Passive exercise in a multisensory environment in order to manage adverse effects in physically inactive patients with dementia: a randomized controlled trial

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Marelle Heesterbeek m.heesterbeek@rug.nl
Rijksuniversiteit Groningen
Corresponding Author
ORCiD: 0000-0002-9831-116X

Eddy van der Zee
Rijksuniversiteit Groningen Afdeling Biologie

Anselm Fuermaier
Rijksuniversiteit Groningen Department of Clinical and developmental neuropsychology

Marieke van Heuvelen
Universitair Medisch Centrum Groningen

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Abstract

Background

Since pharmacological treatments to manage dementia remain controversial, development of non-pharmacological alternatives to limit adverse effects of dementia is urgently needed. Passive exercise in a multisensory environment (Therapeutic Motion Simulation (TMSim), Whole Body Vibration (WBV) and a combination (TMSim + WBV)) is proposed to be such a non-pharmacological alternative. This study primarily aimed to investigate the effects of these different forms of passive exercise on Quality of Life (QoL) and Activities of Daily Living (ADLs) of inactive institutionalized patients with dementia. The secondary aim was to assess the effects on cognitive and physical function.

Methods

In this randomized controlled trial 120 inactive institutionalized persons with dementia (age 85.3 ± 6.8 years, 64.5% female, 59.2% walking aid/wheelchair users, mini mental state examination 12.9 ± 6.6) were assigned to TMSim, WBV, TMSim + WBV or a control group (regular care). The passive exercise groups followed a six-week intervention program consisting of four 4-12 minute sessions a week. QoL, ADLs (proxy-report questionnaires), cognitive and physical function (performance based tests) were measured at baseline, after 6 weeks of intervention, and 2 weeks after the intervention had ended.

Results

Outcome measures did not differ between groups at baseline. No consistent effects of passive exercise on QoL, ADLs, cognitive and physical function were observed after six weeks of intervention or during follow-up.

Conclusion

In the current setting passive exercise did not affect any of the outcomes measures. This may be due to the short intervention period, limited sensitivity to change of the
assessment instruments in this specific vulnerable population or short lasting effects of the interventions. Future research into passive exercise should consider measuring acute and short term effects as well as longer intervention periods looking into alternative outcome measures (e.g. seated balance and behavioral and psychological symptoms of dementia).

Background

The number of patients with dementia is rapidly increasing. It is predicted that in 2050 over 130 million people will suffer from this disease [1]. Dementia is characterized by progressive cognitive decline and physical impairment, causing high burden to both patients and caregivers. With the progression of the disease, patients’ quality of life (QoL) and their ability to perform activities of daily life (ADLs) rapidly decline, with the latter often resulting in institutionalization. To date no cure has been developed to effectively manage dementia. Therefore, a shift towards the use of non-pharmacological alternatives to limit the adverse effects of dementia has been deployed.

To date the most described and examined non-pharmacological intervention is physical exercise. In numerous studies physical exercise is reported to improve cognitive and physical function, ADLs and QoL in patients with dementia [2-4]. However, due to motor deficits, comorbidity and behavioral problems there is a large patient group that cannot be or stay involved in physical exercise programs. For these patients, passive exercise in a multisensory environment might be an effective alternative. It has already been shown that passive exercise in a multisensory environment is feasible to apply in institutionalized older adults with dementia regardless of their cognitive and physical disabilities [5]. However, it remains unclear whether passive exercise in a multisensory environment has beneficial effects in this population.

In this study we distinguish three different forms of passive exercise in a multi-sensory
environment: Therapeutic Motion Simulation (TMSim), Whole body vibration (WBV) and a combination of both (TMSim + WBV). All forms of passive exercise are employed with robotized movement platforms as depicted in Figure 1. During TMSim tactile, proprioceptive, auditory and visual stimuli are provided to the user by activity videos accompanied by simultaneous movements of the robotized movement platform. During WBV tactile and proprioceptive stimulation is provided by mechanical vibrations (30 Hz, 1-2 mm) of the platform. To the best of our knowledge effects of multisensory stimulation as provided by TMSim has not been studied yet in this population. However, in studies that employed (multi)sensory stimulation interventions such as ‘snoezelen’, video or music interventions, improvements in alertness and happiness, increased social behavior, and a reduction in behavioral disturbances as well agitated behavior of patients with dementia were found [6-8]. Additionally, mild vibrations (30-40 Hz), as provided during WBV and TMSim + WBV, can be beneficial for physical performance and cognitive functioning. Multiple studies reported increased muscle strength, mobility, balance and lower blood pressure after WBV [9-12]. Moreover, WBV was found to improve attention and inhibition, both acute (in schoolchildren, young adults (with ADHD)) as well as after 5 weeks (in older adults) [13-16]. Based on these findings it is thought that both TMSim and WBV will lead to a diffuse activation of different brain areas, but that the combination of TMSim + WBV will elicit the strongest effects [17]. Altogether we presume that passive exercise in a multisensory environment has the potential to improve QoL, ADLs, and cognitive and physical function in institutionalized older adults with dementia.

The primary aims of this study were to investigate the effects of TMSim, WBV and TMSim + WBV on ADLs and QoL in institutionalized physically inactive older adults with dementia. The secondary aims were to assess the effects of the three different forms of passive exercise in a multi-sensory environment on cognitive and physical function. We
hypothesized that all forms of passive exercise will have positive effects on both the primary and secondary outcome measures when compared to regular care. Due to a more diffuse brain activation we hypothesized TMSim + WBV to elicit the strongest effects.

