Passive exercise, an effective therapy?
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Summary and General Discussion
In this thesis we aimed to examine the feasibility of three different forms of passive exercise (therapeutic motion simulation (TMSim), whole body vibration (WBV) and TMSim + WBV) and its effects on cognitive and physical function, quality of life (QoL) and activities of daily life (ADLs) of institutionalized older adults with dementia. A secondary aim of this thesis was to increase our understanding about possible underlying brain mechanisms of WBV, using mice. Below I reflect on the results of the previous chapters and integrate the findings with the existing body of literature. Next, considerations and future perspectives are discussed. Finally concluding remarks and clinical implications are presented.

7.1 MAIN RESULTS

7.1.1 Whole body vibration, cognition and the cholinergic system

Different studies that report acute, short term and long term cognitive enhancing effects of WBV are discussed in chapter 2. In this chapter we also suggest that the found improvements in cognitive performance after WBV could be induced by enhanced functioning of underlying neurotransmitter systems. As it is known that the cholinergic system responds to behaviorally salient stimuli from the environment [1], and the high density of cholinergic synapses in the thalamus, striatum, limbic system and neocortex support that cholinergic transmission plays a critical role in attention, memory, learning and other higher brain functions [2], response of the cholinergic system was of special interest to us.

To elucidate whether WBV can induce enhancements in the cholinergic system, a study was designed in which the immunoreactivity of the acetylcholine-synthesizing enzyme choline acetyltransferase (ChAT) (a measure for cholinergic activity) was measured in mice after five weeks of WBV. In chapter 3 we reported enhancements of ChAT-immunoreactivity in the amygdala and layer 5 of the somatosensory cortex in WBV mice as compared to the pseudo-WBV mice. This increase in ChAT-immunoreactivity indicates a higher level of ChAT activity and hence acetylcholine (ACh) production and release.

The neurotransmitter ACh plays a critical role in attention, perception and learning and memory [3]. Links between cholinergic stimulation and improved cognitive performance have been found. For example, in rats, stimulation of cholinergic projections to the cortex enhanced attention performance [4]. Moreover, studies on cholinergic drugs (cholinesterase inhibitors) demonstrated improved memory, attention and visuospatial functions in a number of disorders such as Lewy body dementia, multiple sclerosis, Parkinson’s disease, attention hyperactivity disorder and Alzheimer’s disease [5 and references therein]. Also, a link between cholinergic functioning and Stroop test
performance has been shown [6]. Lesions in cholinergic input to the prefrontal cortex strongly reduced attention performance [7]. Overall, these findings indicate that improved cognitive performance found after WBV are likely to be, at least partly, mediated by increased activity of the cholinergic system. Hence, WBV could possibly reduce symptoms of conditions in which reduced cholinergic activity plays a role (e.g. Parkinson’s disease [8] and Alzheimer’s disease [9]). As dysfunction of the cholinergic system and degeneration of cholinergic neurons have been related to cognitive and behavioral symptoms in different dementia types (e.g. Alzheimer’s disease, vascular dementia and Huntington’s disease) [9-13] WBV was thought to be a promising intervention for patients with dementia. Therefore, a clinical trial was designed to examine the feasibility and effects of WBV, TMSim (for rationale see introduction) and a combination of both in institutionalized older adults with dementia. The study protocol is described in chapter 4.

7.1.2 Feasibility of TMSim, WBV and a combination of both in older adults with dementia

In chapter 5 the feasibility of TMSim, WBV and a combination of both (TMSim + WBV) in institutionalized patients with dementia is reported. With high attendance rates (mean 87.9%), pleasant participant experiences (mean 7.3) and no serious adverse events, we concluded that all three forms of passive exercise in a multisensory environment were shown feasible in institutionalized patients with dementia. Moreover, even the most severely affected individuals could successfully engage in the sessions, making passive exercise feasible at all stages of dementia.

