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General Introduction
1.1 CAN EVERYONE BENEFIT FROM PHYSICAL ACTIVITY?

Every generation people in our society are growing older. Although one could think of this as a result of increased health, according to research performed at the ‘National Institute for Public Health and the Environment’ every new generation is unhealthier than the one before [1]. More recent generations have bigger chances to develop health problems such as obesity and high blood pressure at a younger age. With health problems at a younger age combined with higher life expectancies, the risk for comorbidities increases dramatically. As a consequence, the extra years in life as compared to previous generations, are dominated by health problems causing declines in physical and cognitive capacity [2]. Main contributors to these health problems are high calorie intake and inactivity [1].

No wonder that in today’s society there is a growing interest in physical activity (PA) as an instrument to reduce health problems and overall burden of disease. The American College of Sports Medicine even states ‘exercise is medicine’ [3]. Many clinicians recommend PA to reduce symptoms of physical as well as cognitive problems. Numerous studies report that regular PA is thought to reduce adverse effects of and/or the risk to develop metabolic syndrome related disorders (e.g. obesity and diabetes mellitus type II), muscle, bone and joint diseases (e.g. osteoporosis and osteoarthritis), heart and pulmonary diseases (e.g. chronic heart failure and coronary heart disease) and cognitive disorders (e.g. depression and dementia) [3-6]. In general, the side-effects of PA are extremely limited, hence for many conditions PA is preferred as compared to drugs.

However, many people that highly need the benefits from PA can often not be or stay involved in PA. This can be due to multiple reasons, varying from physical and cognitive limitations to practical limitations. For example, in frail populations, (adherence to) PA can be difficult. With increasing age, significant age related loss of functional capacities occur. Exacerbated by inactive and sedentary lifestyles, muscle atrophy [7], poor balance [8], muscle weakness [9], decreased peripheral sensitivity, vestibular dysfunction and loss of aerobic capacity [10] can keep older adults from PA participation. In addition, fear can also prevent people from getting or staying involved in PA. Fear of falling [9] and neighborhood safety [11-14] in older adults and fear of exercise in patients with cardiovascular or heart disease [15] and obesity [16] are reported as great barriers to PA. Furthermore, lack of social support [13,17], lack of exercise facilities [17,18] and difficulties to access exercise facilities [19,20] are found to be major barriers for PA in older adults (with disabilities). Causing large groups of society not being able to be or stay involved in PA.

For many people who cannot be or stay involved in PA, medication often is inevitable in order to manage their condition(s). However almost every type of medications comes with side-effects. Moreover, many conditions cannot even be successfully managed with the use of medication. For
individuals suffering from such conditions, alternatives that can resemble the positive effects of PA could be of great importance in order to limit the amount of medication needed, improve general physical and mental health and reduce the risk of developing comorbidities.

In this thesis two alternative intervention paradigms, referred to as ‘passive exercise’, are presented that can be applied regardless of someone’s physical or cognitive abilities. Both are thought to stimulate the body and the brain, thereby having the potential to improve users’ physical and mental health. The two interventions are whole body vibration (WBV) and therapeutic motion simulation (TMSim).

1.2 WHOLE BODY VIBRATION

WBV is a term used when a vibration source transfers mechanical oscillations to the body, thereby providing proprioceptive and tactile stimulation. In most vibration devices the applied mechanical oscillations are periodic with a sinusoidal shape. This means that the intensity of WBV can be controlled by adjusting the amplitude (peak-to-peak) \((A)\), frequency \((f)\) (see Figure 1.1) and time of exposure \((t)\). WBV can be applied in an active as well as a passive manner. During active WBV exercises are performed while standing on or interacting with the vibrating source.

Numerous studies reported effects of active WBV on physical function and health related components such as increased muscle strength [21], reduced knee osteoarthritis symptoms [22] and lower blood pressure [23]. However, due to the active component of these interventions, it is not suitable for people with physical disabilities. For passive WBV no active contribution is required. Therefore, passive WBV may serve as a suitable intervention for those who are not able to perform PA. Studies employing passive WBV are scarce. Nevertheless, reported results are promising. Passive WBV where participants were standing on the WBV platform was found to increase bone density [24] and improve mobility, balance and general health status [25,26]. Furthermore, in middle aged obese subjects, improvements in body composition, insulin resistance and glucose regulation were found when WBV was added to a dietary intervention [27]. Effects on cognition were found in studies that employed passive, seated WBV. Acute improvements in attention and inhibition after WBV were found in schoolchildren and young adults (with ADHD) [28-30]. In older adults improvements on attention and inhibition were found after 5 weeks of WBV [31].
1.3 THERAPEUTIC MOTION SIMULATION