Method

An extensive description of the study protocol is given in the previously published protocol paper of this study [17]. The study protocol was approved by the Medical Ethics Committee of the University Medical Centre of Groningen, the Netherlands, and conforms to the principles of the Declaration of Helsinki.

Study design

The study was a single blind randomized controlled trial, comparing the effects of TMSim, WBV and TMSim + WBV with each other and to regular care in institutionalized older adults with dementia. Data was collected from October 2016 until December 2018.

Participants

120 residents (64.5% female, age 85.3 ± 6.8 years) from the closed wards of eight different nursing homes in the North of the Netherlands were included in this study. General characteristics of the participants are given in Table 1.

Insert Table 1 about here

Procedures

Written informed consent was provided by the legal representatives of the participants, participants orally agreed to participate in the study. Outcome measures were assessed at baseline (T0), after six weeks of intervention (T1), and two weeks after the interventions had ended (T2). For every participant all three test moments were assessed by the same research assistant at the same time of the day. Questionnaires for QoL, ADLs and care burden were given to the formal caregiver of the participants.

After baseline measurement and stratification for nursing home, age, gender and baseline
participants were randomly assigned to one of the intervention groups or the control group with a 1:1:1:1 allocation ratio. For randomization a random number generator was used by an independent researcher not related to the study.

**Interventions**

Participants in the intervention groups received 4 intervention sessions a week for six consecutive weeks. In these six weeks, participants in the control group received regular care. All forms of passive exercise were applied using two commercially available motion simulation devices (the balancer, Figure 1a and the wheelchair pod, Figure 1b, Pactive Motion, Hoogerheide, The Netherlands).

During a TMSim session, three short, real life activity videos (e.g. motor riding, dancing or horse riding) of approximately four minutes were shown. Matching music and sounds were played and the platform moved synchronically with the movies on the screen. This way, the participant on the platform moved passively and was stimulated multisensorily by means of visual, auditory, tactile and proprioceptive stimuli. During WBV, the platform vibrated with a 30 Hz frequency and an amplitude of 1–2 mm (manufacturer settings). The duration of the WBV sessions was set to four minutes. A stationary motorcycle with idling engine was shown on the screen and matching sounds were played. For the TMSim + WBV intervention, the former two forms of passive exercise were combined. During 12 min participants alternately received TMSim (4 min) and WBV (2 min).

*Insert Figure 1 about here*

**Outcome measures**

An extensive description of the outcome measures and followed procedures to assess these is given in the protocol paper of this study [17].

ADLs and QoL of the participants were determined with questionnaires filled in by the primary formal caregiver. To determine ADLs an adapted version of the Barthel index was
used [18]. In the adapted version performance on ten different items is scored on a 5 point Likert scale. In this study the item stairclimbing was removed from the questionnaire because of irrelevance for this institutionalized population. Sum scores can range between 0 and 90, with higher scores representing better ADL functioning.

QoL was measured with the QUALIDEM and the EQ-5D-5L [19, 20]. Within the QUALIDEM 10 different subdomains of QoL are distinguished. A sum score between 0 and 120 can be obtained with higher scores reflecting better QoL [19]. The EQ-5D-5L consists of five 5-point Likert scale questions in five different QoL related domains: mobility, self-care, usual activities, pain/discomfort, anxiety/depression [20]. From the scores on these five questions an index value can be computed, which can range between 0 and 1, index values closer to 1 resemble better QoL [21].

As stated in the protocol paper of this study, initially we also planned to use different questions from the The Older Persons and Informal Caregivers Survey Minimum DataSet (TOPICS-MDS) in addition to the QUALIDEM, EQ-5D-5L and the adapted Barthel index to determine QoL and ADLs. However, at baseline, posttest and follow-up we had TOPICS-MDS data for less than half of the participants, as many legal representatives did not fill in the questionnaires (in time). Therefore, we decided not to use these items for the analyses.

Cognitive functions were assessed by blinded, trained research assistants with a set of neuropsychological tests. Global cognitive function was measured using the Mini Mental State Examination (MMSE). The digit span forward (DSf) was used to test verbal memory. For measuring different aspects of executive function a simple reaction time task (SRT), 45 second STROOP test, digit span backward (DSB), trail making test part A (TMT A), phonemic fluency and semantic fluency test were used. Extensive descriptions of the assessments of these tests can be found in the protocol paper of this study [17]. In
contrast to what is described in the protocol paper, for the STROOP test, instead of accuracy scores, an interference score is presented, calculated by subtracting the predicted colour-word score \((\text{word score} \times \text{colour score})/\left(\text{word score} + \text{colour score}\right)\) from the actual colour-word score, as this is thought to better reflect inhibition.

To assess physical function, if possible, participants were asked to perform the Timed Up & Go test (TUG), FICSIT-4 and a 6-meter walking test (6MW). For both the TUG and 6MW the fastest trial of the respectively two and three performed trials was used for analyses.

