The Association Between Physical Performance and Hippocampal Volume in Alzheimer's Disease Patients: A Pilot Study

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Abstract

Alzheimer's disease is developing proportionally with the increased aging of the worlds' population. To this date there are no curative treatments, but finding ways treat the disease to lessen the burden of the symptoms could be crucial for these patients' quality of life. An increasing number of studies have looked at non-pharmacological approaches to treat Alzheimer's disease, but there is a lack of high-quality studies in this topic of research. The current thesis served as a pilot study for the Alzheimer and Music Therapy (ALMUTH) project, providing preliminary data on how physical performance and hippocampal volume affects AD patients and their overall well-being. Twelve AD patients were screened at the Haukeland University hospital. Hippocampal volumetry and total intracranial volume was extracted with automated segmentation using the FreeSurfer software package. Physical performance was measured by the Short Physical Performance Battery. The Mini-Mental State Examination, Geriatric Depression Scale and Activities of Daily Living served as cognitive measures. There was found a moderate, albeit non-significant relationship between physical performance and hippocampal volume, and patients with higher hippocampal volume showed significantly less depressive symptoms. Patients with better physical performance also reported that performing daily activities was easier. These preliminary findings suggest a relationship between physical performance and hippocampal volume in Alzheimer's disease patients and serve as proof-of-concept for the ALMUTH study. The data show encouraging prospects for investigating the relationship between physical performance, hippocampal volume, and Alzheimer's disease at a greater scale.

Key words: Alzheimer's disease, physical performance, hippocampal volume, cognition, daily functioning, depression, FreeSurfer

Sammendrag

Alzheimers sykdom utvikler seg proporsjonalt med økningen av en aldrende verdensbefolkning. Det finnes ingen kurative behandlinger for sykdommen, og å finne måter å behandle sykdommen på eller symptomene disse pasientene opplever, kan være avgjørende for deres livskvalitet. Et økende antall studier har sett på medikamentfrie tilnærminger i forbindelse med behandling av Alzheimers, men det er mangel på studier av høy kvalitet på dette området. Denne avhandlingen har fungert som en pilotstudie for Alzheimer og Musikkterapi (ALMUTH) prosjektet, og gir foreløpige data om hvordan fysisk funksjon og hippocampalt volum påvirker Alzheimers pasienter og deres generelle velvære. Tolv personer diagnostisert med Alzheimers ble testet på Haukeland Universitetssykehus. Volum av hippocampus og totalt intrakranielt volum ble ekstrahert med automatisk segmentering ved hjelp av programvarepakken FreeSurfer. Fysisk funksjon ble målt med Short Physical Performance Battery. Mini-Mental State Examination, Geriatrisk Depresjonsskala, og Aktiviteter i Dagliglivet fungerte som kognitive måleinstrumenter. Det var et moderat, ikke-signifikant forhold mellom fysisk funksjon og volum av hippocampus. Pasienter med større hippocampalt volum viste signifikant mindre depressive symptomer, og de som hadde bedre fysisk funksjon fant det enklere å utføre aktiviteter i dagliglivet. Disse foreløpige funnene viser en assosiasjon mellom fysisk funksjon og hippocampalt volum hos Alzheimer's pasienter, og fungerer som 'proof-of-concept' for ALMUTH-studien. Dataene viser gode muligheter for å undersøke forholdet mellom fysisk funksjon, volum av hippocampus, og Alzheimers sykdom i en større skala.

Nøkkelord: Alzheimers sykdom, fysisk funksjon, hippocampalt volum, kognisjon, depresjon, daglig funksjon, FreeSurfer

Preface

It has been a long-held dream of mine to help patients with Alzheimer's disease and I chose to do my master's degree at the University of Bergen because of its excellence in neuroscientific research. I was lucky enough to meet my supervisor, professor Stefan Koelsch, early in the course of my degree, and he took me under his wing and let me be a part of his research group. Thanks to Stefan, I've been a part of the ALMUTH project for an extended period of time and worked with Alzheimer's disease patients in helping them trying to achieve a higher quality of life. Working on a project that resonated with my own ideology has been very meaningful, and I would like to thank Stefan for his professional support, friendly demeanor and for making this thesis possible. A substantial thanks is directed to Bergen Municipality and its staff for welcoming me with open arms, and for letting me see their work, their interactions with their patients, and for their help in spreading the word of the ALMUTH study. I would also like to thank postdoctoral fellow, Stavros Skouras, who has been invaluable in helping me with processing and analyzing the hippocampal volumetry data for this study. Furthermore, everyone involved in the ALMUTH group has been genuinely welcoming and helpful, and I am truly grateful for all of their help and support.

Finally, I would like to thank my family, close friends, and fellow students for supporting me, believing in me, and keeping me on my feet. Thank you for your endless words of encouragement, optimism, and laughter. You have been a source of great inspiration and motivation throughout this process.

Bergen, 15th of May, 2019

Ellen Kristine Kongshaug

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Abbreviations

ADL	Activities of Daily Living
ALMUTH	The Alzheimer and Music Therapy Group
AD	Alzheimer's Disease
BrainAGE	Brain Age Gap Estimation
BDNF	Brain-Derived Neuropathic Factor
CSF	Cerebrospinal Fluid
DM	Diabetes Mellitus
fMRI	Functional Magnetic Resonance Imaging
GDS	Geriatric Depression Scale
GDS-15	Geriatric Depression Scale with 15 questions
GDS-30	Geriatric Depression Scale with 30 questions
GM	Grey Matter
HCV	Hippocampal Volume
I-ADL	Instrumental Activities of Daily Living
IBMP	Institute for Biological and Medical Psychology
MRI	Magnetic Resonance Imaging
MTL	Medial Temporal Lobe
MCI	Mild Cognitive Impairment
MMSE	Mini-Mental State Examination
P-ADL	Physical Activities of Daily Living
SPPB	Short Physical Performance Battery
TIV	Total Intercranial Volume
WM	White Matter

Introduction

Dementia is an overall term for a range of symptoms associated with memory loss and progressive intellectual deficit in elderly. By this date it is approximated that around 70.000 individuals suffer from dementia in Norway, and with relatives and carers included, about 250.000 people in Norway are affected by the disease (Helse og omsorgsdepartementet, 2012). Alzheimer's disease (AD) is the most common form of dementia, affecting about 60% of all patients (Lobo et al., 2000). Hebert and colleagues (2003) predicted that the prevalence of AD will more than double in 40 years, making the disease a major global health concern. Cognitive decline is common in AD and typical symptoms of the disease include hallucinations, memory loss, not understanding one's surroundings etc., strongly affecting the well-being of AD patients. In a systematic review of non-pharmacological approaches to treating dementia (Hulme, Wright, Crocker, Oluboyede, & House, 2010), the authors pointed out that, after music therapy, exercise was defined as the second most effective treatment to dementia. However, their overall conclusion was that there are too few high-quality studies to make a good assessment. Moreover, a study comparing cardiovascular fitness and brain atrophy in normal aging vs. early AD patients showed that higher fitness levels in were associated with less brain atrophy dependent on dementia severity and age (Burns et al., 2008).

The hippocampus is usually one of the first brain structures affected by AD, and tends to atrophy at a steady rate once a patient is affected by the disease (van der Flier et al., 2005). Whether there is a relationship between the hippocampal volume (HCV) of AD patients and their physical performance is an interesting issue there is little research on to this date. Greater brain atrophy, and thereby lower levels of cognitive functioning, is a precursor with those who suffer from AD. To this day, there is no cure for AD, albeit some medication may relieve the symptoms these patients suffer from. Because cognitive decline tends to correlate with the

patient's quality of life, finding a satisfactory, non-medical treatment can thus be extremely valuable for the well-being of these patients. If the current thesis finds encouraging results, the relationship between AD, hippocampal volume and physical performance will be explored further at a greater scale by the Alzheimer and Music Therapy (ALMUTH) research group at the Institute for Biological and Medical Psychology (IBMP) and Haukeland University Hospital in Bergen, Norway.

Alzheimer's Disease

AD was first described by the neurologist Alois Alzheimer (1864-1915) as a type of dementia appearing before the age of 65 (Alzheimer, 1907; Stelzmann, Schnitzlein, & Murtagh, 1995). The disease is characterized by deficits in memory and general cognitive functioning, but also by difficulty in performing daily activities. As the disease progresses, memory loss and confusion grow worse and ultimately, AD patients become entirely dependent on others for their care (National Institute on Aging, 2016). The frequency of AD is higher between the ages of 85-90 (Rocca et al., 1991), but according to Breitner and colleagues (1999), people reaching that age without showing symptoms are less likely to develop the disease altogether. This indicates that AD is, in fact, a brain disorder, and does not come from normal wear and tear in the brain as initially assumed. Alzheimer's disease is thereby a neurodegenerative disorder, characterized by alteration in neurogenesis, abnormal formation of tau-protein positive neurofibrillary tangles in neurons, abnormal extracellular accumulation of amyloid in senile and diffuse plaques, and cortical atrophy with associated synapse and neuron loss (Crews & Masliah, 2010; Masliah & Salmon, 1999).

Brain atrophy. Medial temporal lobe (MTL) structures such as the entorhinal cortex and hippocampus are usually the first to be affected by these neuropathological changes. From there, the atrophy advances to structures such as the basal forebrain and temporal and

frontal lobe association cortices in the lateral and anterior cortical areas of the brain, and finally the association cortices in the occipital and parietal lobe (Braak & Braak, 1991). The primary motor- and sensory cortex typically remain free from AD pathology (Pearson, Esiri, Hiorns, Wilcock, & Powell, 1985). As most subcortical areas (e.g., basal ganglia, thalamus) are relatively spared, AD is often classified as a classic form of diffuse cortical dementia.

Utilizing structural magnetic resonance imaging (MRI) to asses brain atrophy has been shown to be a valid marker of AD-related neurodegeneration with *post-mortem* histology (Bobinski et al., 1999; Whitwell et al., 2012). In recent years, MRI-derived markers of neurodegeneration can currently be used to track disease progression in clinical trials and to support a clinical diagnosis of AD (Dubois et al., 2010; McKhann et al., 2011). Through the use of high-resolution MRI, the neurodegeneration of specific cortical and subcortical grey matter (in terms of morphological changes, volume loss, and cortical thinning) can be accurately quantified *in vivo.* Using diffusion MRI sequences, the white matter (WM) structural damage can also be estimated, and atrophy throughout the brain in one of many markers for AD.

Because the brain is plastic, it changes with age and the hippocampus is no exception. However, in AD, the rate of hippocampal atrophy has been seen in numerous studies to be greater than that of a normal aging brain (Jack et al., 1997; Kesslak, Nalcioglu, & Cotman, 1991; Scheltens et al., 1992; Seab et al., 1988). Memory impairment is characteristic in early symptoms of AD, and it has been consistently reported that structures like the medial temporal lobe, and particularly the hippocampal formation is one of the earliest macroscopical hallmarks of AD. The hippocampus has therefore been named as one of the core biomarkers of AD (Albert et al., 2011; Dubois et al., 2010; McKhann et al., 2011; Sperling et al., 2011), and because of its significant role, earlier articles have gone so far as to call the disease «hippocampal dementia» (Ball et al., 1985; Hyman, Van Hoesen, Damasio, & Barnes, 1984). The

loss of hippocampal volume has been found in numerous MRI studies worldwide, and hippocampal volume has been found to be reduced by 15-30% already at the mild cognitive stage (van der Flier et al., 2005), and by 10-15% in patients with the amnesic variant of mild cognitive impairment (MCI) (Shi, Liu, Zhou, Yu, & Jiang, 2009). According to Jack and colleagues (2000) the annual rate of the hippocampus in healthy elderly adults is at 1.73%, whilst the annual rate of AD patients was measured to be 3.5%/yr. AD is described as a memory deficit disease, and the rapid and significant loss of hippocampal tissue is thought to be the cause of the deficit.

On a cellular level, many factors contribute to the loss of brain tissue. Brain-Derived Neuropathic Factor (BDNF) is a molecule that can be found in high concentrations in both the cortex and the hippocampus. The BDNF molecule is critical in plasticity, cell proliferation and cellular analogs of memory formation, and recent studies are linking changes in the BDNF system to depression, hippocampal atrophy and age-related memory impairment (e.g., Erickson et al., 2010). A study performed by Nagahara and colleagues (2009) on rodents found that BDNF administration showed broad neuroprotective effects, showing that BDNF therapeutic delivery could potentially serve as a therapy for AD. Because BDNF is widely expressed in the entorhinal cortex, and anterogradely trafficked into the hippocampus (Yan et al., 1997), it is hypothesized to underlie learning (Kaplan & Miller, 2000). A possibility is that the molecule could be an independent factor in hippocampal atrophy because of its reduction in the entorhinal cortex and hippocampus in AD pathology (Connor et al., 1997; Hock, Heese, Hulette, Rosenberg, & Otten, 2000; Narisawa-Saito, Wakabayashi, Tsuji, Takahashi, & Nawa, 1996). Although intriguing, neither this thesis nor the ALMUTH project will look at the BDNF molecule, but it is worth noting which underlying processes might lie underneath hippocampal atrophy.

Physical Activity

Beneficial effects of exercise on cognitive functioning has been demonstrated in numerous animal models, and more recently in an increasing number of clinical studies on the elderly population (Erickson & Kramer, 2009; Fillit et al., 2002; Kramer, Erickson, & Colcombe, 2006). Research with results mostly derived from animal studies have found that mechanisms that potentially have a salutary effect from exercise include neuroendocrine response to stress, neuroinflammation, neuronal survivability and function, and brain amyloid burden (Adlard, Perreau, Pop, & Cotman, 2005; Carro, Trejo, Busiguina, & Torres-Aleman, 2001; Cotman, Berchtold, & Christie, 2007; Fordyce & Farrar, 1991; Isaacs, Anderson, Alcantara, Black, & Greenough, 1992; Nagahara et al., 2009; Nichol et al., 2008; Parachikova, Nichol, & Cotman, 2008; Sasse et al., 2008; Um et al., 2008; Van Praag, Shubert, Zhao, & Gage, 2005). Interestingly, exercise has been shown to have positive effects on physiological processes that can increase the risk of developing AD when compromised, namely cardiovascular health and glucoregulation (Craft, 2005; Gasparini & Xu, 2003; Helzner et al., 2009; Kuusisto et al., 1997).

There are several documented cognitive benefits associated with regular exercise and activity. Colcombe and Kramer (2003) did a meta-analytic study on the fitness effects of older adults' cognitive function. The authors mainly focused on the effects of aerobic fitness and intervention studies and found that fitness training had the most robust, albeit selective, benefits for cognition, where the biggest effect was found for the executive functioning processes (i.e., working memory, planning, multi-tasking, scheduling etc.). These findings are specifically intriguing considering that the pathology of executive functioning is the same as where AD patients experience the greatest and earliest atrophy. This might suggest that processes showing substantial age-related atrophy are amendable to change. Thus, the magnitude of the

effects of exercise seems to be substantial and should be taken into account when looking for effective intervention strategies for AD patients.

Health benefits from exercise. Physical activity throughout one's lifespan has been associated with the reduction of a number of mental (e.g., anxiety, depression) and physical (e.g., breast and colon cancer, cardiovascular disease, obesity) disorders (US Department of Health and Human Services, 2000). Norwegian Directorate of Health recommends 150 minutes of moderate activity a week, or 75 minutes of high intensity (Karlsson, Ståhle, Tranquist, & Aadland, 2009). However, only 1 out of 3 Norwegians fulfill these requirements, and 60% of the average Norwegian day is spent in inactivity (Hansen et al., 2015). According to a report from 2012, physical inactivity is the cause of 6-10% of the major non-communicable diseases such as coronary heart disease, breast and colon cancer, and type II diabetes worldwide (Lee, Shiroma, Lobelo, & Puska, 2012). Whether inactivity is a direct cause of AD has not yet been established, but it appears that there is a strong relationship between the two that is worth investigating.

Effective strategies to delay the onset of AD and the progression of this potentially devastating disease is being researched worldwide. A recent retrospective case-control study (Friedland et al., 2001) showed that patients with AD were generally less active in their midlife (both physically and intellectually), and that inactivity was associated with a 250% increased risk of developing AD. Successful and effective prevention strategies would result in considerable benefits through prolonged independent life expectancy, improved quality of life, and reduced social burdens and economic cost. Consequently, regular physical activity, apart from being an important element in overall health promotion (Larson & Wang, 2004), might be an effective strategy for delaying the onset of dementia (Pate et al., 1995).

Balance and falls. AD patients often experience falls as a result of the loss of balance. Falls in the elderly population is associated with major morbidity, long hospital stays, costs, and mortality (Siracuse et al., 2012), and research has shown that it is possible to prevent falls by exercising and improving physical performance. According to Bergen Municipality's report "Trygg på to bein", (Bergen Kommune, 2010), balance training and strength-building exercises have the best results for preventing falls. Moreover, they reported that several studies (Campbell, Robertson, Gardner, Norton, & Buchner, 1999; Helbostad, Leirfall, Moe-Nilssen, & Sletvold, 2007; Skelton, Dinan, Campbell, & Rutherford, 2005) displayed how inactive seniors who had not previously experienced falls had a good effect of a one year training program. The training group reduced the number of falls by 30% compared with the control group and the effect of exercise was also greatest in the elderly with initial or established functional failure.

With aging, major changes in body composition often follow. Changes such as a progressive decrease in muscle strength, mass, and quality accompanied by an increase of fat tissue can negatively affect functional status (Candow & Chilibeck, 2005; Lauretani et al., 2003). According to the «Trygg på to bein» report, muscle strength is the low-impact effect a muscle or muscle-group can develop. One article (Liu & Latham, 2009) suggests that it appears as if elders who exercise muscle strength become stronger and achieve better function in daily activities. Another study (Kalapotharakos, Michalopoulos, Tokmakidis, Godolias, & Gourgoulis, 2005) showed that two groups of elderly people who used to exercise did better on functional tests after a training intervention. According to the Bergen Municipality report, exercise for the elderly, as for young people, must be done 2-3 times a week with a certain intensity (8-12 repetitions and 3 sets) and be done for a minimum duration of 12 weeks to have an effect (2010). Evidently, increasing muscle composition, and thereby increasing phys-

ical performance could substantially decrease the likelihood of falls in the elderly and with that, long and costly hospital stays.

Cardiovascular Problems. Research has increasingly demonstrated a link between the risk of developing dementia to cardiovascular problems (Whitmer, Gunderson, Barrett-Connor, Quesenberry, & Yaffe, 2005a; Whitmer, Sidney, Selby, Johnston, & Yaffe, 2005b). Such risk factors include obesity, high cholesterol, diabetes, and substance abuse, mostly associated with smoking cigarettes. Data obtained from 8845 participants in a retrospective cohort study showed a 20-40% higher risk of developing dementia for individuals suffering from cardiovascular risk factors earlier in their life (Whitmer et al., 2005b). Data derived from longitudinal studies showed that obesity has been found to be the single highest predictor of dementia, increasing its risk by 74% (Whitmer et al., 2005a). Furthermore, compared to participants with a healthy body mass index (BMI), they found that simply being overweight would increase the risk of developing dementia by 35%. These studies by Whitmer and colleagues shows the importance of considering physical health in diagnosing patients with AD and dementia, both individually and combined, as exercise and increased physical performance has been shown to reduce factors implemented in developing AD.

Diabetes. Evidentially, because the risk factors of cardiovascular problems such as high cholesterol and obesity are associated with diabetes, individuals diagnosed with diabetes mellitus (DM) are possibly at a higher risk of developing dementia. Twenty percent of adults above the age of 65 are affected by DM and numerous cross-sectional studies have shown an association between DM and cognitive impairment (Croxon & Jagger, 1995; Desmond, Tatemichi, Paik, & Stern, 1993; Grodstein, Chen, Wilson, & Manson, 2001). Thus, an association between AD and DM is not implausible and studies looking at the association has been carried out with mixed results. A longitudinal study conducted on Catholic nuns, priests and

brothers found that, of the participants that had DM, 65% was at risk of developing AD (Arvanitakis, Wilson, Bienias, Evans, & Bennett, 2004). Depression is also more likely to occur in patients with DM, and for patients with a dual diagnosis of both depression and DM, the risk of developing dementia is two-to-threefold (Katon et al., 2010). Exercise has been found to be therapeutic both for individuals with diabetes (Soman, Koivisto, Deibert, Felig, & DeFronzo, 1979) and for depression (Babyak et al., 2000), and there is thus reason to believe that an active lifestyle could be beneficial in the prevention of developing DM, and accordingly AD.