TMSim is a form of multisensory stimulation in which visual, auditory, tactile and proprioceptive stimuli are simultaneously provided to the user. Different robotized devices can be used to provide TMSim to the user, with a selection presented in Figure 1.2. Activity videos (e.g. horse-riding, dancing or walking) are played on the television screen, matching sounds and music are played and the device on which the participant is seated/lying moves synchronically with the movements on the screen. Thereby, the participant on the platform experiences it as if they engage in the activities on the screen themselves. Until now, no studies have been reported in which this type of passive exercise in a multisensory environment is applied. However, the distinct components of TMSim are associated with improvements in both physical and cognitive performance.

Effects of vibratory tactile and proprioceptive stimulation have been discussed in the previous section about WBV. The large movements in the frontal, sagittal and transverse plane that are applied during TMSim, however, are other forms of tactile and proprioceptive stimulation. These large movements are thought to cause postural perturbations in the seated subject. Postural perturbation in the frontal and sagittal plane in sitting subjects causes alternating contraction and relaxation of the trunk muscles in order to maintain balance [32]. Depending on the plane in which the perturbation takes place, there are either symmetrical or asymmetrical contractions of right/left abdominal/back muscles. Such equilibrium reactions are automatic compensatory movements and can occur in in the head, trunk and limbs in order to retain or regain balance. These reactions make upright sitting, stance and gait possible and provide the background control necessary for the execution of all skilled motor
responses. Based on this knowledge it is thought that the postural perturbations applied in TMSim could improve both static and dynamic balance control.

To the best of our knowledge no literature is available on the type of video therapy as used during TMSim. However, videos of familiar activities are often used for reminiscence therapy, which is a popular psychosocial intervention in dementia care, and is highly rated by staff and participants. There is some evidence to suggest that it is effective in improving cognition, mood and general behavioral function in older adults with and without dementia [33,34]. In older adults without dementia larger effects were found in subjects with elevated depressive symptomatology as compared to other subjects [34].

Music therapy is used in rehabilitation to enable communication and expression and stimulate brain functions involved in movement, cognition, speech, emotions and sensory perceptions [35]. High quality studies that provide evidence for music listening interventions are limited. Nevertheless, there are indications that listening to music may have beneficial effects on anxiety, pain and quality of life in people with cancer [36]. In palliative care patients singing and humming seem to have beneficial effects on mood, anxiety and depression [37]. Listening to preferred music enhanced functional connectivity in patients with Alzheimer’s disease [38]. Moreover, in patients with dementia, music therapy was found to have positive effects on anxiety and behavioral and psychological symptoms of dementia [39].

Although the processes that underlie the improvements found after the different discussed types of sensory stimulation remain unclear, WBV and the distinct components of TMSim were shown to have beneficial effects on a variety of physical and cognitive parameters. Altogether we think WBV and TMSim have the potential to improve mood, physical and cognitive function in (older) adults. Since both WBV and TMSim can be applied regardless of individuals’ cognitive or physical disabilities these interventions are thought to be especially attractive for frail and clinical populations who are not able to be involved in PA anymore.

Figure 1.2. Three different robotized movement platforms that can be used to apply both TMSim and WBV. From left to right; the wheelchair pod, the balancer and the motion lounger (Pactive Motion, Hoogerheide, The Netherlands).
1.4 A ROLE FOR PASSIVE EXERCISE IN DEMENTIA?

A population that could highly benefit from the potential beneficial effects of WBV and TMSim are institutionalized patients with dementia. Dementia is a term that describes the loss of cognitive functioning (memory, communications and reasoning) and behavioral abilities (emotional control, personality change) that can be the result of many different diseases of which Alzheimer’s Disease is best known. In 2016, worldwide, over 47 million people were estimated to live with dementia [40]. As advanced age is the main risk factor for most dementia types, aging of the world population will result in even higher dementia prevalence in the decades to come [41]. The cognitive decline and physical impairments that characterize dementia reduces patients’ their quality of life and their ability to perform activities of daily life. As a result, institutionalization is inevitable for many patients. To date no treatments are available that can cure or effectively manage dementia. Hence, a shift towards the use of non-pharmacological alternatives to limit the adverse effects of dementia has been deployed.