**Statistics**

All statistical analyses were performed using IBM SPSS Statistics 25.0. Baseline characteristics of the participants were compared between groups using one-way analysis of variance for age, MMSE and number of comorbidities and chi-square tests for gender, use of walking aid/wheelchair, type of dementia platform use and dropout rates. Analyses without substitution of missing values as well as analyses in which missing values were substituted by means of maximum likelihood estimation (MLE) were performed. MLE was performed for each group and domain (QoL, ADLs, cognitive function and physical function) separately. For each test/questionnaire within a domain the tests/questionnaires within that domain on the same time point as well as the same test/questionnaire on the other two time points were taken as predictor variables. A variable on a given time point was substituted only if this variable was measured on at least one of the other time points. The maximum number of substituted values per variable was set to 50%, as substitution of larger percentages would suffer from insufficient sample size to generate valid and meaningful substitutes. Substituted scores below the theoretical minimum on a test or item were set at the theoretical minimum for that test or item, substituted scores higher than the theoretical maximum of a test or item were set at the theoretical maximum for that test or item. In addition, data of the primary
and secondary outcome measures were analyzed with both an intention-to-treat and a per protocol analysis. For the intention to treat analysis all participants were included. For the per protocol analysis only participants who attended at least 50% of the scheduled sessions were included.

Primary and secondary outcome measures at baseline were compared between groups using analyses of variance. If data was not normally distributed (positively skewed), the data was log transformed and again checked for normality before performing the analyses of variance. For each outcome measure change scores between T0 and T1, T0 and T2, and T1 and T2 were calculated and presented. The following applies to all following analyses: participants were included in the analyses if at least one outcome measure was available for at least two measurement time points (T0, T1 or T2). If the data satisfied the assumptions analyses of covariance (ANCOVA) were used to test for differences between groups on both the primary and secondary outcome measures at all three time points. Scores on T1/T2 were used as dependent variables, T0/T1 scores as covariates and group as between subjects factor. Repeated measures analyses of variance were used if the assumption of homogeneity of regression slopes was violated. If the assumption of sphericity was violated, a Greenhouse-Geisser correction was used. For all outcome measures, partial eta squared effect sized were calculated. Effect sizes of 0.01 were considered as small, 0.06 as medium and 0.14 as large [22]. Post-hoc tests were performed with Bonferroni corrections for multiple comparisons. P values lower than 5% were considered to indicate statistical significance.

Results

Baseline

A total of 219 patients were screened for eligibility, informed consent was given for 122, of which 120 were enrolled in the study. In Figure 2 the study design, patient flow and
intervention characteristics for each group are shown. Descriptive characteristics, baseline MMSE and type of dementia were not different between the groups (Table 1). There were no between group differences in feasibility measures and drop-out rates [5]. In supplementary table 1 baseline scores on QoL, ADLs, neuropsychological and physical tests at baseline are shown for each group. As indicated by the MMSE scores, the majority of the participants had moderate to severe dementia. At baseline there were no significant between group differences for any of the primary or secondary outcome measures.

*Insert Figure 2 about here*

**Blinded testing**

86.6% of the tests were assessed by a blinded research assistant. In 5.6% of the cases the research assistant knew that the participant was allocated to an intervention group, but he/she was still blinded for the type of intervention. 7.8% of the tests were not performed blinded, either because the participant gave away the group allocation or because of practical constraints.

**Primary outcome measures**

Analyses with substituted missing values did not yield different results than analyses with the original dataset. Moreover, per protocol analyses including participants who attended at least 12 of the scheduled intervention sessions did not yield different results as compared to the intention to treat analyses. Therefore, data from the intention to treat analyses with substituted values were used for the results presented in tables 2-4. For 4.2% of the cases questionnaire scores for the primary outcome measures were substituted by means of MLE. After six weeks of passive exercise all groups seem to improve somewhat on QoL. ADLs scores improve only in the TMSim and TMSim + WBV group. However, at T1 no significant effects of intervention on QoL or ADLs were found (Table 2). After the 2-week follow-up, significant differences were found for the QUALIDEM
and Barthel index. Post hoc tests revealed that QoL in the control group improved as compared to the WBV group after controlling for the effects of T1 ($p=0.017$). When controlling for baseline effects (T0) the TMSim + WBV group scored higher on the Barthel index at follow up (T2) as compared to the control group ($p=0.027$).

Insert Table 2 about here

Secondary outcome measures

Results on the neuropsychological tests and physical tests are presented in Table 3 and 4. In 4.0% of the cases test scores on neuropsychological tests were substituted, for the physical tests this was 6.4%. Scores on the SRT and the TMTA were not substituted since data on these tests were available for less than 50% of the participants. After controlling for baseline scores, except for a significant difference in performance on the DSB between the WBV group and the TMSim + WBV group ($p=0.013$), no significant differences were found in cognitive function after six weeks of passive exercise. At follow up, while controlling for effects of T1, post-hoc tests revealed that the control group performed better on the DSF as compared to all intervention groups (TMSim $p<0.001$, WBV $p=0.018$, TMSim + WBV $p=0.004$). Post-hoc tests for semantic fluency test performance at T2 after controlling for effects of T1 did not yield any significant between group differences. For both $\Delta$ T0-T2 and $\Delta$ T1-T2 a significant time x group interaction was found on the STROOP color-word test. Post hoc tests revealed no group differences.

All intervention groups performed better (negative difference scores represents faster performance) on the TUG and the 6MW test after 6 weeks of passive exercise. On the FICSIT4 performance declined in all groups after six weeks. At T1 no significant intervention effects were found on any of the physical tests. There was a significant time x group interaction on the 6MW at $\Delta$ T0-T2. Post-hoc tests revealed no group differences.