We presume that the extent to which the interventions could be adjusted to participants’ preferences highly contributed to the pleasant experiences of the participants and the high attendance rates. Intensity of the vibration and movements of the platform could be adjusted for all types of passive exercise. Moreover, the videos applied during TMSim were chosen based on preferences known for, or indicated by the participant. As the TMSim and TMSim + WBV interventions could be personalized to a larger extent than the WBV intervention, higher attendance rates and experience scores were expected in the former two. However, no considerable differences were observed in attendance rates or experience scores between the groups (results chapter 5). This may be partly due to differences in intervention duration between the groups (WBV 4 minutes, TMSim and TMSim + WBV 12 minutes). Since, in general, attendance rates tend to decrease with increased intervention demands, the fact that WBV was only applied for a very short time may distort comparisons with the other two interventions. Besides, although subjective, proxy-experiences scores scored by the research assistants indicated that TMSim and TMSim + WBV were appreciated more than WBV. So even though the TMSim and TMSim + WBV interventions did not seem to be more appreciated in the current study, we do think that the
possibility to take into account personal preferences during TMSim has advantages for intervention adherence in the long run.

7.1.3 Effects of TMSim, WBV and a combination of both in older adults with dementia

Contrary to our expectations, we were unable to establish consistent effects of the three forms of passive exercise on daily functioning (ADLs), quality of life (QoL), cognitive and physical (balance) performance of institutionalized older adults with dementia (chapter 6). It might be that the intervention period of six weeks was too short to evoke detectable differences in this population. In addition, even though the chosen instruments to measure outcome variables are internationally recognized and have shown adequate validity and reliability, they might not be sensitive enough to detect potential small differences that may have occurred within those six weeks. Third, effects of the three forms of passive exercise in a multisensory environment may not last very long, and therefore time points at which outcome measures were assessed were not adequate to capture this.

As reported in chapter 2, most studies in which positive effects of WBV on cognitive performance are reported assessed short term effects [14-16]. Positive effects on attention and inhibition were found immediately after WBV was applied. Moreover, in the study of Regterschot et al. (2014) these effects were only present at the first test assessed after WBV, not the second [16]. As this is the first study to examine the effects of TMSim (only and in combination with WBV), comparing results is difficult. As indicated in chapter 1, the separate components of TMSim were thought to activate many different cortical and subcortical areas, thereby enhancing for example neurotransmitter systems and connectivity between different brain areas [1,17,18]. This could potentially induce improvements in cognitive function and consequently QoL. In chapter 6 we discussed problems that were encountered for assessing different outcome measures in patients with dementia. With the used methods we may have been unable to detect potential (short term) effects of TMSim (and WBV) in this clinical population.

On the other hand, in contrast to our assumption, it might be that the extent to which patients with dementia can benefit from the increased cholinergic activation found after WBV (chapter 3) is limited. Human studies assessing the neuropathological diagnosis of Alzheimer’s disease (AD) have shown that the cholinergic loss seen in this disease is based on the degeneration of cholinergic neurons and of the axons they project to the cerebral cortex [9]. So the cholinergic loss is mainly presynaptic rather than postsynaptic. As many presynaptic cholinergic cells have already been lost in clinical stages of AD, less potential enhancement of cholinergic activity is possible. This may partly explain why we did not find improved cognitive performance after six weeks of WBV in institutionalized patients with dementia.
Physical effects of passive exercise were addressed in chapter 6. We reported that no improvements on static balance (FICSIT4), dynamic balance (timed up and go) and walking speed (6-metre walk) were found after six weeks of passive exercise. No previous studies looking into the effects of passive seated WBV or TMSim on physical functions were found. As reported in chapter 2 a clear distinction can be made between active and passive WBV, as well as between side alternating and synchronous WBV. Studies employing passive, standing WBV in older adults showed inconsistent results. One study found improved static balance [19] following passive, standing (side alternating) WBV, while another did not (synchronous WBV) [20]. Improved performance on the timed up and go test was found in two studies (both side alternating) [21,22] while two others reported no effects on this test (both side alternating) [19,23]. No effects of passive WBV on maximal walking speed were found (synchronous) [24]. As compared to passive WBV, WBV exercise (active WBV, side alternating) was found to be more effective in improving balance and mobility related measures [25]. Moreover, beneficial effects on several health related components such as increased muscle strength [26], reduced knee osteoarthritis symptoms [27] and lower blood pressure [28] have been reported.

