinions regarding the exergame device and technological features as well.

Despite these limitations, some strengths should be acknowledged. The number of participants allowed for a rich data collection of experiences and usability opinions. Although the exergame prototype did not adapt to the individual needs of the participant, which might be considered as a limitation from a clinical perspective, it allowed us to investigate a standardized exergame training session. Moreover, interviews were performed directly following the exergame try-out and in the same room, which stimulated participants' recall of the events and experiences during the exergame session. Also, the interviewer was the same person who facilitated the participants' exergame session, and so they were familiar with each other. Furthermore, the facilitator always attempted to adopt a neutral body language, in order not to influence the participants' responses.

CONCLUSION

Based on the current findings, it can be concluded that the VITAAL exergame prototype is considered useful and entertaining by residential older adults with MNCD. Technical issues concerning the sensor reactivity and the challenges regarding the minigame navigation and instructions should be addressed before the prototype can be implemented in a longitudinal trial. Subsequently, investigating whether this exercise solution can overcome sedentary behavior in this population seems warranted.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Medical Ethics Committee of UZ Leuven (registration: S63304/B322201941828). No compensation for participation was given. The participants provided their written informed consent to take part in this study.

AUTHOR CONTRIBUTIONS

NS developed the research question under the lead of DV, MV, and EB. NS established the concept and design while DV, MV, and EB acted as methodological council. NS conducted data processing, analysis, and interpretation of the results with edits and improvement by all authors and produced a first version of the manuscript. All authors have revised and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2021.701319/full#supplementary-material

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frontiers in Aging Neuroscience

ORIGINAL RESEARCH
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Feasibility of Cognitive-Motor Exergames in Geriatric Inpatient Rehabilitation: A Pilot Randomized Controlled Study

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Objective: The aim of this pilot randomized clinical trial was to test the feasibility and efficacy of an exergame-based cognitive-motor training program in geriatric inpatients.

Methods: The study participants were randomly allocated to either the exergame intervention group or the control group. The control group received the standard rehabilitation treatment offered in the clinic. In addition to the standard rehabilitation program, the intervention group conducted supervised exergame training on 5 days per week using the Dividat Senso, an exergame system specifically designed for older adults. The primary outcome was feasibility, as measured by e.g., adherence rate, attrition rate, occurrence of adverse events, System Usability Scale (SUS) and NASA-TLX score. Secondary outcomes included measures of physical and cognitive functioning such as comfortable walking speed, maximal walking speed, dual task walking speed, Short Physical Performance Battery (SPPB), Timed Up and Go test (TUG), Color-Word Interference test (D-KEFS), Trail Making test A and B (TMT), Go/No-Go test and Step Reaction Time test (SRTT). All secondary outcome measures were assessed pre- and post-intervention.

Results: Thirty-nine persons were included in the study. Average adherence rate was 99%, there were no intervention-related dropouts and no adverse events. The mean System Usability Scale (SUS) score was 83.6 and the mean NASA-TLX score 45.5. Significant time-group interaction effects were found for the dual task walking speed, the Go/No-Go test and Step Reaction Time test (SRTT).

Conclusion: Exergaming is a feasible, safe and effective cognitive-motor training approach in inpatient rehabilitation of geriatric patients. Incorporating exergaming in the rehabilitation program of geriatric patients offers potential to reduce fall risk factors and to increase patients' exercise motivation and rehabilitation success.

Keywords: exergaming, balance training, cognitive training, exercise, step training, older adults, fall prevention

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INTRODUCTION

The aging process is accompanied by a decline in physical and cognitive functions such as balance, gait, executive functions and psychomotor speed (Kramer et al., 1999; Park, 2000; Seidler et al., 2010; Reuter-Lorenz et al., 2015; Valenzuela et al., 2018; Cogliati et al., 2019). These declines often lead to loss of independence in daily life, restricted social participation and are major risk factors for accidental falls (Rowe and Kahn, 1997; Kramer et al., 1999; Herman et al., 2010; Khow and Visvanathan, 2017). In Switzerland, approximately 25% of people aged 65 years and older fall at least once a year (Stürze im Laufe eines Jahre, 2017). Falls in older adults often result in injuries, reduced quality of life and increased healthcare costs (Stevens et al., 2006; Hartholt et al., 2011). Frail older adults, such as people undergoing rehabilitation after a surgery or a fall, are exposed to an even higher fall risk (Kojima et al., 2015). Therefore, it is highly important to improve physical and cognitive functioning, which will in turn reduce fall risk in older adults in general but even more so in fall-prone individuals such as rehabilitation patients. A highly important physical function that is reduced with age is balance control. The balance control system consists of several components such as sensory information acquisition, information processing as well as production of an adequate motor response (Van Dieën and Pijnappels, 2017), all of which show age-related impairments. As a result, older adults frequently face difficulties in controlling their balance (Sturnieks et al., 2008), e.g., executing adequate stepping responses. Stepping responses can be divided into volitional stepping responses e.g., in order to proactively avoid an obstacle and reactive stepping responses e.g., in order to react to an external perturbation to avoid falling (Okubo et al., 2021). In older adults, this stepping capacity is frequently reduced: their reactive steps are shorter (Luchies et al., 1994) and they tend to collide the swing foot with the stance leg (Maki et al., 2000). Moreover, in fallers, the maximum step length (Cho et al., 2004; Schulz et al., 2013) and volitional stepping speed (Melzer et al., 2007) is reduced compared to non-fallers. As a result, if stepping capacity is decreased, the risk for falls increases (Okubo et al., 2017, 2021).

Training interventions that aim to improve stepping capacity were shown to reduce fall incidence (Okubo et al., 2017) and are recommended to be incorporated into fall prevention training programs (Cadore et al., 2013; Giannouli et al., 2020; Sibley et al., 2021). Step training using exergames has become an important instrument in fall prevention in the aging population (Donath et al., 2016; Choi et al., 2017). Exergames successfully combine motor and cognitive training by providing cognitively demanding games which are played by executing body movements. Increasing evidence suggests that the combination of motor and cognitive training leads to a superior effect on cognitive and dual task performance compared to motor or cognitive training alone (Levin et al., 2017; Tait et al., 2017; Raichlen et al., 2020). Simultaneous motor and cognitive training stimulates similar neurobiological processes which result in a synergistic response with higher effects on cognitive improvements (Tait et al., 2017). Therefore, such training can also be more effective in reversing the neurodegenerative consequences of aging than motor or cognitive training alone and, therefore, also decrease fall risk to a higher extent (Segev-Jacubovski et al., 2011; Schoene et al., 2014; Raichlen and Alexander, 2017). In geriatric and/or orthopedic rehabilitation however, conventional therapies merely focus on physical functions. To that end, a cognitive-motor training delivered in form of exergames could increase the efficacy of the rehabilitation by addressing also cognitive control and dual tasking. Furthermore, gamification of exercise was shown to have positive effects on training motivation (Proffitt et al., 2015) and self-efficacy (Su and Cheng, 2016) which are factors that can increase rehabilitation success (Bonnechère et al., 2016). Traditional rehabilitation strategies can be monotonous (Kamkarhaghighi et al., 2017) and exergaming offers a suitable supplement to make a rehabilitation program more entertaining and, thereby, increase the patients' motivation to participate and adhere to their exercise routines (Kappen et al., 2019).

Exergaming interventions were shown to be a feasible and effective training approach in healthy older people; with high adherence to exergame interventions (>90%) and only rare and minor adverse events being reported (Valenzuela et al., 2018). In addition to this, exergaming interventions have positive effects on physical and cognitive functioning such as balance, functional mobility, gait and executive functions in healthy older adults (Stanmore et al., 2017; Corregidor-Sánchez et al., 2020a,b; Fang et al., 2020; Pacheco et al., 2020; Wollesen et al., 2020), as well as people suffering from chronic diseases (Bonnechère et al., 2016; Stanmore et al., 2017; Zeng et al., 2017). However, some current gaps in knowledge need to be addressed. In most of these previous studies, commercial exergame systems were used which were mostly designed for young people and recreational purposes. It can be hypothesized that an exergame system specifically designed for clinical purposes may have better effects. Furthermore, evidence regarding the feasibility of exergame training in inpatient rehabilitation settings is scarce (Knols et al., 2016; Cuevas-Lara et al., 2021).

To the best of our knowledge, this is the first study to examine the feasibility and effects of a motor-cognitive training in form of purpose-developed exergames in a geriatric inpatient rehabilitation setting. Aim of this study was to assess the feasibility and effects of such training in a geriatric inpatient rehabilitation clinic. We first hypothesized that the exergame intervention integrated in the inpatient rehabilitation program routines is feasible and safe. Secondly, we hypothesized that the effects on cognitive and physical functions will be more meaningful in the group receiving the exergame intervention compared to the group receiving the conventional rehabilitation therapy only.

MATERIALS AND METHODS

This paper presents the results of inpatient exergame rehabilitation integrated in the program from the orthopedic and geriatric rehabilitation clinic Dussnang. It is the first study within a series of studies examining feasibility of exergame training in different rehabilitation clinics and various inpatient groups.

The study was approved by the cantonal ethics committee of Zurich, Switzerland (Reg.-No.: 2020-02388), and was conducted according to Good Clinical Practice (GCP) guidelines and the Declaration of Helsinki. All participants were required to give written informed consent. The study has been registered at ClinicalTrials.gov (ID: NCT04872153).

Study Design

This is a pilot feasibility randomized clinical trial (RCT) with two arms (one intervention and one control group) adhering to the CONSORT extension for pilot and feasibility trials (Eldridge et al., 2016). The study was conducted at the geriatric and orthopedic rehabilitation clinic Dussnang during a period of 3 months (January to March 2021). Participants were randomly allocated to one of the two groups using a permuted block randomization approach. The intervention group conducted exergame-training using the Dividat Senso in addition to the conventional rehabilitation treatment while the control group received the conventional treatment only. The duration of the intervention period was adjusted to the duration of each participant's stay at the rehabilitation clinic lasting between 2 and 3 weeks. Before beginning and after finishing the intervention or control period, a baseline (T1-meaurement) and a post measurement (T2-measurement) was conducted with each participant of both groups.

Feasibility in this study was adopted as an umbrella term encompassing adherence, attrition, patient acceptability and safety of the intervention. Adherence considered the frequency of participant attendance at the intervention sessions and the attrition considered the proportion of dropouts. Patient acceptability was assessed by enjoyment level during the intervention and two questionnaires at the end of the intervention. Safety was assessed by recording of adverse events and falls that occurred during the intervention and by two questionnaires at the end of the intervention. We a-priori adopted 15% or less attrition and 80% or more adherence as acceptable for inpatient orthopedic exergame rehabilitation (Nyman and Victor, 2011). Furthermore, patients were expected to score 70 or more points on the System Usability Scale (SUS) (Bangor et al., 2009) and 55/100 for the NASA-TLX score (Grier, 2015).

To provide an estimation of the effectiveness of the intervention for future RCTs, secondary outcomes were used to test the hypothesis of effectiveness. To ensure sufficient power, a sample size calculation was performed. Sample size calculation suggested that a total sample size of 16 participants would offer a power of 91% to correctly reject the null hypothesis. The calculation was based on the effect size ($F = 0.4$) of the interaction effect of the outcome measure Timed Up and Go (TUG) as assessed in the study by Morat et al. (2019). The exergame intervention was almost identical to the present study, however, the intervention period was more than twice as long. Because of the much shorter intervention period in this study, the sample size was aimed to be 40 allowing the detection of smaller effect sizes with sufficient power while also allowing some dropouts. Thus, a small effect size ($F = 0.3$) can be detected with a 91% chance of correctly rejecting the null hypothesis.

Participants

At clinic entry, patients were informed in oral form about the study. Interested persons were fully informed with a detailed information sheet and gave written informed consent prior to the onset of their participation in the study. To be included in the study persons had to fulfill following criteria: (Park, 2000) in-patient stay in the orthopedic and geriatric rehabilitation clinic Dussnang, (Seidler et al., 2010) age $\geq$ 50 years, (Valenzuela et al., 2018) able to score $\geq$ 20 on the Mini Mental State Examination (MMSE), (Cogliati et al., 2019) able to provide a signed informed consent, (Reuter-Lorenz et al., 2015) physically able to stand for at least 3 min without external support (self-report). Exclusion criteria were: (Park, 2000) mobility or cognitive limitations or comorbidities which impair the ability to use the training games and overall system, (Seidler et al., 2010) conservatively treated osteoporotic fractures, (Valenzuela et al., 2018) previous or current major psychiatric illness (e.g., schizophrenia, bipolar disorder, recurrent major depression episodes), (Cogliati et al., 2019) history of drugs or alcohol abuse, (Reuter-Lorenz et al., 2015) terminal illness, (Kramer et al., 1999) severe visual (e.g., especially achromatopsia) and auditory impairments, (Khow and Visvanathan, 2017) insufficient knowledge of German to understand the instructions/games.

Exergame Intervention

Participants allocated to the intervention group conducted a supervised motor-cognitive training by playing exergames on the Dividat Senso in addition to the standard rehabilitation treatment offered by the clinic. The Dividat Senso is a device consisting of a pressure-sensitive platform which records movement produced forces. The platform includes 20 sensors (strain gauges), five vibration motors and an LED control. It is certified as a medical device class 1 and was specifically developed for clinical use. The Dividat Senso is connected to a computer and a screen on which the stimuli appear. The Dividat exergames (**Supplementary Table 1**) were used which specifically target cognitive and motor functions required for activities of daily living such as executive and attentional functions and balance and coordination. The games are played by making steps in four directions (front, right, left, back) and body weight shifting. Training sessions were executed on 5 days per week and each session lasted between 10 and 15 min. During each session, the participants played between six and seven different exergames each lasting between 2 and 3 min. The participants played the same composition of games for five training sessions. After every five training sessions, new, more challenging games were introduced to the training plan. To ensure adequate training progression, personalization of the training plan was achieved on the one hand by the training software (DividatPlay), which contains an algorithm that enabled automatic, real-time adaptation of the difficulty of a training to the level of an individual participant. On the other hand, the therapist/trainer adapted the training plan (i.e., substituted single games) in case of insufficient or excessive difficulty as measured by two criteria: (Park, 2000) too low performance in a game, (Seidler et al., 2010) subjective report of the patient that the game is too difficult or too easy.

Control Group

The patients of the control group followed the standard rehabilitation plan offered by the clinic. For each week this usually included: 3× 30 min physiotherapy, 5× 30 min group therapy (knee- / hip- or back-specific group / otago-group therapy for upper extremities), 3× 30 min walking groups (only in patients admitted for issues in the lower extremities), 3× 45 min group therapy (mindfulness therapy, medical training therapy, activating groups).

Primary Outcomes

The primary outcome of this study was the feasibility of the Dividat Senso integrated in the rehabilitation context. For this purpose, adherence, attrition, and the number of adverse events were assessed. In addition, four questionnaires were used to assess usability and safety and filled in by the participants of the intervention group after each training (NASA-TLX, enjoyment) or at T2-measurement only (SUS, self-made questionnaire including several usability and user experience questions).

Adherence, Attrition and Adverse Events

Average adherence rate was calculated as the number of completed training sessions as a percentage of the maximal possible training sessions. Reasons for non-adherence were recorded in the attendance protocol. Additionally, attrition in the intervention and control group was recorded. The attrition rate was calculated as the number of participants that dropped out during the trial as a percentage of the initial sample size. Adverse events occurring during the training sessions and measurements were noted in detail by the treating therapist.

System Usability Scale

To assess usability of the Dividat Senso, the System Usability Scale (SUS) was used (Brooke, 1996). The SUS is often used for the evaluation of software products, websites or games/exergames. It is a validated and reliable scale and consists of ten items rated on a 5-point Likert scale ranging from 0 to 4 (Brooke, 1996; Tullis and Albert, 2008). For this study, a German translation of the SUS was used (Gao et al., 2020). Scores above 70 are regarded as "acceptable" (Bangor et al., 2009).

NASA Task Load Index and Enjoyment Level

The NASA Task Load Index (TLX) developed by Hart (Hart and Staveland, 1988) is a subjective assessment tool to assess workload experienced while working with a human-machine interface system. A multidimensional rating procedure is used which includes ratings on six subscales: Mental Demand, Physical Demand, Temporal Demand, Performance, Fatigue and Frustration. For each subscale, there is one question which are answered on a 20-point Likert scale ranging from "a little" until "too much." For this study, a German translation of the NASA-TLX was used. For evaluation, the raw NASA-TLX was used which is an average workload score between 1 and 100 calculated by multiplying each rating by 5. Additionally, an overall workload score was calculated averaging the ratings on the six subscales (Said et al., 2020). A NASA-TLX score of 55/100 was expected which is based on the average score for the performance of cognitive tasks, physical activity and video gaming (Grier, 2015). Furthermore, after each training session, participants were asked to rate their perceived enjoyment level on a 5-point Likert scale.

Questionnaire Regarding Usability and Safety

A questionnaire was used to assess user experience and safety aspects. The questionnaire included a total of 19 items to assess each participants' subjective perception of the exergame training sessions. Thirteen items were rated on a 5-point Likert scale ranging from 1 to 5 and assessed fun, motivation, excitement and diversification of the games, perceived improvements of motor coordination, perceived improvements of cognitive performance, intention to recommend this type of training to everyone as well as specifically to people with coordinative impairments, or to people with cognitive impairment, frequency of the training sessions, duration of the training sessions, feeling of safety during training, and fear of falling during training. In six further open questions the participants were asked for their favorite game, their least favorite game, their most challenging game, their least challenging game, what kind of positive effects resulting from the training were perceived, and general impressions of the training.

Secondary Outcomes

The effects of the exergame intervention on physical and cognitive functions were examined as secondary outcome to receive first indications whether a full RCT of the intervention will be worthwhile and to determine whether there is a need for further development of the intervention (Abbott, 2014). For that purpose, several physical and cognitive tests were executed before and after the intervention or control period (T1- and T2-measurement).

Timed Up and Go Test

The Timed Up and Go (TUG) (Podsiadlo and Richardson, 1991) is a quickly executed test that only requires a chair and a stopwatch. It measures how much time participants need to perform the following task: Stand up from a chair, walk 3 m with comfortable speed, turn around, return to the chair and sit down again. The participants were asked to stand up without using their arms, if possible. However, if it was not possible, using their arms was allowed and noted. The test measured functional mobility and balance and can be used to detect change over time (Podsiadlo and Richardson, 1991).

Short Physical Performance Battery

The Short Physical Performance Battery (SPPB) developed by the National Institute on Aging (Short Physical Performance Battery (SPPB), 2021) is a tool (Mijnarends et al., 2013) for assessing motor functioning of the lower extremities. The test battery includes three physical tasks: Maintaining balance in different positions, standing up and sitting down five times as fast as possible and walking at comfortable speed. The total points achieved in all tests together as well as the completion time for the five times sit-to-stand subtask were used for further analyses.

Gait Performance

Normal walking speed was measured during single and dual task conditions while maximal walking speed was measured only

TABLE 1 | Demographics of study participants.

Variables	Exergame group	Control group	*P*-values
Number of participants	19	20	
Sex, Female:Male	[11:8]	[10:10]	
Age, years, mean (SD)	73.0 (8.8)	72.2 (9.8)	0.789
MMSE score, mean (SD)	27.3 (2.1)	28.0 (1.3)	0.208
BMI, kg/m2, median (IQR)	27.3 (5.3)	25.1 (5.3)	0.740
Reason for rehabilitation, %	(47) knee prosthesis (16) hip prosthesis (26) upper extremities (5) back (5) general rehabilitation	(30) knee prosthesis (45) hip prosthesis (15) upper extremities (5) back (5) general rehabilitation	
Time between pre- and post-measurement, days, median, (IQR)	15.0 (3.0)	12.0 (5.3)	0.075
Participants with fall history during last 12 months, %	26	45	
Years of education, years, mean (SD)	11.8 (2.4)	12.2 (3.0)	0.641
Regularly physically active, %	79	85	
Physically active, h/week, mean (SD)	4.3 (3.3)	6.3 (5.4)	0.165
Polypharmacy, %	79	60	
Comorbidities, %	(74) cardio-vascular diseases (68) internal / endocrine diseases (79) orthopedic diseases (5) neurological / psychiatric diseases (21) gastrointestinal diseases (5) eye/ear diseases (16) tumor	(65) cardio-vascular diseases (55) internal / endocrine diseases (95) orthopedic diseases (15) neurological / psychiatric diseases (20) gastrointestinal diseases (10) eye/ear diseases (10) tumor	

during single task condition. In all tasks, participants had to walk along a straight walkway of 14 m. The time was measured during the 10 m in the middle providing the participants with 2 m for acceleration and deceleration, respectively. The 14- and the 10-m zones were marked with taped lines and the time was measured with a stopwatch as soon as the toes of the participant crossed the starting or the finishing line of the 10-m zone, respectively. For each task, the test was repeated twice and the average time was used for further analysis. If required, the use of assistive devices was allowed and documented by the local investigator. For the dual task condition participants had to count backward from 250 (first walk) and 245 (second walk) in steps of 7 (or 3, in case counting in steps of 7 was too difficult) during walking. Both are often used cognitive tasks in dual task paradigms (Bayot et al., 2020).

Step Reaction Time Test

The Step Reaction Time test (SRTT) was performed on the Dividat Senso. It measures psychomotor speed in terms of reaction to a visual stimulus using the lower extremities. On the screen, six gray triangles are depicted. As soon as one of these triangles turns black, participants have to react by stepping as quickly as possible in one of the six possible directions in which the stimulus appeared (right, front left, right, left, back right and back left). Average reaction time was used for further analyses.

Go/No-Go Test

The Go/No-Go Test was also performed on the Dividat Senso and measures selective attention and inhibition. Participants have to focus on a small gray dot in the middle of the screen. In a randomized order, crosses (+) and Xs (x) appear on the right and left side of the gray dot. Participants are asked to ignore the crosses and only react to the Xs by stepping as quickly as possible in the right direction. Average reaction time was used for further analyses.

Trail Making Test

The Trail Making Test (TMT) is a paper-pencil test consisting of two parts. Part A (TMT-A) mainly assesses processing speed (Crowe, 1998). Circled numbers from 1 to 25 are allocated randomly on a sheet which participants have to connect in the right order. Part B (TMT-B) mainly assesses mental flexibility (Crowe, 1998). Here, circled numbers and letters are randomly allocated on a sheet and the participants have to connect circled numbers and letters in the right order and in alternating manner. The required time to complete each task was measured in both parts (Tombaugh, 2004).

Color-Word Interference Test (D-KEFS)

The Color-Word Interference Test is a version of the Stroop Test (Stroop, 1935) and was developed as a part of the Delis–Kaplan Executive Function System, which is a battery of neuropsychological tests (Delis et al., 2001). The Color-Word Interference Test is an instrument to assess inhibition, mental flexibility and shifting consisting of four trials (Homack et al., 2005; Shunk et al., 2007; Jones Chesters, 2008). First is the *color naming trial* in which a sheet containing differently colored squares (red, green, blue) is presented to the participant who has to name the colors as quickly as possible. In the second *word reading trial*, the participant is presented with a sheet containing the words "red," "green" and "blue" printed in black ink which the participant has to read aloud as quickly as possible.

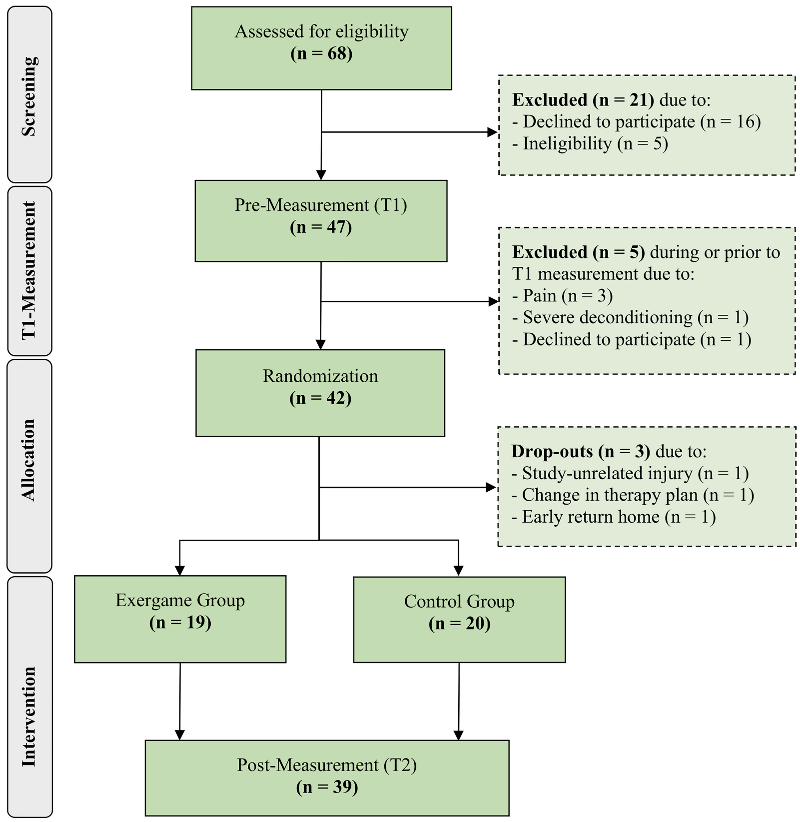

FIGURE 1 | Flow diagram of screening and group allocation (based on Eldridge et al., 2016).

Third, the *inhibition trial* follows which is based on the Stroop test (Stroop, 1935). During this trial, the sheet presented to the participant contains the words "red," "green" and "blue" printed incongruently in red, green or blue ink. The participant is asked to name the color of each word as quickly as possible while inhibiting reading the words. In the final *inhibition/switching trial,* the sheet looks the same as in the inhibition trial but additionally, half of the words are enclosed within boxes. The task is the same as in the inhibition trial expect for the enclosed words: The participant has to name the color of the non-enclosed words but read the word of the enclosed words. The time required to perform each trial was measured in each trial and errors counted in the third and fourth trial.