Generally, there is an extensive body of research linking exercise to beneficial outcomes both neuropsychologically and physically. A link between cardiovascular problems and AD has been well established, and exercising on a regular basis seems to have a positive effect on AD-and age-related brain atrophy. Additionally DM and falls, problems often occurring in the AD population, can seemingly be prevented by engaging in physical activity. There is thus reason to believe that not only can the quality of life be enhanced in active AD patients, but the rate at which their brain decays can evidently be slowed down.

Hippocampal Volumetry

This thesis is a part of the ALMUTH project at IBMP and Haukeland University Hospital, and only addresses a small part of the project. The ALMUTH project will utilize, among other methods, the newly developed BrainAGE paradigm to determine how the brain of the patients differentiate from that of a healthy person in the same age group. Throughout the normal aging process, the brain is prone to change due to both regressive (e.g., cell death and atrophy) and progressive (e.g., myelination and cell growth) neuronal processes. One study showed that grey matter (GM) volume increases from birth until the age of four, followed by a continuous decline until the age of around 70 (Pfefferbaum et al., 1994). Furthermore,

through the very crude geometrical method for the segmentation of MRI data, Pfefferbaum and colleagues also found a WM increase up until the age of 20 when it plateaus. A more recent study (Good et al., 2001) with 465 normal subjects between the ages of 17 and 79 suggested a linear decline in GM to be prevailing in normal aging. Moreover, micro-structural changes in WM and local areas of GM atrophy was reported, suggesting a complex and heterogeneous pattern of atrophy across the adult life span. Evidence for a non-linear and region-specific pattern of neurodegenerative age-related changes in GM volume was also reported by longitudinal data comparisons (Resnick, Pham, Kraut, Zonderman, & Davatzikos, 2003) and cross-sectional morphometric analyses (Terribilli et al., 2011). The hypothesis of normal age-related GM decline is thus supported by these results to the phylogenetic origin of each specific brain region, with younger structures being the last to develop and mature, and thus being more vulnerable to neurodegeneration. Diseases such as AD alter brain structures in abnormal and diverse modes (Ashburner et al., 2003), and another study has recently provided additional evidence supporting this view by showing that the atrophied regions in normal-aging patients are closely related to the regions detected in AD patients (Dukart, Schroeter, Mueller, & the Alzheimer's Disease Neuroimaging Initiative, 2011).

BrainAGE. In order to differentiate a pattern of brain atrophy that deviates from normal brain aging, Franke and colleagues (Franke, Luders, May, Wilke, & Gaser, 2012; Franke, Ziegler, Klöppel, Gaser, & for the Alzheimer's Disease Neuroimaging Initiative, 2010) developed the novel BrainAGE approach. The BrainAGE approach is based on a database of single time-point structural MRI data, which aggregates the multidimensional, complex aging patterns across the entire brain into one single value, being the estimated brain age. This is determined by applying established kernel regression methods to the MRI images. The BrainAGE framework applies RVR, a machine-learning pattern recognition method based on T1-

weighed images developed by Tipping (2001) to estimate individual brain ages. The age estimation accuracy did not show any improvement with non-linear kernels, thus as suggested by Franke and colleagues (2010) the kernel used was a polynomial of degree 1. The training period does accordingly not need parameter optimization. The BrainAGE model is trained with preprocessed whole brain structural MRI data of the training sample.

Hippocampal volume is seen as one of the core biomarkers for MCI converting to AD (Apostolova et al., 2006b; Devanand et al., 2007) and the BrainAGE paradigm has successfully been applied to predict progression of AD (Franke & Gaser, 2012; Gaser et al., 2013; Löwe, Gaser, Franke, & the Alzheimer's Disease Neuroimaging Initiative, 2016). Moreover, it has been successful in examining neurodevelopmental effects in children and adolescents (Franke et al., 2012), examine the hormonal influences and lifestyle factors (Franke, Hagemann, Schleussner, & Gaser, 2015; Franke, Ristow, & Gaser, 2014; Luders, Cherbuin, & Gaser, 2016), to determine brain-aging effects in psychiatric and non-psychiatric diseases (Franke, Gaser, Manor, & Novak, 2013; Koutsouleris et al., 2013), and to determine the impact of long-term instrumental music making on the mature brain (Rogenmoser, Kernbach, Schlaug, & Gaser, 2018). There are thus promising prospects for finding interesting results by looking at physical performance and BrainAGE for the ALMUTH project.

BrainAGE is ideal for the purpose of ALMUTH that will use longitudinal data, and it requires a sophisticated setup which is semi-proprietary. It is furthermore required to scan a large number of control subjects for algorithmic calibration purposes, which is not feasible for a thesis running over the course of one year. Therefore, for the purposes of this thesis, the more well-established HCV will be used, which can be computed in a standardized way using the FreeSurfer software package.

FreeSurfer. For the past 20 years, the hippocampus has been implicated in regulating emotion, forming memories, and in a number of neuropsychiatric diseases, such as epilepsy, depression, sleep disorders, schizophrenia, and dementia (Geuze, Vermetten, & Bremner, 2005b). Because of this, trying to optimize MRI-based hippocampal volumetry through various manual (Geuze, Vermetten, & Bremner, 2005a) and automated (Carmichael et al., 2005; Chupin et al., 2007; Csernansky et al., 1998; Duchesne, Pruessner, & Collins, 2002; Fischl et al., 2002; Ghanei, Soltanian-Zadeh, & Windham, 1998; Haller et al., 1997; Hsu et al., 2002) protocols has been investigated. Although throughout the literature the general understanding is that manual hippocampal volumetry is the 'gold standard,' it is dependent on rater experience and it is highly time-consuming. Therefore, several automated volumetric methods have been developed. The FreeSurfer (Fischl et al., 2002) software package (http://surfer.nmr.mgh.harvard.edu) is an observer-independent subcortical volume and segmentation technique, which provide volumes for individual subcortical nuclei from conventional MR images. The accuracy of using an automated method for labelling and volumetry of subcortical structures have been independently validated with respect to manual volumetric techniques, mainly for the hippocampus (Cherbuin, Anstey, Réglade-Meslin, & Sachdev, 2009; Dewey et al., 2010; Morey et al., 2009; Pardoe, Pell, Abbott, & Jackson, 2009; Shen et al., 2010; Tae, Kim, Lee, Nam, & Kim, 2008). The software provides completely automated parcellation of the cortex and of subcortical structures. It calculates individuals' brain subvolumes by allocating a neuroanatomical label to each voxel of the MRI scan, and the allocation is based on a manually trained training set. Compared to most other automated measures of hippocampal volumetry, the FreeSurfer package is publicly available to researchers, making it a suitable application for the current thesis.

Hippocampal Volume, Physical Performance, and Cognitive Impairment

Testing for physical performance in an Alzheimer's Disease Population. Neuropsychological tests have been developed for various clinical outcomes. Tests to identify early clinical AD has become important to start treatment plans in the early course of the AD progression. Standardized tests of physical performance have been found to be predictive of important outcomes such as nursing home admission, hip fractures, and death. These tests are thus highly associated with several measures on health status and have consequently been applied to geriatric assessment setting and research increasingly (see Guralnik et al., 1994 for an overview). One of the most common tools to measure physical performance in population studies on aging is through the Short Physical Performance Battery (SPPB) (Guralnik, Ferrucci, Simonsick, Salive, & Wallace, 1995). The test includes chair stands tests, walking, and balance, and has been used in a broad spectrum of epidemiological studies on aging (Cesari et al., 2004; Guralnik et al., 2000; Guralnik et al., 1995; Guralnik et al., 1994; Onder et al., 2005; Penninx et al., 2000; Rolland et al., 2006). Patients scoring low in the SPPB have been predicted to have a higher chance of developing a range of health outcomes: hospitalization, length of hospital stay, disability, nursing home admission, mobility loss, and death (Guralnik et al., 2000; 1994; Penninx et al., 2000; Volpato et al., 2008).

In the Leukoaraiosis and Disability Study (LADIS), researchers aimed at determining the influence of age-related WM changes on several objective measures of balance and gait (Baezner et al., 2008). Here, they tested walking speed, balance, and used the SPPB to test patients mobility. They found a clear association between higher SPPB scores and individuals who were physically active. The presence of severe age-related WM changes was also found to be a significant determinant of a pathologic SPPB. Furthermore, it was found that old age, peripheral vascular disease, and diabetes interfered with their test on walking speed. In con-

clusion, the researchers stated that exercise could have a protective effect in delaying disability.

In the literature, it is generally agreed upon that such tests of physical performance supplement, rather than replace, self-report measures of activity and disability. However, patients diagnosed with AD does not have the same ability to correctly self-report their exercising habits, physical performance, and disabilities. It is thus of great importance to find a test measuring these patients' physical performance both in a reliable and valid manner. The SPPB has been shown to have a high test-retest reliability in several studies. In a study on the elderly population in Columbia, the test-retest reliability was high at 0.87 (Gómez, Curcio, Alvarado, Zunzunegui, & Guralnik, 2013). This has shown to be consistent with earlier studies, such as in a study comparing Canadian and Brazilian populations, where the intra-observer reliability in Canada was at 0.89 (95% CI, 0.83-0.93) and at 0.83 (95% CI, 0.73-0.89) in Brazil (Freire et al., 2012). The within-group correlation coefficients have been found to be between 0.88 and 0.92 in the U.S. population (Ostir, Volpato, Fried, Chaves, & Guralnik, 2002; Volpato et al., 2010). The test-retest reliability from Spanish elderly in five primary care centers ranged from 0.6 (95% CI, 0.35-0.70) for the balance test, and 0.8 (95% CI, 0.67-0.86) for gait speed (Cabrero-García et al., 2012). The SPPB has thus been tested and shown to be reliable in various populations, which can increase its clinical application around the world.

Physical performance and brain atrophy. As previously mentioned, an active lifestyle may contribute positively to both cognitive and psychological processes. However, recent evidence has suggested that exercise may also moderate AD-related brain atrophy. In a study on cardiorespiratory fitness and brain atrophy in AD patients, Burns and colleagues (2008) demonstrated that higher levels of fitness in early AD patients were associated with less brain atrophy, independent of dementia severity and age. A more recent study (Niemann,

Godde, & Voelcker-Rehage, 2014) looked at, not only the effects of cardiovascular exercise on the hippocampus but also coordinative exercise. The effects of motor fitness and coordination training have shown to for example facilitate synaptic re-construction and growth (synaptogenesis; Anderson et al., 1994; Black, Isaacs, Anderson, Alcantara, & Greenough, 1990). There were also evidence for motor fitness (e.g., movement speed, balance, fine coordination), but not metabolic fitness (muscle strength and cardiovascular fitness), being associated with hippocampal volume (Niemann et al., 2014).

Most research on the neuropathological effects of exercise has been conducted on animals, and it is thus difficult to draw any reliable conclusions on whether the effects apply to humans as well. Nevertheless, there is an extensive animal literature indicating that exercise produces increases in insulin-like growth factor and nerve growth factor (for review see Ang & Gomez-Pinilla, 2007 and; Cotman & Berchtold, 2002). In the BDNF molecule as mentioned previously (Neeper, Góauctemez-Pinilla, Choi, & Cotman, 1995; Vaynman, Ying, & Gomez−Pinilla, 2004), exercise promotes angiogenesis (Gómez-Pinilla, So, & Kesslak, 1998), neurogenesis (Van Praag, Christie, Sejnowski, & Gage, 1999; Van Praag et al., 2005), and synaptic plasticity and expression of enzymes that underlie metabolism and glucose use (for review see Cotman et al., 2007). These effects have primarily been observed in the hippocampal regions of rats, and some have reported similar effects in the amygdala (Greenwood, Strong, Foley, & Fleshner, 2009) and the entorhinal cortex (Stranahan, Khalil, & Gould, 2007). A few clinical trials have shown favorable effects of exercise on memory (Erickson et al., 2009; Lautenschlager et al., 2008), though most research supporting a memory benefit derives from animal research (Parachikova et al., 2008; Radák et al., 2001; Van Praag et al., 2005; Vaynman et al., 2004).

Age-related changes in the BDNF system could potentially play a role in the loss of tissue in the hippocampus. The effect of exercise on BDNF levels have shown to be positive in both animal and human studies, and in a review by Erickson, Miller, and Roecklein (2012) it was concluded that decreases in BDNF protein expression are associated with increased rates of geriatric depression and poorer hippocampal function. Results of prospective brain imaging (2006) and cross-sectional (2003) studies in humans performed by Colcombe and colleagues suggests that in cognitively healthy older adults, increased aerobic fitness is related to reduced age-related atrophy and increased perfusion in brain regions that support memory processes and executive control. However, most processes are vulnerable to aging (Colcombe & Kramer, 2003; Daniels, Toth, & Jacoby, 2006). A recent intervention study looked at the effects of dancing and traditional healthy fitness training on hippocampal plasticity and balance in healthy seniors (Rehfeld et al., 2017). An increase in HCV was found for both fitness groups. Hippocampal atrophy is one of the most prominent markers in AD pathology, but the hippocampus is also affected by normal aging processes resulting in deficits in learning, memory, and spatial navigation at old age (Barnes et al., 2009; Driscoll et al., 2003). The findings of Rehfeld and colleagues (2017) linking hippocampal volume increases (mainly in the left hippocampus; areas CA1, CA2, and subiculum, respectively) to exercise are thus very interesting, despite the experiment having a low number of participants and a relatively high drop-out rate. Nonetheless, the literature shows a general agreement of physical performance being linked to HCV and whether this volume can increase or not, remains to be investigated thoroughly. However, studies finding a clear link through greater scale interventional studies such as the ALMUTH project could be of great significance, and pilot data from this thesis will shown an indication on whether to spend time and resources on a full-scale investigation.

H_1: There is a positive correlation between hippocampal volume and physical performance, i.e., greater hippocampal volume in AD patients will be positively associated with higher scores on the SPPB.

Cognitive impairment. Deficits in memory and attention often occur before a clinical diagnosis of AD. Global cognition and executive functioning typically show significant associations with broader neurological measures: ventricular enlargement, whole brain atrophy, and cortical thickness across multiple brain regions (Dickerson, Wolk, & the Alzheimer's Disease Neuroimaging Initiative, 2011; Evans et al., 2010; Nho et al., 2012; Stonnington et al., 2010). Additionally, executive functioning task performance and the regions of the brain that support them may also contribute to episodic memory ability (Chang et al., 2009). Several studies have also found a link between physical activity and the risk of developing cognitive decline (Weuve et al., 2004; Yaffe, Barnes, Nevitt, Lui, & Covinsky, 2001).

One test developed to test cognition is the Mini-Mental State Examination (MMSE). It is commonly used in medicine and psychology for screening dementia, and during the 10-minute test, several cognitive domains are tested such as arithmetics, memory, and orientation. A score of 27 or above is seen as being within the normal range. A score in the interval 20-26 indicates MCI, 10-19 indicates moderate cognitive impairment, and a score of under 10 indicates severe cognitive impairment. It was developed by Folstein and colleagues (1975) to distinguish between psychiatric and neurological patients and is probably the most popular measure to screen for cognitive impairment to this day. The test has shown to have good test-retest reliability (Folstein et al., 1975; O'connor et al., 1989; Tombaugh & McIntyre, 1992), as well as sufficient specificity (0.92) and sensitivity (0.86) in 'organic mental disorders' as defined by the authors (O'connor et al., 1989). The test has been criticized numerous times (e.g., Feher et al., 1992) and is currently under the scope in a plagiarism case. Nevertheless, it main-

tains its significant role in the assessment of the of therapeutic agents on cognitive function (Berger, Fratiglioni, Winblad, & Bäckman, 2005; Meyer, Xu, Thornby, Chowdhury, & Quach, 2002; Tierney, Szalai, Dunn, Geslani, & McDowell, 2000), and in the follow-up (Meyer et al., 2002). The MMSE is a very important test for the current thesis as it can give insight into how far in the progression of the disease the AD patients are and how much cognitive impairment they are experiencing.

H_2: There will be a positive correlation between MMSE and HCV, suggesting that better memory and attention correlates with greater hippocampal volume.

H_3: Greater physical performance will be positively correlated with higher scores of the MMSE, i.e., patients scoring higher on the SPPB will have better cognition.

Depressive symptoms. Depression is an important topic of interest in geriatric patients and can have a significant role in AD patients' welfare. Moreover, good mental health can influence the length of which patients are able to live at home. The Geriatric Depression Scale (GDS) (Brink et al., 1982; Yesavage et al., 1982) is one of the most used assessment scales in the evaluation of depression in the elderly population and is a brief self-report questionnaire which includes a set of 30 yes/no questions. It was the first test developed specifically for older adults, in some part by eliminating sexual and somatic complaints, which often appears on other depression scales. The test taps behavioral and affective (but not vegetative) symptoms of depression. Its concurrent validity and reliability has been established next to psychiatric diagnoses or other well-established diagnostic instruments with healthy, active elderly community residents and patients receiving psychiatric or medical in- or outpatient treatment (Koenig, Meador, Cohen, & Blazer, 1988; Norris, Gallagher, Wilson, & Winograd, 1987; Rapp, Parisi, & Walsh, 1988).

It has been estimated that up to 87% of older adults with AD suffer from depression (Carpenter, Ruckdeschel, Ruckdeschel, & Haitsma, 2003), and exercise has been shown to be an effective treatment in reducing depressive symptoms for normal older adults, cognitively intact older adults with depression, and older adults with medical illnesses (Blumenthal et al., 1999; Mather et al., 2002; Mazzeo et al., 1998; North, McCullagh, & Tran, 1990; Singh, Clements, & Fiatarone, 1997). Little is known about the effects on exercise with regard to depressive symptoms in AD patients, but some studies have started to investigate this relationship. Williams and Tappen (2008) did a 16-week intervention study where they measured the reduction of depression in AD patients after comprehensive exercise, supervised walking, or social conversation. They found that exercise as a behavioral approach to treating depression had a clear benefit for nursing home residents diagnosed with moderate to severe AD. The effects of both social conversation and supervised walking did also yield a positive result, albeit the effect of comprehensive exercise was superior. Considering the prevalence of depression amongst the elderly, this offers evidence for the improvement of life quality for those AD patients who exercise on a regular basis.

Depression can result in more adverse consequences for both patients and their caregivers (Starkstein, Jorge, Mizrahi, & Robinson, 2005). Some papers have even tried to establish that because in many cases, depression precedes clinical diagnosis of AD and in a subgroup of AD patients, depression could have contributed to the development of the disease. This claim has had varying results (e.g., Geerlings, den Heijer, Koudstaal, Hofman, & Breteler, 2008), and it has been concluded with a history of depression being a risk factor for dementia (for review, see Jorm, 2001). This link has been proposed as being present because of prolonged exposure to glucocorticoids through a number of depressive episodes in the past could lead to hippocampal atrophy, and thereby lead to the development of AD (Jacobson & Sapolsky,

1991). Therefore, there are acceptable prospects for believing that both HCV and physical performance could be involved in patients' experienced depressive symptoms. Although past depressive episodes are not screened for here, present depression is an important variable to look at in trying to better the patients' overall well-being.

H_4: Physical performance will correlate positively with depressive symptoms, indicating that better physical performance is associated with lower levels of depression (high scores on the GDS).

H_5: There will be a positive association between HCV and GDS, i.e., greater HCV will be correlated with fewer depressive symptoms.

Activities of Daily Living. Deficits in daily living skills have been associated with an increased use of healthcare, reduced quality of life and an increased distress for both the patient and the caregiver (Hope, Keene, Gedling, Fairburn, & Jacoby, 1998; Severson et al., 1994; Vetter et al., 1999). Several observational studies have suggested that physical exercise on regular basis could be one of the most important factors preventing the onset of late-life daily living skills disability (Ferrucci et al., 1999; LaCroix, Guralnik, Berkman, Wallace, & Satterfield, 1993; Wu, Leu, & Li, 1999). Moreover, when examining the relationship between WM hyperintensity, HCV, and everyday functioning, Farias and colleagues (2004) found a significant correlation, but HCV was no longer significant when they controlled for age.

An important goal in caring for AD patients is to help to maintain their ability to perform basic self-care activities such as dressing, bathing, eating without assistance, and transferring out of a chair or bed (Covinsky et al., 1998; Palmer, Landefeld, Kresevic, & Kowal, 1994). To determine elderly individuals' self-sufficiency and independence, Lawton and Brody (1969) developed the Self-Maintaining and Instrumental Activities of Daily Living assessment (ADL). The questionnaire includes both practical ADLs (e.g., grooming, eating),

and instrumental ADLs (e.g., using the telephone, shopping). The performance on the various ADLs is dependent upon the integrity of numerous motor and cognitive systems. ALD impairment often leads to early loss of independence and hence the capability of being an active and contributing member of society. In clinical AD patients, instrumental ADL (I-ADL) impairment has been linked with global pathologic changes and posterior and frontal hypo-metabolism (Marshall, Fairbanks, Tekin, Vinters, & Cummings, 2006; Rowe et al., 2007; Salmon et al., 2005). Nevertheless, exploring the field of hippocampal atrophy, physical performance and ADLs is an important area of research to help AD patients live independently at home for a longer period of time and increasing their quality of life.