Even though physical and physiological effects have been reported after active WBV, this has not yet been consistently established in passive WBV. More research (in different populations) is needed to elucidate whether seated WBV and TMSim may have similar physical effects as standing WBV. Further examination of underlying mechanisms could also shed a light on whether passive WBV (standing and/or seated) and active WBV may be of similar nature and to possible differences in working mechanisms of synchronous and side alternating WBV.

7.1.4 Summary main results
Taken together, in mice, after five weeks of WBV the cholinergic system is activated, which is thought to underlie the cognitive enhancements found after WBV in both mice and, if translatable, humans. Although expected, in institutionalized patients with dementia we did not find improvements in cognitive performance after six weeks of passive exercise. Neither did we find effects of WBV, TMSim and a combination of both on QOL, ADLs and balance related measures. Encouraging was the finding that TMSim, WBV and a combination of both can be safely applied in institutionalized patients with dementia, even in the presence of physical and cognitive problems. Thereby providing alternatives to breach inactivity levels in institutionalized patients for whom often limited activities are available. Further individualization seems to be key and will be addressed later on in this discussion (see 7.2.5 Further development and personalization of TMSim).
7.2 CONSIDERATIONS AND FUTURE PERSPECTIVES

7.2.1 Doing something is better than nothing

Although in this thesis we could not provide evidence for beneficial effects of three different types of passive exercise in institutionalized patients with dementia, we do think that adding passive exercise to activity programs of this population can be beneficial.

Most hours of institutionalized patients with dementia are spent passively in the shared living room of the nursing home. Even though multiple residents and caretakers are often present in these living rooms, the amount of activity and distraction that takes place in these areas is sparse. In an observational study, cognitively impaired nursing home residents were not involved in any form of activity during 63% of the observations [29]. In addition, limited time (approximately 5% of all observations) was spent in structured activities (e.g. music therapy) or social activities (e.g. receiving visitors). As a result of a lack of suitable activities and of dementia patients being unoccupied, they might become increasingly isolated, frustrated, bored and unhappy. Often this is reflected by people walking around and searching, or becoming apathetic, agitated and/or emotionally distressed. An absence of suitable activities might also affect their ability to perform activities of daily life.

Interestingly, participants in the study of Cohen-Mansfield (1992) manifested greater number of agitated behaviors when they were unoccupied, while fewer agitated behaviors manifested when involved in structural or social activities [29]. These results imply an association between boredom and agitated behavior. A clear message arises from these results: (agitated) institutionalized patients with dementia should be provided with activities or social interactions to occupy their time.

As stated in chapter 6 we think TMSim and WBV have the potential to breach inactivity and be complementary to already existing nursing home activities. Both interventions could be used to reduce boredom and provide occupational therapy to residents, thereby possibly reducing agitated behavior.

In the course of the study described in chapter 4-6 we performed a small pilot study in one of the cooperating nursing homes. In this pilot study we observed agitated behavior on days with and without passive exercise intervention during four consecutive weeks. One participant (TMSim + WBV) showed systematically/consistent less agitated behavior on intervention days, whilst two others (TMSim and WBV) showed systematically more agitated behavior. For all participants the number of observed agitated behaviors reduced over time. Although no clear short term positive or negative effect on agitated behavior was established, these results indicate that passive exercise evokes at least some reaction in the patients that is different for each individual.

In addition, although very subjective, many research-assistants and nursing home staff reported that passive exercise vitalized memories and responses from the patients with dementia,
thereby increasing their social interactions. We tried to quantify this in another pilot study where we observed social behavior and positive and negative affect (e.g. “has a smile around the mouth” and “is cheerful” or “makes an anxious impression” and “is crying”) before and after the passive exercise interventions and at the same time points on days without intervention. We observed more positive social behavior and less negative social behavior after the intervention as compared to before the intervention. However, similar trends were observed on days without intervention. For positive and negative affect on the other hand, we observed more positive affect and less negative affect after the interventions as compared to before (Figure 7.1). While on days without interventions there were less distinct differences in observed positive and negative affect at the two time points. As these are results of a pilot study with small sample sized, and few observed behaviors, future observational studies including larger sample sizes are recommended in order to elucidate whether passive exercise really has an effect on affect, social behavior and agitated behavior.