Insert Table 3 and 4 about here
Discussion

The primary objective of this study was to examine the effects of TMSim, WBV and TMSim + WBV on QoL and ADLs in institutionalized physically inactive older adults with dementia. Secondary we wanted to assess the effects of these three different forms of passive exercise in a multi-sensory environment on cognitive and physical function.

Primary outcome measures QoL and ADLs

Our results did not indicate any effects of passive exercise on QoL and ADLs. This might be attributed to the limited intervention period (six weeks) and/or type of instruments used to quantify QoL and ADLs. Although the instruments used in this study are internationally recognized and have shown adequate sensitivity, validity and reliability to measure QoL and ADLs, sensitivity of these instruments to measure change over a six-week time period may be limited. In addition, assessing QoL and ADLs by means of proxy report may be influenced by personal characteristics of the formal caregiver or their relationship with the participant [23, 24].

Comparing the current results to other findings is challenging since there is a lack in availability of high quality studies examining the effects of (multi)sensory stimulation on various outcome measures in institutionalized patients with dementia [25]. Nevertheless, results of our study are partly in line with some other studies in which no effects were found on QoL and ADLs after exercise or music interventions in patients with dementia [26-28]. However, music therapy was shown to be effective in reducing agitated behavior, irritability, anxiety and depression [29-31]. Moreover, multisensory interventions as ‘snoezelen’ demonstrated improvements in Neuropsychiatric Inventory in patients with severe dementia [32]. In the short term ‘snoezelen’ was effective at managing mood and
behavioral disturbances [33]. However, it must be noted that the type and degree of multisensory stimulation applied during ‘snoezelen’ and TMSim has some major differences (e.g. during ‘snoezelen’ also olfaction and taste can be stimulated, while TMSim is more focused on motor, auditory and visual stimulation). Despite limited evidence on improved QoL after these interventions and differences between TMSim and the types of sensory stimulation as applied in other studies, the different components of passive exercise could have the potential to positively influence QoL related factors such as wellbeing, affect and behavioral and psychological symptoms of dementia (BPSD) in both short and long term. Therefore, further research is recommended in which the acute and short-term effects of passive exercise in a multisensory environment on QoL related factors are examined.

**Secondary outcome measures cognitive- and physical function**

No meaningful effects of passive exercise in a multisensory environment on cognitive function were found. Except from some inconsistent findings on a limited number of neuropsychological tests, there were no between group differences. Significant findings may be attributed to chance instead of intervention effects since level of significance was corrected for the multiple comparisons between groups, but not for multiple tests of outcome measures.

Based on previous findings in both humans and rodents positive results of WBV and TMSim + WBV on cognitive function were expected. In older adults 5 weeks of WBV was found to improve attention and inhibition [14]. Furthermore, in mice, 5 weeks of WBV with daily sessions of 10 minutes was found to increase the amount of the acetylcholine-synthesizing enzyme choline acetyltransferase in layer five of the somatosensory cortex and the amygdala, indicating higher cholinergic activity in these areas [34]. Besides, it is known
that the cholinergic system responds to behaviorally salient stimuli from the environment [35], indicating that TMSim is likely to induce increased cholinergic activity as well. The cholinergic system plays a key role in cognitive function [36] and dysfunction of this system has been suggested to underlie cognitive decline in dementia [37, 38]. Interventions, such as WBV, TMSim and TMSim + WBV, targeting this system could therefore be promising to reduce cognitive decline. However, in the current severely affected population it might have been too late for improvements in the cholinergic system. It is likely that due to the severity of the pathologies in these patients, great losses of forebrain cholinergic neurons already took place [38]. This severe loss of forebrain cholinergic neurons may drastically limit the diffuse projections to and activation of other cortical areas leaving less room for improvements via the cholinergic system.

It is also possible that the effects of passive exercise only last for a limited amount of time. Most studies that reported improved cognitive performance after WBV assessed this immediately after the WBV session [13, 15, 16]. For TMSim it is unknown whether effects are more likely to be short or long lasting. In future studies, assessment of different parameters during or shortly after passive exercise could be used to determine if passive exercise can evoke acute or short term effects in institutionalized patients with dementia.

On the other hand, in older adults and a young adult with ADHD effects of WBV on cognitive performance after respectively five weeks and ten days of stimulation were found [14, 39]. The fact that we did not find improved cognitive functioning in the current population after six weeks of passive exercise may be explained by Another explanation for inconclusive results in cognitive function may be the fact that quantifying cognitive function is challenging in this population. First of all because cognitive functions are complex processes and there is limited knowledge regarding the cortical and subcortical
pathways related to these processes [40]. Second, in the included population many uncontrollable variables (e.g. distress, attention fluctuations and BPSD) can influence test performance and cause large day-to-day fluctuations [41, 42]. In order to limit the effects of such uncontrollable variables and daily fluctuations in test performance larger sample sizes are needed.