H_6: There will be a negative correlation between ADL measures and HCV and SPPB, indicating that lower scores on the ADL (higher ability to perform daily activities) will be associated with greater HCV and better SPPB score.

Objective and Overall Aim

This thesis is a part of a larger project, but only covered a small portion of it. The ALMUTH project will look at music and exercise compared to a passive control group of people in an early stage of AD. The thesis serves as a pilot study for the ALMUTH study and one of the primary scientific goals will be to look at the AD patients' HCV and whether greater HCV correlates with the patients motor performance. If AD patients with better physical performance show to have a greater HCV, this could be valuable information in future treatment plans. Whether cognition, depression, and the ability to perform daily activities is linked to physical performance and HCV will also be addressed.

The objective of this study is to provide valuable information for the ALMUTH project in the form of pilot results to enable the research team to judge whether it is worth pursuing a full-scale investigation using HCV as a measure. By gaining knowledge on how

the brain of AD patients differ according to motor performance, it may change how we treat the disease in the future. In cooperation with Bergen Municipality, findings from the general study at large (the ALMUTH project) will be used to make good treatment plans for patients with AD in Bergen and Hordaland.

Methods

Subjects

Inclusion and exclusion criteria. To secure that the subject-pool in the pilot study consisted of patients who could see the entirety of the ALMUTH project through, several clear criteria were set. The predominant criteria were that the patients had to be diagnosed with early-stage AD, or be under evaluation for AD by their primary physician or by a senior consultant, and the patients had to be able to give informed written consent. Patients were then included based on the following criteria: patient was above the age of 18; patient was in an early stage of the AD disease (lives at home/can give informed consent); patient does not have metal implants in body soft tissue for MRI purposes (pacemaker, stent); patient does not have hearing loss that cannot be corrected with hearing aid; patients had to live in or around the Bergen area to ensure their participation in possible intervention programs allocated through the study. All patients were living at home at the time of their first testing, albeit their age and physical activity variated. The current thesis is connected to IBMP at Haukeland, and a group under the Bergen fMRI group - the Brain and Music group, and the ALMUTH project. The data were thus collected at the university hospital Haukeland. The ALMUTH project has estimated a total of approximately 135 participants, but due to time limitation, the current thesis, and thereby the pilot study performed here, only looked at 12 subjects. Therefore, a total of 12 participants were included in the analyses (mean age 74.8 ± 7.3, range: 59–83 years, female/male (f/m) 7/8). Cognitive functioning was assessed by the Mini-Mental State Examination and depressive symptoms were screened for by the Geriatric Depression Scale. Daily functioning was assessed using Activities of Daily Living, and physical performace was assessed using the Short Physical Performance Battery.

Recruitment. Patients were recruited from in and around the Bergen area through local advertisement and public announcements. An appeal at Fyllingsdalen nursing home was made in front of the memory teams (HUK/hukommelsesteamene) from the Bergen area, who relayed the message to any patients and carers they believed to be interested in the research project. Several interviews with the local press were done, and flyers and posters were posted in places of interest. Appeals through social media were also carried out.

Operationalization of Variables

The study looked at both neuroscientific, cognitive and physical measures. The main physical measure used in this study was the SPPB, which is described in detail in the procedure section. The details and procedure of MMSE, GDS, and the two ADL measures that were used to answer hypothesis two, three, and four are described below. Baseline demographic data from each patient was be obtained, including sex, education level, age, medication usage, and any hearing deficits. HCV extracted with the FreeSurfer software is described later in the methods section.

Depressive symptoms. Depression is very common in the elderly population, and the total score on the *Geriatric Depression Scale (GDS)* was used to identify depressive symptoms (see Appendix A). The measure was looked at specifically to identify any comorbid disorders that might occur within the specific group of participants that are being tested. The test includes a set of 30 yes/no questions and was performed by a trained member of staff. The depression scale was developed by Yesavage and colleagues (1982), and a Norwegian version translated by Knut Engedal was utilized.

Memory and attention. Patients with AD often suffers from attention and memory deficits early in the disease, and these deficits are some of the first symptoms to present. The *Mini-Mental State Examination (MMSE)* was developed in 1975 (Folstein et al., 1975), and a

three-times revised Norwegian version was used (Strobel & Engedal, 2016), see Appendix B. A total score of the MMSE provides an idea of the progression of the disease. The MMSE is used in a lot of AD research and can also be an indicator of the patient's ability to learn and remember. The test has seven categories: orientation to time, orientation to place, immediate recall, mental arithmetic, delayed recall, language, and figure copying. The maximum score on the MMSE is 30 points, and any score above 27 is typical for normal cognitive functioning. A score of 20 to 24 usually suggest mild dementia or MCI, 13 to 20 suggests moderate dementia, and a score of less than 12 indicates severe dementia. On average, the MMSE score of AD patients declines approximately two to four points each year. The test was performed by a trained member of staff and lasted approximately 10 minutes.

Daily living with Alzheimer. In order to determine how self-sufficient the participants are, the total score of the *Instrumental Activities of Daily Living (I-ADL)* and *Physical Activities of Daily Living (P-ADL)* was employed (see Appendix C). As this study had a focus on patients in the early stages of their disease, it was important to test the course of the illness, which can be indicated by their day-to-day activity level and how independent participants are. This was assessed via self-reported ability to independently perform activities of daily living in a scale developed by Lawton and Brody (1969). Eight I-ADLs included using the telephone, household, meal preparation, laundry, traveling beyond walking distance, shopping, managing finances, and taking medications. Seven P-ADLs included bathing, grooming, eating, physical activity, using the bathroom, and getting dressed. Each question was scored on a scale from 0 to either 3, 4 or 5, with higher scores indicating a higher probability of the patient needing help in the different activities. A translated Norwegian version was used (Appendix C).

Physical performance. Patients were asked to perform the *Short Physical Performance Battery (SPPB),* which is a set of objective measures of lower extremity physical performance to determine their overall physical fitness level (see Appendix D). The test was developed by Guralnick and colleagues in 1994 (Guralnik et al., 1994) and a Norwegian version translated in 2013 was utilized here (Bergh, Selbæk, Strand, Taraldsen, & Thingstad, 2013). The procedure of the performance battery is described in detail below.

Procedure

Before recruitment and data collection started, the ALMUTH research project was admitted and approved by the Regional Committees for Medical and Health Research Ethics (REK, see Appendix E) and written informed consent (see Appendix F) was obtained from all participants according to the Declaration of Helsinki. The patients were taken to a room to complete all tests included in the ALMUTH test battery. Here, they completed the GDS, the MMSE, the I-ADL and P-ADL, and the SPPB. After the patients had completed the cognitive and physical screening, they were taken into an fMRI laboratory. They were asked some checklist questions before being guided to remove any metal they were wearing, and were debriefed on the procedure of the MRI machine. Patients were asked whether they had a music preference for them to listen to inside the MR scanner and were given noise-canceling earplugs and a set of headphones with their desired music genre. The cognitive and physical screening lasted for approximately two hours, while the entirety of the MRI scan lasted for 30 minutes. Thus, the total screening time lasted approximately 2,5 hours.

Short Physical Performance Battery. All patients were asked to perform the SPPB as a part of the test battery. Here, patients went through the following tests; 1) balance tests, 2) gait speed test, and 3) chair stand test.

The balance tests (1) consisted of the following; a) a side-by-side stand, where patients were asked to stand with their feet together, side-by-side, for 10 seconds. Patients got 1 point for holding out 10 seconds, and 0 points for not attempting or not holding out the full 10 seconds; b) a semi-tandem stand where patients were asked to put one foot in front of the other (optional order) with the side of the heel on the front foot touching the big toe on back foot. Here, the same scoring as for the side-by-side (a) test applied; the last balance test was a c) tandem stand, where they were asked to stand with the heel of one foot in front of and touching the toes of the other foot. Subjects got 0 points for holding the position for less than 3 seconds, one point for holding 3 to 9.99 seconds, and two points for holding the position for the full 10 seconds. In all balance tests, patients were allowed to move their arms, move their body, or bend their knees in order to maintain balance, but were asked to keep their feet steady.

In the gait speed test (2), the patients were asked to walk a three-meter long test course in their normal gait speed twice and was timed for each walk. If they needed to use a cane or other walking aid, they were allowed to. In both tests, the time of which it took the participants to walk the three meters was taken. The patients were scored in the following way; 1 point if time was more than 6.52 seconds, 2 points if the time was between 4.66 to 6.52 seconds, 3 points if time was between 3.62 to 4.65 seconds, and 4 points if time was less than 3.62 seconds.

Lastly, patients were asked to do chair stand tests (3). In the first part, patients were asked if they thought they could safely to try to stand up from a chair without using their arms, and if yes, they were asked to do so with their arms with their hands folded across their chest. If the patients were able to perform the task, they were asked if they thought they were able to do five repetitive chair stands. If yes, the scoring was as follows; 0 points if partici-

pants were unable to complete five chair stands or used more than 60 seconds, 1 point if chair stand time was 16.70 seconds or more, 2 points if the time was 13.70 to 16.69 seconds, 3 points if chair stand time was 11.20 to 13.69 seconds, and 4 points if the patient spent 11.19 seconds or less when doing five chair stands.

Experimental Design.

For the pilot study, the HCV of the patients was the dependent variable. There were several independent variables, the main variable being the patients physical performance. As described above, several physical and cognitive measures were collected to help answer the hypotheses: the SPPB was performed to measure the patients motor performance and level of fitness, the MMSE was performed to measure the patients' mental state (memory and attention); the GDS was performed to measure patients' depressive symptoms; the ADL tests were performed to measure patients activities of daily living (practical and instrumental). Patients HCV and TIV were extracted from MRI scans. All participants took part in the entirety of the experiment and was measured once.

MRI Acquisition and Pre-Processing

A 3.0 Tesla MRI machine (General Electric MRI machine) at the MRI department of the Haukeland University Hospital in Bergen was used to obtain all participants MRI data, with a 32-channel phased-array head coil. For each subject, 3D T1-weighed, high-resolution anatomical images were acquired using a magnetization-prepared rapid acquisition gradient echo (MP-RAGE) sequence with the following acquisition parameters: echo time (TE) of 30 ms, repetition time (TR) of 2250 ms, with a nominal voxel size of 1x1x1 mm. All participants wore MRI compatible glasses (with either corrective or non-corrective lenses) and was given NNL headphones for presenting music stimuli with high sound quality.

Additional image corrections were applied to the T1 images, using the following processing pipeline: (1) data were organized according to the Brain Imaging Data Structure (https://bids.neuroimaging.io), (2) Ditcom data were converted into NIfTI format using dcm2niix, distributed with MRIcroGL (https://www.nitrc.org/projects/mricrogl), (3) anatomical data were defaced using mri_deface, distributed with FreeSurfer (https://surfer.nmr.mgh.harvard.edu/), (4) HCV and total intracranial volume (TIV) were estimated using recon-all (from FreeSurfer) with default parameters, and (5) bilateral average HCV was normalized by TIV for each participant.

Hippocampal Volume Estimation

All participant scans were processed using FreeSurfer version 5.3.0 (Dale, Fischl, & Sereno, 1999; Fischl et al., 2002; Fischl, 2012) (freely available online at http://surfer.nmr.mgh.harvard.edu/), using a MacBook Pro with OS X 10.10.5, processor 2.5 GHz Intel Core i7 processor, with a 16 GB 1600 MHz DDR3 RAM. FreeSurfer is a tool providing quantitative volume data for a range of brain structures, including the hippocampus. FreeSurfer uses a technique that estimates the probability of each voxel on an MR image to belong to a given structure based on a-priori knowledge of spatial relationships acquired with a training set. The software segments the hippocampus based on these neuroanatomical labels to each voxel. The exact methods of the automated volumetric approach have been described in detail previously (Fischl et al., 2002). A fully automated procedure was utilized using the FreeSurfer *recon-all* pipeline, which performs all of the FreeSurfer cortical reconstruction processes. The following major steps are performed by FreeSurfer's *recon-all* function: intensity normalization, motion correction, skull stripping, removal of non-brain tissue, brain mask generation, cortical reconstruction, WM, and subcortical segmentation, cortical tessellation generating GM-WM and GM-pia interface surface triangulations, and probabilistic atlas based on corti-

cal and subcortical parcellation. The analysis was restricted to the right and left hippocampus, and the total intracranial volume (TIV), respectively, for the purpose of this thesis.

Right and left HCV and TIV were extracted for analysis in SPSS. To control for individual differences in head size, the main HCV used was expressed as a TIV ratio (left+right hippocampus/TIV).

Ethical Concerns

Patients with AD are already an exposed group, even at an early stage of their disease. The current thesis was a part of an intervention study using participants living at home, and as a result of the intervention from the ALMUTH project could hopefully live at home longer. To this day, there are few high-quality studies investigating how long-term musical and exercise therapy can benefit AD patients. The pilot data from this study, and consequently the ALMUTH project has great potential for benefiting patients, and through the therapy that will be implemented in Bergen Municipality from the recommendations ALMUTH study.

Being in an MRI machine may be experienced as uncomfortable or claustrophobic for some of the participants. An MRI scan is not dangerous, and it was necessary for the current research project. To limit the discomfort, however, several measures were taken; participants got to see nice nature pictures whilst inside the scanner and listened to the music of their choosing from one of six different genres. Moreover, some of the physical and cognitive tests may also be considered uncomfortable as they ask about sensitive information. Participants ID was masked by using an ID number rather than the name of the participant. The only documents with their full name were the informed consent form (Appendix F). The papers were locked up at the IBMP in the office of the project leader, Stefan Koelsch. Only the members of the Brain and Music group had access to project leader office.

The hope of the ALMUTH project is to help the patients stay and live independently at home longer. Whether they are assigned to the exercise group or the music group, the hope is that the intervention they receive will contribute to cognitive stimulation and a better quality of life. The current thesis only used data for those who are intended for the ALMUTH project, which will hopefully show beneficial results for the participants. A control group will not be applicable for the current thesis but will be for the ALMUTH project. The patient's score on the SPPB or patient's HCV will not effect which intervention group that they will be randomly assigned to. Participants were not economically compensated for their participation, but they might be in one of the two intervention groups and receive 12 months of free therapy in the form of music therapy or physical exercise. The project is funded by the NRF and has been approved by the REK committee (Appendix E). They will not be allowed to participate in the study unless they are able to give informed consent for their participation. As the REK committee has redeemed the ALMUTH project as health research, submitting the project through Personvernombudet for Forskning (NDS) was not necessary.

Statistical Analysis

All Spearman's rank correlation coefficients were performed using the statistical software IBM SPSS for Mac (version 25, **www.spss.com**). A correlation between SPPB and all HCV measures were performed to investigate the main research question on the relationship between HCV and physical performance. To answer the second hypothesis, correlations between all hippocampal measures and MMSE was performed, and a correlation between MMSE and SPPB was performed to examine the third hypothesis. For the fourth hypothesis, a Spearman's correlation was calculated between GDS and all HCV measures. The fifth hypothesis was answered by performing a correlation between SPPB and GDS. For the sixth and

final hypothesis, a correlation between I-ADL, P-ADL, all hippocampal measures, and SPPB was performed.

The Spearman's Rank Correlation Coefficient (Spearman's Rank-Order Correlation or Spearman's rho) is a nonparametric measure of rank correlation. It differs from Pearson's correlation in that it looks at the monotonic relationship between two variables instead of assessing the linear relationship. There are several benefits to using Spearman's rho, in that its non-parametric technique is unaffected by the population distribution, and it is relatively insensitive to outliers. The disadvantage of using this non-parametric technique is that there can be a loss of information when the raw data is converted to ranks.

Spearman's rank correlation was utilized as the main analysis for significance between all variables in this thesis. Essentially, the Spearman rank correlation test is the nonparametric version of the Pearson correlation coefficient. Usually, Spearman's rho is used when either one or both variables are ranked but can be employed instead of linear regression/correlation if there is a question about the normality of the distribution. When testing the sample for normality using the one sample Kolmogorov-Smirnov test, most variables did not satisfy the normality assumption (I-ADL, P-ADL, GDS, SPPB, left hippocampus, gender & TIV). This was most likely due to the small sample of participants. The MMSE, right hippocampus, total HCV, TIV-adjusted TIV, and age were normally distributed. In their paper on sample size requirements for estimating Pearson, Kendall, and Spearman correlations, Bonnet and Wright (2000) suggested that Pearson correlations should only be utilized if $n > 25$, and if the assumption of bivariate normality cannot be justified, then Spearman correlation should be considered. If the data is normally distributed, a Pearson correlation could be more powerful. However, because of the issue of normality and the small sample of the thesis, the Spearman's rho was used.

Results

Due to the thesis serving as a pilot study, the following results can be seen as a proof-of-concept, meaning that the results found here are only meant to demonstrate the feasibility of the method used in the current thesis, and may have practical potential for the ALMUTH project.

Table 1

Means and standard deviations for age, physical- and cognitive measures, and hippocampal volume estimations

Measure	Mean (SD)
Age	74.75 (7.33)
Short Physical Performance Battery	9.50 (3.12)
Mini-Mental State Examination	21.67 (3.09)
Instrumental Activities of Daily Living	15.08 (7.20)
Practical Activities of Daily Living	7.42 (1.93)
Geriatric Depression Scale	7.17 (4.84)
Hippocampal Volume Adjusted by Total Intracranial Volume	0.004151 (0.00102)
Left Hippocampal Volume, cm^3	3.143 (0.897)
Right Hippocampal Volume, cm^3	3.160 (0.829)
Total Hippocampal Volume, cm^3	6.303 (1.597)
Total Intracranial Volume, cm^3	1518.169 (114.811)

The total sample included 12 participants, where seven were male (58.3%). All participants were right-handed and had finished primary school. Five participants had obtained a Bachelor's Degree or higher. Descriptive statistics and mean scores and measures can be found in Table 1. A Spearman's Rank two-way correlation was performed to assess the non-parametric relationship for all variables (see Table 2).

Table 2

Correlation Matrix for age, physical- and cognitive measures, and hippocampal volume estimations

	1	2	3	4	5	6	7	8	9	10	11	12
1. Hippocampal volume adjusted by total intracranial volume	1											
2. Left Hippocampal Volume	.888**	1										
3. Right Hippocampal Volume	.769**	.580*	1									
4. Total Hippocampal Volume	.944**	.895**	.825**	1								
5. Total Intracranial Volume	-.014	-.021	.462	.252	1							
6. Instrumental Activities of Daily Living	.098	.014	.155	.053	.151	1						
7. Practical Activities of Daily Living	-.241	-.030	-.245	-.260	.030	.526	1					
8. Geriatric Depression Scale	.685*	.638*	.506	.613*	-.115	.418	.052	1				
9. Mini-Mental State Examination	.570	.553	.148	.419	-.563	-.246	-.025	.413	1			
10. Short Physical Performance Battery	.359	.241	.237	.334	-.119	-.580*	-.798**	.258	.251	1		
11. Age	-.099	-.276	-.007	-.149	.103	-.125	-.072	-.361	.100	-.064	1	
12. Gender	-.073	.024	-.426	-.220	-.759**	.025	-.053	.402	.247	.201	-.496	1

Note: $^{*}p < .05$. $^{**}p < .01$.

Hippocampal Volume

Generally, the hippocampal measures show good agreement. Total HCV volume and TIV-adjusted HCV had a very strong, positive correlation $r_s(10) = .944$, $p < .001$. The total HCV and both the left side, $r_s(10) = .895$, $p < .001$, and the right side of the hippocampus $r_s(10) = .825$, $p < .001$ showed a strong positive significant correlation. The left and right hippocam-

pus had a moderate positive significant correlation $r_s(10) = .580$, $p = .048$. TIV-adjusted HCV had a strong, positive correlation with the right hippocampus $r_s(10) = .769$, $p = .003$, and the left hippocampus $r_s(10) = .888$, $p < 0.001$.

Physical Performance and Hippocampal Volume

The relationship between TIV-adjusted HCV and SPPB scores was found to be moderately positive but non-significant, $r_s(10) = .359$, $p = .252$. The correlation for SPPB and left hippocampus was weakly positive for both the left, $r_s(10) = .241$, $p = .451$, and for the right, $r_s(10) = .237$, $p = .458$. The correlation between SPPB and total HCV was positive and moderate at $r_s(10) = .334$, $p = .289$. Generally, there were positive but non-significant, trends for SPPB and all HCV measures.