Taken together, there is a high need for development of innovative ways to breach inactiveness and boredom in residential aged care. Unoccupied patients seem to manifest more agitated behavior as compared to when they are occupied. In addition, sitting in a chair or lying in bed for large parts of the day could greatly affect peoples’ ability to perform ADLs. Passive exercise could be used to provide personalized activities to institutionalized patients with cognitive and physical disabilities. Results from our pilot studies indicate that passive exercise can evoke changes in behavior, different for each individual. This was only established in small sample sizes and with moderate methodology, therefore, high quality studies with larger sample sizes are suggested to examine short term effects of passive exercise on social and agitated behavior and measures related to wellbeing.
7.2.2 Improving measures in the dementia population

As discussed in chapter 6, quantifying outcome measures is challenging in patients with dementia. The number of neuropsychological and physical tests that can be adequately used in patients with dementia is limited [30]. In addition, due to a variety of cognitive, behavioral and physical problems assessment of objective measures such as neuropsychological and physical tests is not possible in a large part of the institutionalized patients with dementia. For obtaining valid and reliable results, the participant should be able to accomplish the presented test according to protocol. Many tests, however, require instructions that are too comprehensive to understand for patients in moderate to severe dementia stages (e.g. STROOP color-word test [31], reaction time task [32] and the trailmaking test [33] as described in chapter 4). Development of suitable neuropsychological and physical tests, with normative data for different dementia stages, types and global cognitive status is necessary for this population in order to adequately measure cognitive and physical functions and place changes in test performance over time in context on the population as well as the individual level. Such tests should be of short duration and require short, straightforward instructions.

Beside assessment of cognitive and physical tests, assessment of questionnaires or interviews in these patients is difficult as well, as this requires a certain level of communication skills that are often tremendously affected [34]. For example, patients may not be able to understand what is asked or have difficulties with expressing themselves. This can cause outcomes of self-reported measures to be
unreliable. Therefore, often subjective measures such as proxy reports are used as an alternative to assess outcome measures. However, proxy measures are accompanied by several limitations. Proxy-measures often show discrepancies from self-reported measures [35]. Personal characteristics of the respondent or their relationship with the participants may influence the outcomes [36,37]. Hence, proxy-measures may not be the right solution to counteract the problems with self-report.

In sum, more feasibility and clinimetric research is needed to create consensus on and empower development of feasible, reliable and valid tests and measures that can be used in future clinical studies that include patients with dementia.

**BOX ‘PASSIVE EXERCISE?’**

In this thesis we refer to TMSim, WBV and TMSim + WBV as forms of passive exercise in a multisensory environment. The term passive exercise implicates that activated processes following TMSim and WBV are similar to those following active physical exercise (PE). As the study described in chapters 4-6 is the first to employ TMSim, it is difficult to indicate whether processes following this intervention are similar to those following PE. For WBV and PE, key processes and mechanisms underlying the positive effects on cognition have, in part, been elucidated, mostly in animal models.

To mimic PE, many animal model studies used voluntary running. Voluntary running was shown to increase synaptic plasticity [38,39], neurogenesis (in the hippocampus) [39,40], angiogenesis and perfusion [41] in brain areas that are important for learning and memory. These processes are mediated, in part, by the activation and production of several key growth factors and neurotransmitters: Brain-Derived Neurotrophic Growth Factor (BDNF), Vascular Endothelial Growth Factor (VEGF), serotonin, dopamine and Insulin-Like Growth Factor-1 (IGF-1) [38,42-44].

Although found in animal models that mimic pathological conditions, similar activation and production of growth factors and neurotransmitters have been reported after WBV. In ischemic rats, increased BDNF levels were found after 30 days of WBV treatment as compared to controls [45]. Additionally, after four weeks of WBV increased levels of dopamine and BDNF were found in the striatum of Parkinson’s disease model mice [46]. In an experiment in which different WBV accelerations and frequencies were applied, increased serotonin levels were found after WBV as compared to control condition [47]. These increases were found after a single, four hour, session of 20 Hz, 0.4G WBV, but not after 5 or 30 Hz, 0.4G WBV. At 20 Hz, serotonin levels were found to increase with increased acceleration (0.4 - 5G).