Similar to cognitive function, no intervention effects on balance related outcome measures were found. To our knowledge, this is the first study into the effects of TMSim. In addition, the only prior studies into the effects of WBV on balance related outcome measures in older adults (without dementia) employed vertical WBV and participants had to stand on the vibrating platform instead of being seated. Results of these studies are inconclusive with a mix of studies reporting improvements [43-45] or no effects in balance related outcome measures [46-49]. Moreover, it must be noted that in all these studies WBV was applied in combination with an exercise program. Although results of previous studies are inconsistent there are implications that WBV has the potential to improve physical function. The lack of result on balance related outcome measures as used in this study may be a result of the seated position during the interventions. Compared to upright stance, when seated, less compensatory muscle activity is needed for maintaining balance during postural perturbations as applied during WBV and TMSim. Therefore, physical response to seated passive exercise might not be intensive enough to potentially improve balance related outcome measures that require upright stance. On the other hand, seated balance, especially relevant for wheelchair bound individuals, may have been improved after passive exercise. However, outcome measures as used in this study could not be performed by wheelchair bound patients, and may not have been able to capture such possible improvements in seated balance. Alternative measures like seated posturography or a seated functional reach test could be used in future studies to measure possible
functional changes in seated balance after passive exercise [50, 51].

Finally, as a result of including a vulnerable population the number of participants that could perform the physical tests, especially the balance tests, was relatively low. The current findings on the physical tests are likely to reflect results for patients with lower disease severity. However, especially in vulnerable older adults WBV and TMSim could have the potential to improve balance and mobility [52]. Future research is suggested with alternative balance and mobility measures appropriate to use in vulnerable populations.

Limitations

We already addressed some limitations regarding difficulties to quantify (changes in) the primary and secondary outcome measures in older adults with moderate to severe dementia. As a result of assessment difficulties there was a considerable number of missing data for the cognitive and physical tests. Reasons for these missing data were largely related to (receptive) aphasia and mood or behavioral problems. Participants suffering from (receptive) aphasia were not able to understand test instructions or to produce answers to the test to which they were subjected. Mood and behavioral problems often resulted in agitated and aggressive behavior, resulting in not answering questions or performing physical tests. In addition, a considerable number of participants were wheelchair bound and therefore not able to perform the physical tests. Finally, some participants simply wished to avoid disruptions in their daily routines. Missing questionnaires from the primary formal caregiver were often the result of limited time, due to understaffing, to fill out the questionnaires.

An additional drawback of this study is that it was not known whether the intensity of the movements that were applied during TMSim and TMSim + WBV could affect possible effects of the interventions. For example, some types of high-intensity activities such as
horse riding or snowboarding could be more effective to improve outcome measures as compared to other lower-intensity activities such as walking or diving. On the other hand, for some patients overstimulation as a result of passive exercise could reduce/eliminate potential effects [53]. Both examples stress the importance of further individualization of the different forms of passive exercise. Intensity of each video and optimal session duration should be formally assessed in future studies to help determine the optimum parameters for individuals with dementia living in nursing homes.

**Strengths of passive exercise**

Even though, in this study, we found no convincing effects of passive exercise on any of the reported outcome measures, we would like to emphasize the potential of passive exercise to breach inactivity levels in institutionalized older adults. As, due to high sedentariness and inactiveness, there is a high need to develop innovative ways of breaching sedentary behavior in residential aged care [54]. Due to reduced cognitive and physical capabilities, many regular activities are difficult to engage in for nursing home residents. We showed that all types of passive exercise are feasible to apply in institutionalized older adults with dementia regardless of their cognitive or physical disabilities [5]. Additionally, in general the participants indicated they really enjoyed the passive exercise sessions [5]. Personal preferences, with regard to type of activities, intensity and duration, can be taken into account, creating possibilities for highly individually tailored interventions. For group activities it has already been shown that individualization based on participants’ preferences can optimize the impact [55]. Moreover, familiar activities, sounds and music can (reminiscence) help patients to recall remote memories which may enhance communication, increase sense of orientation, and improve mood and well-being [56]. Therefore, passive exercise in a multisensory environment can be complementary to existing types of activities in nursing homes in
order to breach inactivity patterns of the residents and provide them with enjoyable occupation.

**Conclusion**

In sum, we did not succeed to demonstrate effects of TMSim, WBV and TMSim + WBV on QoL, ADLs, cognitive and physical function. The six-week intervention period may have been too short and alternative instruments for outcome measure assessment should be considered. Addition of passive exercise to daily routines can be used to breach inactivity in institutionalized older adults with dementia. Future studies are suggested in which passive exercise is applied for a longer period and is even more individually tailored. Moreover, development of neuropsychological tests that can be used to measure change in cognitive performance of patients with dementia is recommended. In addition, we propose future studies examining acute and short term effects of passive exercise as well as the effects of passive exercise on alternative outcome measures (e.g. BSDP and seated balance).

**List Of Abbreviations**

QOL: Quality of life;

ADLs: Activities of daily living;

TMSim: Therapeutic motion simulation;

WBV: Whole body vibration;

TOPICS-MDS: The older persons and informal caregivers survey minimum dataset;

MMSE: Mini mental state examination;

SRT: Simple reaction time;

DSf: Digit span forward;

DSb: Digit span backward;

TMT A: Trail making test part A;
TUG: Timed up & go test;
6MW: 6-meter walking test
BPSD; Behavioral and psychological symptoms of dementia

Declarations

Ethics approval and consent to participate
The study protocol is approved by the Medical Ethical Committee of the University Medical Centre Groningen, the Netherlands (Ref No: NL58022.042.16, 2016/334). Written informed consent to participate was obtained from all participants and/or their legal representatives.

Consent for publication
Not applicable

Availability of data and materials
The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests
The authors declare that they have no competing interests.