Statistical Analysis

Descriptive statistics were used for the primary outcomes. For the statistical analysis of the secondary outcomes, R Statistics software (RStudio, Boston, MA, United States, version 3.6.3) was used. Data was first tested for normal distribution using the Shapiro–Wilk test and QQ plots. Afterward, the data were tested for homogeneity of variance using Levene's test. A two-way mixed ANOVA was used to analyze intragroup differences between pre- and post-measurements, intergroup differences between the intervention and the control group and moreover, the interaction of the factors group and time. The interaction effect provides information whether the group assignment had an influence on the performance difference between pre- and post-measurements. Significance level was set at $\alpha = 0.05$. If the two-way mixed ANOVA reported a significant group, time or interaction effect, data was further analyzed using *post hoc* tests. To calculate effect sizes of intragroup differences between post- and baseline measurements, a dependent T-test or its non-parametric equivalent (Wilcoxon signed rank test) was used. The effect size was interpreted using benchmarks describing the effect size as small ($r \geq 0.01$), medium ($r \geq 0.3$), or large ($r \geq 0.5$) (Tomczak and Tomczak, 2014). In general, "per protocol analysis" was used which means that only participants with a sufficient adherence rate ($\geq$70%) were included in the analysis of the effects.

RESULTS

Demographics and Patient Flow

The demographic data are depicted in **Table 1**. There was no statistically significant difference in age, MMSE score, BMI, time between pre- and post-measurement, years of education or physical activity between the two groups. A total of 39 patients were included in the final analysis (**Figure 1**). The intervention period lasted between 8 and 23 days and the average amount of training sessions was 9.6.

Primary Outcomes

Clinicians were willing to recruit patients, and patients were willing to be randomized in either treatment arm. Within the clinical setting of orthopedic rehabilitation, the exergame intervention could be delivered as intended.

More than 69% of the 68 screened patients agreed to participate and 62% of the 68 screened patients were eventually included into the study and allocated to a study group (**Figure 1**). The attrition rate was 7% (n = 3 participants) and the dropout reasons were all study-unrelated (**Figure 1**). Two participants had to quit prior to the first training and one participant left the clinic after one training due to personal reasons. Consequently, no dropouts occurred for intervention-related reasons and, therefore, the intervention-related attrition rate was 0%. The average adherence rate was 99% and the reasons for non-adherence were acute back-pain and acute stomach-ache. No adverse events occurred during the training sessions (and also not during the pre- and post-assessments). The mean rating of the enjoyment level perceived by the participants in all training session was 4.78 (SD = 0.52) on a 5-point Likert scale. The average scores of each item of the raw NASA-TLX are depicted in **Figure 2A** and the average overall raw NASA-TLX score was 45.5 (SD: 10.40) on a scale from 0 to 100. The mean SUS score was 83.6 (SD: 13.72) on a scale from 0 to 100 and the ratings of each SUS item are depicted in **Figure 2B**. The results of the self-tailored questionnaire are summarized in **Table 2**.

Secondary Outcomes

The Shapiro–Wilk test reported a significant non-normal distribution of the data in all outcome measures expect Stroop1 time, five times sit to stand (FTSST) and Go/No-Go average reaction time, which was confirmed by QQ plots examination. The Levene's test reported non-significant differences between groups and time-points of each outcome and therefore homogeneous variances can be assumed. The results of the robust two-way mixed ANOVA and the corresponding effect sizes are depicted in **Table 3**. *Post hoc* tests reported a significant time effect for normal walking speed ($\Psi = -0.13$, $P < 0.001^{***}$), maximal walking speed ($\Psi = -0.15$, $P < 0.001^{***}$), Stroop3 errors corrected ($\Psi = 0.92$, $P = 0.014^{*}$), Stroop3 time ($\Psi = 7.67$, $P < 0.001^{***}$), Stroop4 time ($\Psi = 7.22$, $P < 0.001^{***}$), SPPB total score ($\Psi = -0.82$, $P = 0.004^{**}$), TUG time ($\Psi = 2.24$, $P < 0.001^{***}$), Go/No-Go average reaction time ($\Psi = 53.61$, $P = 0.002^{**}$) and SRTT average reaction time ($\Psi = 166.8$, $P < 0.001^{***}$) and a non-significant time effect for dual task walking speed ($\Psi = 0.08$, $P = 0.088$) and Stroop 1 time (1.18, $P = 0.178$). Furthermore, *post hoc* tests reported a significant interaction effect for dual task walking speed ($\Psi = 0.23$, $P = 0.002^{**}$), Go/No-Go average reaction time $\Psi = (-81.16$, $P = 0.008^{**})$ and SRTT average reaction time ($\Psi = -134.60$, $P = 0.022^{*}$). In **Figure 3**, the boxplots for the physical and dual-task outcomes and in **Figure 4**, the boxplots for the cognitive outcomes are depicted. Highest performance improvements between pre- and post-measurements were found in the exergame group in the outcome measures SRTT, Go/No-Go and dual task walking speed. The effect sizes for change over time in each group are summarized in **Table 2**.

DISCUSSION

Feasibility

The main aim of this study was to test the feasibility of an exergame intervention in orthopedic inpatient rehabilitation of geriatric patients. All outcome measures regarding usability, safety and acceptability suggest high feasibility and therefore this is an indication that a full RCT of the intervention is worthwhile. There seems to be, furthermore, no pressing need for further development of the intervention before such a RCT can be started for geriatric inpatients. The adherence rate of 99% is very high and goes in line with previous studies examining the adherence to technology-based exercise interventions in older people as reviewed by Valenzuela et al. (2018). However, in the present study and in most studies in that systematic review, the exergame training was supervised closely. It is possible, that the therapeutic alliance contributed to the high adherence rate (Moore et al., 2020). In the present study, many participants emphasized that they appreciated the close supervision by the same person which is not usual in a rehabilitation setting (i.e., exergame training was always supervised by the same person (the study investigator), whereas the rest of the treatments were conducted by different/changing therapists). Similarly, a very low attrition rate was observed, and no dropout occurred due to intervention-related reasons. This results in an intervention-related attrition rate of 0% which has also been observed in several previous studies in older people (Williams et al., 2010; De Bruin et al., 2011; Toulotte et al., 2012; Kim et al., 2013; Lai et al., 2013; Silveira et al., 2013; Lee et al., 2014; Chao et al., 2015). In addition, both, the high adherence and low attrition rate may be further explained by the high motivational potential of exergames (Proffitt et al., 2015; Valenzuela et al., 2018). Many older people enjoy playing exergames (Williams et al., 2010; Franco et al., 2012; Jorgensen et al., 2013) which was also the case in this study in which high motivation and enjoyment levels were perceived during the training sessions. Furthermore, the participants generally felt safe during training and only very few were concerned about falling. The absence of any adverse events confirms this high sense of security and suggests that exergaming is a safe training intervention not only in healthy older people (Valenzuela et al., 2018), but also in more frail people undergoing rehabilitation. However, the applied training load might have been rather low. The raw NASA-TLX score of 45.5 was below the expected score of 55. The score of 45.5 is comparable to executing cognitive tasks (mean score: 46.0), but lower than physical activities (mean score: 62.0) and video gaming (56.5) as summarized in a meta-analysis by Grier (2015). Therefore, it seems that the physical component of the training was perceived as easier compared to other physical activities while the cognitive workload was comparable to other cognitive tasks. In addition, the perceived workload score tends to be higher in other video games, which could mean that overall

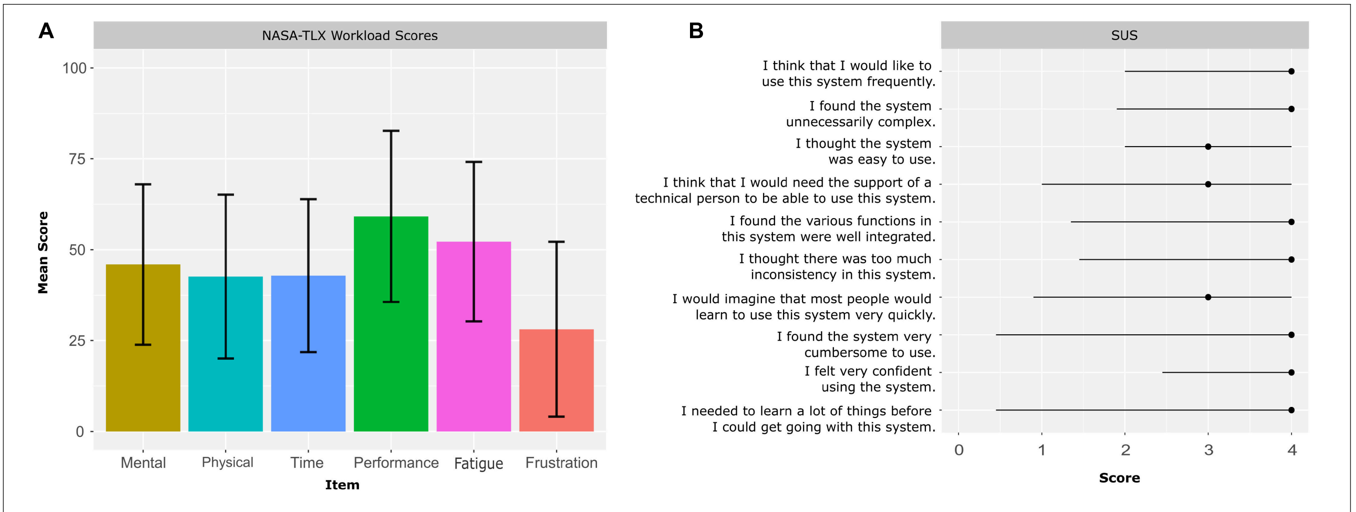

FIGURE 2 | Feasibility outcomes. **(A)** Mean ratings ± standard deviation of each item of the NASA-TLX to assess training workload, **(B)** median and interquartile range of the ratings of each SUS item.

TABLE 2 | Self-tailored Questionnaire regarding usability and safety.

The training on the Dividat Senso was fun.	Completely true (14)	Quite true (5)	More or less true (0)	Rather untrue (0)	Completely untrue (0)
I was motivated for the training.	Completely true (12)	Quite true (6)	More or less true (1)	Rather untrue (0)	Completely untrue (0)
I found the games exciting.	Completely true (12)	Quite true (7)	More or less true (0)	Rather untrue (0)	Completely untrue (0)
I found the games diversified.	Completely true (17)	Quite true (2)	More or less true (0)	Rather untrue (0)	Completely untrue (0)
I think that the training on the Dividat Senso helped to improve my coordination (e.g., balance, reaction).	Completely true (11)	Quite true (6)	More or less true (2)	Rather untrue (0)	Completely untrue (0)
I think that the Training on the Dividat Senso helped to improve my cognitive functions (e.g., memory, concentration).	Completely true (10)	Quite true (7)	More or less true (2)	Rather untrue (0)	Completely untrue (0)
I would recommend the training on the Dividat Senso to people with coordinative or balance impairments.	Completely true (16)	Quite true (3)	More or less true (0)	Rather untrue (0)	Completely untrue (0)
I would recommend the training on the Dividat Senso to people with cognitive impairments.	Completely true (13)	Quite true (2)	More or less true (4)	Rather untrue (0)	Completely untrue (0)
I would recommend the training on the Dividat Senso to other people in general.	Completely true (15)	Quite true (3)	More or less true (1)	Rather untrue (0)	Completely untrue (0)
How would you rate the frequency of the training sessions (5x per week)?	Too low (0)	Rather low (2)	Optimal (14)	Rather high (2)	Too high (1)
How would you rate the duration of the training sessions (approx. 10–15 min)?	Too short (0)	Rather short (3)	Optimal (16)	Rather long (0)	Too long (0)
How safe did you feel during the training sessions?	Very unsafe (0)	Rather unsafe (2)	Not safe nor unsafe (1)	Rather safe (9)	Very safe (7)
Were you afraid of falling during the training sessions?	Never (15)	Hardly ever (2)	Sometimes (2)	Often (0)	Always (0)
Which game did you like the most?	Targets (7), Habitats (6), Simple (2), Ski (2), Hexagon (1), All (1), other games (0)				
Which game did you like the least?	Ski (5), Flexi (3), Hexagon (2), Snake (1), Habitats (1), Simple (1), Simon (1), Targets (1), None (4), other games (0)				
Which game was the most challenging?	Hexagon (5), Flexi (5), Ski (5), Habitats (3), Targets (1), other games (0)				
Which game was the least challenging?	Simple (15), Habitats (3), Flexi (1), other games (0)				
Have you noticed any positive effects (physical, psychological, cognitive) during the training period?	Yes (18), No (1)				
If yes, which positive effects have you noticed?	Reaction (5), attention (3), stability (3), concentration (2), balance (2), coordination (2), psychological well-being (2), cognitive (2), feeling safer (2)				

Numbers in brackets represent absolute values of the frequencies in which each answer was given.

TABLE 3 | Results of each outcome measure across groups and timepoints.

Outcome measures	Exergame group (EG)			Control group (CG)			Q-value (df), *P*-value, Effect size (η^2)		
	T1	T2	*N*	T1	T2	*N*	T1-T2	EG-CG	Interaction
Normal Walking Speed	0.75 (0.40)	0.93 (0.29)	19	0.87 (0.47)	0.96 (0.45)	20	Q(1,21.74) = 16.48 $P < 0.001$***, $\eta^2 = 0.43$	Q(1,21.29) = 0.08 $P = 0.776$, $\eta^2 = 0.00$	Q(1,21.74) = 0.32 $P = 0.577$, $\eta^2 = 0.01$
Maximal Walking Speed	1.05 (0.54)	1.3 (0.57)	19	1.15 (0.50)	1.25 (0.48)	19	Q(1,22.26) = 14.93 $P < 0.001$***, $\eta^2 = 0.40$	Q(1,23.38) = 0.04 $P = 0.846$, $\eta^2 = 0.00$	Q(1,22.26) = 0.62 $P = 0.441$, $\eta^2 = 0.03$
Dual-Task Walking Speed	0.58 (0.28)	0.73 (0.34)	18	0.60 (0.28)	0.69 (0.22)	20	Q(1,17.17) = 10.65 $P = 0.005$**. $\eta^2 = 0.38$	Q(1,20.01) = 0.01 $P = 0.930$, $\eta^2 = 0.00$	Q(1,17.17) = 5.25 $P = 0.035$*, $\eta^2 = 0.23$
TMTA	33.10 (14.77)	30.40 (12.67)	19	36.63 (16.79)	33.85 (22.22)	20	Q(1,19.02) = 4.34 $P = 0.051$, $\eta^2 = 0.19$	Q(1,19.21) = 0.66 $P = 0.428$, $\eta^2 = 0.03$	Q(1,19.02) = 0.34 $P = 0.565$, $\eta^2 = 0.02$
TMTB	123.72 (95.18)	88.75 (86.88)	19	110.19 (56.52)	95.25 (58.47)	18	Q(1,23.23) = 2.98 $P = 0.098$, $\eta^2 = 0.11$	Q(1,23.84) = 0.09 $P = 0.767$, $\eta^2 = 0.00$	Q(1,23.23) = 0.05 $P = 0.646$, $\eta^2 = 0.00$
Stroop1 Time	33.87 (7.45)	31.15 (7.25)	19	35.27 (6.40)	34 (3.57)	20	Q(1,19.78) = 5.14 $P = 0.035$*, $\eta^2 = 0.21$	Q(1,19.82) = 1.27 $P = 0.273$, $\eta^2 = 0.06$	Q(1,19.78) = 0.05 $P = 0.822$, $\eta^2 = 0.00$
Stroop2 Time	23.00 (4.99)	23.19 (5.89)	19	24.88 (6.12)	24.58 (5.19)	20	Q(1,20.02) = 0.03 $P = 0.872$, $\eta^2 = 0.00$	Q(1,22.00) = 1.83 $P = 0.190$, $\eta^2 = 0.08$	Q(1,20.02) = 0.03 $P = 0.860$, $\eta^2 = 0.00$
Stroop3 Time	73.5 (41.61)	70.93 (32.02)	19	70.24 (20.51)	63.60 (19.17)	20	Q(1,20.71) = 24.23 $P < 0.001$***, $\eta^2 = 0.54$	Q(1,17.23) = 0.19 $P = 0.669$, $\eta^2 = 0.01$	Q(1,20.71) = 0.02 $P = 0.878$, $\eta^2 = 0.00$
Stroop3 Errors Not Corrected	0.00 (2.00)	0.00 (2.00)	19	0.00 (0.25)	0.00 (1.00)	20	Q(1,15.49) = 0.18 $P = 0.680$, $\eta^2 = 0.01$	Q(1,15.18) = 1.67 $P = 0.216$, $\eta^2 = 0.1$	Q(1,15.49) = 0.02 $P = 0.879$, $\eta^2 = 0.00$
Stroop3 Errors Corrected	2.00 (1.50)	0.00 (2.00)	19	2.00 (3.25)	1.00 (1.25)	20	Q(1,16.59) = 12.90 $P = 0.002$**, $\eta^2 = 0.44$	Q(1,21.69) = 0.00 $P = 0.995$, $\eta^2 = 0.00$	Q(1,16.59) = 0.19 $P = 0.667$, $\eta^2 = 0.01$
Stroop4 Time	83.00 (37.92)	72.5 (33.7)	19	77.78 (23.37)	68.21 (18.90)	20	Q(1,21.16) = 38.43 $P < 0.001$***, $\eta^2 = 0.64$	Q(1,19.70) = 0.15 $P = 0.699$, $\eta^2 = 0.00$	Q(1,21.16) = 0.13 $P = 0.730$, $\eta^2 = 0.00$
Stroop4 Errors Not Corrected	2.00 (3.50)	1.00 (2.00)	19	1.00 (3.00)	1.00 (2.00)	20	Q(1,18.69) = 1.27 $P = 0.274$, $\eta^2 = 0.06$	Q(1,17.53) = 0.61 $P = 0.445$, $\eta^2 = 0.03$	Q(1,18.69) = 0.48 $P = 0.499$, $\eta^2 = 0.03$
Stroop4 Errors Corrected	1.00 (1.50)	1.00 (2.00)	19	1.00 (2.25)	1.00 (2.25)	20	Q(1,21.68) = 0.01 $P = 0.908$, $\eta^2 = 0.00$	Q(1,19.54) = 0.00 $P = 0.964$, $\eta^2 = 0.00$	Q(1,21.68) = 0.15 $P = 0.698$, $\eta^2 = 0.00$
5TSTS	11.84 (2.97)	12.25 (5.10)	9	11.80 (2.71)	11.43 (3.68)	12	Q(1,7.65) = 0.27 $P = 0.621$, $\eta^2 = 0.03$	Q(1,7.56) = 0.32 $P = 0.589$, $\eta^2 = 0.04$	Q(1,7.56) = 0.02 $P = 0.882$, $\eta^2 = 0.00$
SPPB total score	7.00 (4.50)	10.00 (4.50)	19	7.00 (2.25)	8.00 (3.25)	20	Q(1,21.92) = 15.63 $P < 0.001$***, $\eta^2 = 0.42$	Q(1,19.99) = 1.07 $P = 0.313$, $\eta^2 = 0.06$	Q(1,21.92) = 0.07 $P = 0.794$, $\eta^2 = 0.00$
TUG	15.16 (4.19)	13.21 (3.16)	19	16.78 (6.54)	13.19 (4.36)	19	Q(1,23.67) = 26.28 $P < 0.001$***, $\eta^2 = 0.53$	Q(1,23.96) = 0.45 $P = 0.508$, $\eta^2 = 0.02$	Q(1,23.67) = 1.01 $P = 0.325$, $\eta^2 = 0.04$
Go/No-Go average Reaction Time	986.83 (144.08)	894.24 (149.28)	19	964.04 (254.37)	955.30 (226.55)	19	Q(1,23.38) = 16.77 $P < 0.001$***, $\eta^2 = 0.42$	Q(1,19.54) = 0.02 $P = 0.879$, $\eta^2 = 0.00$	Q(1,23.38) = 6.71 $P = 0.016$*, $\eta^2 = 0.22$
SRTT average Reaction Time	1,223.1 (245.53)	996.2 (167.32)	19	1,173.55 (265.61)	1,078.21 (245.56)	20	Q(1,20.16) = 27.73 $P < 0.001$***, $\eta^2 = 0.58$	Q(1,20.83) = 0.13 $P = 0.725$, $\eta^2 = 0.00$	Q(1,20.16) = 5.23 $P = 0.033$*, $\eta^2 = 0.21$

*Data presented as median (IQR, Interquartile range); TMT, Trail Making Test, Stroop1, Color naming trial; Stroop2, Word reading trial; Stroop3, Inhibition trial; Stroop4, Inhibition/Switching trial; 5TSTS, 5 times standing up from a chair (part of SPPB); SPPB, Short Physical Performance Battery; TUG, Timed Up and Go; SRTT, Step Reaction Time Test. *p < 0.05, **p < 0.01, ***p < 0.001.*

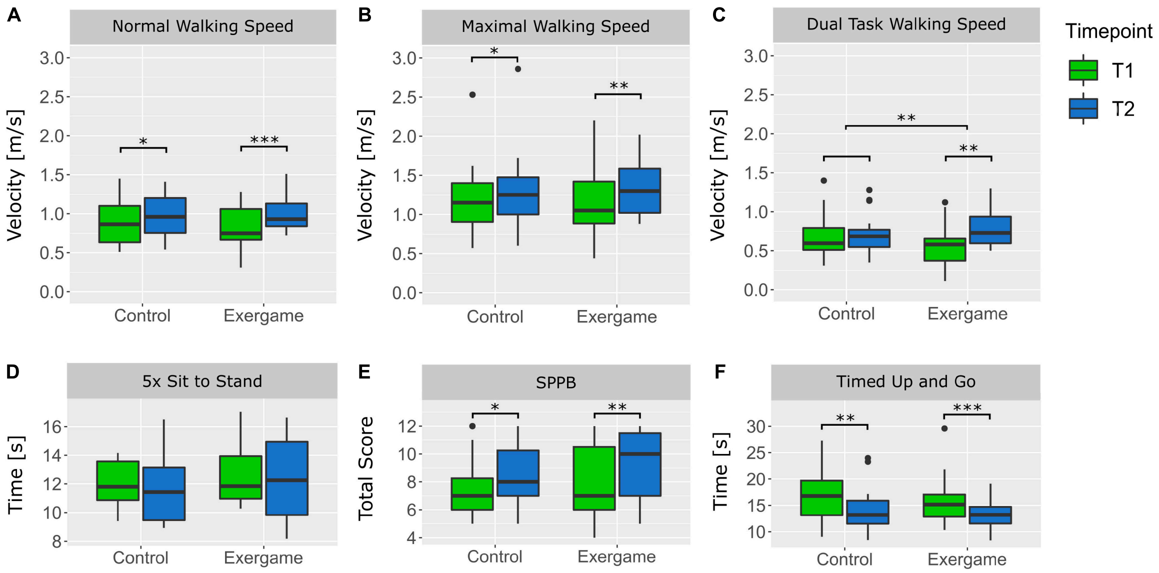

FIGURE 3 | Boxplots of physical outcomes of each group at pre- and post-measurements. **(A)** Velocity for normal walking 10 m, **(B)** maximal velocity for walking 10 m, **(C)** velocity for walking 10 m while dual tasking, **(D)** Time required to stand up five times, **(E)** Total Score achieved in the Short Physical Performance Battery (SPPB), **(F)** Time required for the Timed Up and Go (TUG). *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

workload of the conducted training might have been rather low. Nevertheless, most participants rated the frequency and duration of the training sessions as optimal. This could mean that the workload in terms of number of training sessions per week and duration of training sessions were sufficient, but the training intensity tended to be low. The SUS score of 83.6 can be described as good (Bangor et al., 2009) and suggests that the participants generally had a positive user experience and no major problems in their interaction with the training device were perceived. However, the item-specific SUS ratings suggest that technical support is required for a successful use of the exergame system. Since the Dividat Senso was created for clinical purposes mostly under supervision, the supervisor is indirectly part of the training system. Consequently, the training supervisor should be familiar with the Dividat Senso to ensure fast problem-solving of potential technical problems. In general, the participants were very satisfied with the exergame intervention. Almost all participants subjectively noticed positive effects on physical, cognitive, or psychological aspects during the intervention period and would recommend the exergame training to other people. Moreover, twice as many participants of the intervention group were willing to prolong the stay at the rehabilitation clinic compared to the control group. This might be because some of the participants saw the benefits of the additional exergame training and wanted to profit more from this opportunity. To summarize, in this study, it was shown for the first time that exergaming on the Dividat Senso in geriatric patients is feasible in terms of usability, safety, and acceptability. Thus, exergaming can be successfully incorporated in the rehabilitation program of geriatric patients in inpatient rehabilitation clinics.