PA is thought to be effective in limiting the progressive course of dementia [42-45]. However, due to physical, cognitive and organizational limitations, PA often is not possible. The lack of activity and initiative, decline in the ability to communicate and perform everyday activities can cause severe sensory deprivation in these patients. In turn this facilitates a faster decline in cognitive and physical function. We believe that WBV and TMSim, two types of (multi)sensory stimulation that can be applied regardless of someone’s cognitive or physical disabilities, could be viable interventions to limit the adverse effect of dementia in institutionalized patients with dementia. However, it is unknown whether these types of (multi)sensory stimulation can be safely and successfully applied (feasibility) in these patients.

**BOX ‘SENSORY PROCESSING IN THE BRAIN’**

As indicated before, the underlying processes of WBV and TMSim that could potentially have beneficial effects on cognitive and physical performance are unclear. Nevertheless, based on scientific knowledge about the processing of sensory information it is thought that the tactile, proprioceptive, visual and auditory stimulation that is provided during these types of (multi)sensory stimulation activates many different cortical and subcortical regions (Figure 1.3).

Many different receptors in our body transduce external sensory information in order to be able to process it. For example, transduction of tactile stimulation takes place by skin mechanoreceptors and auditory information is transduced by hair cells in the organ of Corti. After transduction, sensory information travels to the brain via specialized, structured pathways consisting of highly interconnected networks of neurons [49] (e.g. tactile and proprioceptive information...
travels via the spinothalamic and medial lemniscus pathway both ending in the somatosensory cortex [46-48]). Key in sensory processing is the thalamus. It is often referred to as the “gateway to the cortex” because, with the exception of some olfactory inputs, all sensory modalities make synaptic relays in the thalamus before continuing to the primary receiving areas [50]. From the primary receiving sensory areas, information is send to secondary and higher order association areas (see Figure 1.3). As the before mentioned primary and association areas have reciprocal connections with many subcortical structures that also play a role in the processing of sensory information, for both TMSim and WBV a diffuse activation throughout the brain will take place [51].

Figure 1.3. Left the cortex with the primary sensory, motor, visual and auditory areas and surrounding association areas. Information flows from primary areas to secondary association areas and from there to higher order association areas which are spread across the cortex. Right the limbic system with some of the structures that are relevant to sensory processing.

Other than relaying primary sensory information, the thalamus also receives and sends out information to the basal ganglia, cerebellum, neocortex (e.g. prefrontal cortex), and medial temporal lobe and together with these structures creates circuits involved in many different functions (e.g. integrative functions, arousal and selective attention) [52]. In addition, other parts of the limbic system such as the amygdala and hippocampus have widespread and reciprocal cortical-subcortical connections that contribute to the integration of sensory information and play a major role in emotional processing, learning and memory. Activation of the mentioned an illustrated (Figure 1.3) areas and pathways may induce increased blood flow in and connectivity between these specific areas. Furthermore, neurite outgrowth and activation of underlying neurotransmitter systems could be enhanced [53-55].
1.5 OUTLINE OF THIS THESIS

The main objective of this thesis is to study the feasibility of WBV and TMSim and its effects on quality of life and daily functioning in institutionalized older adults with dementia. In addition, an animal study is conducted to increase our understanding about possible neurobiological underlying mechanisms of WBV. **Chapter 2** presents an elaborate description on the concept of WBV and what is currently known about the potential effects of WBV on cognition and the mechanisms that may underlie these effects. In **chapter 3** measures of cholinergic activity after five weeks of WBV in C57Bl/6j mice are presented in order to test whether the cholinergic system possibly contributes to the found improvements in attention after WBV. Based on the outcomes of **chapter 3** and earlier findings, a clinical trial was developed, investigating the feasibility and effects of WBV, TMSim and a combination of both in institutionalized older adults with dementia. An extensive study protocol of this clinical trial is presented in **chapter 4**. In **chapter 5** the feasibility of WBV, TMSim and TMSim + WBV in institutionalized older adults with dementia is reported. The effects of these interventions on quality of life, daily functioning, cognition and physical function of institutionalized older adults are described in **chapter 6**. To conclude, a summary of the results from previous chapters and a general discussion of the studies, their limitations, the potential of TMSim and WBV and implications for future research are presented in **chapter 7**.
REFERENCES