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Authors' contributions
EZ and MvH developed the idea for this study and designed it. AF helped developing the neuropsychological test battery. MH coordinated the study under supervision of EZ and MvH. MH was the primary author of this manuscript, EZ, AF and MvH helped draft the
manuscript. All authors read and approved the final manuscript.

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Tables

Table 1. General characteristics of all included participants.

| Characteristic                  | TMSim group (n=30)      | WBV group (n=30)       | TMSim + WBV group (n=30) |
|--------------------------------|-------------------------|------------------------|--------------------------|
| Age (years), M(SD)             | 84.9(6.6)               | 86.2 (4.7)             | 84.3(8.1)                |
| Range                          | 69-95                   | 75-96                  | 69-103                   |
| Females, %                     | 70.0                    | 63.3                   | 66.7                     |
| Walking aid/wheelchair         | 11/6                    | 13/4                   | 15/3                     |
| Dementia type                  |                         |                        |                          |
| Alzheimer's Disease            | 53.3                    | 43.3                   | 60                       |
| Vascular Dementia              | 10                      | 16.7                   | 13.3                     |
| Lewy body Dementia             | 3.3                     | 3.3                    | 0                        |
| Fronto-temporal Dementia       | 3.3                     | 0                      | 0                        |
| Combination                    | 10                      | 13.3                   | 3.3                      |
| Other/Unknown                  | 20                      | 23.3                   | 23.3                     |
| Comorbidities (number), M±SD, N| 2.8±1.8, (26)           | 3.6±2.0, (2)           | 3.4±2.0, (16)            |
| Drug burden index              | 0.65±0.49, (26)         | 0.73±0.45, (26)        | 0.64±0.49, (25)          |
| MMSE, M(SD)                    | 12.2(7.5)               | 14.0(5.9)              | 13.6(6.7)                |
| Range                          | 0-29                    | 5-22                   | 3-28                     |
Table 2. Baseline and difference scores for QoL and ADLs from-the-intention to treat analyses with substituted missing values.
Table 3. Baseline and difference scores for the neuropsychological tests from-the-intention to treat analyses with substituted missing values.

| Test characteristic | TMSim group | WBV group | TMSim + WBV group |
|---------------------|-------------|-----------|------------------|
| EQ-5D-5L index      |             |           |                  |
| T0                  | 30          | 0.45 (0.27)| 30 0.55 (0.21)   | 30 0.52 (0.22)   |
| ∆ T0-T1             | 29          | +0.02 (0.13)| 29 -0.03 (0.18)  | 30 -0.01 (0.19)  |
| ∆ T0-T2             | 29          | +0.03 (0.13)| 29 -0.03 (0.22)  | 30 +0.03 (0.18)  |
| ∆ T1-T2             | 29          | +0.002 (0.10)| 29 -0.008 (0.12) | 30 +0.03 (0.19)  |
| QUALIDEM Sum        |             |           |                  |
| T0                  | 30          | 77.2 (18.8)| 30 85.0 (17.0)   | 30 78.8 (19.2)   |
| ∆ T0-T1             | 29          | +0.86 (9.3) | 29 +1.6 (13.1)   | 30 +2.9 (12.0)   |
| ∆ T0-T2             | 29          | -1.3 (12.0)| 29 -2.8 (17.1)   | 30 +1.2 (13.5)   |
| ∆ T1-T2             | 29          | -2.1 (8.5) | 29 -4.4 (9.8)    | 30 -1.7 (7.2)    |
| Barthel Sum         |             |           |                  |
| T0                  | 29          | 53.5 (23.5)| 28 59.9 (24.6)   | 29 53.9 (24.2)   |
| ∆ T0-T1             | 28          | +1.4 (10.3)| 27 -1.8 (16.9)   | 29 +2.1 (16.9)   |
| ∆ T0-T2             | 28          | -1.7 (7.1) | 27 -1.3 (11.3)   | 29 +5.8 (20.1)   |
| ∆ T1-T2             | 28          | -3.1 (6.9) | 27 +0.46 (10.1)  | 29 +3.7 (14.5)   |

Positive difference scores indicate improvements in QoL or ADLs, negative scores indicate decline. Group effects and partial eta-squared effect sizes are presented. Baseline measures were compared using one-way analysis of variance. Other group effects were tested with ANCOVA. * indicates statistical significance.
|                   | T0  | T1  | T2  |
|------------------|-----|-----|-----|
| \( \Delta T_0-T_2 \) | -0.22 (2.3) | +0.43 (2.4) | -0.09 (3.9) |
| \( \Delta T_1-T_2 \) | +0.62 (2.5) | +0.83 (2.3) | -0.61 (2.9) |

### SRT Mean (ms)

|       | T0     | T1     | T2     |
|-------|--------|--------|--------|
| \( \Delta T_0-T_1 \) | -2.5 (346.9) | +134.0 (519.3) | -17.22 (453.0) |
| \( \Delta T_0-T_2 \) | -68.1 (334.2) | +178.9 (218.2) | +23.3 (348.0) |
| \( \Delta T_1-T_2 \) | -53.6 (154.0) | -126.7 (350.8) | -12.3 (189.8) |

### SRT SD (ms)

|       | T0     | T1     | T2     |
|-------|--------|--------|--------|
| \( \Delta T_0-T_1 \) | -51.2 (193.0) | -18.1 (159.2) | -15.1 (248.9) |
| \( \Delta T_0-T_2 \) | -124.3 (205.5) | +47.2 (216.2) | +80.4 (271.8) |
| \( \Delta T_1-T_2 \) | -48.3 (86.5) | -45.5 (275.3) | +15.6 (109.7) |