Physical and Cognitive Functioning

We hypothesized that the program with additional exergaming would be more meaningful for patients when compared to the traditional rehabilitation program. In all physical and cognitive outcome measures, the exergame group made equal or higher performance improvements compared to the control group. Both groups significantly improved in most physical and cognitive outcome measures. The exergame group also significantly improved in Go/No-Go and SRTT reaction time, and dual task walking speed. Effect sizes ranged between 0.25 and 0.85 and mostly favor the exergame training group (**Table 4**). A significant interaction effect between group and time reveals that the group allocation had a significant influence on the performance in these tests. In the intervention group, stepping capacity could therefore be improved in terms of a reduced choice reaction time which was also shown by Crotty et al. (2011). In addition, the intervention group was able to increase their walking speed while executing a cognitive task. Furthermore, this group showed walking speed change well beyond the 0.13 m per second Minimal Detectable Change Values (MDC) that can be expected in short term rehabilitation (Middleton et al., 2015) whereas the values for the control group remained within the MDC. This result is consistent with previous findings describing the combination of physical-cognitive training to have superior effects on dual task walking speed than physical training alone (Tait et al., 2017; Raichlen et al., 2020). It can, thus, be concluded that the exergame intervention in this study had a superior effect on the physical-cognitive tasks compared to the rehabilitation program alone. Furthermore, the effect sizes of most outcome measures are higher in the exergame training group compared to the control group (**Table 4**). However, no significant differences

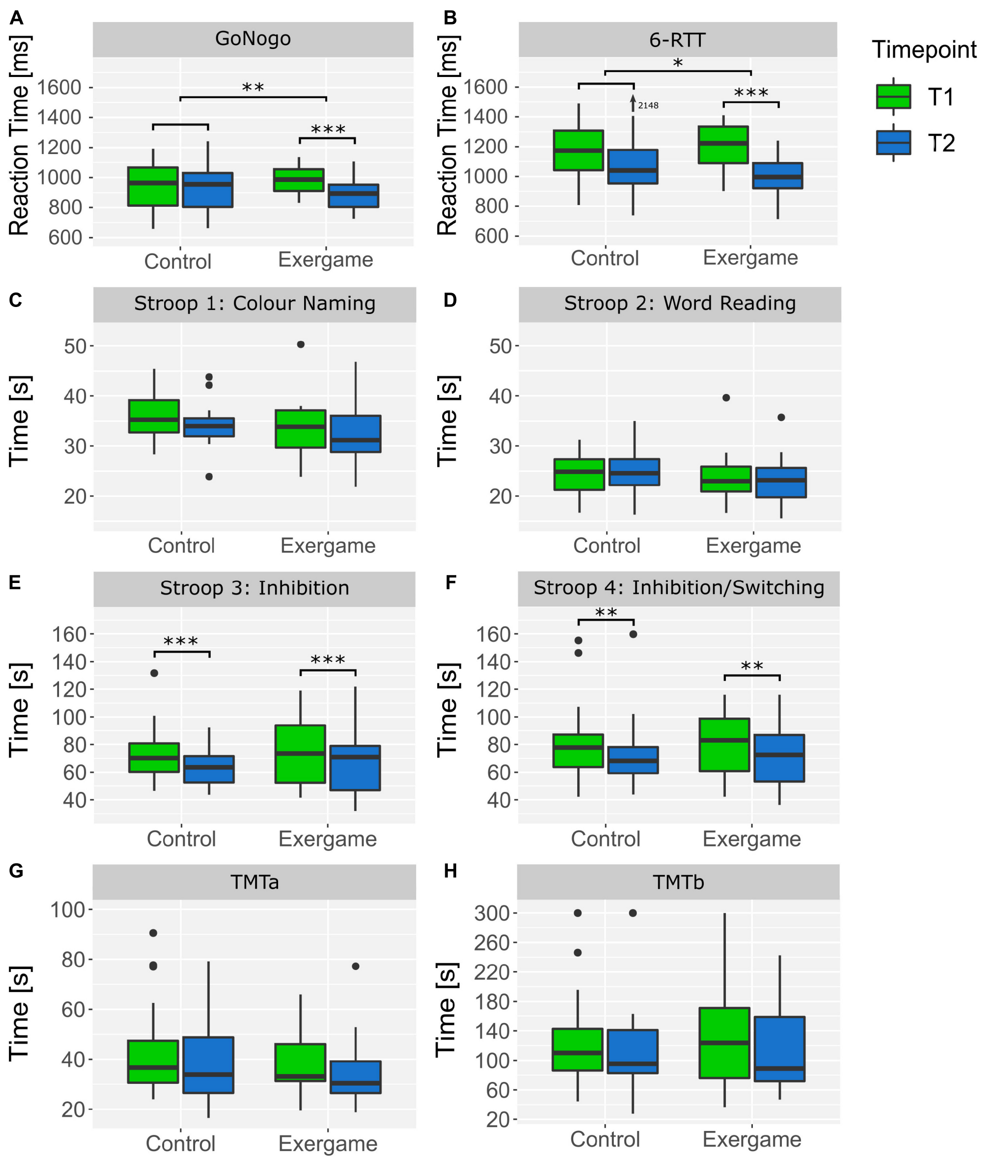

FIGURE 4 | Boxplots of cognitive outcomes of each group at pre- and post-measurements. **(A)** Reaction Time in the Go/No-Go Test on the Dividat Senso, **(B)** Reaction Time in the 6-Step Reaction Time test (SRTT) on the Dividat Senso, **(C)** Time required for the first Stroop task (Color Naming), **(D)** time required for the second Stroop task (Word Reading), **(E)** time required for the third Stroop task (Inhibition), **(F)** time required for the fourth Stroop task (Inhibition/Switching), **(G)** time required for the Trail Making Test (TMT) part A, **(H)** time required for the Trail Making Test (TMT) part B. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

were found between the groups regarding the outcome measures assessing either physical or cognitive functions alone. This is in contrast to previous studies which reported significant effects of exergaming on cognitive functions (Stanmore et al., 2017), functional mobility or balance (Crotty et al., 2011; Jorgensen et al., 2013; Jung et al., 2015; Park et al., 2015; Padala et al., 2017). However, in most of these studies, the intervention period lasted for at least 8 weeks and for balance assessment, the Berg Balance Scale (BBS) was used. Moreover, in some studies (Jorgensen et al., 2013; Schoene et al., 2013), a passive control group was used. These methodological differences might explain the absence of significant differences between the groups in the individual cognitive and physical outcomes in this study. On the one hand, it is possible that the exergame training was cognitively and/or physically not sufficiently demanding to achieve the optimal training stimulus to induce plastic alterations measurable by the outcome measures (Lövdén et al., 2010). On the other hand, a previously reported dose-response effect between cognitive-motor training and cognitive benefits suggests that the benefits of the applied exergame training could increase and become measurable by increasing training dosage (Bamidis et al., 2015). Thanks to the gamification of exercise, exergaming has the potential to increase patients' motivation and long-term adherence to exercise routines (Proffitt et al., 2015;

TABLE 4 | Effect sizes representing change over time in each group.

Outcome measures	Exergame group (EG)	Control group (CG)
	T1-T2	T1-T2
Normal Walking Speed	$r = 0.76$, $P < 0.001$***	$r = 0.48$, $P = 0.032$*
Maximal Walking Speed	$r = 0.66$, $P = 0.004$**	$r = 0.46$, $P = 0.044$*
Dual-Task Walking Speed	$r = 0.77$, $P = 0.001$**	$r = 0.25$, $P = 0.263$
TMTA	$r = 0.42$, $P = 0.073$	$r = 0.43$, $P = 0.053$
TMTB	$r = 0.34$, $P = 0.137$	$r = 0.33$, $P = 0.157$
Stroop1 Time	$r = 0.35$, $P = 0.131$	$r = 0.43$, $P = 0.143$
Stroop2 Time	$r = 0.40$, $P = 0.083$	$r = 0.23$, $P = 0.314$
Stroop3 Time	$r = 0.71$, $P < 0.001$***	$r = 0.74$, $P < 0.001$***
Stroop3 Errors Not Corrected	$r = 0.12$, $P = 0.447$	$r = 0.15$, $P = 0.504$
Stroop3 Errors Corrected	$r = 0.64$, $P = 0.006$**	$r = 0.48$, $P = 0.025$*
Stroop4 Time	$r = 0.70$, $P = 0.001$**	$r = 0.59$, $P = 0.006$**
Stroop4 Errors Not Corrected	$r = 0.02$, $P = 0.97$	$r = 0.24$, $P = 0.235$
Stroop4 Errors Corrected	$r = 0.20$, $P = 0.592$	$r = 0.09$, $P = 0.645$
5TSTS	$r = 0.22$, $P = 0.515$	$r = 0.56$, $P = 0.173$
SPPB total score	$r = 0.76$, $P = 0.001$**	$r = 0.40$, $P = 0.036$*
TUG	$r = 0.77$, $P < 0.001$***	$r = 0.64$, $P = 0.005$**
Go/No-Go average Reaction Time	$r = 0.77$, $P < 0.001$***	$r = 0.27$, $P = 0.268$
SRTT average Reaction Time	$r = 0.85$, $P < 0.001$***	$r = 0.38$, $P = 0.092$

Results of Wilcoxon signed rank test. r = effect size, calculated: $\mathbf{r} = \frac{\mathbf{Z}}{\sqrt{\mathbf{n}}}$ *(Z, Absolute standardized test statistic; n, number of pairs); P, P-Value; TMT, Trail Making Test; Stroop1, Color naming trial; Stroop2, Word reading trial; Stroop3, Inhibition trial; Stroop4, Inhibition/Switching trial; 5TSTS, 5 times standing up from a chair (part of SPPB); SPPB, Short Physical Performance Battery; TUG, Timed Up and Go; SRTT, Step Reaction Time Test. *p < 0.05, **p < 0.01, ***p < 0.001.*

Kappen et al., 2019; Randriambelonoro et al., 2020), that stretch beyond their stay in the inpatient clinic. Exergaming can make a rehabilitation program more entertaining and therefore increase the success of the entire rehabilitation program (Bonnechère et al., 2016). Our data warrant performance of a RCT that is performed over a longer (outpatient) rehabilitation period and that should assess effectiveness. Furthermore, it was shown that exergaming has a significant effect on stepping capacity and walking during dual task conditions. Since both are known fall risk factors (Muir-Hunter and Wittwer, 2016; Okubo et al., 2017, 2021; Bayot et al., 2020), exergaming on the Dividat Senso could be a beneficial supplement to conventional rehabilitation therapies to reduce fall risk of geriatric patients.

Study Limitations

In this study, the exergame intervention was examined in geriatric patients undergoing inpatient rehabilitation and the generalization to other population groups and settings is limited. Further studies are required to test the feasibility and effects of exergaming on the Dividat Senso in other patient groups undergoing inpatient rehabilitation but also in geriatric patients and other patient groups undergoing outpatient rehabilitation for longer durations. Another limitation is that all measurements and training sessions were conducted and supervised by the same local investigator. Consequently, blinding was only possible for the pre-measurements but not for group assignment and post-measurements. A further limitation is the short duration of the intervention. A longer intervention period is needed where effectiveness should be investigated. However, the standard prescription for rehabilitation in an orthopedic or geriatric rehabilitation clinic in Switzerland ranges between 2 and 3 weeks. Since this study aimed to test exergaming in a realistic rehabilitation setting it was important not to artificially extend the duration of the rehabilitation. Another point that should be critically discussed is the chosen outcome measures. No feasibility measures were assessed for the control group which received just the standard treatment; thus a direct comparison of e.g., the required resources is impossible. In addition to this, about half of the participants were not able to execute the Five Times Sit to Stand Test which is a part of the SPPB. Still, the SPPB total score revealed high performance differences between pre- and post-measurements in the intervention group above the substantial change estimates (Perera et al., 2006). However, the use of an easier sit to stand test such as the modified 30 Second Sit to Stand Test (m30STS) (McAllister and Palombaro, 2020) would provide additional information on functional mobility for a future RCT in this frail population group. A further limitation is that the dual task performance was only assessed by walking speed while information about the cognitive performance was not assessed. Therefore, no statement can be made if the improvements in the exergame group is a result of the task prioritization or improved task switching ability. Finally, despite the strategies for individual training adaptations described in the "Materials and Methods" section, it is possible that the training intensity was not sufficiently high to provide the optimal stimulus to each participant. The quantitative assessment of the patients' subjective perception of game difficulty would be a further option to individually adapt training load.

Conclusion and Outlook

In this pilot feasibility study, it was shown that exergaming using the Dividat Senso is a feasible, safe and effective intervention that can readily be integrated in the rehabilitation programs of geriatric inpatients. The high adherence rate, low attrition rate and high acceptability suggest that exergaming offers a great opportunity to make a rehabilitation program more entertaining and increase the motivation of the patients to adhere to their exercise routines while staying in a rehabilitation clinic. Moreover, exergaming on the Dividat Senso has the potential to improve stepping capacity and dual task walking speed in only a few weeks. Both are important fall risk factors and therefore exergaming could be beneficial in reducing fall risk in geriatric patients as previously indicated by a systematic review (Schoene et al., 2014). Furthermore, if the intervention period could be prolonged, more beneficial effects, also on single cognitive and physical functions, might be expected. Consequently, the continuation of the exergame training within the scope of outpatient rehabilitation or as a home-based approach after the end of the inpatient rehabilitation is warranted. The development of home-based exergame systems seems to offer potential for future fall-prevention strategies. Future studies using longer time frames should place a focus on adjusting the training load to each participants' level and also assess dose-response effects while progressing through a rehabilitation program.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

This study's design was reviewed and approved by the Cantonal Ethics Committee of Zurich, Switzerland (Reg. No. 98 2020-02388). All participants provided their written informed consent.

AUTHOR CONTRIBUTIONS

EG, MA, and EB designed the study. FG was responsible for the recruitment. FG, EG, and MA supervised the data collection process. PA collected and analyzed the data and drafted the first manuscript. All authors critically revised the manuscript and approved the final submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2021.739948/full#supplementary-material

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The remaining 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.

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METHODS
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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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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' (Li et al., 2020).

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.

Keywords: cognition, development, exercise, exergames, neurosciences, technology, training

INTRODUCTION

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 (Boletsis and McCallum, 2015; Stanmore et al., 2017). *"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"* (Oh and Yang, 2010). Specifically designed and/or implemented games within these training settings are also called 'serious games'; games developed with a purpose beyond play (Michael and Chen, 2005; Rego et al., 2010). Using exergames for therapeutical interventions complements traditional exercises by using virtual reality, feedback principles and gamification to increase patient motivation and engagement (Matallaoui et al., 2017). 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"* (Aminov et al., 2018). Recent meta-analytic reviews have synthesized that exergame-based training interventions significantly improved various health-related outcomes, including cognitive performance (Howes et al., 2017; Stanmore et al., 2017) and functional physical outcomes (i.e., balance, mobility, exercise capacity) (Howes et al., 2017; Pacheco et al., 2020) 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 (Zhao et al., 2020).

Exergames are a form of simultaneous motor-cognitive training with incorporated cognitive task demands (Herold et al., 2018). According to the 'guided-plasticity facilitation' framework (Fabel and Kempermann, 2008; Kempermann et al., 2010; Herold et al., 2018), acute physical exercise is assumed to enhance brain metabolism and promote neuroplastic processes, whereas these changes in brain plasticity are guided by cognitive stimulation (Fabel and Kempermann, 2008; Kempermann et al., 2010; Joubert and Chainay, 2018). 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 (Lauenroth et al., 2016; Joubert and Chainay, 2018). 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 (Chen et al., 2020; Gavelin et al., 2021) and older adults with mNCD (Wu et al., 2019; Biazus-Sehn et al., 2020; Gavelin et al., 2021). This is also evidenced by slightly superior effects of exergames on cognitive functioning when compared to physically or cognitively active control interventions (Howes et al., 2017; Stanmore et al., 2017; Wang et al., 2019). 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 (Lauenroth et al., 2016; Levin et al., 2017; Tait et al., 2017; Joubert and Chainay, 2018; Yang et al., 2019) or exergame-based (Ogawa et al., 2016; Howes et al., 2017; Stanmore et al., 2017; van Santen et al., 2018; Sokolov et al., 2020; Zhao et al., 2020) 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"* (Stanmore et al., 2017) in older adults with NCDs (Lauenroth et al., 2016; Stanmore et al., 2017; van Santen et al., 2018; Haeger et al., 2019; Moreno et al., 2019; Yang et al., 2019; Sokolov et al., 2020; Swinnen et al., 2020b; Zhao et al., 2020).

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"* (Panza et al., 2018). 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"* (Robison and Rogers, 1994). In short, adherence to training interventions is key to obtain and preserve health benefits (Robison and Rogers, 1994).

"Adherence can be intended as 'maintaining an exercise regimen for a prolonged period following the initial adoption phase'" (Lox et al., 2016; Di Lorito et al., 2020) and is

usually calculated as *"the proportion between the number of sessions attended and the number of sessions offered, reported in percentage"* (Di Lorito et al., 2020). Adherence rates are generally high in exergame-based intervention studies including HOA (Valenzuela et al., 2016; Pacheco et al., 2020) and older adults with NCDs (Swinnen et al., 2020b; Zhao et al., 2020). 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"* (Howes et al., 2017). 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)"* (Stanmore et al., 2017).

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) (Picorelli et al., 2014), 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 (Rhodes et al., 1999). "*Because adherence (or lack thereof) is so crucial to obtain study outcomes, effective strategies and adequate resources should be deployed to address this issue*" (Di Lorito et al., 2020). 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"* (van der Wardt et al., 2017).

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 (Diaz Baquero et al., 2021). Ideally, this process fulfills *"the international standards proposed by ISO9241-210 (International Organization for Standardization, 2019) 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"* (Diaz Baquero et al., 2021). However, it was shown that only half of the studies took the standard 'specification of user requirements' into account (Diaz Baquero et al., 2021). 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"* (Diaz Baquero et al., 2021). Additionally, their finding indicates *"the need to apply this methodology in a more standardized way"* (Diaz Baquero et al., 2021).

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' (Li et al., 2020). 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 (Li et al., 2020). 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 (Li et al., 2020).

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.

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.

CASE STUDY

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 1**.

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.

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"* (Li et al., 2020). 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

TABLE 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 Feasibility Study	"Step 4: Playtesting of Exergame-based Training Concept"
	Step 5:	Modification of Exergame- and Intervention Components		"Step 5: Modification of Exergame-based Training Concept"
Phase 3 – System Evaluation (Start: April 2022)				
Evaluation 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) as secondary outcomes.		Randomized Controlled Trial	"Phase 3: System Evaluation"

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"* (Li et al., 2020).

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 (Lampit et al., 2014; Toril et al., 2014; Mewborn et al., 2017; Joubert and Chainay, 2018; World Health Organization [WHO], 2019; Gates et al., 2020). 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 (Lampit et al., 2014; Toril et al., 2014; Joubert and Chainay, 2018; Bonnechère et al., 2020; Gates et al., 2020) vs. no effect (Sala et al., 2018; Vaportzis et al., 2019; Mansor et al., 2020)], executive function {i.e., improvement (Bonnechère et al., 2020) vs. mixed results [improvements in cognitive inhibition, but no effect on cognitive shifting (Mansor et al., 2020)] vs. no effect (Lampit et al., 2014; Toril et al., 2014; Vaportzis et al., 2019; Gates et al., 2020)}, learning and memory [i.e., improvement (Lampit et al., 2014; Toril et al., 2014; Bonnechère et al., 2020) vs. no effect (Sala et al., 2018; Vaportzis et al., 2019; Gates et al., 2020; Mansor et al., 2020)], visuo-spatial skills [i.e., improvement (Lampit et al., 2014) vs. no effect (Melby-Lervåg et al., 2016; Sala et al., 2018; Vaportzis et al., 2019; Bonnechère et al., 2020)], and working memory [i.e., improvement (Lampit et al., 2014; Melby-Lervåg et al., 2016; Joubert and Chainay, 2018; Bonnechère et al., 2020) vs. no effect (Vaportzis et al., 2019; Gates et al., 2020)]. Although transfer-effects are still debated (Sala and Gobet, 2018; Nguyen et al., 2019), and three meta-analyses have shown smaller improvements in non-trained compared to trained outcomes (Karbach and Verhaeghen, 2014; Melby-Lervåg et al., 2016; Mewborn et al., 2017), these effects were still significant in two of these meta-analyses (Karbach and Verhaeghen, 2014; Mewborn et al., 2017).

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 (Hill et al., 2017; Sherman et al., 2017; Bahar-Fuchs et al., 2019; Gates et al., 2019; Zhang et al., 2019) and working memory (Hill et al., 2017; Sherman et al., 2017; Bahar-Fuchs et al., 2019; Gates et al., 2019; Zhang et al., 2019) have been shown, whereas the evidence for cognitive training remains inconsistent for complex attention [i.e.. improvement (Hill et al., 2017; Bahar-Fuchs et al., 2019) vs. no effect (Sherman et al., 2017; Gates et al., 2019)], executive function [i.e., improvement (Sherman et al., 2017; Bahar-Fuchs et al., 2019) vs. no effect (Hill et al., 2017; Gates et al., 2019; Zhang et al., 2019)], global cognition [i.e., improvement (García-Casal et al., 2017; Hill et al., 2017; Mewborn et al., 2017; Sherman et al., 2017; Bahar-Fuchs et al., 2019; Gates et al., 2019; Zhang et al., 2019) vs. no effect (Liang et al., 2018)], verbal fluency {i.e., improvement (Hill et al., 2017; Sherman et al., 2017) vs. mixed effects [improvement in verbal category fluency but not in verbal letter fluency (Bahar-Fuchs et al., 2019)] vs. no effect (Gates et al., 2019)}, or psychosocial factors like anxiety or depression [i.e., improvement (Hill et al., 2017; García-Casal et al., 2017; Chan J.Y.C. et al., 2020) vs. no effect (Liang et al., 2018; Bahar-Fuchs et al., 2019; Gates et al., 2019)], while cognitive training seems to exert no significant effect on visuo-spatial skills (Hill et al., 2017), functional physical performance or activities of daily living (García-Casal et al., 2017; Hill et al., 2017; Bahar-Fuchs et al., 2019; Gates et al., 2019), and quality of life (Bahar-Fuchs et al., 2019; Gates et al., 2019). Reviewed neuroimaging studies have indicated a training induced *"increase in brain activation (particularly in frontoparietal regions) and either an increase or maintenance in connectivity"* (Miotto et al., 2018). This is consistent with another systematic review, that has found *"no effects [. . .] on hippocampal volumes post-training, but cortical thickening and increased gray matter volumes"* (Beishon et al., 2020), suggesting that the brain remains highly plastic in older adults with NCD (Canu et al., 2018; Miotto et al., 2018). 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 (Gomes-Osman et al., 2018; Joubert and Chainay, 2018; Northey et al., 2018; Etnier et al., 2019; Sanders et al., 2019; World Health Organization [WHO], 2019). Regarding specific cognitive outcomes, physical training (including aerobic, resistance, and multicomponent training) was shown to significantly improve complex attention (Levin et al., 2017; Gomes-Osman et al., 2018; Joubert and Chainay, 2018; Northey et al., 2018; World Health Organization [WHO], 2019), executive functions (Gomes-Osman et al., 2018; Joubert and Chainay, 2018; Northey et al., 2018; Sanders et al., 2019; World Health Organization [WHO], 2019; Chen et al., 2020), learning and memory (Northey et al., 2018; Sanders et al., 2019), visuo-spatial skills (World Health Organization [WHO], 2019), and working memory (Northey et al., 2018; World Health Organization [WHO], 2019), although these effects didn't always reach statistical significance and depend on exercise and training variables (Kelly et al., 2014; Northey et al., 2018; Sanders et al., 2019). Additionally, physical training interventions were shown to reduce fall rates (Sherrington et al., 2017) and exert a positive effect on cardiac autonomic control (Raffin et al., 2019) and hippocampal volumes (Firth et al., 2018) 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 (Sanders et al., 2019; Biazus-Sehn et al., 2020; Chen et al., 2020; Zhou et al., 2020) and visuo-spatial skills (Zhou et al., 2020), whereas no significant changes in complex attention (Kelly et al., 2014; Biazus-Sehn et al., 2020; Law et al., 2020), and mixed findings for global cognition [i.e., improvement (Groot et al., 2015; Ströhle et al., 2015; Gomes-Osman et al., 2018; Northey et al., 2018; Panza et al., 2018; Etnier et al., 2019; Jia et al., 2019; Sanders et al., 2019; Wang et al., 2019; Biazus-Sehn et al., 2020; Law et al., 2020; Zhou et al., 2020) vs. no effect (Kelly et al., 2014; Forbes et al., 2015; Liang et al., 2018)], language [i.e., improvement (Zhou et al., 2020) vs. no effect (Kelly et al., 2014; Biazus-Sehn et al., 2020; Law et al., 2020)], learning and memory {i.e., improvement (Zhou et al., 2020) vs. mixed effects [i.e., improvement in delayed recall and no effect on immediate recall (Biazus-Sehn et al., 2020)] vs. no effect (Kelly et al., 2014; Gomes-Osman et al., 2018; Sanders et al., 2019; Law et al., 2020)}, and working memory [i.e., improvement (Law et al., 2020) vs. no effect (Kelly et al., 2014; Gomes-Osman et al., 2018; Biazus-Sehn et al., 2020)] were synthesized. Additionally, meta-analytic results have synthesized significant improvements in activities of daily living (Forbes et al., 2015; Groot et al., 2015; Lam et al., 2018), balance (Lam et al., 2018), behavioral problems (Law et al., 2020), endurance (Lam et al., 2018), gait (i.e., step length and walking speed) (Lam et al., 2018), and mobility (Lam et al., 2018). Furthermore, positive effects on depressive symptoms (Forbes et al., 2015) and inconsistent findings on fall rate [improvement (Sherrington et al., 2017) vs. no effect (Lam et al., 2018)] 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.

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 (Firth et al., 2018; Joubert and Chainay, 2018; Haeger et al., 2019; Herold et al., 2019b; Marinus et al., 2019; Stillman et al., 2020). There are already meta-analytic results that corroborate some of these effects by showing that aerobic training slows down the decline in hippocampal volume (Firth et al., 2018) and strength training or combined training increase peripheral BDNF concentration (Marinus et al., 2019) that might be related to changes in cognitive abilities (Joubert and Chainay, 2018). 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 (Canu et al., 2018; Haeger et al., 2019; Herold et al., 2019b; Stillman et al., 2020). 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"* (Haeger et al., 2019; Stillman et al., 2020). 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"*) (Herold et al., 2019b). 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 (Groot et al., 2015; Panza et al., 2018; Sanders et al., 2019; Law et al., 2020), while cognitively engaging training appears to have the strongest effect on cognition (Lauenroth et al., 2016; Howes et al., 2017; Levin et al., 2017; Stanmore et al., 2017; Joubert and Chainay, 2018; van Santen et al., 2018; Stojan and Voelcker-Rehage, 2019; Wang et al., 2019; Wu et al., 2019; Biazus-Sehn et al., 2020; Chen et al., 2020; Gallou-Guyot et al., 2020; Mansor et al., 2020; Zhu et al., 2020; Gavelin et al., 2021). These findings are consistent with the 'guided-plasticity facilitation' framework (Fabel and Kempermann, 2008; Kempermann et al., 2010; Herold et al., 2018): Acute physical exercise is assumed to enhance brain metabolism and promote neuroplastic processes, whereas these changes in brain plasticity are guided by cognitive stimulation (Fabel and Kempermann, 2008; Kempermann et al., 2010; Joubert and Chainay, 2018). 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 (Lauenroth et al., 2016; Joubert and Chainay, 2018). 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 (Howes et al., 2017; Chen et al., 2020; Mansor et al., 2020) and working memory (Mansor et al., 2020) in response to sequential or simultaneous motor-cognitive training while the evidence for global cognition [i.e., improvement (Stanmore et al., 2017; Northey et al., 2018; Chen et al., 2020; Zhu et al., 2020; Gavelin et al., 2021) vs. no effect (Wu et al., 2019)] and learning and memory {i.e., mixed findings [improvement in updating memory but no effect on delayed memory (Mansor et al., 2020)]} remains conflicting, and no significant effects were synthesized for complex attention (Vaportzis et al., 2019; Mansor et al., 2020), and verbal fluency (Stanmore et al., 2017). Additionally, improvements in balance (Howes et al., 2017; Pacheco et al., 2020) and functional exercise capacity (Howes et al., 2017) have been synthesized while the evidence for mobility remains conflicting [i.e., improvement (Pacheco et al., 2020; Gavelin et al., 2021) vs. no effect (Howes et al., 2017)] and no significant effects have been synthesized for activities of daily living (Corregidor-Sánchez et al., 2020). When considering meta-analytic results for exergaming specifically, significantly larger improvements in complex attention (Stanmore et al., 2017), executive functions (Howes et al., 2017; Stanmore et al., 2017), global cognition (Stanmore et al., 2017), visuospatial processing (Stanmore et al., 2017), and also functional physical outcomes (i.e., balance, mobility) (Howes et al., 2017), and fear of falling (Howes et al., 2017), but not activities of daily living (Corregidor-Sánchez et al., 2020) or functional exercise capacity (Howes et al., 2017) have been synthesized compared to physically or cognitively active control interventions.