Cognition

A moderate positive relationship was found for TIV-adjusted HCV and MMSE, $r_s(10) = .570$, $p = .053$. Similar results were found for the relationship between MMSE and the left hippocampus with a moderate, but non-significant correlation, $r_s(10) = .553$, $p = .062$, and the total HCV, $r_s(10) = .419$, $p = .175$. The relationship between MMSE and the right hippocampus was positive, although the correlation coefficient was very weak, $r_s(10) = .148$, $p = .646$. These results are approaching significance, and could generally indicate that a larger hippocampus is associated with a better ability to learn and remember. The relationship between SPPB and MMSE showed a non-significant, weak positive correlation coefficient, $r_s(10) = .251$, $p = .431$.

Depression

The association between TIV-adjusted HCV and GDS was found to be a strong positive relationship, $r_s(10) = .685$, $p = .014$. The relationship between GDS and the left hippocampus was strong and positive, $r_s(10) = .638$, $p = .26$, and for GDS and the right hippocampus the

association was moderate and not significant, $r_s(10) = .506$, $p = .094$, leaving the correlation for GDS and total HCV at a strong positive and significant result, $r_s(10) = .613$, $p = .034$. Generally, these results indicate a high probability of patients' depression symptoms is affected by or effects HCV. There was no significant relationship between GDS and SPPB $r_s(10) = .258$, $p = .481$.

Daily functioning

There were two measures indicating the self-sufficiency and daily functioning of the patients, namely the I-ADL and P-ADL. The relationship between SPPB and both the ADLs yielded significant results. For the relationship between P-ADL and SPPB there was a strong negative correlation $r_s(10) = -.798$, $p = .002$. There was a moderate negative correlation for SPPB and I-ADL, $r_s(10) = .580$, $p = .048$. Higher scores in I-ADL and P-ADL indicate a lower level of self-sufficiency and -independency, and higher scores in SPPB indicate better physical performance. These results, therefore, suggest that patients who have better physical performance have a tendency to be more independent and self-sufficient.

There was found no apparent relationships between any hippocampal measures and the ADLs. For P-ADL, the association with TIV-adjusted HCV was negative and weak $r_s(10) = -.241$, $p = .451$, and for I-ADL there was no relationship with TIV-adjusted HCV, $r_s(10) = .098$, $p = .761$.

Discussion

The present study set out to explore the relationship between HCV and physical performance in AD patients at an early stage of their disease. The aim was to provide valuable pilot data for the ALMUTH project to evaluate whether to spend time and resources on investigating the relationship between hippocampal atrophy and motor performance further at a greater scale. Implications from the literature could suggest that high scores on the SPPB could be associated with greater HCV. The study failed to find any significant relationship between either measures, albeit the correlations showed positive trends. The ALMUTH study will use both healthy controls and a larger sample. Therefore, because the relationship between HCV and SPPB was moderate, these pilot data suggest that there is a possibility for a significant association to be seen in the longitudinal interventional study ALMUTH will carry out.

Physical Performance

The data suggest a moderate, and non-significant relationship between SPPB and TIV-adjusted HCV, which could indicate that when the patients' motor performance is better, the HCV would be equally great to some extent. Although the relationship was non-significant, it had a positive direction and demonstrates a proof-of-concept, meaning that if the participant number were higher, it might have yielded a stronger result. The correlations between SPPB and the right and left hippocampus was weak, but the total HCV showed a moderate correlation. Nevertheless, TIV-adjusted HCV is the most important measure to look at as it takes participant head size into account and adjusts for it with regard to HCV. These results are confirming the main hypothesis to a certain extent and as pilot data, they provide valuable information in the future of the ALMUTH project. Seeing these moderate, positive results with a very small sample, could yield significant results in the future with larger data sets. The ALMUTH

project cooperates with Bergen Municipality in finding good treatment plans for AD patients in and around the Bergen area. If the ALMUTH group find these data encouraging and chooses to go forward with these promising results, then the project could provide valuable insight into which treatment plans to follow in the primary care of AD patients.

The SPPB is a standardized measure of lower extremity physical performance that includes balance, walking, and strength tasks. The main outcome of the ALMUTH project is to help AD patients stay at home longer after they have received an AD diagnosis. Low scores of the SPPB has been associated with clinically relevant outcomes that are independent of other socioeconomic factors and health conditions, a claim that have been confirmed across divergent populations and settings (Guralnik et al., 2000; Guralnik et al., 1995; Guralnik et al., 1994; Onder et al., 2005; Ostir, Markides, Black, & Goodwin, 1998; Penninx et al., 2000; Rolland et al., 2006). The loss of independence is a major concern when considering how to help AD patients live at home. It is evident that low scores on the SPPB can cause this loss of independence to occur much earlier than necessary. Therefore, it is interesting to see whether SPPB scores and thus independence, can be improved through physical activity intervention that the ALMUTH study will provide. A study looking at over 400 sedentary persons at risk for disability in the age-range 70 to 89 years did a randomized controlled trial to investigate the effects of physical activity interventions on measures of physical performance (LIFE Study Investigators*, 2006). Here, subjects were allocated to either a moderate-intensity physical activity intervention or to a successful aging health education intervention and were followed for an average of 1.2 years. The researchers found that a structured physical activity intervention improved the SPPB performance and other measures of physical performance and that such intervention improving SPPB scores may offer benefit on more distal health outcomes, such as mobility impairment. Their physical activity intervention consisted of a

combination of balance, strength, aerobic, and flexibility exercises, and a full overview can be found in their article. Although it does not seem as though a similar study has been performed on AD patients, these results are very promising. The ALMUTH project will, similarly, do a randomized controlled trial where one group will receive song intervention, one group will serve as controls, and the last group will receive physical activity intervention. If the results from the physical activity group yield similar outcomes as reported earlier in the literature, it will become very useful in helping caregivers and physicians to administer alternative, non-pharmacological approaches to treating dementia. Moreover, if the ALMUTH study chooses to go forward with these data, and HCV and SPPB scores still show a moderate relationship, there is a possibility hippocampal atrophy slowing down for the patients included in the study.

Validity and reliability of the SPPB have been confirmed across several populations and age-groups as mentioned earlier in this thesis. A Finnish intervention study (Pitkälä et al., 2013) did, however, find that the SPPB was found difficult to conduct on AD patients. They found that instructing dementia patients to perform the test correctly proved difficult. While the paper does not comment on the progression of the AD in their participants, patients had to be on the AD drug reimbursement register of the Social Insurance Institution of Finland, suggesting they could be further along in their disease progression than patients included here. As patients in the current study were in an early stage of their disease and did not express confusion around the various SPPB tasks, it was concluded that patients found the SPPB instructions manageable.

The SPPB has been considered a good measure of not only present physical performance but also for representing how physically active subjects are on a general basis. Beneficial effects of physical activity on cognitive functioning has been demonstrated recurrently, albeit most research is derived from animal models (Erickson & Kramer, 2009; Fillit et al.,

2002; Kramer et al., 2006). Cardiovascular health and glucoregulation can be part of increasing the risk of AD when compromised (Craft, 2005; Gasparini & Xu, 2003; Helzner et al., 2009; Kuusisto et al., 1997), and exercise has been shown to have positive effects on these processes. Furthermore, the presence of midlife cardiovascular risk factors such as high cholesterol, obesity, hypertension, and smoking could substantially increase the risk of late-life dementia (e.g., Whitmer et al., 2005b). Physical activity has shown to improve or entirely remove some of these risk factors, and it can be assumed that a healthy and active lifestyle throughout the course of one's life could generally lessen the risk of developing dementia altogether, but this would need a large-scale longitudinal study to scrutinize. Nonetheless, HCV and physical performance do seem to have an association, and it will be of common neuropsychological interest to see the findings of the ALMUTH study to further the results obtained here.

Cognition

The study demonstrated a positive association between MMSE and TIV-adjusted HCV. Although the relationship, amongst other hippocampal measures, was not significant, the relationship was moderate, and very close to significance at the $p<.05$ level. With this, H_2 is confirmed with reservation. The relationship between SPPB and MMSE showed a non-significant, weak positive correlation coefficient, indicating that there could be a small association between the patients' memory and attention, and their physical abilities. The correlation shows a positive trend but would need further attention with a larger sample for any conclusive judgements. Therefore, for the current thesis, the third hypothesis is disconfirmed.

In primary care, screening for dementia and memory deficits often relies on cognitive screening tests, such as the MMSE, and persons with multimodal functional deficits, such as AD, typically score less than 24. The mean MMSE score in the sample in this study was at

21.7, which is an indication of MCI. Typically, for persons in the preclinical stages of AD, MMSE scores are less sensitive and scores tend to fall within the normal range (≥ 24) (Pasqualetti et al., 2002). Pasqualetti and colleagues conclude in their study that traditional MMSE cutoff values should be approached with warning, as they may not be appropriate in detecting early dementia. Looking at the MMSE scores, patients were in an early stage of the disease, and most patients had an MMSE score of 24 or below. It could be argued that the lack of significance in the relationship between HCV and MMSE is due to patients' AD not having progressed enough to see greater hippocampal atrophy. Nonetheless, it is well-established that early pathological changes, especially in the MTL and hippocampus, often occurs years before clinical symptoms of AD present. HCV has consistently shown to be reduced by up to 40% in patients who have been clinically diagnosed with a moderate severity of AD (Jack, Petersen, O'brien, & Tangalos, 1992; Kesslak et al., 1991; Seab et al., 1988). Moreover, the extent to which the hippocampus atrophies have been shown to correlate with memory impairment and overall severity (Deweer et al., 1995; Kesslak et al., 1991; Laakso et al., 1995). Patients with similar MMSE scores to our sample at >21 have shown to already have lost about 25% at this stage of AD when compared to healthy controls (Killiany et al., 1993; Lehericy et al., 1994; Laakso et al., 1995).

General cognition has been seen in many studies worldwide to correlate with increased physical activity and performance (for a review, see Hillman, Erickson, & Kramer, 2008). SPPB measures strongly correlate with present physical activity level, and seeing a link between MMSE and SPPB is therefore to be expected. This study did not have healthy controls for comparison, albeit the ALMUTH project will. Hence, it is to be expected that both with the large sample size, and healthy controls for comparison, the results will yield more significant relationships between MMSE, SPPB and HCV.

Depression

There was found a strong, significant relationship for depressive scores and hippocampal measures. The right hippocampus did not have a significant relationship with GDS but was moderate and positive. The left hippocampus and the total hippocampus had a significant association with depressive symptoms, and the correlation was stronger when TIV was accounted for. The fourth hypothesis is thereby confirmed. These findings are along the lines of previous research into HCV of depressed subjects. It has been hypothesized that a history of depression, and by prolonged exposure to glucocorticoids through several depressive episodes, could lead to hippocampal atrophy and subsequently lead to the development of AD (Jacobson & Sapolsky, 1991). This study did not screen for previous depressive episodes and whether patients displaying depressive symptoms at the time of the screening have a history of depression is therefore difficult to account for. However, seeing such a strong association between current depressive symptoms and HCV in a pilot study is compelling.

There was no significant relationship between GDS and SPPB, disconfirming the fifth hypothesis. There are varying results on physical activity and depression in the literature. In a meta-analysis Craft and Landers (1998) reported a relatively large effect size (d=0.72) when looking at the effect of exercise on clinically depressed individuals. Little research has been conducted on AD patients, depression, and physical performance, but as mentioned in the introduction, Williams and Tappen (2008) found that AD patients had a clear benefit of exercise as a behavioral approach to treat depression. This thesis did not look at exercise intervention such as Williams and Tappen did, and little research has looked at specifically physical performance and depression in AD patients. It is therefore difficult to draw any conclusions based on previous literature. Nonetheless, the results from this thesis did not yield any signifi-

cant results, but the ALMUTH project utilizing intervention similar to Williams and Tappen might find more positive results.

One paper has concluded that the GDS is not adequate for detecting depression in AD patients, and found a marked decrease of internal consistency in the AD group (Müller-Thomsen, Arlt, Mann, Maß, & Ganzer, 2005). These patients were in later stages of AD, and other research has suggested that cognitive decline can affect the results of the GDS (Zarb, 1996). In the current study, patients had a mean MMSE score of 21.7, indicating a mild cognitive impairment, so it should be assumed that the internal consistency is adequate. On average, after being diagnosed with AD, patients' MMSE score worsens by two to four points each year. It seems like there is no need for concern with patients in the early stages of the disease, but a longitudinal study such as the ALMUTH study should, therefore, investigate whether the GDS is the best measure for screening depression in their group of patients.

Activities of Daily Living

Looking at the results, it seems as though HCV does not play a part in patients ability to perform ADLs. There is little research in this field, but some studies have found an association between instrumental ADLs and brain volume. The results from the current study yielded a significant relationship for neither P-ADL nor I-ADL with HCV, which again could be due to a number of reasons. When Farias and colleagues (2004) examined the relationship between HCV and ADL, the association was significant, but when controlling for age, the correlation disappeared. Another study used a community-dwelling population to investigate whether structural and microstructural brain changes were associated with ADLs, and found that smaller brain, HCV and higher diffusivity were associated with changes in ADLs (Verlinden et al., 2014). Nevertheless, their study did not do follow-up MRIs, making it difficult to establish whether changes in brain pathology coincided with a change in ADLs. The population was

also relatively healthy, not affected by AD, so it is impossible to say whether their findings can be generalized to an AD population. Moreover, the relationship between neuropsychological test performance and ADL in elderly psychiatric patients has shown to be moderate (Nadler, Richardson, Malloy, Marran, & Brinson, 1993; Richardson, Nadler, & Malloy, 1995). Thus, the lack of association between HCV and ADL is not surprising and in line with previous research. Although it was not a focus for the analysis, worth mentioning is the relationship between I-ADL and GDS. From looking at Table 2, there is a moderate, although non-significant relationship between the two. It is interesting that P-ADL has no association with GDS, but not being able to perform activities such as doing one's own shopping and using the phone (I-ADL activities) can play a role in these patients quality of life.

There was found a strong relationship between P-ADL and SPPB, and a moderate relationship between I-ADL and SPPB. This is most likely due to patients who score high on the SPPB does have better physical performance, making it easier to perform activities such as shopping and bathing. Where patients are not able to, for example, walk five meters without help, it is likely that they will struggle to perform daily activities without help from a caregiver. The P-ADLs are very personal, physical activities such as getting dressed and using the toilet. Such activities correlate closely with the physical abilities tested by the SPPB, and a strong correlation here is to be expected if the AD patients are able to correctly self-report in the ADL. Therefore, the sixth hypothesis is somewhat confirmed in that it appears easier for patients to perform daily activities if they score higher on the SPPB, but HCV does not seem to be involved in daily functioning.

Guralnik and colleagues (1994) reported that physical performance and self-reported disability was strongly associated, and were both independent predictors of nursing home admission and short-term mortality. Liu and Latham (2009) found that elderly exercising muscle

strength, and thereby increasing their physical performance, achieve better function in daily activities. Therefore, these findings on SPPB and ADL are along the lines of previous research linking physical performance and daily functioning.

Hippocampal Volume

In the present study, an automated approach by FreeSurfer (Dale et al., 1999; Fischl et al., 2002; Fischl, 2012) was used to determine HCV. The results show good agreement across the different hippocampal measures, indicating that the measures are consistent across the participants. Looking through the literature, the HCVs of the participants of this study is slightly larger than usual. The mean HCV for the patients in the present study was measured to 6.303 cm^3, which is larger than what one would expect in AD patients. A study by Tae and colleagues (2008) validating HCV measures in patients with chronic major depressive disorder and controls found that when using the Freesurfer automated hippocampal volumetric method, HCV was 35% larger. This was thus to be expected, and although not desirable, due to time limitations it was necessary to utilize an automated approach, and not the «gold standard» manual segmentation. In an article from 2014, a group of quantitative researchers looked at the differences in HCV change and the reproducibility of two automated approaches (FreeSurfer and FIRST) and expert manual outlining (Mulder et al., 2014). They found that quantitative reproducibility values of 1-year microliter and percentage HCV change were about the same for all three approaches, but that the FreeSurfer reproducibility was statistically significantly superior to both FIRST and manual outlining after exclusion of failed segmentations. Consequently, using FreeSurfer with the *recon-all* function for the current thesis is well-founded.

Due to time limitations, it was not possible to look at the hippocampal volumetric changes over time. This will be done in the ALMUTH project, independent of the outcomes

of this thesis, which can offer valuable information when taking the different intervention programs into account. If the patients in the current study do show hippocampal atrophy differentiation from that of healthy age-matched controls, it could be due to BDNF. In AD patients, there is a loss of BDNF of the hippocampus (Connor et al., 1997; Hock et al., 2000; Narisawa-Saito et al., 1996). Because BDNF is believed to contribute in the loss of neuronal tissue, it can be assumed due to it being anterogradely trafficked into the hippocampus by the entorhinal cortex (Yan et al., 1997), it may play a big role in hippocampal atrophy. Recently, research has looked into how exercise can contribute to increasing the level of BDNF in the hippocampus (for review see Cotman et al., 2007). Although this is a very interesting area of research, it would need a different methodology on a cellular level to investigate further. Nevertheless, if it is so that exercise can slow down hippocampal atrophy, the various underlying processes should be considered.

It was not feasible to utilize the BrainAGE paradigm developed by Franke and colleagues (2010) for this thesis, but it will be included for the ALMUTH project. It has been claimed that if the estimated BrainAGE is higher than a patient's chronological age, a positive BrainAGE score indicates accelerated atrophy, which is considered a risk factor for conversion to AD. The BrainAGE framework's ability to correctly identify persons with MCI who will convert to AD has been compared to biomarkers from cerebrospinal fluid (CSF), cognitive scales, and to HCV (Gaser et al., 2013). It was found that BrainAGE outperformed all cognitive measures as well as CSF biomarkers. Interestingly, even though HCV has previously shown to represent an independent risk factor for AD and in predicting MCI conversions to AD (Apostolova et al., 2006b; Devanand et al., 2007), the BrainAGE approach outperformed this prediction utilizing baseline HCVs in other recently published classification studies (Costafreda et al., 2011; Risacher et al., 2009; Risacher et al., 2010). Although for the purpose

of this thesis, it was not necessary to look at conversion from MCI to AD, it would be interesting to look at the patients of this thesis' BrainAGE as it helps differentiate a pattern of brain atrophy that deviates from that of a normal, healthy brain.

It is crucial to address that although the evidence for hippocampal atrophy in AD is compelling, it may lack both specificity and sensitivity at the MCI stage, as it can present in other, non-AD forms of dementia, such as frontotemporal lobar degeneration (van de Pol et al., 2006), semantic dementia (Chan et al., 2001), and vascular dementia (Bastos-Leite et al., 2007; Laakso et al., 1996). Our patients had, however, been diagnosed with AD by their primary physician or by an attending physician. Although looking at the MMSE scores, patients were mildly cognitively impaired, it could also mean they were in an early stage of their disease. Withal, it is difficult to draw any conclusions from such a small sample as has been used in this thesis.

The hippocampus consists of several subfields and recognizing the differentiated patterns of atrophy in AD is important. Studies looking at hippocampal subfields through the use of MRI scans found a consistent alteration in the subfield CA1 of the hippocampus, both for volumetric (Boutet et al., 2014; de Flores et al., 2015; Iglesias et al., 2015; La Joie et al., 2013; Mueller & Weiner, 2009; Wisse et al., 2014b) and surface-based methods (Apostolova et al., 2006a; Apostolova et al., 2012; Chételat et al., 2008; Frisoni et al., 2006; Frisoni et al., 2008; Gerardin et al., 2009; Mak et al., 2016; Tepest et al., 2008; Wang et al., 2006). When comparing healthy controls to MCI patients, CA1 had the most consistent shape alteration (Apostolova et al., 2012; Chételat et al., 2008; Gerardin et al., 2009; Tang et al., 2015; Tepest et al., 2008) or volume reduction (La Joie et al., 2013; Pluta, Yushkevich, Das, & Wolk, 2012; Yushkevich et al., 2015). Moreover, MCI patients who converted to AD showed greater CA1 and subiculum atrophy than of those who did not convert (Apostolova et al., 2006a; Chételat

et al., 2008) with similar results for healthy controls converting to AD (Apostolova et al., 2010; Csernansky et al., 2005). The FreeSurfer software has received various criticisms with regard to hippocampal subfield segmentation (Wisse, Biessels, & Geerlings, 2014a). In their critical appraisal, Wisse and colleagues conclude that the boundaries of the parcellation scheme of FreeSurfer version 5.3.0 (as used for this thesis) are in a mismatch with known anatomical boundaries, impacting the reliability of subfield atrophy in neuropsychiatric diseases. Therefore, recognizing these criticisms, if the current study were to look at the subfields of the hippocampus, it would be necessary to employ a different segmentation methodology. As mentioned previously, the validity of FreeSurfer has been confirmed numerous times concerning total HCV segmentation, and it is accordingly of no concern utilizing the software for the purpose of total HCV.