### Stroop Word

|       | T0     | T1     | T2     |
|-------|--------|--------|--------|
| \( \Delta T_0-T_1 \) | +4.53 (10.0) | -2.3 (10.2) | -4.0 (12.6) |
| \( \Delta T_0-T_2 \) | +3.4 (13.7) | -1.9 (14.5) | -2.7 (9.0) |
| \( \Delta T_1-T_2 \) | -1.1 (10.6) | 0.37 (15.1) | -0.80 (13.4) |

### Stroop Colour

|       | T0     | T1     | T2     |
|-------|--------|--------|--------|
| \( \Delta T_0-T_1 \) | +2.9 (7.5) | -0.94 (10.9) | -4.0 (13.0) |
| \( \Delta T_0-T_2 \) | +3.5 (9.7) | +0.78 (5.9) | -1.1 (11.9) |
| \( \Delta T_1-T_2 \) | +0.44 (11.4) | +1.7 (10.3) | +2.9 (9.1) |

### Stroop Color-Word

|       | T0     | T1     | T2     |
|-------|--------|--------|--------|
| \( \Delta T_0-T_1 \) | +1.3 (6.0) | +2.7 (7.7) | +0.61 (5.7) |
| \( \Delta T_0-T_2 \) | -2.4 (5.6) | -0.01 (3.3) | +1.9 (5.9) |
|                          | T1-T2 | T0    | T1    | T2    |
|--------------------------|--------|-------|-------|-------|
| \(\Delta T_1 - T_2\)    | 19     | -3.7  | 21    | -2.7  |
|                          | 20     | -7.6  | 22    | -12.7 |
|                          | 19     | -3.9  | 21    | +0.36 |
|                          | 19     | -3.2  | 21    | -2.5  |
|                          | 19     | -3.2  | 21    | -2.5  |
|                          | 19     | -3.7  | 21    | -2.7  |
|                          | 20     | +1.3  | 20    | +1.3  |
|                          | 20     | +0.36 | 20    | +1.3  |
|                          | 20     | +0.26 | 20    | +0.26 |
| Stroop Interference T0   | 20     | -7.6  | 22    | -12.7 |
| \(\Delta T_0 - T_1\)    | 19     | -0.73 | 21    | +2.9  |
|                          | 19     | -3.9  | 21    | +0.36 |
|                          | 19     | -3.2  | 21    | -2.5  |
|                          | 20     | +1.1  | 20    | +1.1  |
|                          | 20     | +1.3  | 20    | +1.3  |
|                          | 20     | +0.6  | 20    | +0.6  |
| DSF T0                   | 21     | 5.5   | 24    | 5.9   |
| \(\Delta T_0 - T_1\)    | 20     | +0.34 | 23    | -0.33 |
|                          | 20     | -0.03 | 23    | -0.03 |
|                          | 20     | -0.36 | 23    | +0.30 |
|                          | 20     | -0.22 | 23    | 0.46  |
|                          | 20     | 0.22  | 23    | 0.50  |
|                          | 19     | +0.03 | 23    | -0.17 |
|                          | 20     | -0.22 | 23    | 0.46  |
|                          | 20     | +0.22 | 23    | 0.50  |
|                          | 19     | +0.03 | 23    | -0.17 |
|                          | 19     | -0.22 | 23    | 0.46  |
| DSB T0                   | 21     | 2.2   | 24    | 2.6   |
| \(\Delta T_0 - T_1\)    | 20     | +0.22 | 23    | -0.63 |
|                          | 19     | +0.03 | 23    | -0.17 |
|                          | 19     | -0.22 | 23    | 0.46  |
|                          | 20     | +0.22 | 23    | 0.50  |
|                          | 19     | +0.03 | 23    | -0.17 |
|                          | 19     | -0.22 | 23    | 0.46  |
| TMT-A (s) T0             | 15     | 120.2 | 19    | 114.1 |
| \(\Delta T_0 - T_1\)    | 11     | +14.3 | 14    | -8.2  |
|                          | 11     | +17.7 | 14    | +34.1 |
|                          | 11     | +3.4  | 13    | +50.5 |
|                          | 11     | -20.3 | 12    | -23.7 |
|                          | 11     | -0.25 | 13    | -0.12 |
|                          | 12     | +13.6 | 14    | +13.6 |
|                          | 11     | -0.25 | 13    | -0.12 |
|                          | 12     | -23.7 | 13    | -23.7 |
|                          | 12     | -23.7 | 13    | -23.7 |
|  |                          | 11     | -0.25 | 13    | -0.12 |
|                          | 12     | -23.7 | 13    | -23.7 |
| Phonemic fluency T0      | 21     | 8.6   | 23    | 9.5   |
| \(\Delta T_0 - T_1\)    | 19     | -0.15 | 22    | +1.2  |
|                          | 20     | -0.26 | 22    | +1.1  |
|                          | 19     | -0.25 | 22    | -0.12 |
|                          | 19     | -0.25 | 22    | -0.12 |
|                          | 19     | -0.15 | 22    | +1.2  |
|                          | 20     | -0.26 | 22    | +1.1  |
Group effects and partial eta squared effect sizes are presented. Baseline measures were compared using one-way analysis of variance. For all other effects, ANCOVA was used unless indicated otherwise. Except for time-related outcome measures positive difference scores indicate improvements in test performance, negative difference scores indicate decline in test performance. For time related outcome measures (RT Mean, RT SD and TMTA) negative difference scores indicate improvements in test performance, positive difference scores indicate decline in test performance. * indicates statistical significance.