For older adults with mNCD or dementia, significant improvements in complex attention (Chan J.S.Y. et al., 2020), global cognition (Stanmore et al., 2017; Wang et al., 2019; Wu et al., 2019; Biazus-Sehn et al., 2020; Chan J.S.Y. et al., 2020; Zhu et al., 2020; Gavelin et al., 2021), learning and memory (Biazus-Sehn et al., 2020; Chan J.S.Y. et al., 2020), and visuo-spatial skills (Chan J.S.Y. et al., 2020) have been meta-analytically synthesized, whereas there is conflicting evidence for executive functioning [i.e., improvement (Biazus-Sehn et al., 2020) vs. no effect (Chan J.S.Y. et al., 2020)] and language (Zhu et al., 2020), and no effects have been synthesized for working memory (Chan J.S.Y. et al., 2020). Additionally, improvements in physical outcomes (e.g., mobility, balance) (Gavelin et al., 2021) and psychosocial factors (i.e., neuropsychiatric symptoms, depression, quality of life) (Gavelin et al., 2021) 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 (Stanmore et al., 2017). Moreover, exergame-based training interventions are greatly accepted in individuals with mNCD and increase training adherence and engagement through facilitating training motivation and satisfaction (Zhao et al., 2020).

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 (Stanmore et al., 2017; van Santen et al., 2018; Stojan and Voelcker-Rehage, 2019; Swinnen et al., 2020b; Zhao et al., 2020; Gavelin et al., 2021). 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 (Lauenroth et al., 2016; Tait et al., 2017; Joubert and Chainay, 2018; Haeger et al., 2019; Stojan and Voelcker-Rehage, 2019; Yang et al., 2019). 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"* (Muiños and Ballesteros, 2021). 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"* (Stojan and Voelcker-Rehage, 2019). 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 (Canu et al., 2018; Haeger et al., 2019; Yang et al., 2019). 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"* (Stanmore et al., 2017) in older adults with NCDs (Lauenroth et al., 2016; Stanmore et al., 2017; van Santen et al., 2018; Haeger et al., 2019; Moreno et al., 2019; Yang et al., 2019; Sokolov et al., 2020; Swinnen et al., 2020b; Zhao et al., 2020). 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"* (Li et al., 2020). 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 (Manser et al., 2022a[1]).

Clinical Picture

The clinical picture of mNCD represents an intermediate stage of cognitive impairment between the normal aging process and dementia (Petersen et al., 1997, 2014; American Psychiatric Association, 2013; Lindbergh et al., 2016; Sanford, 2017; Janelidze and Botchorishvili, 2018; World Health Organization [WHO], 2018). 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*

[1] Manser, P., Adcock, M., and de Bruin, E. D. (2022a). Design Considerations for an Exergame-based Training Intervention for Older Adults with mild Neurocognitive Disorder.

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)" (American Psychiatric Association, 2013). 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"* (Stokin et al., 2015). 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) (Petersen, 2011; Roberts and Knopman, 2013; Janelidze and Botchorishvili, 2018). Deteriorations in episodic memory and executive function represent the most prevalent cognitive impairments (Chehrehnegar et al., 2020). 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 (Schuff and Zhu, 2007; Janelidze and Botchorishvili, 2018; Chehrehnegar et al., 2020). Especially the structural changes in the hippocampus predict the conversion of MCI to dementia (Kantarci et al., 2005; Apostolova et al., 2006).

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 (Petersen et al., 2009, 2014, 2018; Hu et al., 2017; Janelidze and Botchorishvili, 2018; Parnetti et al., 2019). The global incidence of MCI is estimated to increase from 2% at age 75 – 79 increasing up to 7% (Janelidze and Botchorishvili, 2018; Gillis et al., 2019). 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% (Mitchell and Shiri-Feshki, 2009). Fortunately, between 14% (clinical populations) and 31% (community-based cohort) revert to normal cognitive functioning for their age (Malek-Ahmadi, 2016; Kasper et al., 2020). Nonetheless, a recent meta-analysis reported a pooled progression rate of 34%, more than twice as high as the pooled reversion rate of 15% (Hu et al., 2017). This dichotomy between conversion to dementia and reversion to normal cognition suggests the presence of modifiable risk factors contributing to this cognitive decline (Sanford, 2017; Kasper et al., 2020).

Risk Factors, Prevention and Treatment Options

Age is considered to be the strongest risk factor for developing mNCD (Hu et al., 2017; Sanford, 2017; Janelidze and Botchorishvili, 2018; Levine et al., 2018; Parnetti et al., 2019). Other risk factors include the male sex (Petersen et al., 2010; Roberts et al., 2012; Hu et al., 2017), the presence of the apolipoprotein E allele (Caselli et al., 2009), a family history of cognitive impairment (Ng et al., 2016), the presence of vascular risk factors (i.e., metabolic syndrome, hypertension, hyperlipidemia, coronary heart disease, diabetes mellitus, or stroke) (Roberts et al., 2014; Vassilaki et al., 2015; Pal et al., 2018), or a physically or cognitively sedentary lifestyle (Verghese et al., 2006; Geda et al., 2010). Hence, changes in lifestyle that increase physical activity and/or reduce vascular risk factors are powerful protectors for brain atrophy and cognitive decline (Erickson et al., 2010; Sofi et al., 2011; Beydoun et al., 2014; Blondell et al., 2014; Carvalho et al., 2014; Beckett et al., 2015; Guure et al., 2017; Lee, 2018; Cunningham et al., 2020). When considering therapy options for incident MCI, physical and cognitive training were even shown to outperform pharmacological therapies (Liang et al., 2018). Indeed, *"there is currently no effective pharmacological intervention for MCI"* (Kasper et al., 2020). 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 (Cooper et al., 2013; Fitzpatrick-Lewis et al., 2015; Ströhle et al., 2015; Farina et al., 2017; Butler et al., 2018; Fink et al., 2018). Consequently, it was suggested to focus on multi-domain treatment strategies including physical training and cognitive stimulation (Sanford, 2017; Kasper et al., 2020). 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"* (de Oliveira et al., 2015; Lehert et al., 2015; Chuang et al., 2016; Iadecola et al., 2016; Smith, 2019). 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 (American Psychiatric Association, 2013). 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 (Manser et al., 2022a) (see text footnote 1).

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 (Manser et al., 2022a) (see text footnote 1).

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 (Manser et al., 2022a) (see text footnote 1). 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 (Zhao et al., 2020). Accordingly, adherence to exergame-based training interventions is typically high in older adults with NCD (Swinnen et al., 2020b; Zhao et al., 2020). 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 (Manser et al., 2022a) (see text footnote 1).

Motivators for Treatment

The 'Self-determination Theory' (Deci and Ryan, 2002) has demonstrated considerable efficacy in explaining exercise motivation and behavior (Hagger and Chatzisarantis, 2008). 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 (Hagger and Chatzisarantis, 2007; Murcia et al., 2008; Wilson et al., 2008; Teixeira et al., 2012). 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) (Ryan and Deci, 2000). The 'Self-determination Theory' (Deci and Ryan, 2002) is in line with multiple empirical observations that predicted favorable exercise and training behavior with more autonomous forms of motivational regulation in healthy adults (Duncan et al., 2010; Teixeira et al., 2012; Wilson et al., 2012; Friederichs et al., 2015), HOA (Teixeira et al., 2012; Devereux-Fitzgerald et al., 2016; Gummelt, 2017; Behzadnia et al., 2020), and also in clinical populations like stroke patients (Swanson and Whittinghill, 2015), patients with cardiovascular disease (Russell and Bray, 2009), or patients with NCD (Barrado-Martín et al., 2021). 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 (Duncan et al., 2010). 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"* (Subramanian et al., 2019). For patients with NCDs specifically, a new theoretical model, the 'PHYT in dementia' (Di Lorito et al., 2019), was recently introduced. It includes both individual-level and environment-level constructs with the aim to *"inform effective interventions to promote physical activity"* (Di Lorito et al., 2019) 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 (Di Lorito et al., 2019). To account for these factors, especially for the preference that *"the routine can be performed at home and at different times during the day"* (Di Lorito et al., 2019), 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 (Russell and Bray, 2009).

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 (Manser et al., 2022a) (see text footnote 1).

Step 3: Therapeutic Needs

In step 3, it was aimed to: (1) *"specify the users' fitness goals, training settings, and outcome measures"* (Li et al., 2020); 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)"* (Li et al., 2020). 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 (Manser et al., 2022a) (see text footnote 1).

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)"* (Smith et al., 2018). 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 (Smith et al., 2018). A better self-efficacy is expected to improve perceived quality of life (Langer et al., 2019).

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 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 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 (Chen et al., 2020; Gavelin et al., 2021) and older adults with mNCD (Biazus-Sehn et al., 2020; Gavelin et al., 2021). 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 (Howes et al., 2017; Stanmore et al., 2017). Moreover, exergame-based training interventions are greatly accepted in individuals with mNCD and increase training adherence and engagement through facilitating training motivation and satisfaction (Zhao et al., 2020). 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 (Herold et al., 2018). The content of the exergames should mainly focus on working memory and memory training as part of a multi-domain training program (Mewborn et al., 2017; Sherman et al., 2017; Bahar-Fuchs et al., 2019). 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 (Buitenweg et al., 2012; Herold et al., 2018). 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) (Herold et al., 2018). Furthermore, the preferred postural modality in which exercise is performed should be in a vertical body loading position (Swinnen et al., 2021). Exercise performed in standing position that requires a changing base of support to play the games better meets the specifics for training postural control (Tahmosybayat et al., 2018) and puts a higher demand on spatial processing demands (Dodwell et al., 2019) next to enhancing both processing speed and attentional selectivity (Rosenbaum et al., 2017). Such effects of improved balance and executive functions are not observed for exercise performed pedaling a bicycle in a seated position (Karssemeijer et al., 2019a,b) possibly due to a lack of a dynamic influence on visual working memory performance (Dodwell et al., 2019). 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 (Moreau and Conway, 2014).

TABLE 2 | Moderating effects of exercise and training parameters on the effectiveness of cognitive, physical, and cognitive-motor training in healthy older adults and older adults with 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	Bahar-Fuchs et al., 2019	• Higher (>3x/week) (Bahar-Fuchs et al., 2019)	Groot et al., 2015	• Higher (≥ 4x/week) (Sanders et al., 2019)	NR	NR	High frequency (≥5x/week)
	HOA	NR	• Lower [≤2x/week (Mewborn et al., 2017), ≤3x/week (Lampit et al., 2014)]	NR	• Higher [≥2x/week (Sanders et al., 2019), ≥3x/week (Chen et al., 2020), ≥5x/week (Northey et al., 2018)] • Lower (≤3x/week) (Jia et al., 2019)	Mansor et al., 2020	• Higher [≥3x/week (Chen et al., 2020), ≥5x/week (Northey et al., 2018)]	
Intensity/ Complexity	mNCD	NR	NR	Sanders et al., 2019; Chen et al., 2020	• Moderate intensity (Biazus-Sehn et al., 2020) • moderate to high intensity (Law et al., 2020)	Chen et al., 2020	• Moderate physical exercise intensity (Biazus-Sehn et al., 2020)	Physical load: moderate intensity motor complexity: high challenge cognitive load: unknown
	HOA	Toril et al., 2014	NR	Sanders et al., 2019	• Moderate to vigorous (Northey et al., 2018) • high motoric challenge (Sherrington et al., 2017)	NR	• high motoric challenge (Sherrington et al., 2017)	
Type (of training)	mNCD	García-Casal et al., 2017; Bahar-Fuchs et al., 2019; Chan J.Y.C. et al., 2020)	• Computer-based (García-Casal et al., 2017) • Individual training (Sherman et al., 2017)	Law et al., 2020	• Aerobic training (Groot et al., 2015; Panza et al., 2018) • Multicomponent (Groot et al., 2015; Sanders et al., 2019)	Wu et al., 2019	• Simultaneous training (Gavelin et al., 2021) • Combined training (Biazus-Sehn et al., 2020)	Individually applied simultaneous motor-cognitive training
	HOA	NR	• Video-game based training (Lampit et al., 2014; Toril et al., 2014)	Sanders et al., 2019	• Multicomponent (Northey et al., 2018)	NR	• Simultaneous training (Chen et al., 2020; Gavelin et al., 2021) • Exergaming (Mansor et al., 2020)	
Time (exercise duration)	mNCD	NR	NR	NR	• Shorter (≤30 min) (Sanders et al., 2019)	NR	NR	≤30 min
	HOA	Lampit et al., 2014	• Shorter (≤30 min) (Mewborn et al., 2017)	Raffin et al., 2019; Sanders et al., 2019; Chen et al., 2020	• Shorter (≤30 min) (Jia et al., 2019) • Longer (≥45 min) (Northey et al., 2018)	Chen et al., 2020; Mansor et al., 2020	• Shorter (Mansor et al., 2020)	
Duration (of the intervention)	mNCD	Bahar-Fuchs et al., 2019	• Longer (≥3 months) (Bahar-Fuchs et al., 2019)	Sanders et al., 2019; Wu et al., 2019	NR	Wu et al., 2019	NR	≥12 weeks

(Continued)

TABLE 2 | (Continued)

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	
	HOA	Bonnechère et al., 2020	• Shorter (≤6 weeks) (Toril et al., 2014)	Sanders et al., 2019	• Shorter (≤12 weeks) (Northey et al., 2018; Chen et al., 2020) • Longer (>16 weeks) (Jia et al., 2019)	Biazus-Sehn et al., 2020	• Longer (≥12 weeks) (Stanmore et al., 2017) • Shorter (≤12 weeks) (Biazus-Sehn et al., 2020; Chen et al., 2020; Gavelin et al., 2021)	
Volume (i.e., total intervention/ exercise time)	mNCD	Sherman et al., 2017; Zhang et al., 2019	NR	Law et al., 2020	• Higher [≥24 h (Law et al., 2020)] • Moderate (60 – 120 min/week) (Wu et al., 2019) • Lower (Biazus-Sehn et al., 2020) (≤2h/week) (Jia et al., 2019)	NR	• Moderate (60 – 120 min/week) (Wu et al., 2019)	Moderate (60 – 120 min/week)
	HOA	Lampit et al., 2014	• Higher (≥20 h, ≥20 sessions) (Mewborn et al., 2017)	Raffin et al., 2019	• Higher [≥3 h/week (Sherrington et al., 2017)]	Mansor et al., 2020	• Higher volume (≥120 min/week) (Howes et al., 2017)	
Progression and 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 (Toril et al., 2014)	NR	NR	NR	NR	
Specificity	mNCD	Bahar-Fuchs et al., 2019; Zhang et al., 2019	Multi-domain training (Sherman et al., 2017; Bahar-Fuchs et al., 2019) including memory (Sherman et al., 2017) -memory-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 (Mewborn et al., 2017; Sherman et al., 2017) including working memory (Mewborn et al., 2017) and memory (Mewborn et al., 2017; Sherman et al., 2017) -memory-specific training	NR	NR	NR	NR	

HOA, healthy older adults; NR, not reported; mNCD, mild neurocognitive disorder.

TABLE 3 | 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 and 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 and 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)

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 (Biazus-Sehn et al., 2020) and a moderate training volume (60 – 120 min/week) (Wu et al., 2019) 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 (Chen et al., 2020), ≥5x/week (Northey et al., 2018)], higher challenging motor tasks (Sherrington et al., 2017), shorter session durations (Mansor et al., 2020), and either longer (≥12 weeks) (Stanmore et al., 2017) or shorter (≤12 weeks) (Biazus-Sehn et al., 2020; Chen et al., 2020; Gavelin et al., 2021) intervention durations have been shown to improve effectiveness of motor-cognitive training interventions. However, these conclusions are opposed by other meta-analyses (Biazus-Sehn et al., 2020; Chen et al., 2020; Mansor et al., 2020). In older adults with mNCD, higher training frequencies have been shown to improve effectiveness of physical- (i.e., ≥4x/week) (Sanders et al., 2019) and cognitive training (i.e., > 3x/week) (Bahar-Fuchs et al., 2019), while shorter session durations (i.e., ≤ 30 min) (Sanders et al., 2019) of physical exercise and longer intervention durations of cognitive training interventions (i.e., ≥ 3 months) (Bahar-Fuchs et al., 2019) 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 (Toril et al., 2014) 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 (Mewborn et al., 2017; Sherman et al., 2017; Bahar-Fuchs et al., 2019) including memory (Mewborn et al., 2017; Sherman et al., 2017) and working memory specific training (Mewborn et al., 2017) 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) (Toril et al., 2014) 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.

Herold et al. (2019a) 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 (Herold et al., 2019a). 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) (Impellizzeri et al., 2019). This adapted exercise prescription approach is believed allowing further insights into dose-response relationships and to result in more distinct training effects (Herold et al., 2019a; Stojan and Voelcker-Rehage, 2019). 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) (deBettencourt et al., 2015; Mishra et al., 2016; Sokolov et al., 2020), *"games that do not have entertainment, enjoyment or fun as their primary purpose"* (Lau et al., 2016). 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** 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. Regarding the monitoring of neurocognitive demands (i.e., game complexity), and in line with the adapted exercise prescription proposed by Herold et al. (2019a), 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"* (Pope et al., 1995, 2014; Fairclough, 2015; Muñoz et al., 2018). *"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"* (Ewing et al., 2016). Optimally, it would work on basis of specific markers of internal training load to adapt the external training demands (Herold et al., 2019a). However, the optimal marker(s) for internal training load remain to be determined (Herold et al., 2019a). 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 (Panza et al., 2018; Sanders et al., 2019). 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 (Gray and Lindstedt, 2017). These are behavioral markers that relate to motor skill acquisition and can be analyzed with a focus on micro dynamics of individual performance curves (Gray and Lindstedt, 2017). 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 (Gray and Lindstedt, 2017), 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

TABLE 4 | Possible ideas/concepts for training monitoring.

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 and 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

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.

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 (Manser et al., 2022a) (see text footnote 1).

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 5**). As can be seen in **Table 5**, 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 (Li et al., 2020).

Step 4: Technology Scoping

A previous study showed good results in people with major neurocognitive disorders using a Dividat Senso platform (Swinnen et al., 2021). 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 (Swinnen et al., 2020a). 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 3**. 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 5 | Overview of preferred training parameters and final decision for Brain-IT.

Exercise and training parameters	Preferences based on:			Requirements for a theoretically optimal 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 and 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

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*" (Li et al., 2020).

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.

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 (Li et al., 2020). 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"* (Li et al., 2020), and *"to establish a mutual exergame design expectation"* (Li et al., 2020).

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 (Manser et al., 2022a) (see text footnote 1). 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 (Manser et al., 2022a) (see text footnote 1).

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 (Manser et al., 2022a) (see text footnote 1).

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 (Lehrer and Gevirtz, 2014). 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 (Netz, 2019). 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) (Halson, 2014; Hoffman, 2014; Slade et al., 2016; American College of Sports Medicine et al., 2017; Herold et al., 2019a). 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 (Garber et al., 2011). 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 (Jamnick et al., 2020). Nonetheless, *"studies involving only moderate exercise intensity (e.g., B60% VO2max) might reasonably choose %VO2max, %HRmax, %VO2R, or %HRR over threshold-based relative exercise intensity prescription"* (Mann et al., 2013). For the neurocognitive demand – that serves as the driving mechanisms for task-specific neuroplasticity (Netz, 2019) – 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 (Herold et al., 2019a). To be able to differentiate between the physical- and neurocognitive demands during exergaming, a theoretical model was proposed (**Figure 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% heart rate reserve (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 (Herold et al., 2019a). 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 (Herold et al., 2019a). 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

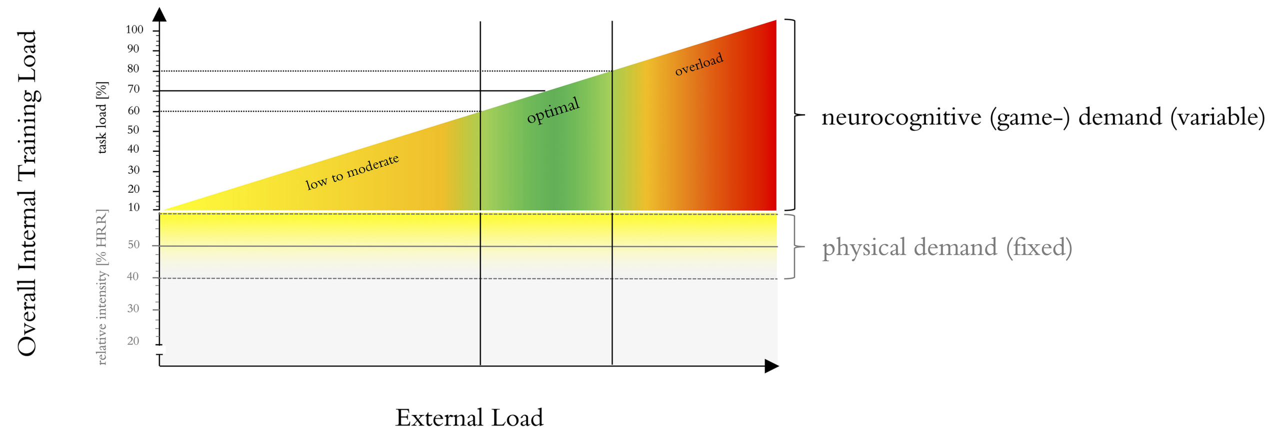

FIGURE 1 | Methodological framework for the contribution of physical- and neurocognitive- (i.e., game-) demands during exergaming.

training load that is easily measurable (Manser et al., 2021). Based on the findings of this study (Manser et al., 2022c[2]), 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.

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 5** 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) (Slade et al., 2016) [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 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 2**).

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"* (Fissler et al., 2013; Herold et al., 2018) while additionally using *"cognitive stimulation [...] to "guide" these neuroplastic processes"* (Fissler et al., 2013; Bamidis et al., 2014; Herold et al., 2018). 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,

[2]Manser, P., Adcock, M., and de Bruin, E. D. (2022c). Quantification of Individual Exergame Demands – Validity, and Reliability of vagally-mediated Heart Rate. (Variability)Reactivity to Measure Internal Training Load in Older Adults.

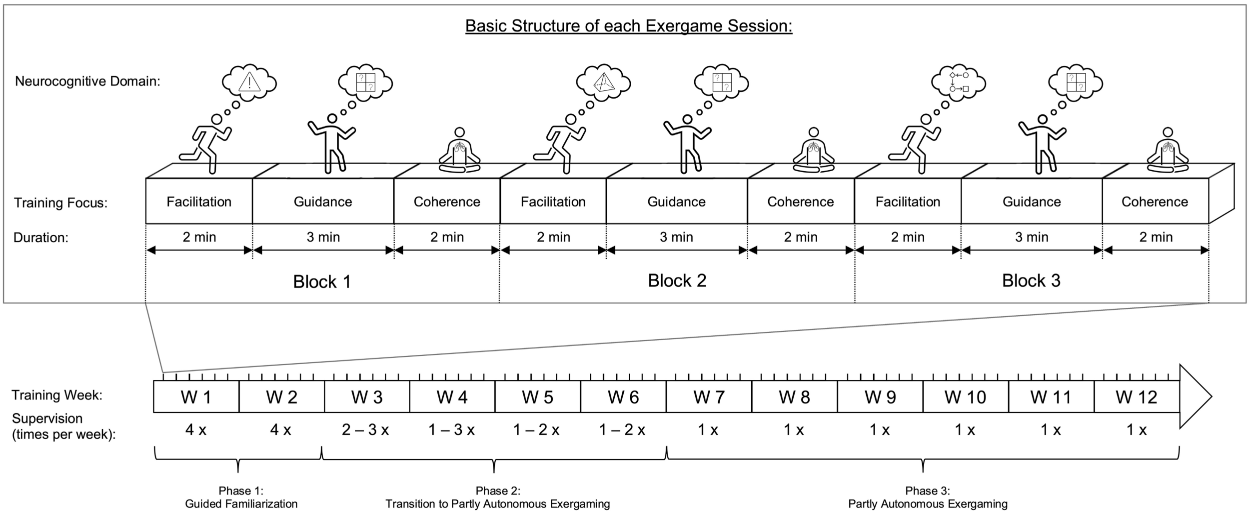

FIGURE 2 | Overview of the exergame-based intervention concept and the basic structure of each exergame session (here as an example for a patient with amnestic-single domain mNCD with a training focus on learning and memory in week 1).

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% heart rate reserve (HRR) (Garber et al., 2011)]. 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 (Ismail et al., 2017; Ma, 2020). 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 (Lehrer and Gevirtz, 2014; Shaffer et al., 2014). 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 (Schwerdtfeger et al., 2020). An increased HRV is predicted to increase vagal afferent transmission to the forebrain, activate the prefrontal cortex, and improve executive function (Shaffer et al., 2014). 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 (Goessl et al., 2017; Zaccaro et al., 2018; Lehrer et al., 2020). The evidence for older adults (i.e., $\geq$ 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 (Jester et al., 2019). 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"* (Lehrer et al., 2020). 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). 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 (Garber et al., 2011)]. 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: $HR_{target} = (HR_{max} - HR_{rest}) \cdot 0.40 + HR_{rest}$ (Karvonen et al., 1957; Karvonen and Vuorimaa, 1988). For this calculation the age-predicted maximal heart rate: $HR_{max} = 208 - 0.7 \cdot \text{age}$ 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 (Di Lorito et al., 2019). According to the 'Optimizing Performance through Intrinsic Motivation and Attention for Learning (OPTIMAL)' theory of motor learning (Wulf and Lewthwaite, 2016), 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"* (Wulf and Lewthwaite, 2016). 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"* (Wulf and Lewthwaite, 2016; Lemos et al., 2017). 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"* (Li et al., 2020).

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" (Eldridge et al., 2016; Manser et al., 2022b[3]).

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 (Manser et al., 2022b) (see text footnote 3), the intervention concept will be modified for its final evaluation on effectiveness with expected contributions from end users, clinicians, researchers, and data analysts.

Phase 3: System Evaluation

Goal: To systematically evaluate the exergame system "*to ensure the exergames meet their intended goals*" (Li et al., 2020) regarding therapeutic outcomes, user experience, and technology performance (Li et al., 2020).