One study in which PE and WBV were directly compared was performed in leptin receptor–deficient mice, a model for type II diabetes. Metabolic and osteogenic effects of 20 minutes WBV (32 Hz, 0.5G) and 45 minutes of treadmill exercise (10m/min) were compared. For both types of
intervention, similar effects were found on insulin sensitivity, pancreatic response to glucose, muscle fiber diameter, reduced adipocyte hypertrophy in visceral fat, attenuated hepatic steatosis and enhanced glycemic control [48]. In addition, in older adults increased levels of IGF-1 were found immediately, one hour and two hours after a single session of WBV as compared to pseudo-controls [49].

To conclude, comparisons across findings in both human and rodent literature reveal similarities between exercise and WBV in activation and production of several growth factors and neurotransmitters. However, WBV studies were often performed in models resembling pathological conditions. Furthermore, it is unclear whether working mechanisms of active and passive WBV are identical. Therefore, it remains unknown if WBV as applied in animal models reflects passive and/or active WBV (discussed in the section 7.2.4 Animal models). Altogether the comparison between exercise and WBV (as well as TMSim) warrants further investigation in order to determine whether we can rightfully refer to WBV (and TMSim) as being passive exercise.

7.2.3 Optimal characteristics of vibration?
As processing of vibratory stimuli by the skin mechanoreceptors is thought to be a crucial underlying mechanism of WBV, it can be questioned whether vibration of the whole body is necessary. Density of mechanoreceptors is highest in glabrous skin which is typically more sensitive than hairy skin. In humans for example, the fingers have many receptors with small receptive fields (more sensitive), while the legs and trunk have fewer receptors with large receptive fields (less sensitive). A study in which only the fingertips are stimulated could provide evidence for the hypothesized role of mechanoreceptors in WBV. This may also verify whether vibration of the whole body is necessary. It is known that the number and mean density of mechanoreceptors in the skin decreases with age [50-52]. Therefore, research in different aged study populations is recommended.

Furthermore, given the characteristics of the mechanoreceptors that are sensitive to the type of vibration that is applied during WBV (in most studies 20-40 Hz), the continuous nature of the applied WBV could be impeached. Meissner and Pacinian corpuscles are rapidly adaptive receptors [53], meaning they respond to changes in the environment instead of to continuous stimuli (Figure 7.2). Hence, in order to fire, these corpuscles need constantly changing stimuli. During WBV we apply the same stimulus for several minutes, while it is likely that with such continuous stimulation the firing of the targeted mechanoreceptors only lasts for several seconds. On the other hand, random WBV, for example with changing frequency and/or amplitude, could potentially cause the mechanoreceptors to keep firing. So far, only one study examined both continuous and random WBV [54]. Six weeks random (three series of alternately 30 seconds, 20 Hz and 30 seconds, 50 Hz), but not constant (six times 30
seconds, 35 Hz) WBV in series of 30 seconds improved performance on the time up and go test (dynamic balance). However, no between group comparisons were made and data for the constant WBV group was not presented, therefore from this study it cannot be concluded that random WBV is more effective than constant WBV. Nevertheless, it is worth investigating whether providing more variable types of WBV might be more effective than applying the same stimulus for several minutes, as we currently do in WBV.

7.2.4 Animal models

Although mouse models can be very useful to study specific neurobiological processes that underlie passive WBV and other types of sensory stimulation, important differences between the human and animal models should be recognized. As the exact underlying mechanisms of passive WBV remain unknown, it also remains unknown whether the processing of this type of sensory stimulation in mice actually resembles the processing of WBV in humans.

In seated, passive WBV it is thought that information processing via the skin mechanoreceptors plays a key role in the observed positive effects on cognitive performance found after (seated) WBV. Similar to human, in animals touch is also detected by means of skin mechanoreceptors and processed in the somatosensory area. However, unlike human, rodents (and other animals) heavily rely on their whiskers for tactile sensing, complementary to sensing via the skin. In the barrel cortex, a region of the somatosensory cortex, information of the whiskers is processed. Different neurons of the barrel cortex

![Receptive field size](image)

**Figure 7.2.** Touch is the detection of a mechanical stimulus impacting the skin. Four types of mechanoreceptors are localized in various layers of the skin where they detect a wide range of mechanical stimuli (e.g. pressure, stretch and vibration). Each type of receptor has its own characteristics in terms of receptive field size, adaptation speed and perception (e.g. stimulus type and frequency), thereby is sensitive to specific aspects of the physical environment.
have different frequency preferences [55]. Whisking generally occurs at frequencies between 5 and 15 Hz [56,57]. However, results from different studies suggest sensitivity of the whiskers to stimulation up to 1500 Hz [55,58-60]. It is likely that WBV in mice, at least to a large extent, activates signaling from the whiskers and related brain areas. To what extent this difference between animal models and the human situation affects the possibility to translate results remains unknown.