Limitations

The ALMUTH project was in the beginning phase of testing participants for their intervention study, leaving this study with a sample of 12 participants. Due to the study being connected to the ALMUTH study, being a longitudinal intervention study, recruiting participants was found to be difficult. All participants had to have been diagnosed with AD, and they needed to make their way to Haukeland University Hospital in a time-slot appropriate for both the participant, their caregiver, and for the MR department at the Haukeland University Hospital. This, alongside with other predicaments, made it difficult to start the project at the planned time. The current thesis had already been postponed 6 months waiting for more participants to sign up for the study, and it was thus determined to go forward with the 12 participants and wait no longer. Nevertheless, the study only serves as a pilot study for the ALMUTH project, allowing a sample of 12 participants, and its promising results will serve as

good predicaments for future research. The small sample size will, therefore, serve as a good future benchmark for the ALMUTH study.

Alzheimer's disease patients is a very vulnerable group, and understanding a variety of questions and tasks in a small amount of time can be difficult. The testing session with physical and cognitive measures lasted for an entirety of approximately two hours before patients were taken to the MR machine for scanning for another 30-45 minutes. This is a lengthy process for any individual, let alone an AD patient. The GDS is a well-established measure for depression in geriatric patients. With the long set of tests our patients were asked to perform, it could be useful to utilize the GDS questionnaire with only 15 questions, as opposed to the 30-question scale our patients performed. Its validity has been confirmed across several populations (e.g., Conradsson et al., 2013; Durmaz, Soysal, Ellidokuz, & Isik, 2018; Fountoulakis et al., 1999), and it could be useful utilizing the GDS-15 to shorten the time spent on the test battery. All patients were allowed to take breaks when desired and had a primary caregiver in the neighboring room if they needed help. No patients expressed exhaustion or discomfort, and it can only be assumed that their needs were taken care of. Nevertheless, shortening the time to accommodate the patients could have yielded a higher participant number, or for the purpose of the ALMUTH study, lessen the drop-out rate if applicable.

All measures used here is well established and has shown to have both good reliability and validity. Some measures, however, have proved difficult employing on AD patients. As mentioned previously, some researchers have reported AD patients having trouble understanding the directions of the SPPB (Pitkälä et al., 2013). A measure of physical performance developed specifically for this patient group is thus desired. Nonetheless, our patients were in an early stage of the disease, and no patients expressed difficulty understanding any SPPB directions. Further, it would be interesting looking at the different subsets of the SPPB (gait speed,

chair stands, and tandem) and their independent relation with each cognitive measure and HCV, but due to an omission with the first few patients, it was only feasible to look at the total score.

Using automated segmentation methods for hippocampal volumetry was necessary for this study. Although its validity and agreement with manual segmentation have been documented in various research (Cherbuin et al., 2009; Dewey et al., 2010; Morey et al., 2009; Pardoe et al., 2009; Shen et al., 2010; Tae et al., 2008), the manual 'gold standard' will always be the best way to determine HCV for MR images. It has been reported in one study on manual vs. automated segmentation that the mean HCV is larger with the FreeSurfer package than with manual segmentation (Tae et al., 2008). Looking through the literature on reported mean HCVs, both for healthy elderly, and AD patients, it is evident that the mean reported here of approximately 6 cm^3 is larger than what is reported elsewhere with manual hippocampal volumetry. However, the data is consistent with other research using FreeSurfer and the recon-all pipeline, and because it has been reported to have good agreeableness with manual segmentation, it is assumed that these hippocampal measures correlate with other research.

Theoretical Implications

In recent years, researchers have looked at the relationship between physical performance and AD. Because HCV is seen as one of the core biomarkers for converting from MCI to AD (Apostolova et al., 2006b; Devanand et al., 2007), finding ways to slow down the hippocampal atrophy has been a topic of great interest. There is substantial research into pharmacological ways to slow down the progression of AD, but recently, non-pharmacological approaches has emerged as a topic-of-interest. This study have shown that there might be a link between hippocampal atrophy and physical performance. In the literature, there is a general agreement that physical performance is beneficial to both physical and mental health (US De-

partment of Health and Human Services, 2000; Whitmer et al., 2005a; Whitmer et al., 2005b), and to some degree, on subregions of the brain (Burns et al., 2008; Niemann et al., 2014), such as the hippocampus and the findings of this study supports this. The results showed a positive correlational association, albeit non-significant. This could be due to the small sample size but proves itself as important findings as a pilot study for the ALMUTH project.

The findings here suggest a correlational relationship between depressive symptoms and HCV, confirming the general agreement in the literature (Erickson et al., 2012; Geerlings et al., 2008; Jacobson & Sapolsky, 1991; Jorm, 2001). Because depression often is seen in AD patients, finding solutions to treat depression is crucial for a better quality of life. The findings here did not suggest a strong relationship between physical performance and depression. This could be due to this thesis not comparing previous depressive episodes to present depressive symptoms. The literature suggests that there is an association between the two, and it can be assumed that these findings will differ with the ALMUTH project. Nonetheless, the findings on HCV and depression will withal be a positive contribution to studies linking HCV and depression.

In their systematic review in trying to find good-quality non-pharmacological approaches to treating dementia, Hulme and colleagues (2010) found that physical exercise is one of the most effective ways to treat dementia. Here, they concluded that there are too few high-quality studies on this topic, and most research looking at hippocampal atrophy and physical performance stems from animal research. There have also been a few clinical trials showing favorable effects of physical performance on memory, but most of these findings are also derived from animals (for review see Ang & Gomez-Pinilla, 2007 and; Cotman & Berchtold, 2002). The findings from this study will serve as pilot data for the grand ALMUTH project which will hopefully yield promising contributions to the literature on the elderly

population, especially on AD patients. Hopefully, the ALMUTH study will come forward with excellent longitudinal data on how the brain, and specifically the hippocampus, is affected by physical performance. Furthermore, the project can contribute to the literature on how to help AD patients stay at home longer by finding good intervention strategies.

Practical Implications

Burns and colleagues (2008) found in their study that higher levels of physical performance in early-onset AD patients were associated with less brain atrophy. Seeing positive results between physical performance and hippocampal atrophy here will prove important in the future of the ALMUTH project. Patients from this pilot study have been randomly assigned to one of three one-year intervention groups, one of which is physical exercise. Because an interesting association between SPPB and HCV has been seen here, it is recommended that the researchers of the ALMUTH project should pursue the effect of physical performance on hippocampal atrophy. The findings from the project will be shared with Bergen Municipality to find more effective ways to non-pharmacological treatments of dementia in and around the Bergen area. Seeing these promising results with such a small sample size is substantial, and can prove to become important for the grand project in the future. Because the ALMUTH project will look at both healthy controls and AD patients, it will become easier to draw conclusions on the effect of exercise and physical performance on hippocampal atrophy, and possibly disease progression. Moreover, a clear link between falls, balance and exercise has come forward from Bergen Municipality report «Trygg på to bein» (Bergen Kommune, 2010) amongst other research. The literature suggests that effects from physical exercise can help reduce falls, and thus lengthy hospitalizations, by 30%. These results were found even for patients with established functional failure, such as patients scoring low on the SPPB (Campbell et al., 1999; Helbostad et al., 2007; Skelton et al., 2005). Although this the-

sis did not screen for falls and lengthy hospital stays, it can be assumed through the literature that the patients scoring low on the SPPB will be more prone to this. If physical intervention can help AD patients, especially for patients scoring low on the SPPB in the current research project, it could have a substantial effect on these patients' quality of life.

Future Research

The scientific literature on hippocampal atrophy and AD patients suggest HCV is usually smaller already at the MCI stage (Shi et al., 2009; van der Flier et al., 2005). Future research should, therefore, include healthy controls to capture differences employing automated segmentation from the FreeSurfer software. Because such automated measures of hippocampal volumetry using FreeSurfer yields larger HCV than with manual segmentation, it is important to look at how AD patients differ from healthy controls when using this method. Future research should also include looking at the subregions of the hippocampus, as research suggests that mainly the left hippocampus, the CA1 and CA2, and the subiculum is greatly affected by AD. Seeing whether this atrophy can be altered through physical exercise could be eminently valuable.

There was found a strong relationship for depressive symptoms and HCV, indicating that more depressed patients had lower HCV. Alzheimer's disease patients often present with depressive symptoms and links have been made between hippocampal atrophy, depression, and dementia. The literature generally agrees upon a history of depression, rather than present depressive symptoms, are associated with AD, and future research should include the history of previous depressive episodes of both the patient and their close family.

For AD patients, any task can seem excessive. The patients in the ALMUTH study needs to go through a long test battery, and for any healthy individual, up to three hours of testing is very long. Even so, including all tests in the test battery is necessary to ensure full

research benefits. An easy way to cut down time would be to employ the GDS-15 instead of the longer 30-question scale. The correlation between the two tests is very strong, and there should be no need to utilize the GDS-30 with an already long set of tests. Moreover, the GDS has been criticized for not being adequate in testing AD patients (Müller-Thomsen et al., 2005). In the future, one should look at other, more AD adapted, tests - especially for longitudinal studies with AD patients such as the ALMUTH project where patients cognition tend to deteriorate rapidly.

Conclusions

The findings from this thesis have shown that there could be a relationship between HCV and physical performance. Hippocampal atrophy is seen as one of the core biomarkers for converting to AD, and although it is not possible to see causal relationships from the current study, the ALMUTH project could provide valuable contributions to the literature with regard to hippocampal atrophy and exercise. Because they will test the patients over time (before, during, and after intervention), and use data of healthy controls, seeing how HCV changes over time with physical exercise intervention is possible. Moreover, a strong relationship between HCV and depressive symptoms was found. One goal of the ALMUTH study should be to, through improving physical performance, lessen patients' depressive symptoms. A possibility could be that through exercise, physical performance will increase, and thus hippocampal atrophy will slow down. Even though the literature suggests a significant relationship between past depressive episodes and conversion to AD, helping patients with current depressive symptoms through increasing physical performance could be consequential in helping these patients live more independently.

Consequently, improving physical performance through exercise has been shown to benefit various comorbid disorders for AD patients, such as general physical health, diabetes, cardiovascular problems, diabetes, and obesity. It has also been seen to improve mental health illnesses, such as anxiety and depression. A few studies have pointed out that dementia is linked to such health issues, and by increasing physical performance in AD patients, comorbid risk factors might go away all-together, and possibly slow down the progression of AD. The goal of this study, and consequently the ALMUTH project, is to help AD patients live independently at home longer, and this thesis has shown that the positive effects of physical performance could be substantial in this goal. Finding ways to either slow down hippocampal

atrophy or ultimately, reverse it, could be momentous for this already vulnerable group of patients. The further investigation of the relationship between SPPB and HCV in AD patients is therefore recommended for the ALMUTH project.

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Appendix

Appendix A - Geriatric Depression Scale (GDS)

GDS

Geriatrisk Depresjonsskala

Om GDS

GDS er en selvevalueringsskala som avdekker depresjon hos eldre. Skalaen er et screeningsinstrument med 30 Ja/Nei spørsmål som pasienten fyller ut selv. Norske undersøkelser anbefaler skalaen brukt som intervju (1). Den ser ut til å være en meget god skala. Den anbefales også av British Geriatric Society og blir ofte brukt i internasjonale studier.

Vurdering av skalaens anvendbarhet

GDS kan med fordel anvendes av helsepersonell uten psykiatrisk spesialkompetanse. Den er robust og kan brukes blant somatisk syke eldre og lett til moderat demente pasienter.

Validitet

God validitet. En skår på $\geq$11 indikerer depresjon; sensitivitet 84 % og spesifisitet 95 %. Dersom man øker cut off skår til $\geq$14, er sensitiviteten 80 % og spesifisiteten 100 % (2).
For pasienter med demensdiagnose er imidlertid sensitivitet og spesifisitet noe lavere uansett cut off skår (3).

Reliabilitet

God reliabilitet. Intern konsistens: Cronbachs alpha: 0.94 (2).
Test-retest (n=20, etter en uke) er 0.85 (2).
Retest i norsk undersøkelse ga en gjennomsnittlig Kappa-verdi på 0.77 (1).

Brukervennlighet

Utfylling av skalaen tar vanligvis 10 minutter.

Konstruksjon

Endimensjonal.

Brukerveiledning

Det følger med to nesten identiske skjemaer. Hvis pasienten fyller ut skjemaet selv, gi vedkommende skjemaet uten stjerner. Erfaringer tilsier at en med fordel kan hjelpe pasienten med utfyllingen eventuelt fylle ut skjemaet selv ved å intervjue pasienten.
Det kan være i tilfeller hvor pasienten er engstelig, har nedsatt syn, er dement eller er deprimert og derfor har nedsatt utholdenhet. Et JA på spørsmålene 2, 3, 4, 6, 8, 10, 11, 12, 13, 14, 16, 17, 18, 20, 22, 23, 24, 25, 26 og 28 gir en skår på 1, mens et NEI på spørsmålene 1, 5, 7, 9, 15, 19, 21, 27, 29 og 30 også gir skåre 1. Intervjuer må selv avgjøre om det er mest naturlig å tiltale pasienten med du eller De. Det får ingen betydning for resultatet hvilken tiltaleform en bruker så lenge intervjuet foregår på en respektfull måte og under rolige forhold. Gi pasienten god tid til å svare og gi rom for assosiasjoner rundt hvert spørsmål.
Dersom skår $\geq$11, bør man følge opp og utføre MADRS intervju.

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GDS

Geriatrisk depresjonsskala

Yesavage J A, 1983 - Norsk versjon ved Knut Engedal

Pasientens navn: _____

Fødselsår/dato: _____ Dato utfylt: _____

Utfylt av: _____ Stilling: _____

Nedenfor finner du 30 spørsmål om hvorledes du har følt deg den siste uken.
Vær vennlig å krysse av for det svaralternativ som passer for deg.

1. Føler du deg jevnt over tilfreds med livet _____ ☐Ja ☐Nei
2. Har du oppgitt eller sluttet med mange interesser_____ ☐Ja ☐Nei
3. Føler du at livet er tomt_____ ☐Ja ☐Nei
4. Synes du ofte at tilværelsen er kjedelig _____ ☐Ja ☐Nei
5. Ser du lyst på fremtiden_____ ☐Ja ☐Nei
6. Er du plaget med tanker som du ikke får ut av hodet _____ ☐Ja ☐Nei
7. Er du vanligvis i godt humør _____ ☐Ja ☐Nei
8. Er du engstelig for at det skal hende deg noe alvorlig _____ ☐Ja ☐Nei
9. Føler du deg vanligvis lykkelig_____ ☐Ja ☐Nei
10. Føler du deg ofte hjelpeløs_____ ☐Ja ☐Nei
11. Føler du deg ofte urolig og rastløs _____ ☐Ja ☐Nei
12. Foretrekker du å være hjemme fremfor å gå ut å oppleve nye ting ____ ☐Ja ☐Nei
13. Er du bekymret for din egen fremtid_____ ☐Ja ☐Nei
14. Føler du at du har større problem med hukommelsen enn mange andre (jevnaldrende)_____ ☐Ja ☐Nei
15. Føler du i øyeblikket at det er godt å leve_____ ☐Ja ☐Nei
16. Føler du deg ofte nedtrykt og ensom_____ ☐Ja ☐Nei
17. Føler du deg verdiløs slik du nå er_____ ☐Ja ☐Nei
18. Bekymrer du deg ofte over fortiden_____ ☐Ja ☐Nei

19. Synes du livet er spennende_____ ☐Ja ☐Nei
20. Er det et tiltak å ta fatt på noe nytt_____ ☐Ja ☐Nei
21. Føler du deg opplagt_____ ☐Ja ☐Nei
22. Synes du at din egen situasjon er håpløs_____ ☐Ja ☐Nei
23. Synes du at folk flest har det bedre enn deg_____ ☐Ja ☐Nei
24. Blir du ofte forstyrret av bagateller_____ ☐Ja ☐Nei
25. Føler du ofte trang til å gråte_____ ☐Ja ☐Nei
26. Har du vansker med konsentrasjonen_____ ☐Ja ☐Nei
27. Liker du å stå opp om morgenen_____ ☐Ja ☐Nei
28. Forsøker du å unngå sosiale sammenkomster_____ ☐Ja ☐Nei
29. Faller det deg lett å ta bestemmelser_____ ☐Ja ☐Nei
30. Er du like lys til sinns som tidligere_____ ☐Ja ☐Nei

Appendix B - Mini-Mental State Examination (MMSE)

Aldring og helse
Nasjonal kompetansetjeneste

NORSK REVIDERT MINI MENTAL STATUS EVALUERING (MMSE–NR3)

Carsten Strobel & Knut Engedal, 2016

Pasient (PAS)/fødselsdato: _____ Språk/tolk: _____

Skolegang/utdanning/antall år: _____ Yrke: _____

Hørsel/høreapparat: _____ Syn/briller: _____ Geriatrisk leseprøve: _____

Testleder (TL): _____ Dato/kl: _____ Teststed: _____

Er PAS testet med MMSE-NR før? Nei ☐ Ja ☐► Når/hvor/oppgavesett nr./skåre: _____

Administrasjons- og skåringsveiledning

Screeningtesten MMSE-NR brukes til kognitiv utredning og forløpskontroll ved demens, hjerneslag og andre sykdommer som påvirker kognitiv funksjon, og for å vurdere behandlingseffekt, kognitiv egnethet for bilkjøring o.l. Testen alene er ikke tilstrekkelig til å diagnostisere demens. Diagnosekriteriene for demens *må* også være oppfylt. MMSE-NR supplerer annen utredning så som somatisk undersøkelse, legemiddelgjennomgang, komparentintervju (med bl.a. spørsmål om type/forløp/varighet av ev. kognitiv svikt og endret ADL-funksjon) og vurdering av stemningsleie. Eksekutiv svikt, f.eks. etter hjerneslag og ved frontotemporal demens, kan være vanskelig å påvise med MMSE-NR. Skåre og kvalitativ utførelse kan over tid endre seg ved flere psykiatriske og somatiske sykdomstilstander og sykdomsfaser: av og til med bedre utførelse og skåre, som ved behandling av depresjon eller delirium, ev. dårligere, som ved progredierende demens.

TL bør ha fått opplæring i bruk av MMSE-NR og kjenne til manualens innhold (se www.aldringoghelse.no). Gjennomføring som ikke er i tråd med retningslinjer for administrasjon, oppfølgende spørsmål og skåring, kan gi for høy eller lav skåre. Dette kan få betydning for utredning, konklusjon, oppfølging og behandling. Følg derfor standardisert instruksjon under hver oppgave og overhold retningslinjer i manual og på skjema. Har PAS lav norskspråklig kompetanse og annet morsmål enn norsk, bruk fagutdannet tolk (*ikke* slektninger) og språktilpasset stimulusark på oppgave 18.

Utfør testing en-til-en uten pårørende til stede. Slå av mobiltelefoner. Sørg for at PAS ved behov bruker briller/hørselshjelpemidler. Minn ev. på bruk underveis. Unngå at PAS ser skåring og svaralternativer på skjema. Les **uthevet** tekst høyt, langsomt og tydelig. Still samtlige spørsmål, også om PAS har besvart oppgaveledd under tidligere stilte spørsmål. All instruksjon kan gjentas med unntak av spesifiserte begrensninger på oppgave 12 og 17. Ikke gi hint om hvordan oppgavene kan løses eller om svar er rett eller galt. Skriv ordrett ned svar på hvert spørsmål. PAS kan på eget initiativ korrigere svar underveis. Ved flere svar på et spørsmål må PAS velge hvilket svar som skal skåres. Dersom PAS har vansker med å gi adekvate muntlige svar, f.eks. ved afasi og andre talevansker, be PAS prøve å skrive svar på eget ark. Lar heller ikke dette seg gjennomføre, bruk tilrettelagte MMSE-NR pekeark på aktuelle orienteringsoppgaver. Sett kryss i ruten for «0» ved feil svar og i ruten for «1» ved rett svar. Gi aldri ½ poeng. Gir PAS utrykk for ikke å klare en eller flere av oppgavene, oppfordre likevel til å gjøre et forsøk. Gjenta oppfordring om nødvendig. Er PAS *ikke* testbar på en oppgave pga. ikke-kognitiv funksjonsbegrensning, notér hvorfor og sett ring rundt ruten for «0». Inkluder likevel oppgaven i totalskåren, da totalskåren skal angis i antall poeng av 30 mulige (det er f.eks. ikke tillatt å gi 23 av 25 poeng).

Ved retesting: For å redusere læringseffekt fra tidligere testing, bytt til riktig oppgavesett (ordsett og starttall) som spesifisert på oppgave 11–13.