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) (O'Caoimh, 2015). As secondary outcomes, domain-specific assessments for the evaluation of the key neurocognitive domains [as defined by Sachdev et al. (2014) in line with DSM-V (American Psychiatric Association, 2013)] of learning and memory, complex attention, executive function, and visuo-spatial skills will be incorporated as recommended (Janelidze and Botchorishvili, 2018). 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.

[3]Manser, P., Adcock, M., and de Bruin, E. D. (2022b). Feasibility, Usability and Acceptance of a Newly Developed Exergame-Based Intervention Concept for Older Adults with Mild Neurocognitive Disorder – A Pilot Randomized Controlled Trial.

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 (Li et al., 2020).

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 (Slade et al., 2016) in line with the CONSORT 2010 statement (Begg et al., 1996; Moher et al., 2010)] when serious games for motor-cognitive rehabilitation purposes are to be developed.

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.

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.

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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

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Effects of Exergaming-Based Tai Chi on Cognitive Function and Dual-Task Gait Performance in Older Adults With Mild Cognitive Impairment: A Randomized Control Trial

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Background: Declined cognitive function interferes with dual-task walking ability and may result in falls in older adults with mild cognitive impairment (MCI). The mind-body exercise, Tai Chi (TC), improves cognition and dual-task ability. Exergaming is low-cost, safe, highly scalable, and feasible. Whether the effects of exergaming-based TC is beneficial than traditional TC has not been investigated yet.

Objectives: The objective of this study was to investigate effects of exergaming-based TC on cognitive function and dual-task walking among older adults with MCI.

Methods: Fifty patients with MCI were randomly assigned to an exergaming-based TC (EXER-TC) group, a traditional TC (TC) group, or a control group. The EXER-TC and TC groups received 36 training sessions (three, 50-min sessions per week) during a 12-week period. The control group received no intervention and were instructed to maintain their usual daily physical activities. The outcome variables measured included those related to cognitive function, dual-task cost (DTC), and gait performance.

Results: The EXER-TC and TC groups performed better than the control group on the Chinese version of the Stroop Color and Word Test, the Trail Making Test Parts A and B, the one-back test, gait speed, and DTC of gait speed in cognitive dual-task conditions after training. However, there were no significant differences between the EXER-TC and TC groups. Compared with the control group, only the EXER-TC group experienced beneficial effects for the Montreal Cognitive Assessment.

Conclusion: EXER-TC was comparable to traditional TC for enhancement of dual-task gait performance and executive function. These results suggested that the EXER-TC approach has potential therapeutic use in older adults with MCI.

Keywords: MCI, dual task gait, exergaming, tai chi, cognition

INTRODUCTION

Gait control requires higher-level cognitive function, especially executive function. Gait control shares common brain networks with cognitive processes essential for planning and goal-directed behaviors (Yogev-Seligmann et al., 2008). Dual-task walking (i.e., walking while performing a cognitive task) can challenge gait control, especially in with cognitive impairment. Slowing dual-task gait velocities correlate with declines in executive function, visual working memory, and processing speeds in older adults with mild cognitive impairment (MCI) (Doi et al., 2014). Gait control declines in speed and variability are also associated with greater injurious fall risk in older adults with MCI (Pieruccini-Faria et al., 2020). This dual-task interference or cost might represent a surrogate motor marker and be associated with advancement toward dementia in older adults with MCI (Sakurai et al., 2019). Reduced entorhinal cortex volumes in older adults with MCI are linked to higher dual-task costs under subtracting serial sevens conditions (Sakurai et al., 2019). Examination of dual-task gait performance can provide evidence that gait control and cognitive performance are linked (Hausdorff and Buchman, 2013). These gait parameters may also be helpful for early diagnosis and intervention in with MCI.

The mind-body exercise, Tai Chi (TC), has physical and cognitive components. Used as an intervention, TC might be an effective way to reduce rates of cognitive decline in healthy and in cognitively impaired older adults. A systematic review and meta-analyses found that TC has potential to improve cognitive function in older adults, particularly in executive function domain (Wayne et al., 2014). Evidence for improvements in cognitive function after TC training is supported by functional changes in cortical areas and in physiological biomarkers such as brain-derived neurotrophic factor (BDNF) (Tao et al., 2016, 2017; Sungkarat et al., 2018). TC is a multi-task with a high attention resource demand (Li et al., 2014; Wayne et al., 2014). Practicing TC improves dual-task gait variability in healthy older adults and patients with Parkinson's disease (Wayne et al., 2015; Vergara-Diaz et al., 2018). However, evidence that TC improves dual-task walking ability in older adults with MCI has not been investigated yet.

Exergaming is body movement-controlled computer gaming. The exergaming device, Kinect, is low-cost, interactive, scalable, and feasible for use in clinical populations (Barry et al., 2014). Interactive exergaming effectively enhances cognitive function in older adults in community settings, increases short-term memory and executive function in healthy older adults, and improves visuospatial perception in adults with neurological disease (Monteiro-Junior et al., 2017; Mura et al., 2018; Gallou-Guyot et al., 2020). It remains unclear whether combining interactive exergaming with TC benefits on cognitive function and dual-task gait performance in older adults with MCI. This study investigated effects of exergaming-based TC training on cognitive function, dual-task cost, and gait performance, compared with traditional TC and control groups in older adults with MCI.

MATERIALS AND METHODS

Participants

We recruited participants in communities of Taipei, Taiwan. The inclusion criteria were: (1)≥65 years of age, (2) a diagnosis of MCI based on Petersen's criteria (Petersen, 2004), and (3) physical ability sufficient to allow walking more than 10 m independently. The exclusion criteria were: (1) a diagnosis of dementia, (2) brain tumor, (3) any musculoskeletal problems that would preclude exercise training, (4) diagnosis of hand movement disorders, dysgraphia, or color vision deficiency, and (5) education level < 6 years. Each participant provided written informed consent before study enrollment. A power of 80%, an effect size of 0.43, and an alpha level of 5% were used for the sample size estimate of 45 participants (15 per group) for an ANCOVA model (Liao et al., 2019). We recruited 54 participants (18 per group) to accommodate a 15% dropout rate.

Study Design

The study protocol was approved by the Institutional Human Research Ethics Committee of Taipei City Hospital. This single-blind (assessor), parallel, randomized controlled trial was registered at http://www.clinicaltrials.in.th/ (TCTR TCTR20210530003). Each participant was randomly assigned to the exergaming-based Tai Chi (EXER-TC), traditional Tai Chi (TC), or control group via a sealed envelope. Another blinded assessor performed the cognitive and gait assessments (pre- and post-intervention) described in the Outcomes Measures section.

Intervention

Three, 50-min training sessions per week were performed by the EXER-TC and TC group participants. An experienced certified TC coach supervised all training in small group settings of three to four participants. Participant in the EXER-TC and TC groups wore smartwatch to observe heart rate during training. The rate of perceived exertion (RPE) were also set at 12-14 (somewhat hard) during training to ensure the training intensity was consistant between these two groups.

Tai Chi Group

Participants were taught Yang Style TC for 12 weeks. Simplified 24 form Yang Style TC was taught because it required less time and consisted of fewer postures. This TC type is appropriate for older adults with MCI because it is easier to learn and remember. The "warm-up" was the first part of each three-part TC session. The warm-up consisted of simple motions to help participants learn to relax muscles and joints. The second part of the session consisted of "TC instruction." The entire set of unique Yang style simple form movements was taught to each group. The coach taught the participants to move in low-speed circular motions and to focus on breathing and muscle coordination. Each session ended with a "cool-down," which included activities that ended the TC and rested the body.

Each Participant Was Randomly Assigned to the Exergaming-Based Tai Chi Group

EXER-TC group participants performed 50 min of TC training during exergaming. The infrared light component of the Kinect system (Microsoft Corporation, Redmond, WA, United States) was used to capture and track changes in limb segment motion. The system was then used to create a virtual full-body 3D map. During the TC exergames (LongGood software, Taiwan), participants imitated a virtually-presented TC coach and responded to instant feedback by real-time adjustments in movement. The EXER-TC program is also modified from Yang Style TC which includes changing standing from wide to narrow base, body mass weight shifting, squats, and slow symmetrical to diagonal coordination arm-leg movements. Therefore, the programs in TC and EXER-TC are similar. Movement accuracy scores for each participant were presented simultaneously on the monitor while TC was in progress. Each session consists of 10 min warm-up, 35 min main exercise, and a 5 min cool-down.

Control Group

Control group participants were instructed to maintain their usual daily physical activities. No exercises or specific behavioral management training were assigned to this group.

Outcome Measures

Cognitive Function

Global Cognition

The Montreal Cognitive Assessment (MoCA) is an effective cognitive impairment screening instrument for MCI subjects (Nasreddine et al., 2005). A good reliability and validity were proved between MoCA scores and Mini-Mental State Examination (MMSE) scores. A higher score in the 0 to 30 score range indicates better global cognitive function. The MoCA Taiwanese version has a reliability of 0.88 and a validity of 0.86 (Tsai et al., 2012).

Executive Function

Executive function was represented using the Trail Making Test (TMT). The TMTA consisted of 25 encircles randomly distributed on a paper. Participants connect the 25 serial numbers ascendingly and quickly. For the Chinese version of the TMTB, participants draw a line continually connecting 12 encircled numbers and Chinese animal zodiac in alternating order. The score on each part is the time (seconds) required to complete the task. Delta TMT (the difference between TMT B and TMT A) was also recorded as our TMT outcome.

Verbal Memory

The Chinese version of California Verbal Learning Test (CCVLT) was used to assess immediate recall and recall after a 10-min delay. Participants are required to recall 9 two-character nouns over 4 repeating assessment. The sensitivity of this test is 0.852 (Chang et al., 2010).Verbal memory and delayed recall were assessed by calculating the total number of nouns accurately recalled.

Attention

Selective attention and inhibition were assessed using the Stroop Color and Word Test (SCWT), Chinese version. In the incongruous condition, the character of color was printed in a different color. Participants were asked to indicate the color of the ink rather than the word/character. The outcomes were the number of correct answers given in 45 s (SCWT number) and time taken to name 45 characters (SCWT seconds).

Working Memory

The spatial n-back task test was utilized to assess working memory. This test is frequently used in neuroimaging and neuropsychology research. Spatial n-back test position matching consisted of one-back and two-back tasks. Test-retest reliability is 0.71 for the one-back test and 0.82 for the two-back test (Soveri et al., 2018). A square was shown in nine possible locations in a 3 × 3 grid randomly. Participants determine whether the presented square appeared in the same location as the previous square (the one-back task) and the square two positions ago (the two-back task). Twenty-one trials were used for the one-back tests. Twenty-four trials were used for the two-back tests. The total number of correctly answered trials was calculated for each participant.

Gait Performances and Dual-Task Costs

Gait performances were evaluated by the wearable GAIT Up system (Gait Up, Lausanne, Switzerland). This inertial sensor device has high agreement and consistency with the pressure sensing system (Rudisch et al., 2021). During the experiment, we fixed two wearable sensors on the dorsal side of the participant's left and right shoes. Each participant walked three trials under the following condition: (1) a single task condition: walking at their usual speed, (2) a cognitive dual-task condition: walking while performing serial-3-subtractions task from a random number between 90 and 100 (3) a motor dual-task condition: walking while carrying a tray with glasses of water. The sensors recorded gait speed (cm/s), stride length (cm), and cadence (step/min) during single and dual task walking. The mean values of three trials in each condition were used for the statistical analysis. Dual-task interference was quantified using dual-task cost (DTC), which was calculated as: DTC [%] = 100 x (single task performance – dual task performance)/single-task performance (Muir et al., 2012).

Data Analysis

Sociodemographic, neuropsychological, and gait data analyses were performed using SPSS 20.0 software (SPSS Inc., Chicago, IL, United States). Descriptive statistics (mean ± standard deviation values or as numbers) were generated for all variables. One-way analysis of variance (ANOVA) was used to compare the three groups with respect to continuous variables in baseline demographic characteristics (e.g., age, weight, height, body weight and MMSE). Chi-square test was used to compare the categorical variables such as sex. In cognition and gait outcome measures, the influence of pre-intervention values was adjusted as the covariate, and the corrected post-intervention values

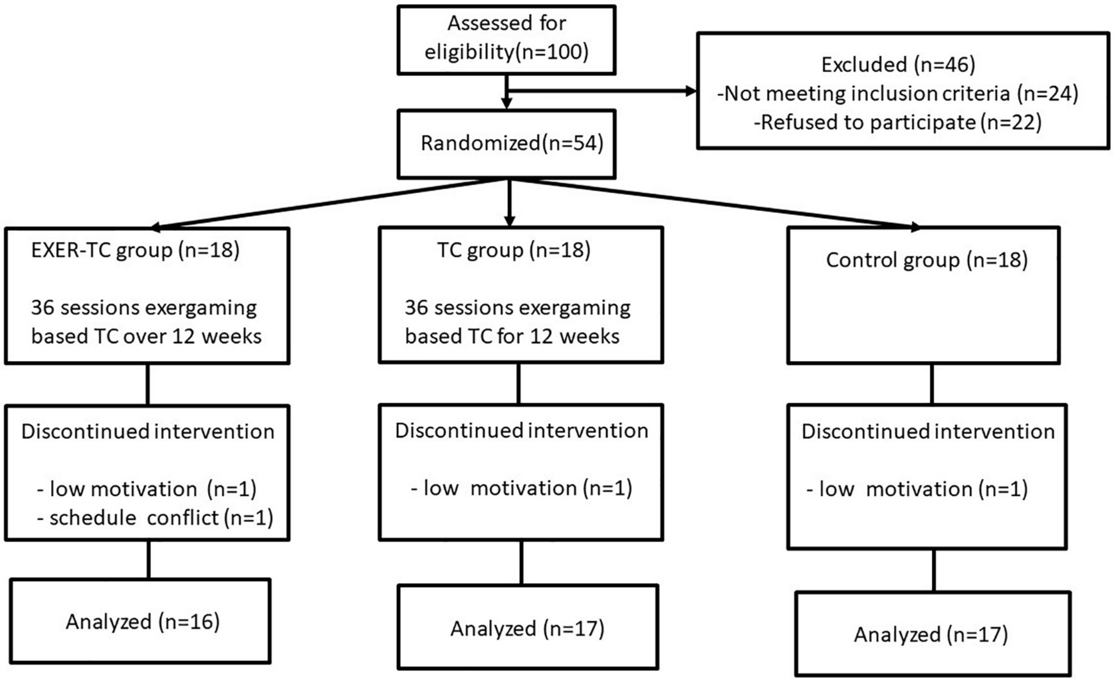

FIGURE 1 | Flow chart of the study design.

were generated after analysis of covariance (ANCOVA). One-way ANCOVA was used to compare corrected post-intervention values between the three groups at the end of the trial. Bonferroni correction was used in *post hoc* comparisons among three groups, and the adjusted significance level was set at $p < 0.017$. Eta-squared (η2) was calculated to indicate the effect size.

RESULTS

One-hundred individuals were screened, and 54 were enrolled and randomly assigned to the EXER-TC, TC, or control group in this study (**Figure 1**). Four participants did not complete the study. One participant in the EXER-TC group, one in the TC group, and one in the control group withdrew due to low motivation. One participant in the EXER-TC group withdrew due to scheduling conflicts. A total of 50 participants ($n = 16$ in the EXER-TC group, $n = 17$ in the TC group, and $n = 17$ in the control group) completed all interventions and assessments; these data were used in the final statistical analysis. Adverse events were not reported by any participants. The results for demographic characteristics are presented in **Table 1**; there were no significant between-group differences.

Cognitive Performances

The results for cognitive performance, before and after intervention, are presented in **Table 2**. The ANCOVA results indicated significant group effects for the MoCA, TMTA, TMTB, Delta TMT, SCWT number, SCWT seconds, and one-back test. *Post hoc* analysis found that both the EXER-TC and TC groups performed better than the control group for the TMTA, TMTB, Delta TMT, SCWT seconds, and one-back test after training (TMTA: EXER-TC vs. control, $p < 0.001$, TC vs. control, $p = 0.006$; TMTB: EXER-TC vs. control, $p < 0.001$, TC vs. control, $p = 0.004$; Delta TMT: EXER-TC vs. control, $p = 0.001$, TC vs. control, $p = 0.007$; SCWT seconds: EXER-TC vs. control, $p = 0.001$, TC vs. control, $p = 0.003$; one-back test: EXER-TC vs. control, $p = 0.001$, TC vs. control, $p = 0.005$). *Post hoc* analysis also revealed that after training, only the EXER-TC group had a significantly higher mean score for MoCA and SCWT number compared with the control group (MoCA: EXER-TC vs. control, $p = 0.008$; SCWT number: EXER-TC vs. control, $p = 0.001$).

Gait Performances

The results for gait performance before and after intervention are presented in **Table 3**. The ANCOVA results indicated significant group effects for gait speed ($p < 0.001$) and cadence ($p = 0.022$),

TABLE 1 | Baseline demographic characteristics of patients (N = =50).

	Control group (*N* = 17)	TC group (*N* = 17)	EXER-TC group (*N* = 16)	*P* value
Age (year)	73.4 ± 6.5	73.2 ± 6.3	74.6 ± 6.1	0.7
Sex (female/male)	11/6	12/5	12/4	0.8
Height (cm)	157.6 ± 7.8	155.1 ± 7.2	154.4 ± 6.9	0.4
Body weight (kg)	58.4 ± 10.6	59.2 ± 9.2	56.0 ± 7.5	0.5
MMSE (score)	26.6 ± 2.2	25.8 ± 2.4	25.1 ± 1.7	0.1

MMSE: Mini-Mental State Examination.

TABLE 2 | The ANCOVA analysis and *post hoc* comparisons of cognitive task performance between the control group, TC group, and EXER-TC group after 36 training sessions (N = 50).

	Control group (N = 17)		TC group (N = 17)		EXER-TC group (N = 16)		Group effect (*p* value)	Effect size
	Pre-intervention	Corrected Post-intervention (original post-intervention)	Pre-intervention	Corrected Post-Intervention (original post-intervention)	Pre-intervention	Corrected Post-intervention (original post-intervention)		
MoCA (score)	23.2 ± 2.8	22.7 ± 0.39 (23.2 ± 2.5)	21.8 ± 3.6	23.4 ± 0.38 (22.8 ± 3.6)	22.6 ± 2.5	24.5 ± 0.38 (24.6 ± 2.1)	0.008†	0.190
TMTA (seconds)	81.9 ± 30.6	80.3 ± 1.9 (81.7 ± 31.9)	81.5 ± 38.3	71.7 ± 1.9 (72.8 ± 34.9)	77.0 ± 30.4	65.8 ± 1.9 (63.0 ± 19.2)	< 0.001*†	0.375
TMTB (seconds)	198.4 ± 58.1	192.7 ± 8.2 (191.8 ± 46.1)	204.5 ± 78.3	152.1 ± 8.2 (154.5 ± 64.3)	197.3 ± 54.9	137.1 ± 8.5 (135.6 ± 32.2)	< 0.001*†	0.339
Delta TMT (seconds)	116.5 ± 47.6	111.4 ± 6.8 (110.0 ± 28.8)	122.9 ± 71.1	80.5 ± 6.8 (81.8 ± 46.8)	120.3 ± 51.7	72.4 ± 7.0 (72.6 ± 30.5)	< 0.001*†	0.283
CVVLT (number)								
Verbal memory	22.4 ± 4.1	21.8 ± 0.9 (22.0 ± 3.3)	22.1 ± 6.4	21.3 ± 0.9 (21.4 ± 6.3)	21.7 ± 3.4	24.3 ± 0.9 (24.1 ± 3.2)	0.07	0.108
Delayed recall	6.1 ± 2.3	5.4 ± 0.5 (5.7 ± 2.4)	5.1 ± 3.4	7.2 ± 0.5 (6.9 ± 2.7)	5.6 ± 2.6	6.8 ± 0.5 (6.8 ± 2.7)	0.05	0.122
SCWT (number)	23.5 ± 9.3	22.6 ± 0.8 (23.5 ± 9.9)	22.6 ± 11.6	25.6 ± 0.8 (25.7 ± 12.3)	21.6 ± 10.0	27.3 ± 0.8 (26.4 ± 9.9)	0.001†	0.248
SCWT (seconds)	102.0 ± 50.7	110.1 ± 3.9 (111.4 ± 57.7)	101.8 ± 48.2	90.2 ± 3.9 (91.4 ± 54.2)	98.0 ± 40.5	86.9 ± 4.0 (84.1 ± 36.2)	< 0.001*†	0.302
***N*-back test (number)**								
1-back	12.4 ± 3.4	12.9 ± 0.4 (12.1 ± 4.3)	13.2 ± 3.2	14.4 ± 0.4 (14.8 ± 3.4)	13.1 ± 2.4	15.2 ± 0.4 (15.3 ± 2.5)	< 0.001*†	0.332
2-back	4.7 ± 1.9	5.2 ± 0.3 (4.5 ± 2.1)	5.9 ± 2.9	6.2 ± 0.3 (6.5 ± 3.1)	5.6 ± 3.0	6.4 ± 0.3 (6.9 ± 3.6)	0.06	0.116

EXER-TC, exergaming-based Tai Chi; TC, traditional Tai Chi; MoCA, Montreal Cognitive Assessment; TMT, Trail Making Test; CVVLT, The Chinese version of California Verbal Learning Test; SCWT, Stroop color and word test;
**Significance level < 0.017 for post hoc comparisons (TC vs. Control).*
†Significance level < 0.017 for post hoc comparisons (EXER-TC vs. Control).

DTC of speed (p = 0.002), and DTC of cadence (p = 0.032) during cognitive dual-task performance. The *post hoc* analysis revealed that the EXER-TC and TC groups performed better than the control group in gait speed and DTC of speed during cognitive dual-tasks after training (gait speed: EXER-TC vs. control, p < 0.001, TC vs. control, p = 0.001; DTC of speed: EXER-TC vs. control, p = 0.002, TC vs. control, p = 0.017).

DISCUSSION

We compared the effects of EXER-TC with those of TC and control on cognitive function and dual-task gait performance. First, both the EXER-TC and TC groups had better performance than the control group in the executive function and attention domains as measured by TMT, SCWT, and one-back test after training, but only EXER-TC exerted a more beneficial effect than the control for the global cognition (MOCA) and SCWT number. Second, compared with the control group, both the EXER-TC and TC groups experienced beneficial effects for gait speed and DTC of speed during cognitive dual-task walking after training. Finally, there were no significant between-group differences for EXER-TC vs. TC for cognitive and dual-task gait performance after training.

Both the TC and EXER-TC groups improved in cognitive function in the executive function domain. The TMT, SCWT, and one-back test are indicators of executive control abilities associated with cognitive flexibility, inhibitory control and working memory (Sánchez-Cubillo et al., 2009). These results were consistent with previous study, which found that TC training improves TMT test scores (Sungkarat et al., 2017). TMTA represents visuoperceptual ability, TMTB reflects working memory and task-switching ability, and Delta TMT indicates mental flexibility. Practicing TC requires use of a series of cognitive activities, including movement recall, switching, attention, inhibitory control and visuospatial orientation devoted to multisegmental movement. Study results suggest that TC practice may activate the prefrontal cortex and improve working memory, attentional focus, and processing speed through concurrent physical and mental activity (Wayne et al., 2014; Kim et al., 2016; Tsang et al., 2019). Therefore, we suggest practicing the TC program in a real or virtual scenario effectively facilitated complex executive function as reflected in the TMT, SCWT, and one-back test improvements.

The beneficial effect on the MoCA score implies that EXER-TC may lead to a variety of cognitive improvements. The possible explanation is the interactive advantage of exergaming. Participants are required to be alert to contextual feedbacks, recruit cognitive resources, and adjust body posture according to the command of the virtual coach. In addition, the advantage of enjoyment and attractiveness in the environment of exergaming may further augment the training effect of TC and lead to improvement in cognitive dual-task performance. Frontal and subcortical-frontal cortex volumes are associated with single and dual-task gait performance in older adults with MCI (Doi et al., 2017; Allali et al., 2019; Beauchet et al., 2019). Previous studies have shown evidence that VR and exergaming improve

TABLE 3 | The ANCOVA analysis and *post hoc* comparisons of dual-task gait performance between control group, TC group, and EXER-TC group after 36 training sessions (*N* = 50).