In addition to differences in the processing of tactile information, also differences in posture between animal and human passive WBV could be problematic in translating results. In human, during passive WBV participants are seated or statically standing on the vibrating plate. While in rodent experiments the animals often can freely move around (albeit in a limited space). In our own experiments it was observed that during WBV mice were moving and changing posture. Therefore, rodent WBV experiments may be more likely to resemble active WBV instead of passive WBV. Moreover, direct contact of the mice with the vibrating source may be less consistent as compared to the human situation.

Finally, even though the use of different mouse strains is relevant as they may represent differences as seen in human population, the outcomes can differ for different strains. Studies on different strains in which effects of WBV on cognitive and physical performance was examined yielded inconsistent results. For example, improved performance in a reference memory Y-maze test was observed in C57BL/6 mice, but not in CD-1 mice (chapter 2). Additionally, in two studies with similar protocols joint degeneration following WBV was found in CD-1 mice, but not in C57BL/6 mice [61,62]. These results indicate that WBV induced effects may vary in a strain-specific matter.

All in all, the use of animal models could potentially elucidate underlying mechanisms of WBV. Besides, investigating differences in effectiveness of WBV in different strains could help examine factors or areas specifically susceptible to WBV. Future research is needed to examine the similarities between the processing of WBV in human and animal models and to check whether current methods applied in animal models may resemble active or passive WBV.

7.2.5 Further development and personalization of TMSim
TMSim is a relatively new intervention in which passive exercise in a multisensory environment can be applied to the user. In chapter 5 we already showed that TMSim (in combination with WBV) was highly adjustable to participants their preferences. We also discussed that personalization is thought to affect attendance rates and experience scores and that TMSim has the potential to breach inactivity patterns in residential aged care (this chapter). More research to provide a scientific foundation for further development of TMSim is key.
Determining optimal duration, frequency (how often) and intensity are important to determine the optimal dose of TMSim. In CD1 mice for example five, but no 30 minutes of WBV was effective for improving cognitive and physical performance [63]. Apart from the intervention characteristics of TMSim, personalization of the content of TMSim is also needed. The extent to which effectiveness of TMSim could depend on different types of music played during TMSim for example remains open to question. It is known from the literature that effectiveness of music therapy highly depends on familiarity and preferences of the participant [64,65]. Activation of the supplementary motor area may underlie the effectiveness of familiar and preferred music [66]. Also widespread increased functional connectivity in cortico-cortical and cortico-cerebellar networks following preferred music was found [66]. The latter study indicates, that familiar sensory stimulation are powerful instruments to evoke emotions and retrieve memories. Thereby supporting further personalization of the music, sounds, videos and type of activities that are applied during TMSim.

More research on the underlying mechanisms involved in TMSim can potentially increase our knowledge about which populations might benefit from this type of stimulation and what the optimal dose could be. So, further research, development and personalization of TMSim could potentially further improve feasibility and effectiveness.

### 7.3 CONCLUSION AND PRACTICAL IMPLICATION

Taken all results and considerations into account we conclude that passive exercise is a feasible intervention that can be successfully applied in all stages of dementia. Effectiveness of passive exercise in institutionalized patients with dementia has not been established. So for now, we conclude that passive exercise by itself may not have the capacity to replace established pharmacological and non-pharmacological approaches to alleviate adverse effects of dementia. However, we do suggest it can be used as an adjunct treatment, complementary to current activity programs and is a useful strategy to breach inactivity patterns. Not only in institutionalized older adults with dementia, but for all persons that are inactive due to cognitive, physical or organizational limitations.
REFERENCES


Summary and General Discussion