Lavere alder og høyere utdanning gir ofte bedre skåre, likeså testing utført i omgivelser som er velkjente for PAS pga. stedsorienteringsoppgavene. Notér faktorer som kan påvirke utførelse negativt, så som liten eller ingen skolegang, høy alder, svekket syn/manglende briller, svekket hørsel, dårlig dagsform, smerter, lav oppgaveinnsats, trettbarhet, afasi, lese- og skrivevansker, dyskalkuli, ikke-kognitiv funksjonsbegrensning, skriving/tegning med ikke-dominant hånd (f.eks. ved lammelse), rusmidler (inkl. alkohol), akutt somatisk sykdom, depresjon, lav norskspråklig kompetanse, stress og testangst. Legemiddeleffekter kan tidvis påvirke resultat negativt/positivt og krever egen vurdering. Totalskåre alene gir ikke informasjon om spesifikke kognitive sviktområder som kan være diagnostisk og klinisk relevante. Journalfør derfor også påfallende utførelse (lang tidsbruk, mange korrigeringer o.l.), og hvilke oppgaver PAS ikke får til. Skåringsprofil og kvalitativ vurdering av utførelse kan i tillegg gi informasjon om kognitive restressurser og kompenserende mestringsstrategier som kan være nyttige for tilrettelegging av aktivitet og samhandling.

Skåring MMSE-NR3. Journalfør oppgavesett (ordsett og starttall oppgave 11–13) brukt i dag: 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐

		KOMMENTARER TIL SPESIFIKKE OPPGAVELEDD:	
Orientering	*(oppgave 1–10)*		**/10**
Umiddelbar gjenkalling	*(oppgave 11)*		**/3**
Hoderegning	*(oppgave 12)*		**/5**
Utsatt gjenkalling	*(oppgave 13)*		**/3**
Språk og praksis	*(oppgave 14–19)*		**/8**
Figurkopiering	*(oppgave 20)*		**/1**
Total poengskåre			**/30**

Versjon 3, 11.09.2016

Vurderer du som TL at samarbeid/motivasjon/testinnsats var uten anmerkning? Ja ☐ Nei ☐ Usikker ☐

Vurderer du som TL at oppmerksomhet/bevissthetsnivå/våkenhet var uten anmerkning? Ja ☐ Nei ☐ Usikker ☐

Vurderes ikke resultat som valid/gyldig, angi årsak(er): _____

Merknader (atferd, bruk av pekeark, legemidler [inkl. dårlig legemiddeletterlevelse] som kan påvirke kognitiv funksjon, glemt briller/høreapparat e.l.):

_____

_____

Basert på: Folstein, M.F., Folstein, S.E. & McHugh, P.R. (1975). "Mini-Mental State": A practical method for grading the cognitive state of patients for the clinician. Journal of Psychiatric Research, 12, 189-198.
Engedal, K., Haugen, P.K., Gilje, K. & Laake, P. (1988). Efficacy of short mental tests in the detection of mental impairment in old age. Compr Gerontol A, 2, 87-93.
Strobel, C. & Engedal, K. (2008). MMSE-NR. Norsk Revidert Mini Mental Status Evaluering. Revidert og utvidet manual. Oslo. Nasjonal kompetansetjeneste for aldring og helse.

Start med spørsmålet: **Synes du hukommelsen din er blitt dårligere nå enn den var tidligere?** Ja ☐ Nei ☐ Usikker ☐
Jeg skal nå stille deg noen spørsmål som vi bruker for bl.a. å undersøke hukommelsen. Svar så nøyaktig du kan.

ORIENTERING

Prøv å unngå at PAS bruker ledetråder: ser ut av vindu (årstid, måned, sted, etasje), bruker kalender, avis, innkallingsbrev (årstall, måned, ukedag, dato, sted), sjekker dato på klokke, mobiltelefon e.l. På oppgave 8 og 9, sett ring rundt valgt stedsalternativ.

1. Hva er din fødselsdato? Dag, måned og år må være rett for poeng _____ 0☐ 1☐
(Sa PAS kun deler av sin fødselsdato, si: **Si *hele* fødselsdatoen med dag, måned og år.**)

2. Hvor gammel er du? (Sier PAS kun fødselsdato, si: **Jeg mente, hvor mange år *er* du?**) _____ 0☐ 1☐

3. Hvilket årstall har vi nå? Gi kun poeng for fullt årstall med 4 sifre _____ 0☐ 1☐
(Sa PAS kun siste 2 sifre, si: **Si *hele* årstallet med alle tall. Hva heter det mer enn…** [gjenta sifrene PAS sa]**?**)

4. Hvilken årstid har vi nå? Ta hensyn til vær og geografiske forhold ved skåring (se manual) _____ 0☐ 1☐

5. Hvilken måned har vi nå? Gi kun poeng for rett navn på måned, ikke for nummer på måned _____ 0☐ 1☐

6. Hvilken dag har vi i dag? Gi kun poeng for rett navn på ukedag _____ 0☐ 1☐

7. Hvilken dato har vi i dag? Gi poeng dersom dato for dag er rett, selv om måned eller år er feil _____ 0☐ 1☐

8. Hvilken by/kommune/bygd (e.l.) **er vi i** (*eller:* **er vi like i nærheten av**) **nå?** _____ 0☐ 1☐

9. Hva heter dette stedet/sykehuset/sykehjemmet/legekontoret (e.l.)**?** (*eller:* **Hvor er vi nå?**) _____ 0☐ 1☐

10. I hvilken etasje er vi nå? Still spørsmålet selv der bygg kun har én etasje _____ 0☐ 1☐
Avhengig av hvilken inngang PAS brukte, vil noen bygg i skrånende terreng kunne ha flere poenggivende svar for samme etasje (f.eks. under-, 1. og 2. etasje). Gi også poeng om PAS med annet morsmål, i tråd med sitt språk, benevner norsk 1. etasje som grunnplan (stuen [dansk], ground floor [engelsk]), og tilsvarende for andre etasjer (norsk 2. etasje: 1. sal [dansk], first floor [engelsk]).

UMIDDELBAR GJENKALLING

Bytt til riktig ordsett ved retesting for å redusere læringseffekt fra tidligere testing: 2. gang PAS testes bruk ordsett 2 (tak-banan-nål), 3. gang bruk ordsett 3 (saft-lampe-båt) osv., 6. gang bruk ordsett 1 på nytt, 7. gang bruk ordsett 2 osv. Sett ring rundt dagens ordsett.

11. Jeg vil nå si 3 ord som du skal gjenta, etter at jeg har sagt alle 3. Disse skal du prøve å huske, for jeg kommer til å spørre deg om dem litt senere. 1 sek pause etter hvert innlæringsord.
Ordene du skal gjenta er: …… (1 sek)**, ……** (1 sek)**, ……** (1 sek)**. Vær så god!**
Repeter hele ordsettet inntil PAS gjentar alle 3 ord i samme forsøk. Maks 3 presentasjoner. Gi *kun* poeng for riktige ord etter 1. presentasjon, også for lydlike ord (f.eks. pga. hørselsvansker: mål for nål, hatt for katt). Rekkefølgen PAS sier ordene i, er uten betydning for skåring. Antall presentasjoner: ____ stk.

Ordsett (nr. 1–5) brukt i dag:	1	2	3	4	5		
Ordene du skal gjenta er...	**Stol**	**Tak**	**Saft**	**Katt**	**Fly**	_____	0☐ 1☐
	Ekorn	**Banan**	**Lampe**	**Avis**	**Eple**	_____	0☐ 1☐
	Tog	**Nål**	**Båt**	**Løk**	**Sko**	_____	0☐ 1☐

Etter 3 gjenkalte ord eller 3 presentasjoner, si: **Husk disse ordene, for jeg vil spørre deg om hvilke de er litt senere.**

HODEREGNING

Bytt til riktig starttall ved retesting: 2. gang bruk 50 osv., 6. gang bruk 80 på nytt, 7. gang 50 osv. PAS får ikke bruke blyant og papir, men kan på eget initiativ telle på fingrene. Gi poeng når svar er minus 7 fra forrige tall, uavhengig av om forrige svar var rett eller galt.

12. Nå litt hoderegning. Hva er ..... minus 7? Før 1. subtraksjon (å trekke 7 fra starttallet) kan all instruksjon gjentas. (Gir PAS uttrykk for ikke å beherske hoderegning, oppfordre likevel til å gjøre et forsøk.) Rett etter tallsvaret, si: **Fortsett med å trekke fra 7, helt til jeg sier stopp.** Etter 1. subtraksjon kan *kun* instruksjon om å trekke fra 7 gjentas, men det er ikke lenger tillatt å informere om starttallet og heller ikke om hvilket tall PAS var kommet til. Etter 2. subtraksjon er det heller ikke tillatt å informere om hvor mye PAS skulle trekke fra (-7). Notér tallsvar og hvor mye PAS trakk fra (-), ev. la til (+).

Starttall (nr. 1–5) brukt i dag:	1	2	3	4	5		-7 = 1 poeng	
Starttall: **Hva er ..... minus 7?**	**80**	**50**	**90**	**40**	**60**	PAS tallsvar:	PAS trakk fra (-), ev. la til (+):	
Fortsett med å trekke fra 7, helt til jeg sier stopp →	73	43	83	33	53	_____	----------	0☐ 1☐
	66	36	76	26	46	_____	----------	0☐ 1☐
Ved behov, si: **Og så videre.**	59	29	69	19	39	_____	----------	0☐ 1☐
Ved behov, si: **Og så videre.**	52	22	62	12	32	_____	----------	0☐ 1☐
Ved behov, si: **Og så videre.**	45	15	55	5	25	_____	----------	0☐ 1☐

Etter 5 subtraksjoner (eller færre tallsvar hvis oppgaven ikke fullføres), si: **Fint, det holder. Tell nå nedover fra 100 slik som dette: 100, 99, 98, osv. til jeg sier stopp. Vær så god!** Etter ca. 30 sek, si: **Fint, det holder.** Bruk alltid oppgaven for å få lang nok tid med distraksjon for å sikre reell kartlegging av langtidshukommelse fremfor arbeidshukommelse på oppgave 13. Distraksjonsoppgaven skåres ikke, men notér ev. vansker med å telle baklengs, da dette kan gi klinisk relevant informasjon.

UTSATT GJENKALLING

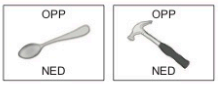
13. Hvilke 3 ord var det jeg ba deg om å huske? Ikke gi stikkordshjelp/hint, sett ring rundt dagens ordsett.

Ordsett (nr. 1–5) brukt i dag:	1	2	3	4	5		
	Stol	Tak	Saft	Katt	Fly	_____	0☐ 1☐
	Ekorn	Banan	Lampe	Avis	Eple	_____	0☐ 1☐
	Tog	Nål	Båt	Løk	Sko	_____	0☐ 1☐

Er PAS i tvil om et ord var med, be PAS gjøre et valg. Sier PAS rett ord, men så hevder at ordet likevel ikke var med, gi 0 poeng. Ved flere enn 3 ord be PAS velge hvilke 3 ord som skal være svaret, *kun disse* skåres. Rekkefølgen PAS sier ordene i, er uten betydning for skåring. Gi *kun* poeng for eksakt gjengitte ord fra *dagens* ordsett (både best. og ubest. form entall gir poeng). Beslektet ord, målord i sammensatt ord, flertallsform, synonym, omskrivning: stoler, skip, pus, gnager, togbane, lokomotiv o.l. gir ikke poeng. Sa PAS lydlikt ord på umiddelbar gjenkalling (f.eks. pga. hørselsvansker: mål for nål, hatt for katt), og samme ord gjentas på utsatt gjenkalling, gi poeng.

BENEVNING

Ved testing og retesting bruk kun stimulusarkene i farger med skje og hammer, aldri andre objekter. Alternative poenggivende svar: ord med skje/skjei, f.eks. spiseskje/plastskjei, ord med sleiv, f.eks. grøtsleiv, ord med øse/ause, f.eks. grautause, ord med hammer, f.eks. snekkerhammer.



14. Hva heter dette? Vis stimulusarket, pek på skjeen _____ 0☐ 1☐

15. Hva heter dette? Vis stimulusarket, pek på hammeren _____ 0☐ 1☐

FRASEREPETISJON

16. Gjenta *ordrett* denne frasen nå (si tydelig)**: «Aldri annet enn om og men».** (Ved behov, si: **Start nå.**)
Gi *kun* poeng når hele frasen gjentas korrekt etter 1. presentasjon med *alle* 6 ord i riktig rekkefølge. Godta dialektvarianter.
Gjentar ikke PAS frasen korrekt, gi 0 poeng og si frasen inntil 2 ganger til. Antall presentasjoner: ____ stk.

Aldri annet enn om og men _____ 0☐ 1☐

3-LEDDET KOMMANDO

Legg A4-arket på bordet nærmere TL enn PAS med kortsiden mot PAS. For å unngå at PAS starter før hele instruksjonen er gitt, legger TL sin hånd på arket til all instruksjon er gitt. 1 sek pause etter hvert ledd. Gi 1 poeng for hver riktig utførte delhandling.

17. Hør godt etter, for jeg skal be deg gjøre 3 ting i en bestemt rekkefølge. Start først når all instruksjon er gitt. Er du klar? Gi instruksjon om alle delhandlingene samlet og *kun én* gang: **Ta dette arket med kun én hånd** (1 sek)**, brett arket på midten kun én gang, med én eller begge hender** (1 sek)**, og gi arket til meg** (1 sek)**. Vær så god!**

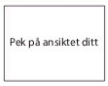
Tar arket med *kun én* hånd _____ 0☐ 1☐

Bretter arket på midten *kun én* gang (med én/begge hender, brett trenger ikke være helt på midten) _____ 0☐ 1☐

Gir arket til TL (gi også poeng om arket legges på bordet tydelig foran TL) _____ 0☐ 1☐

LESNING

18. Nå vil jeg at du gjør det som står på arket. Vis stimulusarket* mens instruksjon gis.
PAS må peke mot ansiktet sitt for poeng. Peker *ikke* PAS mot ansiktet sitt, gjenta instruksjon inntil 2 ganger til.
Alle 3 presentasjoner gir mulighet for poeng. Antall presentasjoner: ____ stk. *Bruk språktilpasset stimulusark.



Pek på ansiktet ditt (PAS kan bruke én eller begge hender) _____ 0☐ 1☐

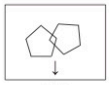
SETNINGSGENERERING

Legg skjemaet på neste side med pil (↓) mot PAS. Gi PAS en blyant.

19. Skriv en meningsfull setning* her. Pek på **X** på øvre del av skjemaet neste side _____ 0☐ 1☐
Skriver PAS kun ett ord, f.eks. en imperativform som «Spis», et subjekt som «Snøvær» eller et egennavn, si: **Skriv en hel setning.** Skriver ikke PAS noe eller tidligere gitt setning/frase, f.eks. «Pek på ansiktet ditt», si: **Skriv en setning du lager selv.** Skriver ikke PAS noe nå heller, si: **Skriv en setning om noe i dette rommet.** *Kan være på norsk eller morsmål.
For poeng må setningen gi mening, men trenger ikke ha objekt og tidvis heller ikke subjekt eller verb. Se manualeksempler.
Stave- og grammatikalske feil er uten betydning for skåring. Gi poeng for spørresetning om kriterier ellers er innfridd.

FIGURKOPIERING

Legg figurarket riktig vei (med pil [↓] mot PAS) over øvre del av neste side (over setningen PAS skrev).
Legg et viskelær ved siden av (skal ikke brukes som linjal). Figurarket skal forbli liggende riktig plassert til PAS er helt ferdig (dette er ikke en hukommelsesoppgave).



20. Kopier figuren så *nøyaktig* du kan her. Pek på nedre del av skjemaet neste side.
Du kan bruke viskelær. Ta deg god tid. Si fra når du er ferdig. _____ 0☐ 1☐
Gi poeng når femkantene overlapper og danner en firkant: 5-4-5. Er 5-4-5 innfridd, er det uten betydning for skåring hvor de overlapper, om det er innbyrdes størrelsesforskjell mellom dem, rotert utførelse eller størrelsesforskjell mellom figur og kopi.
Se manualeksempler. Er PAS misfornøyd med utførelse, og denne *er* feil (jf. 5-4-5), be PAS korrigere eller tegne figuren på nytt.
Maks 3 forsøk. Skår beste forsøk. Er TL i tvil om poengkriterier (jf. 5-4-5) er innfridd, be PAS tegne figuren på nytt.

OPPGAVE 19. SETNINGSGENERERING

X

OPPGAVE 20. FIGURKOPIERING

↓

Appendix C - Activities of Daily Living (I-ADL & P-ADL)

Utredningsverktøy til bruk for HELSE- OG OMSORGSPERSONELL

ADL vurdering

Lawton og Brody, 1969

Utgangspunkt for avkrysning er hva pasienten faktisk utfører i hverdagen og ikke hva han/hun kan klare eller er i stand til å mestre fysisk sett.

Jo høyere skåre på et område, jo mer sannsynlig er det at pasienten kan være i behov av hjelp på det området.

0 skåres kun dersom området ikke er aktuelt. F.eks. skåres pasienten til 0 (ikke aktuelt) på ansvar for egne medisiner dersom han/hun ikke har noen medisiner.

Instrumentelle aktiviteter i dagliglivet (I-ADL)

A. Bruk av telefon

0 ☐ Ikke aktuelt.
1 ☐ Benytter telefon på eget initiativ, slår opp nummeret og ringer.
2 ☐ Ringer noen få velkjente telefonnummer.
3 ☐ Svarer telefonen selv, men ringer ikke selv.
4 ☐ Bruker ikke telefon.

B. Innkjøp

0 ☐ Ikke aktuelt.
1 ☐ Tar hånd om innkjøp alene.
2 ☐ Gjør mindre innkjøp på egen hånd.
3 ☐ Trenger hjelp til hver handletur.
4 ☐ Er ikke i stand til å gjøre innkjøp.

C. Matlaging

0 ☐ Ikke aktuelt.
1 ☐ Planlegger, forbereder og serverer måltider selvstendig.
2 ☐ Lager tilstrekkelig med måltider dersom ingrediensene er tilstede.
3 ☐ Varmer opp og serverer ferdiglagde måltider, men opprettholder ikke diett.
4 ☐ Må ha måltidene ferdiglaget og servert.

D. Hushold

0 ☐ Ikke aktuelt.
1 ☐ Opprettholder husarbeid alene eller har hjelp til større oppgaver innimellom.
2 ☐ Gjør lettere oppgaver som oppvask og rer opp sengen.
3 ☐ Gjør lettere oppgaver, men klarer ikke holde et akseptabelt nivå av renhold.
4 ☐ Trenger hjelp til alt husholdningsoppgaver.
5 ☐ Deltar ikke i noen husholdningsoppgaver.

E. Vasking av klær

0 ☐ Ikke aktuelt.
1 ☐ Vasker alle klærne selv.
2 ☐ Vasker småting, skyller strømper etc.
3 ☐ All vasking av klær må gjøres av andre.

F. Transport

0 ☐ Ikke aktuelt.
1 ☐ Reiser selvstendig med offentlig transport eller kjører egen bil.
2 ☐ Reiser på egenhånd med drosje, men bruker ikke annen offentlig transport.
3 ☐ Reiser med offentlig transport med hjelp eller sammen med andre.
4 ☐ Begrensende reiser med drosjer eller bil med hjelp av andre.
5 ☐ Reiser ikke i det hele tatt.

G. Ansvar for egne medisiner

0 ☐ Ikke aktuelt.
1 ☐ Tar ansvar for å ta medisiner i korrekte doser til riktig tid.
2 ☐ Ansvar for å ta medisiner dersom de på forhånd er klargjort i korrekte doser.
3 ☐ Klarer ikke ta hånd om egen medisinering.

H. Håndtere egen økonomi

0 ☐ Ikke aktuelt.
1 ☐ Bestyrer økonomien selvstendig (betaler regninger og bruker bank/post/brevgiro/ nettbank).
2 ☐ Håndterer daglige innkjøp, men trenger hjelp med bankoppgaver, store innkjøp osv.
3 ☐ Kan ikke håndtere penger.

Personnære aktiviteter i dagliglivet (P-ADL)

A. Toalett

0 ☐ Ikke aktuelt.
1 ☐ Klarer seg selv på toalettet.
2 ☐ Trenger å bli påminnet, og/eller hjelp til å vaske seg, har sjelden uhell (høyst en gang i uken).
3 ☐ Er inkontinent (blære eller tarm) i søvne mer enn en gang i uken
4 ☐ Er inkontinent (blære eller tarm) i våken tilstand mer enn en gang i uken.
5 ☐ Ingen kontroll over blære eller tarm.