	Control group (*N* = 17)		**TC group (*N* = 17)**		**EXER-TC (*N* = 16)**		**Group effect (*p* value)**	**Effect size**
	Pre-intervention	**Corrected Post-intervention (original post-intervention)**	**Pre-intervention**	**Corrected Post-intervention (original post-intervention)**	**Pre-intervention**	**Corrected Post-intervention (original post-intervention)**		
Single task gait								
Speed (cm/s)	112.4 ± 22.5	113.9 ± 6.3 (113.2 ± 30.1)	115.2 ± 32.7	111.5 ± 6.3 (112.0 ± 28.5)	114.6 ± 23.7	110.4 ± 6.5 (110.6 ± 26.2)	0.9	0.003
Stride length (cm/s)	119.5 ± 18.1	116.7 ± 4.4 (117.1 ± 21.4)	120.1 ± 21.8	118.1 ± 4.4 (118.7 ± 17.1)	115.9 ± 21.0	114.2 ± 4.6 (113.2 ± 20.7)	0.8	0.008
Cadence (step/min)	113.0 ± 9.5	114.1 ± 2.3 (113.6 ± 8.7)	113.0 ± 11.2	114.5 ± 2.3 (114.0 ± 11.7)	116.0 ± 15.0	112.7 ± 2.4 (113.8 ± 14.1)	0.8	0.007
Cognitive dual-task gait								
Speed (cm/s)	55.0 ± 22.4	48.9 ± 3.8 (50.5 ± 19.0)	51.1 ± 20.8	69.8 ± 3.8 (69.3 ± 21.9)	49.9 ± 28.4	73.5 ± 4.0 (72.4 ± 20.2)	< 0.001*†	0.332
DTC of speed (%)	49.0 ± 22.3	53.3 ± 4.2 (51.7 ± 22.2)	53.1 ± 19.9	36.1 ± 4.2 (36.5 ± 20.4)	54.4 ± 25.9	31.7 ± 4.2 (32.8 ± 17.3)	0.002*†	0.240
Stride length (cm/s)	97.2 ± 20.7	90.3 ± 4.5 (93.0 ± 20.5)	94.5 ± 21.6	99.0 ± 4.5 (100.4 ± 25.1)	81.8 ± 25.	96.2 ± 4.8 (91.7 ± 17.3)	0.3	0.039
DTC of stride length (%)	18.3 ± 13.2	22.0 ± 2.8 (20.3 ± 10.5) ±	20.4 ± 16.6	15.3 ± 2.8 (14.4 ± 15.1)	29.4 ± 18.2	15.2 ± 2.9 (17.9 ± 12.7)	0.1	0.078
Cadence (step/min)	66.5 ± 24.8	64.8 ± 4.6 (66.0 ± 24.2)	61.2 ± 17.5	79.9 ± 4.6 (78.0 ± 17.5)	65.2 ± 25.0	82.5 ± 4.7 (83.0 ± 25.2)	0.02	0.154
DTC of cadence (%)	39.9 ± 24.3	42.1 ± 4.1 (40.9 ± 23.4)	44.3 ± 16.9	29.3 ± 4.1 (30.1 ± 15.2)	43.2 ± 21.2	27.4 ± 4.2 (27.7 ± 18.0)	0.03	0.139
Motor dual-task gait								
Speed (cm/s)	81.7 ± 21.3	90.2 ± 3.9 (89.9 ± 15.2)	82.6 ± 22.3	91.5 ± 3.9 (91.5 ± 20.6)	83.0 ± 22.5	93.3 ± 4.0 (93.5 ± 18.6)	0.8	0.006
DTC of speed (%)	26.3 ± 16.5	23.7 ± 4.4 (2.37 ± 24.6)	25.3 ± 21.0	16.6 ± 4.4 (16.3 ± 16.2)	27.2 ± 14.6	11.3 ± 4.5 (11.5 ± 13.0)	0.1	0.079
Stride length (cm/s)	98.4 ± 18.0	101.6 ± 3.3 (103.3 ± 15.7)	96.8 ± 17.3	101.4 ± 3.3 (102.2 ± 17.9)	91.4 ± 20.6	102.7 ± 3.4 (100.2 ± 19.0)	0.9	0.002
DTC of stride length (%)	17.3 ± 11.3	11.4 ± 2.3 (10.7 ± 9.4)	18.2 ± 13.8	12.3 ± 2.3 (12.0 ± 13.8)	21.3 ± 10.0	10.4 ± 2.4 (11.3 ± 7.5)	0.8	0.007
Cadence (step/min)	100.1 ± 11.0	104.8 ± 3.2 (103.8 ± 14.0)	101.7 ± 14.4	105.1 ± 3.2 (104.7 ± 12.7)	106.6 ± 13.7	109.4 ± 3.3 (111.0 ± 15.7)	0.5	0.024
DTC of cadence (%)	11.0 ± 9.7	8.0 ± 3.2 (8.1 ± 12.9)	9.5 ± 12.4	5.6 ± 3.1 (5.6 ± 15.7)	7.6 ± 8.2	2.6 ± 3.3 (2.3 ± 8.5)	0.4	0.030

EXER-TC: exergaming-based Tai Chi; TC: traditional Tai Chi; DTC: dual task cost.
**Significance level < 0.017 for post hoc comparisons (TC vs. Control).*
†Significance level < 0.017 for post hoc comparisons (EXER-TC vs. Control).

brain activation (Liao et al., 2020, 2021). Although we did not measure brain function, we suggest that EXER-TC improved brain plasticity in older adults with MCI. Therefore, beneficial transfer effects to global cognitive function and dual-task walking ability may result from the consolidation of the neural circuit provided by exergaming.

The advantage of TC on enhanced dual-task walking capacity in older adults at high risk of falling has been reported (Li et al., 2019). The benefit of exergaming on enhanced dual-task walking performance in community-dwelling older adults has also been stated (Wang et al., 2021). This study is the first to investigate either with traditional or exergaming-based TC in older adults with MCI. Executive function correlated highly with gait speed and variability in dual-task walking (Hausdorff et al., 2008; Wang et al., 2021). Both TMT and Stroop performance are tasks of executive function linked to cognitive flexibility, divided attention, and inhibitory control in older adults (Hobert et al., 2011; Ikeda et al., 2014; Wollesen et al., 2016). Dealing with different stimuli simultaneously and reacting to surroundings are essential parts of cognitive dual-task gait performance. We suggest that the improvements in executive function (TMT and Stroop test) contribute to gains of gait speed during cognitive dual-task waking in both the TC and EXER-TC groups.

Older adults with MCI may be easily affected by dual-task interference due to lesser neural network available for concurrent action on secondary tasks. The DTC presents the interference in dual-task performance compared to the single-task performance. In this study, the DTC of speed during cognitive dual-task performance reduced 17% after TC training and 22% after EXER-TC training. Based on the bottleneck and capacity-sharing theories (Tombu and Jolicoeur, 2003), we suggest that both traditional and interactive exergaming TC increases cognitive capacity, improves processing speed, and reduces interference between cognitive dual-task walking tasks (Redfern et al., 2002). A cognitive DTC $\geq$ 20% can destabilize gait and increase fall risk (Hollman et al., 2007). Likewise, a DTC > 20% is associated with progression to dementia in older adults with MCI (Montero-Odasso et al., 2017). In this study, the cognitive DTC of speed for the TC and EXER-TC groups were > 20% before and after training. This result suggested that the routine TC training programs were required for the study participants, even though they had much improvement after intervention.

Improvements in gait performance and DTC were only apparent for the cognitive dual-task, not the motor dual-task. One possible reason for this difference is that our motor task is not as challenging as our cognitive task to cause dual-task interference; therefore, the training improvements were not significant. The previous finding supports this explanation that older adults with MCI showed more apparent gait deviations in walking while doing serial subtraction than walking while carrying a glass of water on a tray (Hunter et al., 2018). Another reason is that the task of TC resembled the cognitive dual-task because performing TC requires concurrent physical and mental activity. Therefore, the practicing effects of both TC and EXER-TC were more easily transferred to cognitive dual-tasks rather than motor dual-tasks.

As far as we know, this is the first study to validate the influence of exergaming-based TC intervention on dual-task walking costs in older adults with MCI. Limitations of this study include the long-term effects of EXER-TC on cognitive and dual-task performance remain unknown due to lack of follow-up assessment. Second, there is limited physiological evidence to support the training-induced cognitive improvements. Use of brain imaging and measurement of physiological factors such as BDNF may be included in a future study. Third, training intensities were difficult to match. However, we monitored heart rates and perceived exertion, and ensured that the session times of the two groups were equal. Fourth, the learning effect may affect performance in the post-intervention improvement for most tasks. However, we assume that the learning effect was negligible because of the long pre-to-post assessment interval of 3 months. Fifth, the control group had no intervention and probably less contact with the study personally.

CONCLUSION

This study found that the benefits of EXER-TC were equal to traditional TC for the executive function domain, gait speed, and DTC of speed during cognitive dual-task walking in older adults with MCI. The benefit in global cognitive function were found only after EXER-TC group. These results support the hypothesis that exergaming facilitates positive effects of TC and has potential therapeutic use in older adults with MCI.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Human Research Ethics Committee of Taipei City Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

C-LL and Y-YL conceived and designed the experiments, and wrote the article. F-YC and M-JW performed the experiments. F-YC, M-JW, and Y-YL analyzed the data. All authors reviewed the manuscript.

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Development and Co-design of NeuroOrb: A Novel "Serious Gaming" System Targeting Cognitive Impairment in Parkinson's Disease

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Whilst Parkinson's disease (PD) is typically thought of as a motor disease, a significant number of individuals also experience cognitive impairment (CI), ranging from mild-CI to dementia. One technique that may prove effective in delaying the onset of CI in PD is cognitive training (CT); however, evidence to date is variable. This may be due to the implementation of CT in this population, with the motor impairments of PD potentially hampering the ability to use standard equipment, such as pen-and-paper or a computer mouse. This may, in turn, promote negative attitudes toward the CT paradigm, which may correlate with poorer outcomes. Consequently, optimizing a system for the delivery of CT in the PD population may improve the accessibility of and engagement with the CT paradigm, subsequently leading to better outcomes. To achieve this, the NeuroOrb Gaming System was designed, coupling a novel accessible controller, specifically developed for use with people with motor impairments, with a "Serious Games" software suite, custom-designed to target the cognitive domains typically affected in PD. The aim of the current study was to evaluate the usability of the NeuroOrb through a reiterative co-design process, in order to optimize the system for future use in clinical trials of CT in individuals with PD. Individuals with PD (n = 13; mean age = 68.15 years; mean disease duration = 8 years) were recruited from the community and participated in three co-design loops. After implementation of key stakeholder feedback to make significant modifications to the system, system usability was improved and participant attitudes toward the NeuroOrb were very positive. Taken together, this provides rationale for moving forward with a future clinical trial investigating the utility of the NeuroOrb as a tool to deliver CT in PD.

Keywords: cognitive training, Parkinson's, serious games, co-design, dementia, brain training, cognitive impairment

INTRODUCTION

Whilst Parkinson's disease (PD) is primarily characterized as a motor disorder, many individuals also experience some degree of cognitive impairment (CI). Impairments in one or more cognitive domains may be observed even in early PD (<5 years) (Goldman et al., 2015), with many individuals also at risk of progression to mild CI (PD-MCI) and dementia (PD-D) (Litvan et al., 2012). Even in newly diagnosed individuals, PD-MCI is a common finding, with one study, the ICICLE-PD study, reporting that 42.5% of newly diagnosed individuals met criteria for PD-MCI using level 2 criteria (1.5 SDs lower than normative values) (Yarnall et al., 2014). By 3–5 years post-diagnosis, an estimated 20–57% of individuals qualify for diagnosis of PD-MCI (Caviness et al., 2007), with 20% converting to PD-D within 3 years (Saredakis et al., 2019). After 8 years, approximately 80% of individuals with PD develop PD-D (Aarsland et al., 2003). PD-D, classified as one of the Lewy Body dementias, is thought to be at least partially related to Lewy body pathology within limbic and neocortical areas (Smith et al., 2019), with Braak et al. (2005) reporting a correlation between declining scores on the Mini-Mental State Exam (MMSE) and higher neuropathologic state (Braak et al., 2005). Nevertheless, Lewy body pathology is only one contributor to the complex pathophysiology of PD-D, with other factors, including degeneration of neurotransmitter systems, the co-occurrence with Alzheimer's disease-related pathology, and genetic factors also playing a role (for review, see Aarsland et al., 2021).

Cognitive impairment in PD may manifest in multiple domains, including executive function, attention, processing speed, visuospatial function, memory and verbal fluency, although not all domains are equally affected, particularly early in the course of the disease (Kehagia et al., 2010). Additionally, CIs, particularly those affecting executive function, are a key contributor to deficits in motor learning observed in PD, which may lead to increased gait and balance symptoms for individuals, and, ultimately, heightened risk of adverse events, such as falls (Olson et al., 2019). In support of this, the regulation of gait variability and rhythmicity, while an automatic process in healthy individuals, requires active attention in those with PD, with executive function deficits further exacerbating the increases in gait variability seen during dual-task performance (Yogev et al., 2005). Overall, CI represents the single biggest predictor of quality of life, mortality and caregiver burden for individuals with PD (Duncan et al., 2014).

Despite the prevalence and significant burden of CI in PD, however, interventions are limited. Whilst dopamine (DA) replacement therapies, such as levodopa, are effective at providing symptomatic relief for motor impairments, evidence for the treatment of CI is mixed, with some studies noting that intervention may paradoxically worsen cognition in certain domains (Schneider et al., 2013; Poston et al., 2016). The only currently approved treatment specifically for CI in PD is the use of cholinesterase inhibitors (Sun and Armstrong, 2021). These are, however, associated with prominent side effects (Ravina et al., 2005), variable efficacy between patients (Emre et al., 2014), and may even exacerbate the motor-symptoms of the disease (Collins et al., 2011). Furthermore, such therapies only address symptomatic presentation of established CI, unable to prevent or slow the development of cognitive dysfunction in PD (Cerasa and Quattrone, 2015). Consequently, current pharmacological interventions fall short in addressing CI in PD and, as such, interest has grown in non-pharmacological interventions, such as cognitive training (CT) (Guglietti et al., 2021; Sun and Armstrong, 2021).

Cognitive training is defined as training programs providing cognitive stimulation that offer structured practice on specific cognitive tasks (Clare and Woods, 2004). Multiple studies have established the efficacy of CT in improving or maintaining cognitive function in various neurological patient populations in areas such as global cognition, executive functions, learning, visuospatial abilities and memory (Sinforiani et al., 2004; Mohlman et al., 2011; Naismith et al., 2013; Petrelli et al., 2015; Folkerts et al., 2018). CT has also been shown to be effective both in cognitively healthy PD patients (Glizer and MacDonald, 2016), as well as those with PD-MCI (Reuter et al., 2012; Maggio et al., 2018), and the benefits may be maintained long-term up to 12 months (Petrelli et al., 2015; Bernini et al., 2019). Despite this, however, recent reviews of the literature as a whole have reported mixed results on the benefits of CT in PD (see, for example, Guglietti et al., 2021), with a Cochrane review evaluating the effectiveness of CT for PD-MCI and PD-D reporting no difference between CT intervention and control groups in measures of global or specific cognitive skills (Orgeta et al., 2020). It is important to note, however, that this review had strict inclusion criteria, capturing only randomized control trials.

The variability in outcomes for CT in the PD population may potentially be linked to differences in implementation strategies between programs, with many not optimized for use specifically in individuals with PD. In particular, the motor impairments observed in PD may represent a significant barrier to traditional CT modalities, with activities requiring a high level of manual dexterity, such as the use of pen and paper, which proves challenging for individuals with dyskinesia/akinesia (Thomas et al., 2017). Whilst the move from traditional pen-and-paper techniques to more computer-based programs may address some of these barriers, a 2010 survey found that nearly 80% of PC-users with PD have significant and severe difficulties using a computer due to their illness (Nes Begnum, 2010). In particular, muscle stiffness, inertia and tremor were frequent problems, resulting in significantly higher severe difficulties using a standard mouse (42%) and keyboard (27%) (Nes Begnum, 2010). Similarly, previous studies have shown one-third to half of computer users' time is spent dragging a cursor via the mouse, which is considered a complex motor operation (Johnson et al., 1993) and represents a major obstacle to successful computer use for people with motor difficulties (Trewin and Pain, 1999; Kouroupetroglou, 2014). As such, this could represent a significant barrier to the delivery of CT in PD, potentially confounding the evaluation of outcomes. To address such barriers, assistive technologies and appropriate hardware, adapted for the PD population, are needed.

Engagement with the CT paradigm itself may also be key to the ultimate success of the intervention. In support of this, CT in a cohort of psychiatric patients determined engagement during

FIGURE 1 | The Orby Controller, which consists of several features specifically adapted for motor dysfunction, including: (1) a spherical shape to allow for ergonomic bimanual control, (2) gray grip pads (partially obscured during use) and optional hand straps to support hand placement, (3) an adjustable sensitivity threshold, to prevent random movements from being interpreted as purposeful, (4) vibration to provide haptic feedback to the player, and (5) a large red selection button on the front of the controller to reduce the fine motor requirement (not shown).

training was a significant independent predictor of cognitive gains, irrespective of simple exposure (Harvey et al., 2020). Given that individuals with PD experience decreased reward sensitivity in an off-dopaminergic medication state, as well as increased apathy (Muhammed et al., 2016), this may be a particularly relevant concern for use of CT in this population. One strategy that may improve engagement is the addition of game-like features (gamification) into CT programs (Lumsden et al., 2016; Van De Weijer et al., 2019). This can be attributed to the incorporation of features such as high-score and reward incentives, narrative, personalization, self-directed challenge, exploration, free-play, competition and graphics into the training platform (Nagle et al., 2015). Gamification may also have benefits beyond improvement of engagement alone, with a systematic review of the literature of gamification in CT highlighting seven reasons researchers opted to gamify CT programs, including increased usability/intuitiveness for target age groups, increased ecological validity, increased suitability for the target disorder, and increased brain stimulation (Lumsden et al., 2016). The review concluded that gamified training is highly engaging and motivational and found evidence that gamification may be effective at enhancing CT in the elderly and ADHD populations (Lumsden et al., 2016). Similarly, recently, the Parkin'Play study showed enhanced global cognition scores after 24-weeks of individuals with PD participating in a home-based, gamified CT intervention (Van De Weijer et al., 2019).

To date, however, a system that targets the motor impairments that limit the use of traditional CT delivery methods in PD, while also incorporating elements of gamification that may improve engagement and treatment adherence, is lacking. In order to address this, we aimed to develop a novel "Serious Gaming" system, NeuroOrb, that would incorporate both assistive hardware and a custom gaming suite, designed to target the cognitive domains most affected in PD. Prior to deciding to embark on a large-scale trial to evaluate the potential cognitive benefits of CT delivered using the NeuroOrb system, we first engaged with individuals with PD in a reiterative co-design process, in order to evaluate the usability of the system in this population. Following incorporation of all feedback into system design, individuals were again asked to engage with the NeuroOrb system and evaluate the effectiveness of the changes. This manuscript details the outcomes of that co-design process, with future clinical trials planned to evaluate the cognitive benefit of the NeuroOrb system in individuals with PD.

PARTICIPANTS AND METHODS

Participants

Participants (*n* = *13*) were recruited from the community via Parkinson's South Australia. Participation was voluntary and no incentive to participate was provided. Inclusion criteria included a prior diagnosis of PD by a registered neurologist and fluency in English. Exclusion criteria included significant hearing and visual impairments not corrected by glasses/contacts, a neurological disorder other than PD, or a previous diagnosis of a learning disability. All participants provided written informed consent prior to testing and the research conducted was approved by the Human Research Ethics Committee of the University of Adelaide (H-2020-214).

The NeuroOrb System

The NeuroOrb serious gaming system involves two main components. The first is the use of an assistive hardware via the 'Orby' controller (**Figure 1**). Orby is an innovative novel controller that was custom co-designed by one of the authors of the current study (DH) to address barriers associated with motor dysfunction, such as reduced fine motor control and tremor

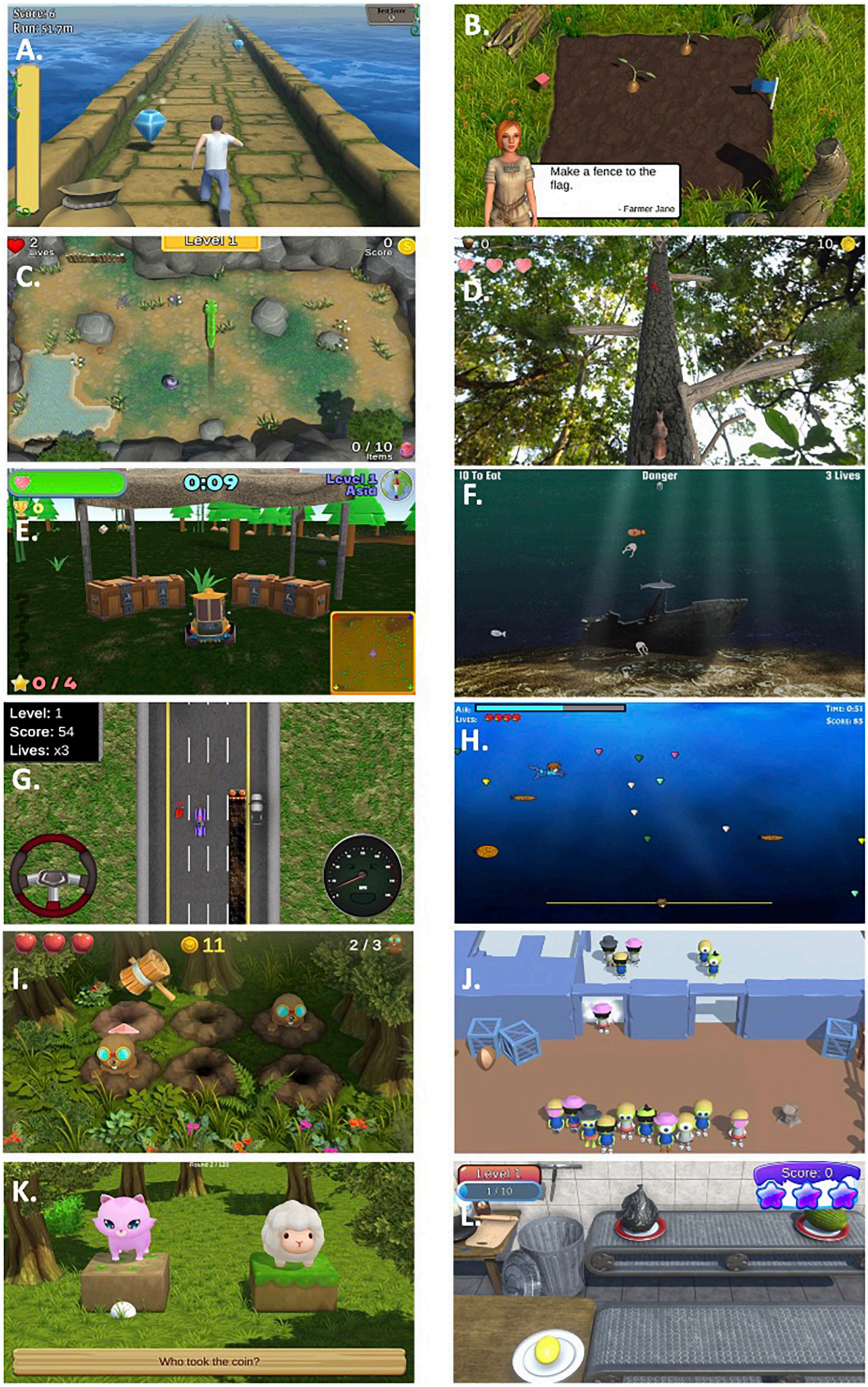

FIGURE 2 | Representative screenshots from each of the games included within the NeuroOrb suite: **(A)** A Bridge Too Far; **(B)** Farm Quest; **(C)** Snake; **(D)** Squirrel; **(E)** Sunday Driver; **(F)** Marine Life; **(G)** Driving Maniac; **(H)** Swimma; **(I)** Whack-a-Mole; **(J)** Munchkinis; **(K)** Who's the Boss?; **(L)** Chow Time!

(Walker and Hobbs, 2014; Hobbs et al., 2019). The spherical "Orb" part of the controller is 200 mm in diameter and the top of the controller is 230 mm above the table surface. The spherical shape allows for ergonomic bimanual control, with grip pads on either side to indicate ideal hand placement. Importantly, the sensitivity of responsiveness can be adjusted for the individual, with the movement recognized as "purposeful" altered to take into account the extent of motor impairment. This is particularly important for PD patients with resting tremor or drug-induced dyskinesias, as unintentional tremors can be ignored, leaving only intentional movements to direct the controller during CT. The controller also includes vibration, which allows for haptic feedback triggered by actions within each game. Finally, the large red button for selection minimizes the requirement for fine motor control that may be required with devices such as iPad or keyboard keys, which may otherwise be a concern for PD patients. Orby has previously been trialed successfully in individuals with hand impairments due to disability, such as cerebral palsy and in adults post-stroke (Hobbs et al., 2017), but has not previously been trialed in individuals with PD.

Secondly, to improve user engagement, a custom serious gaming suite was designed to target the cognitive domains most affected in PD, including executive function (working memory, attention, cognitive flexibility, problem solving), visuospatial function and learning (Watson and Leverenz, 2010; **Figure 2**). Some of these games were adapted from existing games designed by one of the authors of this study (DH). Other games were developed specifically for the NeuroOrb system. Each game is described below, with further information on the cognitive domains that each game targets summarized in **Table 1**. Due to the nature of gameplay, several of the games encompass training in multiple domains. This gamification of the CT paradigm introduces elements of high-user control, self-directed challenge, exploration and free-play, which have previously been shown to improve outcomes in home-based CT compared to more automated task delivery (Nagle et al., 2015).

Assessment of NeuroOrb

In order to assess overall acceptability of NeuroOrb, the well-validated System Usability Scale (SUS) was administered both pre- and post-modification (Peres et al., 2013). Additionally, to investigate participants' perceptions of the Orby controller, games catalog and NeuroOrb system overall, two surveys were developed in-house. These surveys were specifically developed for the purposes of this co-design trial and have not been externally validated.

The first of these assessed feedback on the NeuroOrb system, with questions regarding whether individuals enjoyed the system as a whole (calculated as % responding yes), whether they found the system challenging to use (calculated as % responding yes), how enjoyable/difficult they found the games/Orby controller to use (rated on a scale of 1–10, with 1 = very poor/easy and 10 = very challenging/enjoyable), and their confidence in whether they thought that routine engagement with the NeuroOrb system would result in improvement or maintenance of cognitive function (rated on a scale of 1–10, with 1 = not at all confident and 10 = very confident). This survey was repeated both pre- and post-modification of the NeuroOrb system, with an additional question added post-modification asking whether participants felt that their comments had been addressed.

The second survey, given both pre- and post-modification of the NeuroOrb system, focused on the content and usability of the individual games themselves. Participants were asked whether they enjoyed each game, whether they found the game challenging, whether they found the instructions for each game clear, and whether they found the game easy to play (all calculated as % responding yes). Further, for each game, participants were asked to rate their enjoyment of the game, as well as how difficult they found each game (each rated on a scale of 1–10, with 1 = very poor/easy and 10 = very challenging/enjoyable). Finally, features of each game (i.e., color/animation/sound) and features of the game control were both rated on a scale of 1–3, with 1 = poor/not good, 2 = average and 3 = good.

Procedure

Eligible participants ($n = 13$) attended the Brain and Body Fitness Studio (BBFS) at Parkinson's South Australia and completed three 60-min sessions with NeuroOrb over the course of a week (**Figure 3**). All participants were tested in the "on"-stage of their medications (i.e., the period in which motor symptoms are well-controlled by the medication). While caregivers were not present during the training sessions, participants were supervised during game play by a member of the research team with prior expertise in using the NeuroOrb system. A pre-exposure battery, consisting of demographic questions, the Mini-Mental State Examination (MMSE) to assess baseline cognitive function (Folstein et al., 1975), the Parkinson's Disease Questionnaire-39 (PDQ-39) to assess disease-specific quality of life (QoL; Jenkinson et al., 1997) and the Geriatric Depression Scale (GDS) as a self-report measure to assess depression in older adults (Pocklington et al., 2016), was administered on day 1, followed by a 60-min NeuroOrb session. Day 2 involved 60-min of supervised gameplay and day 3 involved 60-min of gameplay, followed by a post-exposure battery. This post-exposure battery consisted of a series of questionnaires on previous game experience, system feedback and individual game feedback. Additionally, the System Usability Scale (SUS) was administered to assess overall acceptability of NeuroOrb (Peres et al., 2013).