\(^a\) Repeated measures analyses of variance, time x group effects presented

| Semantic fluency | T0  | 22  | 2.6 (2.4) | 23  | 3.2 (2.1) | 22  | 2.5 (2.0) |
|------------------|-----|-----|-----------|-----|-----------|-----|-----------|
| Δ T0-T1          | 21  | -0.17 (0.89) | 22  | -0.14 (2.4) | 22  | +0.37 (1.8) |
| Δ T0-T2          | 21  | -0.47 (1.6) | 22  | +0.50 (2.3) | 22  | +0.17 (1.9) |
| Δ T1-T2          | 21  | -0.30 (1.9) | 22  | +0.64 (1.7) | 22  | -0.20 (1.9) |

Table 4. Baseline and difference scores for the physical tests from the intention-to-treat analyses with substituted missing values.
| Test characteristic | TMSim group |           | WBV group |           | TMSim + WBV group |           |
|---------------------|-------------|-----------|-----------|-----------|-------------------|-----------|
|                     | N           | Mean(±SD) | N         | Mean(±SD) | N                 | Mean(±SD) |
| Wheelchair          | 6           |           | 4         |           | 3                 |           |
| TUG (s)             |             |           |           |           |                   |           |
| T0                  | 15          | 19.2 (10.1) | 19       | 27.0 (23.6) | 23               | 24.3 (13.7) |
| Δ T0-T1             | 15          | -3.2 (7.8)  | 18       | -5.1 (13.3) | 23               | -0.76 (5.3)  |
| Δ T0-T2             | 15          | -1.4 (4.5)  | 18       | -4.1 (10.7) | 23               | -0.85 (5.1)  |
| Δ T1-T2             | 16<sup>b</sup> | +2.2 (5.1)  | 18       | +1.0 (2.9)  | 23               | -0.09 (5.3)  |
| FICSIT4             |             |           |           |           |                   |           |
| T0                  | 15          | 2.2 (1.7)   | 18       | 2.2 (1.6)   | 23               | 1.8 (1.8)   |
| Δ T0-T1             | 15          | -0.19 (1.0) | 16       | -0.64 (0.82)| 21               | -0.31 (1.1) |
| Δ T0-T2             | 15          | -0.61 (0.71)| 16       | -0.56 (0.95)| 19               | -0.25 (1.2) |
| Δ T1-T2             | 16<sup>b</sup> | -0.40 (0.98)| 16       | +0.09 (1.1)| 19               | +0.09 (0.97)|
| 6MW (s)             |             |           |           |           |                   |           |
| T0                  | 20          | 8.1 (3.7)   | 21       | 9.3 (4.5)   | 24               | 9.4 (4.4)   |
| Δ T0-T1             | 20          | -0.43 (2.2) | 20       | -1.1 (1.5)  | 24               | -1.4 (2.5)  |
| Δ T0-T2             | 20          | -0.13 (1.6) | 20       | -0.49 (1.3) | 24               | -1.8 (1.7)  |
| Δ T1-T2             | 21<sup>b</sup> | +0.12 (2.1)| 20       | +0.65 (1.0) | 24               | -0.43 (1.8) |

Group effects and partial eta squared effect sizes are presented. Baseline measures were compared using one-way analysis of variance. For all other effects, ANCOVA was used unless indicated otherwise. For the TUG and 6MW negative difference scores indicate improvements in test performance, positive difference scores indicate decline in test performance. For the FICSIT4 positive difference scores indicate improvements in test performance, negative difference scores indicate decline in test performance. * indicates statistical significance, <sup>a</sup> Repeated measures analyses of variance, time x group effects.
Due to a bone fracture one participant of the TMSim was unable to perform the physical tests during T0.

Figures

Figure 1

A) The balancer with a chair, screen and control panel, and B) the wheelchair pod with a wheelchair platform and television screen (identical control panel as in Fig. 1A is not depicted). A wheelchair as well as a normal chair could be safely secured on the wheelchair platform. Both platforms were used to provide the TMSim, WBV and TMSim + WBV intervention sessions. Images from Pactive Motion (Hoogerheide, The Netherlands).

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| Assessed for eligibility (n=219) |
|----------------------------------|
| T0 Baseline measurement (n=120)  |
| Randomization (n=120)            |
| TMSim intervention (n=30) 6 weeks|
| WBV intervention (n=30) 6 weeks  |
| TMSim + WBV intervention (n=30) 6 weeks |
| Control group (n=30) Regular care |

- No informed consent (n=97)
- Did not meet inclusion criteria (n=2)
Figure 2

Flowchart of the study design, intervention characteristics and participant flow.

IIT, intention to treat analysis; PP, per protocol analysis. *Number includes participant that is also included in ‘died n=2’, as this participant dropped-out of the interventions due to illness and eventually passed away, therefore dropped-out of the T1 and T2 measurements.

Supplementary Files

This is a list of supplementary files associated with the primary manuscript. Click to download.

CONSORT 2010 Checklist.doc
Additional file.docx