B. Spising

0 ☐ Ikke aktuelt.
1 ☐ Spiser uten hjelp.
2 ☐ Trenger litt hjelp under måltidene, eller trenger spesialtilberedte måltider, eller trenger annen hjelp i måltidssituasjonene.
3 ☐ Spiser med moderat hjelp og "søler".
4 ☐ Trenger mye hjelp ved alle måltider.
5 ☐ Spiser ikke selv, og motsetter seg forsøk på å bli matet av andre.

C. Påkledning

0 ☐ Ikke aktuelt.
1 ☐ Kler av og på seg selv, velger ut klær fra egen garderobe.
2 ☐ Kler av og på seg selv med noe hjelp.
3 ☐ Trenger moderat hjelp ved påkledning og/eller utvelgelse av klær.
4 ☐ Trenger mye hjelp ved påkledning, men samarbeider med den som hjelper.
5 ☐ Motsetter seg aktivt andres hjelp til personlig stell.

D. Personlig stell (Hår, negler, hender, ansikt, klær)

0 ☐ Ikke aktuelt.
1 ☐ Alltid pent kledd og velstelt, uten hjelp.
2 ☐ Steller seg selv, men trenger f.eks hjelp til barbering.
3 ☐ Trenger moderat og regelmessig hjelp eller veiledning til personlig stell.
4 ☐ Trenger hjelp til alt personlig stell, men holder seg ren og velstelt ved hjelp fra andre.
5 ☐ Motsetter seg aktivt andres hjelp til personlig stell.

E. Fysisk bevegelse

0 ☐ Ikke aktuelt.
1 ☐ Går utendørs, i jevnt og ulent terreng.
2 ☐ Går i nærmiljøet.
3 ☐ Kan forflytte seg ved hjelp av (kryss av en)
- ☐ A. Annen person
- ☐ B. rekkverk
- ☐ C. Spaserstokk
- ☐ D. Gåstol
- ☐ E1. Rullestol, kommer i og ut på egen hånd
- ☐ E2. Rullestol, trenger hjelp til å komme i og ut.

4 ☐ Kan ikke gå, men sitter oppreist uten støtte i stol eller rullestol, men kan ikke bevege seg uten hjelp.
5 ☐ Sengeliggende mer enn halvparten av tiden.

F. Bading

0 ☐ Ikke aktuelt.
1 ☐ Bader selv uten hjelp (badekar, dusj).
2 ☐ Bader selv, men trenger hjelp i og ut av badekaret/dusjen.
3 ☐ Vasker kun ansikt og hender, og kan ikke bade/vaske resten av kroppen.
4 ☐ Vasker seg ikke selv, men er samarbeidsvillig når andre hjelper.
5 ☐ Vasker seg ikke selv og gjør motstand når andre gjør et forsøk på å hjelpe.

Kommentarer:

Appendix D - Short Physical Performance Battery (SPPB)

Short Physical Performance Battery (SPPB)

Oversatt til norsk april 2013 v/Sverre Bergh[1], Heidi Lyshol[2], Geir Selbæk[1], Bjørn Heine Strand[2], Kristin Taraldsen[3], Pernille Thingstad[3] *1. Alderspsykiatrisk forskningssenter, Sykehuset Innlandet HF 2. Folkehelseinstituttet 3. Forsknings gruppe for geriatri, St. Olavs hospital og NTNU*

Innhold:

1. Manual for testprotokoll
2. Registreringsark for testing
3. Scoringsark for poengberegning
4. Vedlegg:
   - Scoring for 3m gangtest der 4m ikke er praktisk mulig
   - Tillegg til originaltesten:
     Registrering av ganghastighet og reise/sette seg x5 med bruk av armene

Bakgrunn:
Short Physical Performance Battery er en test for screening av fysisk funksjon hos eldre. Testen var opprinnelig utviklet for bruk i en større amerikansk studie av eldre over 65 år, EPESE studien. Testen har vist seg å ha god prediksjonsevne for død og sykehjemsinnleggelser [1], fremtidig funksjonsfall og økt hjelpebehov [4], sykehusinnleggelser [5] og reinnleggelser i sykehus [6]. Den har vist seg egnet til bruk i sykehus på akutt syke eldre [7], som screeningtest i primærhelsetjenesten[8] og på hjemmeboende eldre [9]. Testen er oversatt fra engelsk til norsk i tråd med gjeldende retningslinjer og den norske versjon er gratis og fritt tilgjengelig for bruk.

Tillegg til originalversjonen:
Utregning og registrering av ganghastighet er ikke en del av originaltesten. Ganghastighet kan brukes som en selvstendig test, er et anbefalt mål på helse og funksjon hos eldre og har veletablerte referanse verdier [10]. Den originale SPPB versjonen kan ha en gulveffekt ved testing av eldre med lavt funksjonsnivå. For eldre som scorer 0 poeng på reise/sette seg kan tiden med bruk av armene registreres i tillegg. Denne tiden regnes ikke inn i totalscoren SPPB, men registreres som en egen test.

Testprosedyre:
Nødvendig utstyr: Stoppeklokke, målebånd, farget markerings teip, stol
Det anbefales at manualen og instruksjoner innøves på forhånd. Kun registreringsarket brukes under testing, og beregning av totalscore gjøres i etterkant. Det anbefales å laste ned instruksjonsvideo og informasjonsmateriell fra hjemmesiden til originaltesten: http://www.grc.nia.nih.gov/branches/ledb/sppb/.
Ganghjelpemiddel kan brukes under gangtesten om nødvendig. Det er viktig å registrere og bruke samme ganghjelpemiddel ved retest, evt. velge det pasienten går raskest med for å kunne fange opp bedring. Ved testing av statisk balanse og reise/sette seg x5 settes eventuelle ganghjelpemiddel til siden (ikke ha rullator foran pasienten). Årsak til at deltageren ikke gjennomfører testen er viktig å registrere for å skille mellom deltagere som fysisk ikke er i stand til å gjennomføre testen pga utrygghet og redusert funksjon (scorer null poeng) og de som kan fysisk, men ikke lar seg teste av andre grunner (missing). Denne vurderingen baseres på tester sin kliniske vurdering.

Tolkning [1, 2]**:**

Lav score: 0-6 poeng	< 10 poeng indikerer økt risiko for funksjonssvikt
Middels score: 7-9 poeng	< 8 poeng indikerer begynnende svikt i ADL funksjoner
Høy score: 10-12 poeng.	

Klinisk meningsfull endring (totalscore): 1 poeng [3]

For mer detaljerte referanseverdier i forhold til alder og kjønn anbefales originalartikkelen [2]. Referanseverdier for ganghastighet som selvstendig test er oppgitt i vedlegget.

1. Guralnik, J.M., et al., *A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission.* J Gerontol, 1994. **49**(2): p. M85-94.
2. Guralnik, J.M., et al., *Lower extremity function and subsequent disability: consistency across studies, predictive models, and value of gait speed alone compared with the short physical performance battery.* J Gerontol A Biol Sci Med Sci, 2000. **55**(4): p. M221-31.
3. Perera, S., et al., *Meaningful change and responsiveness in common physical performance measures in older adults.* J Am Geriatr Soc, 2006. **54**(5): p. 743-9.
4. Guralnik, J.M., et al., *Lower-extremity function in persons over the age of 70 years as a predictor of subsequent disability.* N Engl J Med, 1995. **332**(9): p. 556-61.
5. Studenski, S., et al., *Physical performance measures in the clinical setting.* J Am Geriatr Soc, 2003. **51**(3): p. 314-22.
6. Volpato, S., et al., *Predictive value of the Short Physical Performance Battery following hospitalization in older patients.* J Gerontol A Biol Sci Med Sci, 2011. **66**(1): p. 89-96.
7. Volpato, S., et al., *Performance-based functional assessment in older hospitalized patients: feasibility and clinical correlates.* J Gerontol A Biol Sci Med Sci, 2008. **63**(12): p. 1393-8.
8. Cavazzini, C., et al., *Screening for poor performance of lower extremity in primary care: the Camucia Project.* Aging Clin Exp Res, 2004. **16**(4): p. 331-6.
9. Freiberger, E., et al., *Performance-based physical function in older community-dwelling persons: a systematic review of instruments.* Age Ageing, 2012. **41**(6): p. 712-21.
10. Studenski, S., *Bradypedia: is gait speed ready for clinical use?* J Nutr Health Aging, 2009. **13**(10): p. 878-80.

1

SHORT PHYSICAL PERFORMANCE BATTERY, TEST MANUAL

Alle testene bør gjennomføres i samme rekkefølge som de er presentert i denne manualen. Instruksjoner til deltagerne er vist i uthevet kursiv og skal formuleres på nøyaktig samme måte som beskrevet i dette dokumentet.

1. STATISK BALANSE

Deltageren må være i stand til å stå uten støtte, uten hjelp av stokk eller rullator. Du kan hjelpe deltageren opp i stående.

> ***La oss nå begynne kartleggingen. Nå vil jeg at du skal prøve å innta ulike stillinger. Jeg vil først beskrive og vise hver stilling for deg. Så vil jeg at du skal prøve å gjøre det samme. Du skal ikke gjøre noe du føler er utrygt eller noe du ikke klarer.***
>
> ***Har du noen spørsmål før vi starter?***

A. Stående stilling, samlede føtter

1. ***Nå vil jeg vise deg den første stillingen.***
2. (Demonstrer) ***Jeg vil at du skal forsøke å stå med føttene samlet, inntil hverandre, i ca 10 sekunder.***
3. ***Du kan bruke armene, bøye knærne eller bevege kroppen for å holde balansen, men prøv å ikke flytte på føttene. Prøv å holde stillingen helt til jeg ber deg stoppe.***
4. Stå ved siden av deltagerne for å hjelpe han/henne inn i stillingen.
5. Gi akkurat nok støtte til deltagerens arm for å unngå at han/hun mister balansen.
6. Når deltageren står med føttene samlet, spør **"Er du klar?"**
7. Slipp så taket og start tidtakingen idet du sier, **"Klar, start"**
8. Stopp stoppeklokken og si **"stopp"** etter 10 sekunder eller hvis deltageren flytter føttene og forlater stillingen eller griper tak i armen din.
9. Hvis deltageren ikke klarer å holde stillingen i 10 sekunder, noter resultatet og gå videre til ganghastighetstesten.

B. Stående stilling, semi-tandem

1. ***Nå vil jeg vise deg den andre stillingen.***
2. (Demonstrer) ***Nå vil jeg at du skal forsøke å stå med siden av hælen på den ene foten inntil stortåen på den andre foten i ca 10 sekunder. Du kan velge hvilken fot du har fremst, den som føles mest naturlig for deg.***
3. ***Du kan bruke armene, bøye knærne eller bevege kroppen for å holde balansen, men prøv å ikke flytte på føttene. Prøv å holde stillingen helt til jeg ber deg stoppe.***
4. Stå ved siden av deltageren for å hjelpe han/henne inn i semi-tandem stilling.
5. Gi akkurat nok støtte til deltagerens arm for å unngå at han/hun mister balansen.
6. Når deltageren står med føttene samlet, spør **"Er du klar?"**
7. Slipp så taket og start tidtakingen idet du sier, **"Klar, start"**
8. Stopp stoppeklokken og si **"stopp"** etter 10 sekunder eller hvis deltageren flytter føttene og forlater stillingen eller griper tak i armen din.
9. Hvis deltageren ikke klarer å holde stillingen i 10 sekunder, noter resultatet og gå videre til ganghastighetstesten.

C. Stående stilling, tandem

1. ***Nå vil jeg vise deg den tredje stillingen.***
2. (Demonstrer) ***Nå vil jeg at du skal forsøke å stå med hælen på den ene foten foran og inntil tærne på den andre foten i ca 10 sekunder. Du kan velge hvilken fot du har fremst, den som føles mest naturlig for deg.***
3. ***Du kan bruke armene, bøye knærne eller bevege kroppen for å holde balansen, men prøv å ikke flytte på føttene. Prøv å holde stillingen helt til jeg ber deg stoppe.***
4. Stå ved siden av deltageren for å hjelpe han/henne inn i tandem stilling.
5. Gi akkurat nok støtte til deltagerens arm for å unngå at han/hun mister balansen.
6. Når deltageren står med føttene samlet, spør **"Er du klar?"**
7. Slipp så taket og start tidtakingen idet du sier, **"Klar, start"**
8. Stopp stoppeklokken og si **"stopp"** etter 10 sekunder eller hvis deltageren flytter føttene og forlater stillingen eller griper tak i armen din.

2. 4m GANGTEST

Nå skal jeg observere hvordan du vanligvis går. Hvis du bruker stokk eller andre ganghjelpemidler, og føler at du trenger det for å gå en kort distanse, kan du bruke det.

A. Første test av ganghastighet

1. ***Dette er distansen du skal gå. Jeg vil at du skal gå til den andre enden, i din vanlige hastighet, som om du gikk nedover gaten til butikken.***
2. Demonstrer øvelsen for deltageren
3. ***Gå hele lengden, over og forbi teip-markeringen før du stopper. Jeg kommer til å gå sammen med deg. Føler du at dette er trygt?***
4. La deltageren stå med begge føttene inntil startlinjen.
5. ***Når jeg vil du skal starte, sier jeg: "Klar, start".*** Når deltageren bekrefter å ha forstått instruksjonen, si: ***"Klar, start."***
6. Start tidtakingen idet deltageren begynner å gå.
7. Gå bak og til siden for deltageren.
8. Stopp tidtakingen når en av deltagerens føtter er helt over mållinjen.

B. Andre test av ganghastighet

1. ***Nå vil jeg at du skal gjøre det samme en gang til. Husk å gå i din vanlige hastighet, og gå helt over og forbi teip-markeringen.***
2. La deltageren stå med begge føttene inntil startlinjen.
3. ***Når jeg vil at du starter, sier jeg: "Klar, start".*** Når deltageren bekrefter å ha forstått instruksjonen, si: ***"Klar, start."***
4. Start tidtakingen idet deltageren begynner å gå.
5. Gå bak og til siden for deltageren.
6. Stopp tidtakingen når en av deltagerens føtter er helt over mållinjen.

3. REISE SEG TEST

Reise seg fra stol én gang

1. ***Dette er den siste øvelsen. Er det trygt for deg å reise deg opp fra stolen uten å bruke armene?***
2. ***Den neste testen måler styrken i beina dine.***
3. (Demonstrer og forklar øvelsen.) ***Først, kryss armene over brystet, og sitt slik at føttene er plassert på gulvet; så reiser du deg opp, behold armene i kryss over brystet.***
4. ***Nå vil jeg at du skal prøve å reise deg opp med armene i kryss over brystet.*** (Noter resultatet)***.***
5. Hvis deltageren ikke klarer å reise seg uten å bruke armene, si ***"OK, prøv å reise deg med bruk av armene."*** Dette avslutter testen. Noter resultatet og gå til scoringsarket.

Reise/ sette seg x5

1. ***Tror du det vil være trygt for deg å reise deg opp fra stolen fem ganger uten å bruke armene?***
2. (Demonstrer og forklar øvelsen.) ***Nå vil jeg at du skal reise deg helt opp så RASKT du kan fem ganger, uten stopp. Etter at du har reist deg hver gang, sett deg ned og reis deg opp igjen. Behold armene i kryss over brystet. Jeg tar tiden med en stoppeklokke.***
3. Når deltageren sitter på riktig måte, si: **"Klar? Reis deg"** og start tidtakingen.
4. Tell høyt hver gang deltageren reiser seg, opp til fem ganger.
5. Stopp om deltageren blir sliten eller tungpustet av å reise seg fra stolen flere ganger.
6. Stopp stoppeklokka når han/hun har reist seg helt opp den femte gangen.
7. Stopp også
    - Hvis deltageren bruker armene
    - Etter 1 minutt, hvis deltageren ikke har fullført 5 repetisjoner
    - Hvis du bekymrer deg for deltakerens sikkerhet
8. Hvis deltageren er utslitt og stopper før fem repetisjoner, spør "**Kan du fortsette?"** for å bekrefte dette.
9. Hvis deltageren sier "Ja," fortsett tidtakingen. Hvis deltageren sier "Nei," stopp og nullstill stoppeklokken.

Registreringsark dd/mnd/år: ☐☐ ☐☐ ☐☐☐☐

ID/navn:

1. Balansetest

1.Samlede føtter 10 sekunder

↓

2.Semi-tandem 10 sekunder

↓

3.Tandem 10 sekunder

↓

Gå til gangtest

1. ☐☐.☐☐ sek

2. ☐☐.☐☐ sek

3. ☐☐.☐☐ sek

2. Gangtest

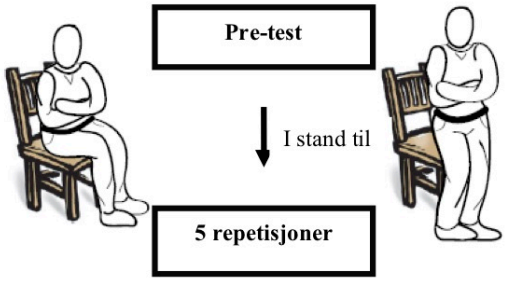
Ganghjelpemidler ved test (kryss av):

1. ☐ uten
2. ☐ krykke/stokk (er)
3. ☐ rollator
4. ☐ Annet (spesifiser)_____

Tid test 1: ☐☐.☐☐ sek

Tid test 2: ☐☐.☐☐ sek

3. Reise/ sette seg



→ Avslutt

Ikke i stand til

Setehøyde ☐ cm

Tid 5 repetisjoner uten armbruk: ☐☐.☐☐ sek

Tester:

SCORING SPPB:

dd/mnd/år: ☐☐ ☐☐ ☐☐☐☐

ID/navn:

1. Score statisk balanse

Hvis deltageren ikke har forsøkt eller mislyktes, kryss av hvorfor:

1. ☐ Forsøkte, men ikke i stand til(0p)
2. ☐ Deltageren kunne ikke holde stillingen uten hjelp(0p)
3. ☐ Ikke forsøkt, tester følte det utrygg(0p)
4. ☐ Ikke forsøkt, deltager følte seg utrygg(0p)
5. ☐ Deltager tar ikke instruksjon(missing)
6. ☐ Annet (spesifiser)_____
7. ☐ Deltager nektet(missing)

Samlede føtter =10 sek = 1 p <10 sek = 0 p ☐

+

Semi-tandem =10 sek = 1 p <10 sek = 0 p ☐

+

Tandem =10 sek = 2 p 3 - 9.99 sek = 1 p < 3 sek = 0 p ☐

=

Sum poeng balanse: ☐

2. Score 4m gangtest

Hvis deltageren ikke har forsøkt eller mislyktes, kryss av hvorfor:

1. ☐ Forsøkte, men ikke i stand til(0p)
2. ☐ Deltageren kunne ikke gå uten assistanse(0p)
3. ☐ Ikke forsøkt, tester følte det utrygg(0p)
4. ☐ Ikke forsøkt, deltager følte seg utrygg(0p)
5. ☐ Deltager tar ikke instruksjon(missing)
6. ☐ Annet (spesifiser)_____
7. ☐ Deltager nektet(missing)

Deltager var ikke i stand til: = 0 poeng
Hvis tiden var > 8.7 = 1 poeng
Hvis tiden var 6.21 - 8.70 = 2 poeng
Hvis tiden var 4.82 - 6.20 = 3 poeng
Hvis tiden var < 4.82 = 4 poeng

Poeng ganghastighet (beste av to forsøk): ☐

3. Score reise/sette seg x5

Hvis deltageren ikke har forsøkt eller mislyktes, kryss av hvorfor:

1. ☐ Forsøkte, men ikke i stand til(0p)
2. ☐ Deltageren kunne ikke reise seg uten hjelp(0p)
3. ☐ Ikke forsøkt, tester følte det utrygg(0p)
4. ☐ Ikke forsøkt, deltager følte seg utrygg(0p)
5. ☐ Deltager tar ikke instruksjon(missing)
6. ☐ Annet (spesifiser)_____
7. ☐ Deltager nektet(missing)

Deltager var ikke istand til/brukte >60 sek = 0 poeng
Hvis tiden var ≥16.7 sek = 1 poeng
Hvis tiden var 13.7 – 16.69 sek = 2 poeng
Hvis tiden var 11.20 – 13.69 sek = 3 poeng
Hvis tiden var ≤ 11.19 sek = 4 poeng

Poeng reise/sette seg x5: ☐

tester:

TOTAL SCORE SPPB 1.+2.+3.: ☐

Vedlegg/tillegg til orginaltesten:

1. Ganghastighet-test
2. Reise/sette x5 m/armbruk
3. Scoring for 3m gangtest (der 4m ikke er mulig)

Ganghastighet-test:

Ganghastighet = Distanse(m)/ tid (sekunder):

Test 1. ☐m / ☐☐.☐☐sek = ☐.☐☐ m/sek

Test 2. ☐m / ☐☐.☐☐sek = ☐.☐☐ m/sek

Tolkning [1-3]:

Skrøpelig:	**Begynnende funksjonssvikt:**	**Normal:**
Økt risiko for fall Økt risiko for funksjonssvikt Økt risiko for sykehusinnleggelse Redusert innendørs og utendørsmobiltiet	Økt risiko for fall og funksjonsvikt Selvhjulpen i ADL Redusert utendørsmobilitet	Ingen økt risiko eller begrensninger i ADL og mobilitet

Reise/sette seg x5 m/armbruk: Samme instruksjon som SPPB, men med bruk av armlener på stolen.