Participants were provided with a brief controller demonstration and written instructions for each game and assistance was provided if requested during the first session to help familiarize individuals with the controller and game objectives. Play for each game was restricted to 15 min over the course of the week to ensure an even spread of training across multiple domains. Feedback was collected via both written surveys and verbal communication across the three sessions and adjustments to the gaming suite and controller setup were made based on this feedback.

Participants were invited back 1-month and 6-months later for two additional 60-min sessions with the adjusted setup to provide feedback on implementation of suggested changes. The 1-month session was conducted to allow individuals to assess the success of changes overall, while the original gameplay experience was still fresh in their minds. Conversely, the 6-month session was

TABLE 1 | Overview of primary and supplementary cognitive domains trained in the gaming suite and game descriptions.

Game	Primary rationale	Supp 1	Supp 2	Supp 3	Game description
A Bridge Too Far	Working Memory	Cognitive Flexibility/ Set Shifting	Visuospatial		A running game that requires the player to collect coins, cans of soda (for energy) and the correct color gem, while navigating a never-ending path and avoiding gaps.
Farm Quest	Problem Solving/ Abstract Reasoning	Planning	Attention		A puzzle game that requires problem solving skills to separate different farm produce into like groupings and reach a flag on the other side of a vegetable patch.
Snake	Visuospatial Function	Avoidance Learning	Attention		A snake character needs to be navigated within an arena, avoiding obstacles, boundaries and its own body, whilst collecting different "orbs." Additionally, an eagle intermittently flies across the arena requiring the player to decide if they will risk their life to collect the orbs or seek safety in a nearby lake.
Squirrel	Attention	Working Memory	Cognitive Flexibility/ Set Shifting	Visuospatial	A squirrel character requires navigation around a never-ending tree, avoiding branches, with speed and number of obstacles increasing as the player progresses. Prior to the start of each level, players are presented with a "shopping list" of colored berries and the number of each that they are required to collect. Players must avoid all other colored berries not specified for collection.
Sunday Driver	Attention	Working Memory	Spatial Navigation	Cognitive Flexibility	A driving game that requires players to navigate a large area to find and collect different characters that are spread around the course through trial and error, and to return them to a central tent.
Marine Life	Attention/ Working Memory	Cognitive Flexibility/ Set Shifting	Avoidance Learning	Spatial Navigation	A deep ocean game that requires different sea creature characters to be navigated around to eat a specified number of other sea creatures before progressing to the next level. Each level includes a "danger" creature (or creatures) that the player must avoid, with the player's character and those they are asked to eat and avoid changing with each level.
Driving Maniac	Visuospatial	Attention			A vertical-scrolling driving game that involves navigation of a car along a road where the player must avoid obstacles such as other cars, oil slicks and roadblocks, whilst collecting extra lives and fuel-tanks. Speed increases with distance traveled, to increase the difficulty.
Swimma	Attention	Working Memory	Problem Solving/ Abstract Reasoning	Cognitive Flexibility/ Set Shifting	A side-scrolling game that requires navigation of a scuba diver character through a constantly moving underwater environment, whilst avoiding other sea creatures, collecting certain gems, avoiding a particular gem, and collecting air bubbles and extra lives to stay alive.
Whack-A-Mole	Attention	Working Memory	Sequence Learning		A game that requires players to hit dirt burrows with a hammer in the same sequence that moles appear and then hide, to reveal each mole. The number of burrows increases with each stage, the number of moles appearing in a sequence increases, and the rate of appearance varies between moles (e.g., first and second moles might pop up quickly, but the third may be slightly delayed).
Who's the Boss?	Problem Solving/ Abstract Reasoning	Working Memory	Risk-Taking Behavior		A puzzle game that presents the player with a pair of characters (e.g., Cat/Sheep) and asks them to guess who they believe the "boss" is, with feedback (correct/incorrect) provided instantaneously. Subsequent pairs of characters (e.g., Penguin/Chicken) are then presented, and through a series of exposures of different combinations of paired characters, the player must determine the correct hierarchy of characters, receiving coins depending on the number of paired exposures they required to make their guess. The player can also choose to bet on their confidence in their final decision.
Munchkinis	Abstract Reasoning	Cognitive Flexibility/ Set Shifting			A puzzle game requiring the guidance of "Munchkinis" characters through a series of gates, in order to guide them home. Each level involves a series of gates (2 or 4) that allow entry based on a particular trait (e.g., glasses vs. no glasses, hat vs. hair, etc.). The player must use trial and error to determine the sorting criteria and allocate each Munchkinis through their respective gate.
Chow Time	Response Inhibition	Attention	Working Memory		Players are presented with a moving conveyer belt with various foods/items and must sort the edible food (e.g., melon) from the non-edible items (e.g., an old boot). To select, players must make an intentional selection of the edible food by moving the controller toward the second conveyer belt to collect; however, no movement is required when faced with inedible food. The conveyer belt increases in speed with each level.

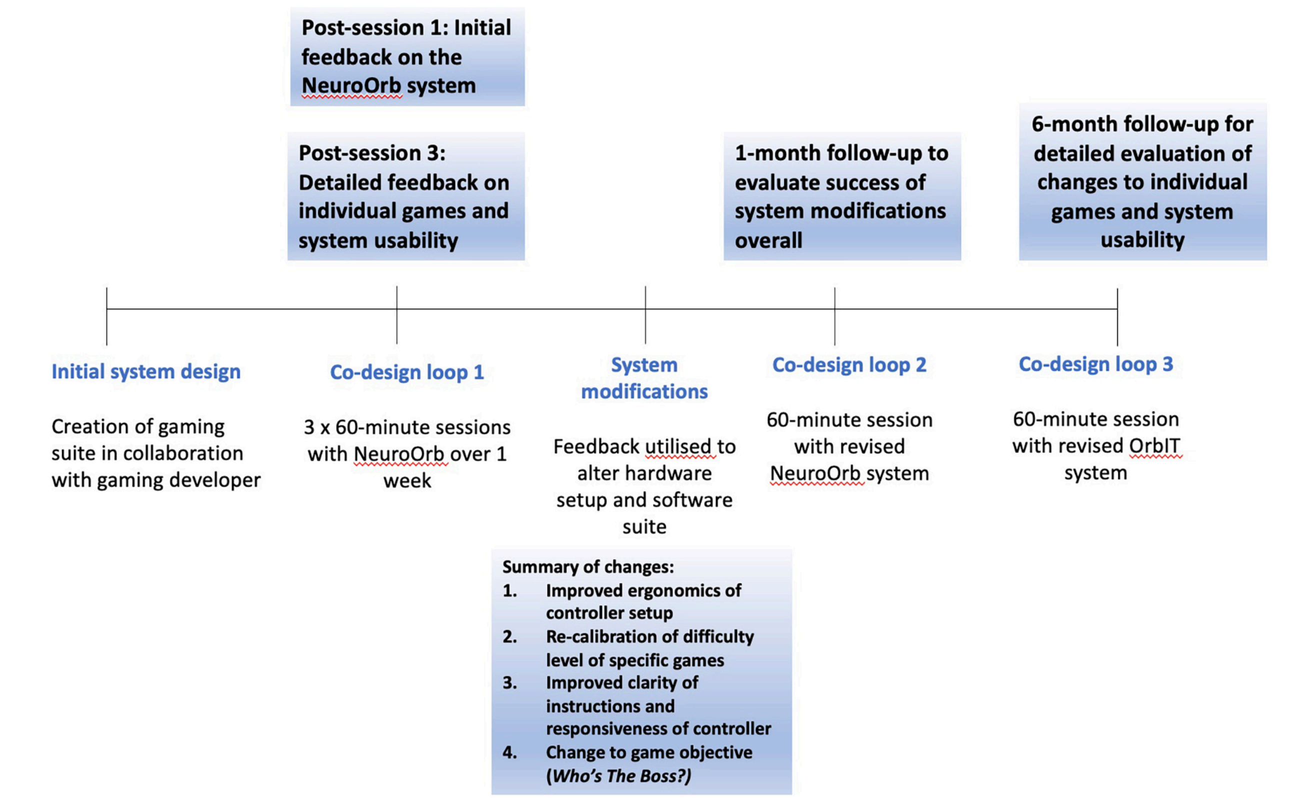

FIGURE 3 | A timeline of the co-design trial. The NeuroOrb system was first developed in collaboration with a gaming developer (BW). Participants were then invited to participate in three 60-min sessions over the course of a week, spaced 48 h apart. Extensive survey and verbal feedback was collected at the end of the first and third sessions. This feedback was then used to make significant changes to both the hardware and software of the NeuroOrb system. Following these changes (~1-month post-exposure), participants were invited back for another 60-min gaming session and were encouraged to provide initial feedback on the changes made. They were then invited back a second time (~6 months post-exposure) for a further 60-min session with the NeuroOrb system, followed by the completion of detailed feedback about the gaming suite and system as a whole.

conducted to allow enough time to have passed from the initial system engagement to minimize carry-over effects that could potentially bias the final system and games evaluation. During co-design loop 2 (~1-month post-engagement), follow-up feedback on the overall changes to NeuroOrb, as well as assessment of overall system enjoyment, was collected. During co-design loop 3 (~6 months post-engagement), individuals again completed the SUS and were asked for feedback on the individual games. Throughout all sessions, observations were recorded and verbal feedback was noted by trained members of the research team.

Statistical Analysis

Demographic data are presented as either Mean (±SD) or Range/Proportion, depending on the variable. For rating scales, each item was scored on either a 10-point or 3-point Likert scale. Data are presented as Mean (±SD), with the exception of measures presented as the percentage of participants endorsing "yes" for a particular measure. For pre- to post-modification improvement, the absolute increase in percentage for percentage-based measures and the absolute increase in points for scale-based measures was calculated. Data were analyzed using SPSS (Version 26).

RESULTS

Participant Demographics

Thirteen participants were included in the pilot (6M/7F, Mean Age 68.15 ± 8.54) years), with an average disease duration of 8 ± 5.43 years. Demographics are summarized in **Table 2**. Twelve of the 13 participants completed all 3 sessions of the CT training period, with 1 completing 2/3 due to time constraints. Eleven of the 12 participants (92%) attended the 1-month follow-up and nine of the 12 participants (75%) attended the 6-month follow-up. Participants did not appear to be cognitively impaired, with MMSE scores all > 27 (Mean 29 ± 0.82). Despite not scoring in the CI range on the MMSE, a subjective survey revealed participants commonly reported cognitive concerns, including remembering events (30.1%), remembering information (38.5%), paying attention (15.4%), learning new tasks (15.4%), remembering words (15.4%) and managing day-to-day tasks (15.4%). In addition, 38.5% self-reported experiencing motor difficulties.

Unfortunately, neither the MDS-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) nor Hoehn and Yahr (HY) staging was available for the current sample. However, previous work has suggested that the median disease duration for HY staging is 4 years for Stage 1, 5 years for Stage 2, 7 years for Stage 3, 10 years for Stage 4 and 14 years for Stage 5, with individuals with disease duration from 6 to 10 years, which represents the majority of individuals in the current sample, evenly represented across all five stages (Skorvanek et al., 2017). From observations carried out during game play with the NeuroOrb system, motor impairments did not appear to prevent any participant from actively engaging with the system, and no participant expressed concerns to this effect in their comments.

At baseline, PD participants did not report a decrease in health-related QoL in any domain measured by the PDQ-39 compared with normative data (Jenkinson et al., 1997). Furthermore, participants mean GDS (3.42 ± 4.08) did not indicate depression, with scores > 11 indicating depression on this measure (Mondolo et al., 2006).

With relation to previous game experience, 92.3% of participants reported playing games, with 53.8% reporting a frequency of 1 or more times daily. The preferred gaming formats reported were card games (76.9%), word and number games (76.9%) and puzzle/tile/board games (38.5%). In terms of computerized games, 30.8% reported playing games in an online format, whilst only 1 participant (7.7%) reported a preference for video games, indicating the sample group had minimal experience with computerized video games prior to engaging in the co-design process.

System Feedback- Co-design Loop 1

Session 1: Initial Feedback

After one session, 91% of participants reported that they enjoyed the NeuroOrb gaming system, with an average rating of 7.58 ± 2.19/10 (**Table 3**). 100% of participants reported finding the games challenging, with the average difficulty level of the games rated as 6.25 ± 1.29/10. However, the games were still reported as being enjoyable, with an average overall enjoyment rating of 7.75 ± 2.18/10. Furthermore, participants reported a high degree of confidence in the ability of the NeuroOrb system to improve/maintain cognitive function (7.92 ± 1.78/10). One participant reported that they would not use the system at home, one reported occasional use, six reported use several times a week and five reported the likelihood of daily use.

With regards to accessibility of the Orby controller itself, this received only a moderate rating (5.83 ± 1.85/10) after the first exposure to the system. Observationally, participants appeared to become more comfortable with controller use by the second exposure and proficient by the third session, with one participant noting, "*the gaming platform was not too awkward to operate once I became used to the tension of the [NeuroOrb] i.e., not to be too forceful gripping.*" Encouragingly, with repeated use, participants also optimized their own use of the Orby controller. Despite being shown a traditional grip (one hand over each grip pad) in the initial session, throughout the trial and across different games, participants adopted several different techniques to control the device, including one handed (**Figure 4A**), upper hold (**Figure 4B**) or lower hold (**Figure 4C**), fingertips (**Figure 4D**), and bear grip (**Figure 4E**) for those with more prominent motor dysfunction (**Figure 4**).

Individual Game Feedback: Pre-modification

Following completion of the third session of play, feedback was collected on the individual games. Data were separated into two categories: content (enjoyment, interest, challenge, difficulty and features) and usability (instructions, ease of play and controls). An overall system rating was also obtained. For each game, the number of participant responses received depended on whether the game was played during their sessions. Overall ratings for each game are summarized in **Table 4**.

Overall, the response to the games was positive, with all games (except Snake) receiving an above average (>5) overall rating. These results were probed further based on feedback regarding content and usability. Content was broken down into enjoyment, difficulty and game features. In terms of enjoyment, the majority of games were considered enjoyable, with >90% of participants reporting enjoyment of *A Bridge Too Far* (7.42 ± 1.82/10), *Squirrel* (7.17 ± 1.36/10), *Marine Life* (7 ± 2.23/10) and *Driving Maniac* (7.71 ± 2.18/10) and >50% of participants reporting enjoyment of *Swimma* (6.71 ± 1.50/10), *Sunday Driver* (6.44 ± 1.97/10), *Whack-A-Mole* (7.55 ± 1.58/10), *Munchkinis* (7.64 ± 2.33/10), *Who's the Boss?* (5.85 ± 2.16/10) and *Chow Time*! (6.3 ± 2.64/10). Games with a below average (<50%) number of participants reporting enjoyment included *Farm Quest* (5.73 ± 2.31/10) and *Snake* (4.54 ± 1.83/10).

TABLE 2 | Demographic and patient data (*n = 13*), Mean ± SD.

Patient Data	Mean ± SD	Range/Proportion
Age (Years)	68.15 ± 8.54	48–81
Gender (M/F)	–	6/7
Years Since Diagnosis	8 ± 5.43	1–19
MMSE	29 ± 0.82	–
GDS	3.42 ± 4.08	–
PDQ-39 Summary Index	21 ± 11.25	–
Affected Side (Right/Left/Equal)	–	2/6/5
Dominant Hand Affected	–	7/13
DBS Surgery	–	2/13
Time Since Medication (hours)	1.85 ± 1.11	–

TABLE 3 | Session 1 – Initial feedback on the NeuroOrb system.

Initial Feedback		Mean ± SD
Initial Enjoyment	% Yes	91.7%
	Games	7.75 ± 2.18
	NeuroOrb System	7.58 ± 2.19
Challenging	% Yes	100%
Difficulty	Games	6.25 ± 1.29
	Controller	5.83 ± 1.85
Confidence	Likelihood of improvement/maintenance of cognitive function	7.92 ± 1.78

%, percent of participants who answered "yes." Scores are based on a scale of 1–10 (1 = very poor/easy, 10 = very challenging/enjoyable). n = 12, Mean ± SD.

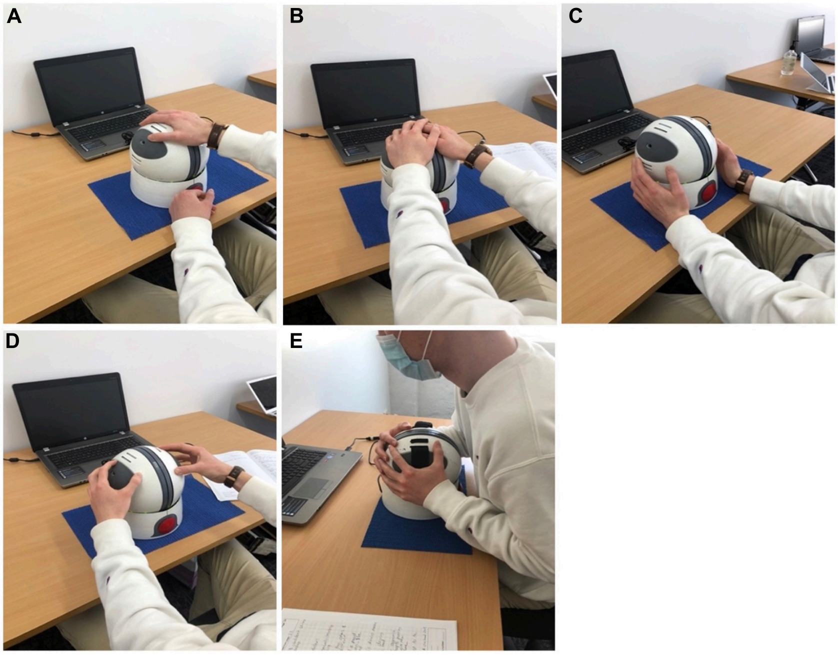

FIGURE 4 | Despite being shown a traditional grip (one hand over each grip pad) in the initial session, following additional exposures to the Orby controller, participants adopted several different techniques to control the device, including one handed **(A)**, upper hold **(B)** or lower hold **(C)**, fingertips **(D)** and bear grip **(E)** for those with more prominent motor dysfunction.

With regards to difficulty, we sought to balance achieving an effective challenge with reducing the "cognitive cost" of games by ensuring that all games fell into a difficulty level of between 6 and 8 on a 10-point scale. All games were within this range, with the exception of *Chow Time!*, with only 30% of participants reporting this game to be challenging. This was corroborated with observations and verbal feedback, with participants reporting the speed of the conveyer belt started off "*too slow*" and did not become challenging until at least level 5. Conversely, although still within an acceptable range, *Munchkinis* was considered the most difficult game included in the suite. Based on observations during the first three sessions, this also appeared to be related to progression. For example, the first level of *Munchkinis* involved the sorting of features based on 2 criteria, before level 2 progressed to sorting based on multiple characteristics. This progression was reported to be "*too steep*," with only one participant observed to successfully complete the second stage.

In terms of game features, including the use of color, animations and sound, all games were rated > 2.5 on a three-point scale, with no notable comments or observations made with regards to the visual features of the games' design. Interestingly, one participant did comment on the reliance on color for sorting in many of the games, particularly *Squirrel*, as this would be a potential barrier for implementation in those with color blindness. Whilst this feedback was not directly addressed in the initial round of changes, future adaptations could include the use of shape, rather than color, to overcome this particular concern.

Usability of the games was assessed based on the ease of play, clarity of instructions provided and controller responsiveness for each game. *A Bridge Too Far* and *Chow Time!* were considered easy to play by 100% of participants. Whilst *Chow Time*'s ease is likely attributed to the slow progression of the game, *A Bridge Too Far* appeared to be quite challenging for participants based on observations. This may be because the game is the first listed in the suite and, as such, all participants chose to begin with this game. This meant that, when observers were guiding participants through the features and use of the controller for the first time, it was via this game. This may have led users to feel particularly supported in how to play the game, raising their confidence level and inflating their perception of the ease of the game. Conversely, games which scored poorly (<60%) for ease of play included *Farm Quest, Snake, Sunday Driver, Swimma* and *Munchkinis*. Based on participant comments, this was attributable to poor clarity of the instructions and poor responsiveness of the controls. For example, participants specifically commented "*instructions not clear*" or "*not easy to follow*" for *Farm Quest*. For *Sunday Driver,* participants commented it was "*not clear had to go to center tent first*." Whereas comments for *Snake* included "*didn't seem to respond to controls*" and "*controlling the snake was difficult, needs refining*."

Concerningly, upon initial rating, only half of all games received an endorsement of >85% for clarity of instructions. For five of the remaining games (*A Bridge Too Far, Farm Quest, Snake, Swimma* and *Who's the Boss?*), a more moderate percentage of participants (65–70%) reported that the instructions were clear. Overall, participants reported that "*having instructions built*

TABLE 4 | Individual game feedback, pre-modification.

		Content					Usability			Overall rating
	Res.	Enjoyed (% yes)	Enjoyment rating (Av interest + Enjoyment)/10	Challenge (% yes)	Difficulty rating/10	Features (color/animation/sound)/3	Clear instruction (% yes)	Ease of play (% yes)	Controls/3	
A Bridge Too Far	13	100%	7.42 ± 1.82	84.6%	7 ± 0.0	2.81 ± 0.27	69.2%	100%	2.62 ± 0.51	**7.69 ±1.60**
Farm Quest	11	36.4%	5.73 ± 2.31	100%	7.36 ± 1.63	2.77 ± 0.44	70%	54.6%	2.7 ± 0.48	**5.5 ±2.36**
Squirrel	12	91.7%	7.17 ± 1.36	81.8%	6.33 ± 1.72	2.73 ± 0.46	100%	81.8%	2.64 ± 0.67	**7.17 ±1.34**
Snake	12	41.7%	4.54 ± 1.83	75%	6.67 ± 2.23	2.64 ± 0.55	70%	33.3%	1.82 ± 0.75	**4.83 ±1.80**
Sunday Driver	9	66.67%	6.44 ± 1.97	100%	7.44 ± 1.24	2.59 ± 0.52	22.2%	22.2%	2.62 ± 0.52	**6.33 ±2.24**
Marine Life	11	90.9%	7 ± 2.23	90%	6.73 ± 1.95	2.83 ± 0.37	88.9%	72.7%	2.5 ± 0.53	**7.27 ±2.15**
Swimma	7	85.7%	6.71 ± 1.50	85.7%	6 ± 1.83	2.56 ± 0.54	66.7%	57.1%	2.33 ± 0.52	**6.43 ±2.37**
Driving Maniac	12	100%	7.71 ± 2.18	100%	7.33 ± 1.23	2.52 ± 0.52	85.7%	75%	2.46 ± 0.53	**7.83 ±1.80**
Whack-A-Mole	10	80%	7.55 ± 1.58	80%	7.2 ± 1.40	2.73 ± 0.45	100%	88.9%	2.33 ± 0.82	**7.7 ±1.77**
Munchkinis	7	85.7%	7.64 ± 2.33	100%	8 ± 1.41	3 ± 0.0	100%	57.1%	3 ± 0.0	**7.57 ±1.90**
Who's the Boss?	10	70%	5.85 ± 2.16	100%	7.3 ± 1.49	2.67 ± 0.49	66.7%	80%	2.67 ± 0.5	**6.3 ±1.34**
Chow Time	10	80%	6.3 ± 2.64	30%	4.2 ± 1.75	2.63 ± 0.51	100%	100%	2.75 ± 0.46	**6.4 ±2.84**

Res, respondents, % indicates percent of participants who answered "yes." Ratings are on a scale of 1–10 (1 = very poor/easy – 10 = very challenging/enjoyable). Features and controls are on a scale of 1–3 (1 = Not Good, 2 = Average, 3 = Good). For all ratings, the table presents Mean (±SD).

into the program would be ideal." This discrepancy was also noticed in observations, with considerable guidance required initially to assist participants in identifying the objectives and features of the games.

Overall Usability: Pre-modification

Following the third session, participants were asked to complete the SUS to assess overall usability of the NeuroOrb System. Results are summarized in **Table 5**. Interpretation of usability based on standard SUS guidelines resulted in an overall score of 65.58/100. According to the SUS grading system, this is considered below the average score of 68 (Gomes and Ratwani, 2019). Furthermore, using the scale developed by Sauro (2011), this score equates to a grade of "C" (approximately 42nd percentile) (Sauro, 2011).

Based on participant feedback, this may, at least in part, be due to general setup/handling issues, with several participants noting comments such as, "*I think the device needs to be anchored to a base, so it doesn't move about the table*." Fatigue/discomfort may also have played a role, with two participants commenting that their shoulders/arms became tired or sore during the session. Additionally, one participant ended 2/3 of their sessions 5 min early due to fatigue.

Modifications Made Following Co-design Loop 1 Feedback

To address the issues identified during the co-design, significant alterations were made, including: (1) improved ergonomics of the controller setup, (2) re-calibration of the difficulty level of tasks within specific games, (3) improved clarity of instructions and responsiveness of controller and, in the case of "*Who's the Boss?*" specifically, (4) a change to the game objective.

Changes to Ergonomics of Controller Setup and Feedback

The controller setup itself was altered, in order to improve user experience and decrease fatigue associated with extended use. This included the introduction of a grip mat, improving how the controller remained in place on the table, as well as the introduction of the optional straps that the controller was designed with, in which participants could place their hands for improved grip/handling of the controller. The straps also enabled participants to "rest" their hands to reduce fatigue and shoulder strain whilst still maintaining control. This reduction of shoulder/arm fatigue was further enhanced through the use of height-adjustable ergonomic chairs with arm rests to provide additional support. Overall, changes to the ergonomics of the set-up and controller were well received, as demonstrated by comments such as, "*mat beneath controller helps*;" "*straps help when moving object on game i.e., are great help when having to just select*" and "*using straps and rubber mat was good*." Most encouragingly, one participant noted, "*the controller was much easier than a mouse and keyboard*" and mentioned that, although they hadn't taken their medication yet, "*it was still easy to navigate on the [NeuroOrb].*" This was also reflected in the follow-up survey where, on a scale of 1 (much worse) to 10 (much better), changes to the controller itself were rated 7.64 ± 1.75/10.

TABLE 5 | Results of the system usability scale questionnaire: pre- versus post-modifications.

Scores are based on a scale of 1–5 (1 = Strongly Disagree, 5 = Strongly Agree). Mean ± SD		
	Pre-modification (*n* = 13)	**Post-modification (*n* = 9)**
System Usability Scale – Questions	**Mean ± SD**	**Mean ± SD**
I think that I would like to use the NeuroOrb System frequently	3.23 ± 0.6	3.67 ± 0.71
I found the NeuroOrb System unnecessarily complex	1.92 ± 0.86	1.67 ± 0.71
I thought the NeuroOrb System was easy to use	3.46 ± 0.78	4.00 ± 1.12
I think that I would need the support of a technical person to be able to use the NeuroOrb System	2.08 ± 0.95	2.11 ± 1.05
I found the various functions of the NeuroOrb System were well integrated	3.46 ± 0.88	3.78 ± 0.44
I thought there was too much inconsistency in the NeuroOrb System	2.39 ± 1.04	1.56 ± 0.53
I would image that most people would learn to use the NeuroOrb System very quickly	3.77 ± 0.93	4.00 ± 1.00
I found the NeuroOrb System very cumbersome to use	2.38 ± 0.96	2.11 ± 1.09
I felt very confident using the NeuroOrb System	3.39 ± 0.96	4.00 ± 1.00
I needed to learn a lot of things before I could get going with the NeuroOrb System	2.31 ± 0.95	2.11 ± 1.20
Overall score	**65.58/100**	**74.17/100**

Changes to the Difficulty Level of Games and Feedback

In order to ensure that all games fell in our ideal range of 6–8/10, modulation of task difficulty was made for both *Chow-Time!* and *Munchkinis*. For *Chow-Time!,* the initial speed of the conveyer belt, and accordingly the required processing speed, was increased. Following modifications, the percentage of participants that reported finding the game challenging increased 37% (from 30 to 67%) and the difficulty rating increased 2.8 points (from 4.2 ± 1.75/10 to 7.0 ± 1.00/10), bringing the game in line with our target difficulty. This was well received, as reflected in verbal feedback in the follow-up session, with participants commenting "*starting speed is better,*" which "*made it more interesting*." Additionally, the overall rating of the game increased 2.93 points (from 6.4 ± 2.84/10 to 9.33 ± 0.58/10). For *Munchkinis*, conversely, an additional level comparable to the first one was added, in order to allow the participants more time to identify and familiarize themselves with the sorting criteria. Following these changes, observers noted an increase in the number of participants reaching the final level at follow-up. This was accompanied by a 1.33 point decrease in difficulty rating (from 8.0 ± 1.41/10 to 6.67 ± 2.31/10), as well as a 1.76 point increase in overall rating (from 7.57 ± 1.90/10 to 9.33 ± 0.58/10). Interestingly, at post-modification rating, three games fell just below the target range of 6–8: *A Bridge Too Far* (5.22 ± 1.56/10), *Snake* (5.75 ± 1.71/10) and *Driving Maniac* (5.75 ± 3.40/10). It is important to note, however, that this was based on a small number of ratings and may be influenced by previous exposure effects.

Improved Clarity of Instructions/Responsiveness of Controller and Feedback

One of the main changes implemented across ***all*** games was the incorporation of instructions into each game's menu, rather than in a separate written booklet. Additionally, images were included in the instructions to assist in familiarizing the participants with elements they encounter during game play. This appeared to have an immediately beneficial effect, with participants commenting that they had not previously recognized elements of gameplay prior to reading the new on-screen instructions. The addition of explanatory pictures seemed to be a key driver of this, with one participant noting, "*I love the pictures in the instructions so I knew what to look for*." Of all games, *Sunday Driver* received the poorest rating of instruction clarity at baseline (22.2%), a finding corroborated by observers, who needed to provide considerable guidance for players. Accordingly, for this game, instructions were incorporated to appear during game play itself, rather than solely all at the beginning. This allowed the player to be guided by instructions based on their game play (e.g., if they stayed stationary, a prompt would appear instructing them of their next goal) (**Figure 5A**), leading to enhanced clarity about what was required at each stage of game play and better engagement with the game during a follow-up session. This was reflected in the post-modification ratings, with an absolute increase of 45% (from 22 to 67%) in the percentage of individuals reporting that the instructions were clear and an absolute increase of 78% (from 22 to 100%) in the percentage of individuals endorsing the game as easy to play.

Overall, changes to the instructions were well-received at follow-up sessions, with one-third of games (*A Bridge Too Far, Snake, Sunday Driver* and *Who's the Boss?)* showing an improvement in the percentage of individuals reporting that the instructions were clear compared to baseline. A further one-third of games (*Squirrel, Swimma, Munchkinis,* and *ChowTime!)* did not show a change from baseline, but this is likely reflective of the fact that all of these, with the exception of *Swimma,* had already obtained a 100% rating for instruction clarity at baseline. For the remaining one-third of games (*Farm Quest, Marine Life, Driving Maniac,* and *Whack-a-Mole)* that showed a decrease in the percentage of individuals reporting that instructions were clear, this may be biased by the small number of ratings (just four per game).

Given that three of these four games, with the exception of *Marine Life,* showed an improvement in overall rating compared to baseline, however, it may also indicate that factors other than

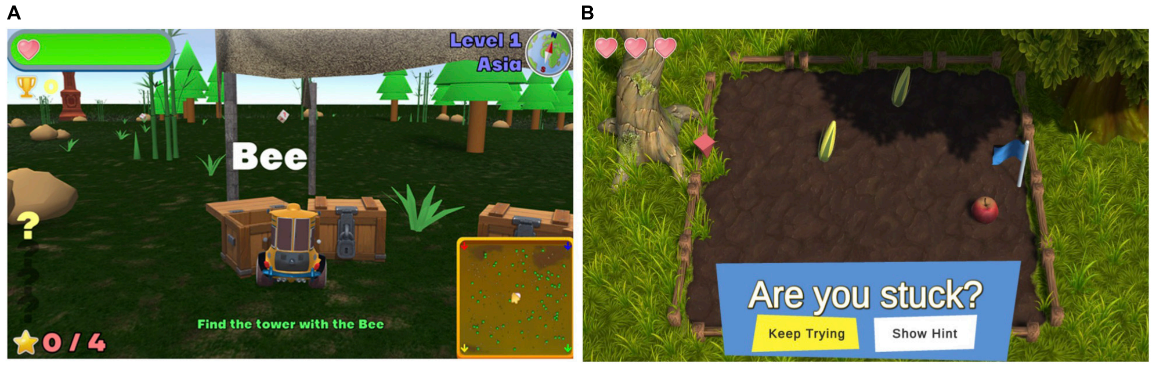

FIGURE 5 | (A) One of the changes made to Sunday Driver included the addition of prompts to instruct individuals based on their gameplay. For example, players would be reminded of the goal if they remained stationary for too long. **(B)** One of the changes made to Farm Quest included the addition of a time-activated hint trigger, offering the player the option of a hint for the next move.

instruction clarity were driving game feedback. In line with this, for *Farm Quest,* participants attributed their difficulty in understanding what was required to progress between levels not to the instructions, but instead to their perceived ability, with one stating, "*problem was mainly me I feel*" and going on to state that their dissatisfaction with the game was "*just due to my comprehending or not understanding the rules*." Given that *Farm Quest* involves problem solving and abstract reasoning, this may reflect particular challenges with this cognitive domain in individuals with PD (Beatty and Monson, 1990; Cronin-Golomb et al., 1994; Young et al., 2010). As such, in order to minimize frustrations, a time-activated hint trigger was added, offering the player the option of a hint for the next move if required (**Figure 5B**). Encouragingly, this was associated with an absolute increase of 64% (from 36 to 100%) in the percentage of individuals reporting that they enjoyed the game and an increase of 2.25 points in the overall rating of the game (from 5.5 ± 2.36/10 to 7.75 ± 0.96/10).

Modification was also made to the controller sensitivity and responsiveness. This modification was particularly noteworthy for *Snake*, which was the only game to initially receive a below average (<2) rating (1.82 ± 0.75/3) of the usability of specific controls within the game. This translated to poor measures of enjoyment, with only 41.7% of participants reporting that the game was enjoyable and an overall rating of just 4.54 ± 1.83/10, the lowest for any game. Participants were not able to pass the first level and did not attempt to play the game after the first exposure. Accordingly, several changes were made, including optimization of the controller sensitivity to movement and directional changes, a reduction in speed of the snake, an increase in arena size and the removal of obstacles from the first three levels, in order to give the player a larger margin of error to make directional decisions and more time to adjust to the controls. These changes were well received, with participants reporting they could "*feel [the controller] responding better,*" and the rating of the usability of controls within the game increasing 0.93 points (from 1.82 ± 0.75/3 to 2.75 ± 0.50/3). Ratings of the game itself also changed strikingly post-modification, with an absolute increase of 58% (from 42 to 100%) in the percentage of individuals endorsing the game as enjoyable and an absolute increase of 67% (from 33 to 100%) in the percentage of those reporting that the game was easy to play. Similarly, the enjoyment rating of the game increased 2.96 points (from 4.54 ± 1.83/10 to 7.5 ± 0.58/10), with overall rating increasing 2.42 points (from 4.83 ± 1.80/10 to 7.25 ± 0.96/10).

Change to Game Objective and Feedback

Who's the Boss? was originally the least successful of all games in the catalog, receiving an average enjoyment score of just 5.85 ± 2.16/10 and a difficulty rating of 7.3 ± 1.49/10. It also received the most negative comments of all games, with participants reporting the game to be "*frustrating,*" "*hard to find a pattern*" and "*just a bit of random guesswork most of the time*." Accordingly, the game was re-pitched entirely, from a confusing and monotonous task based on reinforcement learning principles to a hierarchical structure that required problem solving /abstract reasoning for individuals to identify "the boss" based on the lowest number of exposed pairings, with more coins rewarded for faster guesses. The game was also divided into "stages" to incorporate an element of progression, with the number of new characters increasing by 2 with each stage (e.g., 4, 6, 8, etc.). Additionally, a betting element was added, with participants able to wager based on their confidence in their guess. These changes were well received during follow-up, with participants verbally reporting the game was a "*better format*" and "*much better than last time*." This was also reflected in the post-modification ratings of the game, with an absolute increase of 30% in the percentage of individuals reporting the game as enjoyable (from 70 to 100%) and an overall increase of 1.3 points in the rating of the game (from 6.3 ± 1.34/10 to 7.6 ± 1.67/10). Importantly, these changes also meant that there was a second game available, in addition to *Farm Quest,* that focused on the training of problem solving/logical deduction.

This positive impact of the changes to the games was reflected in a follow-up survey where, on a scale of 1 (much worse) to 10 (much better), changes to the games were rated 7.91 ± 1.04/10.

Table 6 summarizes the individual and overall rating changes per game post-modification, and **Table 7** shows the absolute increase or decrease (in either percentage or point values) from baseline for each individual game, following all modifications.

TABLE 6 | Individual game feedback, post-modification.

	Content						Usability			Overall rating
	Res.	**Enjoyed (% yes)**	**Enjoyment rating (Av interest + enjoyment)/10**	**Challenge (% Yes)**	**Difficulty rating/10)**	**Features (color/animation/ sound)/3**	**Clear instruction (% yes)**	**Ease of play (% yes)**	**Controls/3**	
A Bridge Too Far	9	100%	7.17 ± 1.58	56%	5.22 ± 1.56	2.59 ± 0.55	89%	89%	2.44 ± 0.53	**8.00 ± 1.58**
Farm Quest	4	100%	8.13 ± 1.34	100%	7.25 ± 0.96	2.83 ± 0.19	50%	50%	2.75 ± 0.50	**7.75 ± 0.96**
Squirrel	5	100%	7.00 ± 1.80	60%	6.20 ± 1.48	2.93 ± 0.26	100%	100%	3.00 ± 0.00	**7.4 ± 1.52**
Snake	4	100%	7.50 ± 0.58	75%	5.75 ± 1.71	2.92 ± 0.29	100%	100%	2.75 ± 0.50	**7.25 ± 0.96**
Sunday Driver	3	100%	7.67 ± 0.58	100%	7.33 ± 1.15	2.56 ± 0.58	67%	100%	2.00 ± 1.00	**7.33 ± 1.15**
Marine Life	4	75%	5.63 ± 3.36	50%	6.67 ± 0.58	2.5 ± 0.58	67%	50%	2.75 ± 0.50	**5.50 ± 3.70**
Swimma	4	67%	6.50 ± 3.00	75%	6.00 ± 2.94	2.67 ± 0.53	67%	75%	2.50 ± 0.58	**6.00 ± 2.71**
Driving Maniac	4	100%	8.38 ± 1.72	100%	5.75 ± 3.40	2.50 ± 0.58	75%	100%	2.50 ± 0.58	**8.50 ± 1.29**
Whack-A-Mole	4	100%	8.63 ± 1.04	100%	7.75 ± 0.96	2.67 ± 0.53	67%	50%	2.75 ± 0.50	**9.00 ± 0.82**
Munchkinis	3	100%	9.33 ± 0.58	100%	6.67 ± 2.31	3.00 ± 0.00	100%	67%	3.00 ± 0.00	**9.33 ± 0.58**
Who's the Boss?	5	100%	7.20 ± 1.78	80%	6.60 ± 1.82	2.53 ± 0.55	100%	60%	2.60 ± 0.55	**7.60 ± 1.67**
Chow Time	3	100%	9.33 ± 0.58	67%	7.0 ± 1.00	3.00 ± 0.00	100%	100%	3.00 ± 0.00	**9.33 ± 0.58**

Res, respondents, % indicates percent of participants who answered "yes." Ratings are on a scale of 1–10 (1 = very poor/easy – 10 = very challenging/enjoyable). Features and controls are on a scale of 1–3 (1 = Not Good, 2 = Average, 3 = Good). For all ratings, the table presents Mean (±SD).

TABLE 7 | Absolute increase/decrease from baseline for each individual games following modifications.

	Content					Usability			Overall rating/10
	Enjoyed	**Enjoyment rating/10**	**Challenge**	**Difficulty rating/10**	**Features (color/animation/sound/3**	**Clear instruction**	**Ease of play**	**Controls/3**	
A Bridge Too Far	+0%	−0.25	−29%	−1.78	−0.22	+20%	−11%	−0.18	**+0.31**
Farm Quest	+64%	+2.4	+0%	−0.11	+0.06	−20%	−5%	+0.05	**+2.25**
Squirrel	+8%	−0.17	−22%	−0.13	+0.2	+0%	+18%	+0.36	**+0.23**
Snake	+58%	+2.96	+0%	−0.92	+0.28	+30%	+67%	+0.93	**+2.42**
Sunday Driver	+33%	+1.23	+0%	−0.11	−0.03	+45%	+78%	−0.62	**+1**
Marine Life	−16%	−1.37	−40%	−0.06	−0.33	−22%	−23%	+0.25	**−1.77**
Swimma	−19%	−0.21	−11%	+0	+0.11	+0.3%	+18%	+0.17	**−0.43**
Driving Maniac	0%	+0.67	+0%	−1.58	−0.02	−11%	+25%	+0.04	**+0.67**
Whack-A-Mole	20%	+1.08	+20%	+0.55	−0.06	−33%	−39%	+0.42	**+1.3**
Munchkinis	+14%	+1.69	+0%	−1.33	+0	+0%	+10%	+0	**+1.76**
Who's the Boss?	+30%	+1.35	−20%	−0.7	−0.14	−33%	−20%	−0.07	**+1.3**
Chow Time	+20%	+3.03	+37%	+2.8	+0.37	+0%	+0%	+0.25	**+2.93**

*Absolute increase or decrease from baseline is indicated for each measure, presented as either change in percentage (for measures recording % yes) or change in points (for measures using a rating scale). Pre- and post-modification scores can be seen in **Tables 4**, **6**, respectively.*

Overall Usability- Post-modification

A post-session survey revealed a positive response to the changes made, with 100% of participants reporting they felt their comments were addressed. Confidence in the ability of repeated use of the NeuroOrb gaming system to be beneficial for cognitive function was reported by all participants (100%) and an overall enjoyment rating of the system was 8.18 ± 1.08/10, which represents an 8% improvement upon the initial system rating in the first session. Importantly, the revised SUS score increased from a 65.58 to a 74.17, which is considered above the average score of 68 on the SUS grading system (Gomes and Ratwani, 2019; **Table 5**). Using the scale developed by Sauro (2011), this score equates to a grade of "B" (70th percentile) (Sauro, 2011).

DISCUSSION

This study used a reiterative co-design process to develop a novel serious gaming system, NeuroOrb, for the delivery of CT in individuals with PD. Feasibility was assessed by evaluating a combination of outcomes, including enjoyment, accessibility and acceptability of both the software and hardware. Overall, the NeuroOrb system demonstrated positive feedback in all areas assessed, with integration of feedback resulting in high ratings of enjoyment and confidence in the benefits of the CT program. It is important to note, however, that the lack of a formal motor rating scale, such as the MDS-UPDRS, is a major limitation of the current study, as it is not possible to ascertain from our data whether degree of motor impairment affected participants' perceptions of either the usability or enjoyability of the NeuroOrb, which could have impacted upon system ratings.

The cohort in the current study was high functioning, with no evidence of CI (average MMSE = 29), depression or motor impairment significant enough to interfere with daily activities. This is surprising, as the cohort included a broad range of disease duration, ranging from 1 to 19 years (average 8 years ± 5.43). Given that participants in the co-design trial were not specifically recruited based on cognitive function (i.e., PD without CI, PD-MCI, and PD-D), this may represent a selection bias, with only high functioning individuals volunteering to take place in the study. This may make it difficult to interpret how those with PD-MCI or PD-D would have engaged with the NeuroOrb system and whether they would have been able to understand the game instructions, even post-modification. Additionally, given the lack of sensitivity of the MMSE to detect either MCI or dementia in PD (Hoops et al., 2009), the group may have been more impaired than suggested based on MMSE scores alone. In support of this, a percentage of the participants self-reported cognitive difficulty [remembering events (30.1%), remembering information (38.5%), paying attention (15.4%), learning new tasks (15.4%), remembering words (15.4%), and managing day-to-day tasks (15.4%)]. It is possible that a measure more sensitive to detecting CI in PD, such as the Montreal Cognitive Assessment (MoCA) (Hoops et al., 2009), may have been better able to detect some cases of MCI or mild dementia in the current cohort. Nevertheless, while it may be difficult to extrapolate the results from this small sample to the wider PD population, including those with more severe motor and CIs, this is also likely to represent the target demographic who may derive the most benefit from CT. In support of this, recent research supports that older adults with higher baseline cognitive function are more likely to benefit from CT than those who are already impaired (the so-called magnification effect) (Mohlman et al., 2011; Fu et al., 2020).

Encouragingly, initial impressions of the NeuroOrb system were positive, with the majority of participants reporting that they enjoyed the system and rating it highly. Indications of acceptability for the implementation of the CT program were also high, with most participants expressing confidence in the NeuroOrb system to improve or maintain cognitive function. These are important positive predictors, as game enjoyment and perceptions of cognitive benefit toward gamified CT in an older population have been correlated with motivation (Boot et al., 2016). Accordingly, high levels of initial enjoyment and confidence reported in the NeuroOrb system are likely to reflect motivation to engage further with the system. In support of this, 10 out of 13 of the participants in the current study reported that they would use the NeuroOrb system several times per week, or even daily, if it were available commercially. This is particularly relevant in PD, where ∼40% of individuals experience disorders of motivation (den Brok et al., 2015). Such motivation to engage may, in turn, translate to improvements in adherence to a long-term CT regime, enhancing the efficacy of the CT program overall.

Concerningly, the Orby controller itself received only a moderate rating for accessibility after the first exposure to the system. Given the challenges associated with motor function in the PD population (Mazzoni et al., 2012), it is important for the controller to be considered accessible, and initial accessibility feedback was not as positive as hoped. This rating could be related to several factors; for example, it may indicate issues with handling of the controller sensitivity and responsiveness of the controller to specific games, or ergonomics of the overall set-up. Furthermore, this rating may be reflective of the minimal exposure and unfamiliarity of the participants to computerized games, specifically video games. Minimal experience with handling similar technologies suggests a steeper learning curve, which may also have impacted initial accessibility impressions of the controller. Over time, participants appeared to become more comfortable with controller use and were able to optimize their own use of the Orby controller. This versatility exemplifies a positive adaptive feature of the Orby controller, allowing it to cater for the heterogeneity of motor impairments in the PD population (Greenland et al., 2019).

Although individuals did become more comfortable with the system with repeated exposure, however, some problems persisted, with an overall below-average SUS indicating compromised usability. While unclear exactly what may have driven these difficulties, they may have been due to either general setup/handling issues or to participant fatigue/discomfort. Fatigue is a commonly reported symptom in PD, with a reported prevalence of 50% (Siciliano et al., 2018) and is one of the three Rs (i.e., "Repeatedly") suggested by Kouroupetroglou (2014) to represent particular barriers for computer use in motor impaired populations. As such, it may have affected the ability of participants to engage throughout the session and, in turn, affected their perception of the usability of the system overall. It is also possible, however, that difficulties with the games themselves negatively impacted on overall system usability, making it critical to interpret overall usability in the context of ratings of the gaming suite.

Overall, the response to the games was positive, with all games (except *Snake*) receiving an above average overall rating. In terms of enjoyment, the majority of games were considered enjoyable. This is important, as enjoyment is a strong motivator and positively associated with effortful engagement (Cacioppo et al., 1996). Games with a below average (<50%) number of participants reporting enjoyment included *Farm Quest* and *Snake*. Lower participant enjoyment of these games may have been reflective of a number of factors, such as inappropriate game difficulty or issues with game features.

The relationship between perceived task difficulty and performance is not well understood for CT in PD; however, studies suggest a balance is important. In older adults specifically, Selective Engagement Theory (Hess, 2014) proposes that increased 'cognitive costs' associated with activities later in life results in a reduction in the cost/benefit ratio, reducing the willingness of older adults to engage in demanding activities (Hess et al., 2016). It is critical to balance this, however, against the theoretical framework proposed by Lövdén et al. (2010) for achieving cognitive plasticity in adults. According to this model, the transfer of gains from CT across multiple cognitive domains or to real-world contexts depends on the difficulty of the training task, with sustained cognitive challenges required to induce lasting neural changes. This necessitates a continual mismatch between the demand of the task (i.e., the cognitive load) and the cognitive capacity of the individual. In support of this, adaptive training of working memory (i.e., where task demands are continually increased based on performance) resulted in far transfer to an untrained episodic memory task, as well as accompanying neural changes (Flegal et al., 2019). In light of these considerations, we sought to achieve an effective challenge, while also reducing "cognitive cost." While we were able to achieve this for the majority of games, *Chow Time!* was rated as too easy and *Munchkinis* was rated as too difficult. Interestingly, however, this did not appear to affect enjoyment of these games.

Similarly, enjoyment of the games did not appear to be negatively affected by game features, with use of color, animation and sound all highly rated. This is important, as basic stimuli (images and texts) associated with traditional pen and paper CT can make therapy boring for patients (Alloni et al., 2017). The inclusion of 3D graphics in computerized training is considered beneficial, due to increased entertainment and involvement of the patient, as well as the introduction of new elements (such as spatial perception) into training, ultimately improving direct interaction compared to more abstract 2D counterparts (Alloni et al., 2017). Given that neither game difficulty or features appeared to negatively impact either enjoyment or rating of the game, it may be that usability of the games themselves, including clarity of instructions provided and controller responsiveness for each game, was most important for determining the enjoyability and overall rating of the game. In support of this, both *Farm Quest* and *Snake*, the two lowest rated games for enjoyment, scored poorly for ease of play, with both also receiving only moderate ratings for clarity of instructions.

Encouragingly, through the co-design process and the subsequent alterations made to the NeuroOrb system, we seemed to successfully address all points raised, with 100% of respondents stating that they felt as though their feedback was addressed. Following implementation of these changes, participants rated changes to both the controller and the games extremely highly. Furthermore, overall enjoyment of the system as a whole increased and there was a notable improvement in SUS score from the 42nd to the 70th percentile (Sauro, 2011), indicating that NeuroOrb is likely to have high usability as a tool for individuals with PD.

Importantly, the number of issues that we were able to pre-emptively identify and address through this study highlights the importance of engaging in a co-design process with key stakeholders, prior to engaging in a large-scale intervention trial. Such a cooperative approach is in line with current best practice guidelines for the design of interventions for use in patient populations, and is anecdotally reported to lead to more effective services and better outcomes for individuals (although more rigorous assessment of outcomes and cost-benefit analysis is needed) (Clarke et al., 2017). Co-design has previously been successfully used in many healthcare indications. In PD specifically, co-design has been used to design eHealth services (Revenas et al., 2018), collaborative care (Kessler et al., 2019), and even smart home technology (Bourazeri and Stumpf, 2018). Most recently, and highly relevant to the current work, co-design was used to put forth recommendations for the design of a personalized gaming suite for use by individuals with PD (Dias et al., 2020). Within the current study, without consultation with key stakeholders in a reiterative co-design process, many of the issues we identified would have been missed. This could have had a disastrous impact on any intervention trials, as issues with the games themselves (e.g., understanding what the objective is) or with the hardware (e.g., navigating the controller or avoiding fatigue) could have negatively affected engagement with the system, or even successful completion of the trial. This, in turn, may have confounded the assessment of effects on cognitive function, potentially masking any benefits derived from NeuroOrb. Instead, following our extensive incorporation and evaluation of suggested modifications, we are now well-placed to proceed to a large-scale clinical trial using NeuroOrb to deliver customized CT in individuals with PD, evaluating any potential benefits using a sensitive and comprehensive cognitive assessment battery.

CONCLUSION

Considering the positive ratings of the controller, gaming suite and the NeuroOrb system overall, we have developed a customized "Serious Games" approach to CT, optimized for use in individuals with PD and ready for deployment in subsequent intervention trials designed to assess its efficacy.

Through our co-design process, we believe that the incorporation of novel elements into both the hardware and software of the NeuroOrb system represent a significant improvement on other CT systems developed to date, which often use commercially available software packages or non-validated paradigms, without consultation from key stakeholders (Thompson et al., 2020). Instead, our system allows us to target the areas of cognitive function that present the most concern for individuals with PD in an accessible and highly engaging way. This makes us well-placed to obtain maximal benefit from use of the system to deliver CT in this population. While it ultimately remains to be determined if NeuroOrb will result in cognitive benefits for individuals with PD, or whether such benefits will last or transfer to everyday ADLs, this process nevertheless illustrates the importance of co-design and appropriate consultation of key stakeholders when designing future therapeutic strategies.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Human Research Ethics Committee of the University of Adelaide (H-2020-214). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

BG coordinated the co-design trial, analyzed the data, and drafted the manuscript. DH designed the NeuroOrb system, contributed to the co-design trial, and supervised the project. BW was the game developer for the software suite. BE, AM, and SD contributed to the co-design trial and analyzed the data. LC-P contributed to the design of the software suite, led the co-design trial, conducted data analysis, supervised the project and substantially revised the manuscript. All authors contributed to the final version of the manuscript.

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