Tid 5 repetisjoner m/armbruk: ☐☐.☐☐**sek**

Ved testing av skrøpelige populasjoner anbefales å legge til et ekstra element i tillegg til originaltesten i form av registrert tid på reise/sette seg x5 med bruk av armer (armlener på stol) der deltager ikke klarer å reise seg uten støtte.

Skåring for 3m distanse (hvis 4m ikke er mulig å gjennomføre):

Deltager var ikke i stand til:	= 0 poeng
Hvis tiden var > 6.52	= 1 poeng
Hvis tiden var 4.66 - 6.52	= 2 poeng
Hvis tiden var 3.62 - 4.65	= 3 poeng
Hvis tiden var < 3.62	= 4 poeng

1. Abellan van Kan, G., et al., *Gait speed at usual pace as a predictor of adverse outcomes in community-dwelling older people an International Academy on Nutrition and Aging (IANA) Task Force.* J Nutr Health Aging, 2009. **13**(10): p. 881-9.
2. Studenski, S., *Bradypedia: is gait speed ready for clinical use?* J Nutr Health Aging, 2009. **13**(10): p. 878-80.
3. Fritz, S. and M. Lusardi, *White paper: "walking speed: the sixth vital sign".* J Geriatr Phys Ther, 2009. **32**(2): p. 46-9.
4. Perera, S., et al., *Meaningful change and responsiveness in common physical performance measures in older adults.* J Am Geriatr Soc, 2006. **54**(5): p. 743-9.

Appendix E - REK Approval

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst	Claus Henning Thorsen	22845515	13.03.2018	2018/206 REK sør-øst C
			Deres dato:	Deres referanse:
			09.01.2018	

Vår referanse må oppgis ved alle henvendelser

Stefan Kölsch
Universitetet i Bergen

2018/206 ALMUTH

Forskningsansvarlig: Universitetet i Bergen
Prosjektleder: Stefan Kölsch

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK sør-øst C) i møtet 15.02.2018. Vurderingen er gjort med hjemmel i helseforskningsloven (hfl.) § 10.

Prosjektleders prosjektbeskrivelse
ALMUTH prosjektet skal se på effekten av sang og trening hos personer med Alzheimers sykdom (AS). Deltakere vil deles inn i tre forskjellige grupper, musikkgruppen, treningsgruppen og kontrollgruppen. Intervensjoene skal vare i 12 måneder og deltakerne vil bli testet før og etter med fysiske tester (fMRI, DTI, MR) og mentale tester (nevropsykologiske tester). Mentale tester vil se på kogntive evener som persepsjon, hukommelse og oppmerksomhet. Både de fysiskse og mentale testene vil gjøres to ganger, en gang før intervensjon og en gang etter intervensjon. Deltakere planlegges også å følges opp 2 og et halvt år og 5 år etter avsluttet intervensjon. En gang i uken vil deltakerne i intervensjonsgruppene få en time med sangundervisning for musikkgruppen og gruppetime med ulik trening for treningsgruppen. Deltakere vil også få øvelser som de kan gjøre hjemme og en gang i måneden tilbud om gruppeaktivitet (tur og kor).

Vurdering
I dette prosjektet skal man undersøke effekten av sang, musikk og trening hos personer med Alzheimers sykdom. Hensikten er få en bedre forståelse for hvordan ulike grupper mennesker subjektivt opplever musikk, og også hvordan det å lytte til musikk kan påvirke mennesker rent fysiologisk. Et overordnet mål er bedre helse for denne pasientgruppen herunder at de kan være hjemmeboende lengst mulig.

Deltakere skal rekruttere via musikkterapeut i kommunene, dagsenter, oppslag og annonsering.
Deltakerne skal deles inn i tre forskjellige grupper,: musikkgruppen, treningsgruppen og kontrollgruppen. Intervensjonene skal vare i 12 maneder og deltakerne vil bli testet før og etter med fysiske tester (fMRI, DTI, MR) og mentale tester (nevropsykologiske tester). Ved de mentale testene vil man se pa kognitive evner (persepsjon, hukommelse og oppmerksomhet). Fysiske og mentale testene gjøres to ganger, før og etter intervensjonen.

Intervensjonen består av ukentlig (en gang) sangundervisning (musikkterapi) for musikkgruppen og gruppetime med ulik trening for treningsgruppen. Deltakerne vil ogsa fa øvelser som de kan gjøre hjemme, og en gang i måneden vil de få tilbud om gruppeaktivitet (tur og kor).

Besøksadresse:
Gullhaugveien 1-3, 0484 Oslo

Telefon: 22845511
E-post: post@helseforskning.etikkom.no
Web: http://helseforskning.etikkom.no/

All post og e-post som inngår i saksbehandlingen, bes adressert til REK sør-øst og ikke til enkelte personer

Kindly address all mail and e-mails to the Regional Ethics Committee, REK sør-øst, not to individual staff

Studien har to hovedutfall; nevrovitenskaplig mål (hjerneanatomi) og adferdsmål (livskvalitet/mental tilstand).

Det fremgår at man planlegger å følge opp deltakerne etter henholdsvis 2 ½ år og 5 år etter avsluttet intervensjon, men komiteen legger til grunn at dette ikke er en del av denne søknaden og tar således ikke stilling til dette.

Komiteen oppfatter dette som en grundig og velskrevet søknad, med mye henvisning til litteratur.

Komiteen bemerker at effekten av sang og trening for så vidt har vært undersøkt i tidligere studier, og at det således kan stilles spørsmål ved hvor mye ny kunnskap denne studien kan avstedkomme. Dette prosjektet har imidlertid et design som gjør at det ikke kan utelukkes at man kan finne ut noe nytt, og komiteen vurderer derfor studien til å falle innenfor helseforskningslovens virkeområde.

Komiteen mener det er godt redegjort for styrkeberegning. Det konkluderes med behov for å rekrutterer totalt 135 hjemmeboende personer med Alzheimer, det vil si 45 i hver av de tre gruppene.

Den skisserte beredskap i forhold til utilsiktede funn ved MR-undersøkelse, er etter komiteens mening tilfredsstillende. Det vises til at vanlig prosedyre ved Haukeland er at en lege ser gjennom alle fMRI bilder før de gis til forskerne. Skulle det være noe, tar lege kontakt med pasienter direkte. Det er i tillegg to leger som er tilknyttet prosjektet, og som er tilgjengelig for spørsmål hvis det skulle være aktuelt. Kontaktinformasjon til legene vil bli delt ut ved behov.

Komiteen forutsetter at de som takker nei til deltakelse i studien blir tilbudt standardbehandling**.**

Komiteen forutsetter videre at deltakernes samtykkekompetanse vurderes av kompetent person.

Informasjonsskriv
Komiteen mener vedlagte pasientinformasjonen er god.

Ettersom man i prosjektet ønsker samtykke fra både pasienter og pårørende, må det utarbeides et separat informasjons-/samtykkeskriv til pårørende.

Ut fra dette setter komiteen følgende vilkår for prosjektet:
Det må utarbeides informasjons-/samtykkeskriv til pårørende.

Vedtak
Prosjektet godkjennes under forutsetning av at ovennevnte vilkår oppfylles, jf helseforskningslovens §§ 9 og 33.

I tillegg til vilkår som fremgår av dette vedtaket, er tillatelsen gitt under forutsetning av at prosjektet gjennomføres slik det er beskrevet i søknaden og protokollen, og de bestemmelser som følger av helseforskningsloven med forskrifter.

Tillatelsen gjelder til 01.02.2021. Av dokumentasjons- og oppfølgingshensyn skal opplysningene likevel bevares inntil 01.02.2026. Opplysningene skal lagres avidentifisert, dvs. atskilt i en nøkkel-og en opplysningsfil. Opplysningene skal deretter slettes eller anonymiseres, senest innen et halvt år fra denne dato.

Komiteens avgjørelse var enstemmig.

Klageadgang
Komiteens vedtak kan påklages til Den nasjonale forskningsetiske komité for medisin og helsefag, jfr. helseforskningsloven § 10, tredje ledd og forvaltningsloven § 28. En eventuell klage sendes til REK sør-øst C. Klagefristen er tre uker fra mottak av dette brevet, jfr. forvaltningsloven § 29.

Sluttmelding og søknad om prosjektendring
Prosjektleder skal sende sluttmelding til REK sør-øst på eget skjema senest 01.08.2021, jf. hfl. § 12. Prosjektleder skal sende søknad om prosjektendring til REK sør-øst dersom det skal gjøres vesentlige endringer i forhold til de opplysninger som er gitt i søknaden, jf. hfl. § 11.

Med vennlig hilsen

Britt Ingjerd Nesheim
Prof.dr.med,
Leder REK sør-øst C

Claus Henning Thorsen
Rådgiver

Kopi til: Universitetet i Bergen ved øverste administrative ledelse: post@uib.no

Appendix F - Informed Consent Form

PÅRØRENDE SAMTYKKESKJEMA

«2018/2020 ALMUTH Musikk terapi og Alzheimers prosjektet»

Bakgrunn og hensikt

Dette er et spørsmål til deg som pårørende til en person med hukommelsesproblemer om at du og den du er pårørende for deltar i et forskningsprosjekt. Forskningsprosjektet undersøker hvordan hjernen og adferd kan endre seg ved hjelp av musikk eller fysisk aktivitet for personer med en forhøyet risiko for Alzheimer sykdom. Institutt for Biologisk og Medisinsk Psykologi ved Universitetet i Bergen er ansvarlig for studien. Undersøkelsen er knyttet til Alzheimer sykdom i tidlig fase, og derfor spør vi kun personer som kan ha en forhøyet risiko for å utvikle Alzheimer sykdom, om å delta. Dette inkluderer, men er ikke begrenset til, personer med Alzheimer sykdom i tidlig fase og personer med mild kognitiv svikt. Personer med alvorlige hørselsproblemer vil ikke kunne delta. Videre kan man heller ikke delta hvis man er gravid, lider av klaustrofobi, har andre nevrologiske lidelser, metall-implantater i kroppens bløtvev, bor på sykehjem, eller hvis man står på visse typer medisiner.

Hva innebærer din deltakelse?

Studien er delt opp i tre grupper. En gruppe vil få sangundervisning og delta på kor, en annen gruppe vil få fysisk aktivitet og delta på turer, mens den siste gruppen vil ikke tilbys noen aktiviteter. Det er tilfeldig hvilken gruppe man havner i da dette avgjøres ved loddtrekning. Intervensjonene vil foregå en gang i uken, samt en gang i måneden med flere av de andre i samme forsøksgruppe. Uavhengig av hvilken gruppe man havner i vil deltakere bli bedt om å gjennomføre en rekke undersøkelser og spørreskjemaer. Disse undersøker kognisjon, språk og mulig sykdomsforløp. Alle deltakere vil også gjennomføre en MR-undersøkelse, hvor vi tar en rekke bilder av hjernen deres mens de ligger stille og får høre på musikk og se på bilder. Hele undersøkelsen varer ca. 2 timer, men vil ikke nødvendigvis skje samme dag. Vi er fleksibel og prøver å gjøre det som passer best for dere. De fleste av testene vil tas to ganger; en gang i begynnelsen og en gang etter 12 måneder. Noen av testene vil kun tas i begynnelsen eller kun etter 12 måneder.

Noen deltakere vil også bli spurt om de kan filmes under aktivitetene. Utvalg av deltakere til videoobservasjon vil følge praktiske muligheter og begrensninger. For å forstå hvorfor og hvordan intervensjonen virker (eller ikke virker) er det viktig å analysere gjennomføring av intervensjonen.

Dette bidrar til forståelsen av hvordan terapeuten og deltakeren jobber sammen og hvilke endringer som skjer gjennom forløpet. Deltakere kan når som helst reservere seg mot å bli filmet eller be om å få tidligere filmopptak slettet, uten at dette påvirker aktiviteten vi tilbyr. Videoopptak lagres kun på en lokal datamaskin uten tilkobling til internett, som er sikret med passord og oppbevares på et låst rom på UiB. Etter prosjektslutt vil videomaterialet bli slettet.

Vi ønsker også å innhente informasjon fra **deg** om hvordan det er å være pårørende for en person med kognitiv svikt, og om intervensjonene også kan forbedre dette samspillet. Dette innebærer at du fyller ut to spørreskjemaer angående depresjon og belastning. Disse spørreskjemaene vil også gis to ganger, en gang i begynnelsen og en gang etter 12 måneder.

Alle opplysninger om dere vil bli av-identifisert og ditt personvern vil bli ivaretatt (se avsnitt «Hva skjer med informasjonen om dere?»).

Mulige fordeler og ulemper

De ulike delene av studien har ulike ulemper og fordeler – og her er en kort oversikt over dem.

1. Noen av testene vi utfører og testsituasjonen i seg selv kan oppleves ubehagelig. Noen av spørsmålene er enkle, mens andre er vanskelige. Vi forventer ikke at noen skal klare alt. Spørreskjemaene vi benytter kan også føles ubehagelig for noen da vi spør om personlige ting. Imidlertid vil all informasjon beskyttes og deres personvern vil bli ivaretatt. Disse testene regnes for å være uten risiko.

2. MR-undersøkelsen innebærer at deltakere ligger i en MR-skanner ved Haukeland universitetssykehus. Det finnes en potensiell helse- og sikkerhetsrisiko for enkelte personer i MR eksperimenter. Det sterke magnetfeltet til MR-skanneren kan ha ødeleggende effekt for mennesker som har metalldeler i kroppen (f.eks. kirurgiske klips, pacemaker, metallspon). MR-skanneren kan bråke og deltakere må ligge stille i omtrent 40 minutter i et trangt kammer. Dette kan medføre uro og ubehag.

MR-avbildning av hjernen kan avdekke uregelmessigheter som kan kreve ytterligere medisinsk undersøkelse. Det kan føre til funn av hittil ukjente medisinske tilstander, men det kan også gi falske alarmer – f.eks. oppdagelse av en tilsynelatende skadelig tilstand som egentlig er ufarlig. Slike tilfeldige funn, uavhengig om de viser seg å være skadelige eller ufarlige, kan føre til uro. På den annen side kan eventuelle tilfeldige funn av alvorlige sykdommer som ellers ville vært uoppdaget, føre til tidligere behandling og bedre prognose. Alle MR-bilder vil bli vurdert av en radiolog ved Haukeland universitetssykehus. Bildene vil også bli sett på av en lege ved Haukeland

universitetssykehus før forskerne får bildene. Hvis det dukker opp uvanlige funn på MR bildene vil en lege kontakte dere direkte.

Generelt ansees MR som en trygg metode med ingen kjente korte eller langvarige skadelige effekter for nevrologisk friske deltakere.

3. Dere bidrar til forskning og økt kunnskap om hukommelsesproblemer og Alzheimers sykdom.

Hva skjer med informasjonen om dere?

Informasjonen som registreres om dere skal kun brukes slik som beskrevet i hensikten med studien. Alle opplysningene vil bli behandlet uten navn, fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter dere til deres opplysninger gjennom en navneliste, men denne navnelisten oppbevares alltid adskilt fra svarene i studien. Det vil heller ikke være mulig å identifisere dere i resultatene av studien når disse publiseres. Deres opplysninger er med andre ord av-identifisert, og kun autorisert personell knyttet til prosjektet har tilgang til navnelisten som kan knytte dere til personopplysninger. Deres kontaktinformasjon vil deles med våre samarbeidspartnere (f.eks. musikkterapeuter og fysioterapeuter) for å kunne følge dere opp på best mulig måte og for å kontakte dere i forbindelse med de ulike intervensjonsgruppene. Personopplysningene/deltakerlisten vil slettes når prosjektet er ferdig i 2021, mens innsamlet data lagres med et anonymt referansenummer som ikke lenger kan spores tilbake til dere. Kun prosjektmedarbeidere ved ALMUTH prosjektet på avdelingen for biologisk og medisinsk psykologi har tilgang til data. I løpet av prosjektperioden vil deler av innsamlet materiale imidlertid kunne utveksles med samarbeidende institusjoner (Haukeland universitetssykehus, UNI Research AS). Dette samarbeidet bidrar til å kunne gjennomføre tilleggsanalyse og for å oppnå større grupper og mer relevante funn. Dataene vil eventuelt deles i av-identifisert form og uten navn. Senest fem år etter at prosjektet er avsluttet vil alle kode-nøkler bli slettet, slik at all data er fullstendig av-identifisert.

Frivillig deltakelse

Det er frivillig å delta i studien. Dere kan når som helst og uten å oppgi noen grunn trekke samtykke til å delta i studien. Vi understreker også at å trekke seg fra studien ikke vil få noen konsekvenser for dere. Dersom du ønsker å delta, samt at personen du er pårørende for deltar, undertegner du samtykkeerklæringen på siste side. Om du nå sier ja til å delta, kan du når som helst trekke tilbake ditt samtykke uten at dette får noen konsekvenser. Dersom dere senere ønsker å trekke dere eller har

spørsmål om studien, kan du kontakte Birthe Flo (telefon 55 58 62 09 / 46 88 46 92 eller e-post: birthe.flo@uib.no).

Ytterligere informasjon om studien finnes i kapittel A – utdypende forklaring av hva studien innebærer. Ytterligere informasjon om personvern, økonomi og forsikring finnes i kapittel B – Personvern, økonomi og forsikring. Samtykkeerklæring følger etter kapittel B.

Kapittel A- Utdypende forklaring av hva studien innebærer.

Hvilke rettigheter og forpliktelser har dere som deltakere? Deltakelse er frivillig og krever samtykke hvor dere som deltakere må gjøre dere kjent med dette informasjonsskrivet og undertegner samtykket om dersom dere ønsker å delta. Som deltakere i forskningsprosjektet har dere ingen forpliktelser, og kan når som helst trekke dere fra prosjektet uten å oppgi grunn. Dere kan også be om at data vi har samlet fra dere slettes og ikke brukes. Det vil ikke ha noen konsekvenser for dere å trekke dere fra prosjektet. Fullfører dere prosjektet vil dere få skriftlig tilbakemelding om forskningsprosjektets resultater og konklusjon etter forskningsprosjektet er avsluttet. Prosjektet vil senest være avsluttet 2021.

Kapittel B – Personvern, økonomi og forsikring

Personvern: Opplysninger som registreres om dere er lite person-sensitive, og vil handle om kjønn, alder, høyde og vekt. Resultatene fra MR-undersøkelsen er anonyme og ikke egnet til identifisering. Andre forskere kan få tilgang til de anonymiserte resultatene, spesielt i en analyse-situasjon eller hvis eventuelle resultater fra studien offentliggjøres og bakgrunnsdata etterspørres - men kun autorisert personell med direkte tilknytning til studien vil ha tilgang til navn. Utlevering av materiale og opplysninger til andre: Hvis dere sier ja til å delta i studien, gir dere også samtykke til at deres avidentifiserte opplysninger utleveres til andre forskningsmiljøer og institusjoner, f.eks. gjennom formidling av forskningsresultater. Dette kan være land med lover som ikke tilfredsstiller europeisk personvernlovgivning. Men vi understreker at vi ikke under noen omstendighet vil dele ut opplysninger som kan identifisere dere eller knytte dere til studien.

Rett til innsyn og sletting av opplysninger om dere og sletting av bilder: Hvis dere sier ja til å delta i studien, har dere rett til å få innsyn i hvilke opplysninger som er registrert om dere. Dere har videre rett til å få korrigert eventuelle feil i de opplysningene vi har registrert. Dersom dere trekker dere fra studien, kan dere kreve å få slettet innsamlede opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner.

Finansiering av studien: Studien er finansiert gjennom forskningsmidler fra Norsk Forskningsråd.

Forsikring: Som deltager i studien er man forsikret gjennom Pasientskadeerstatningsloven.

Godkjenning: prosjektet er godkjent av Regional Komite for medisinsk og helsefaglig forskningsetikk, (2018/206)

Samtykke til deltakelse i studien:

Jeg er villig til at jeg og den jeg er pårørende for deltar i studien

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(Signert av prosjektdeltaker, dato)

Jeg bekrefter å ha gitt informasjon om studien

(Signert, rolle i studien, dato)