Alar Kaskikallio

The Effect of Vascular Brain Changes on Cognitive Function in Normal Aging, Mild Cognitive Impairment and Alzheimer's Disease

Åbo Akademi University

The Effect of Vascular Brain Changes on Cognitive Function in Normal Aging, Mild Cognitive Impairment and Alzheimer's Disease

Alar Kaskikallio

Psychology
Faculty of Arts, Psychology, and Theology
Åbo Akademi University
Turku, Finland, 2021

Supervised by:
Dr. Petra Grönholm-Nyman, PhD
Department of Psychology
Åbo Akademi University
Finland

Docent Mira Karrasch, PhD, Clinical Neuropsychologist
Department of Psychology
Åbo Akademi University
Finland

Reviewed by:
Associate Professor Michael Rönnlund, PhD
Department of Psychology
Umeå University
Sweden

Associate Professor Grégoria Kalpouzos, PhD
Aging Research Centre
Karolinska Institutet
Sweden

Opponent:
Associate Professor Grégoria Kalpouzos, PhD
Aging Research Centre
Karolinska Institutet
Sweden

Cover art: Ella Kahila

ISBN 978-952-12-4077-5 (printed)
ISBN 978-952-12-4078-2 (digital)
Painosalama Oy – Turku, Finland 2021

To Tanja and Aatos

Contents

ACKNOWLEDGEMENTS

First, I wish to warmly thank all the participants who took their time to participate in the data collection. This thesis would not exist without you.

I was especially fortunate to have Dr. Petra Grönholm-Nyman as my supervisor. Thank you Petra for always being there and helping me in countless things, be it scientific matters, manuscript editing, baby clothes or instruction for Peppi. The advice, encouragement and warm support that you have showered me (and all the other students!) with is invaluable. I had a another lucky strike with Docent Mira Karrasch being my second supervisor. Thank you Mira for all the scientific and clinical advice, stimulating conversations and weird humor. Your aerial ladyship has a wonderful ability to clarify complex topics into appetizing mental snacks. Both of you have taught me immensely about doing research. Thank you for being awesome.

Associate Professor Michael Rönnlund and Associate Professor Grégoria Kalpouzos provided thorough evaluations and feedback on the manuscript, which helped to improve and refine the final version of the thesis. Additionally, it was an honor having Associate Professor Grégoria Kalpouzos serve as my opponent in the public defense of this thesis.

This thesis would not have been possible without the funding provided by the Department of Psychology as well as the Doctoral training program at the Faculty of Arts, Psychology and Theology at Åbo Akademi University. Furthermore, I am indebted to the National PET-Centre in Turku for providing the research data used in this thesis.

It was a privilege to be able to collaborate with such a group of talented academic minds. Professor Juha Rinne was one of the prime movers behind the original data collection and provided valuable feedback during the project. Additionally, I was fortunate to be able to rely on the solid expertise of Professor Riitta Parkkola and Dr. Terhi Tuokkonen regarding the visual assessments of neuroimaging data and on Dr. Juha Koikkalainen and Dr. Jyrki Lötjönen of Combinostics Ltd. for the quantified analysis of neuroimaging data.

I wish to also thank: the senior academic brains at the department who have helped me along the way; the past and present fellow doctoral students who have similarly dived into the depths of murky statistics and “constructive” reviewer comments, and (hopefully) emerged

triumphant without PTSD; the bright undergraduate students I've had the privilege and pleasure of teaching over the years (too many of you to name!); all the other wonderful people at the Department of Psychology, The Faculty of Arts, Psychology and Theology and other places/dimensions at Åbo Akademi University. Thank you: Dr. Katarina Alanko, Associate Professor Jan Antfolk, Dr. Daniel Fellman, Dr. Katariina Finnilä, Dr. Annika Gunst, Dr. Ada Johansson, Associate Professor Patrick Jern, Linda Karlson, Paula Kresanov, Marianne Källström, Professor Matti Laine, Professor Minna Lehtonen, Dr. Karolina Lukasik, Keni Miettinen, Sabina Nickull, Yasmin Nyqvist, Daniel Sahlgren, Rosa Salmela Dr. Anna Soveri, Catharina Walldén, Dr. Otto Waris, A special thank you to: Liisa Ritakallio for the moral support, creative puns and camaraderie in keeping the office neat and tidy; Dr. Minja Westerlund for the awesome side-collaboration, ångestlådan and video game analyses; Dr.[2] Jussi Jylkkä for the cerebral and mind-bending discussions about philosophy, consciousness and cyborgs, among other things.

I am also indebted to a host of wonderful and talented psychologists and neuropsychologists from other instances. These include Dr. Ulla Ellfolk, Taru Nikkilä, Anna Ryösä and others from TYKS Neuro, as well as Emilia Häyry, Arja Lilja, Sanna Lyly, and Jenni Siikavirta from the Masku Neurological Rehabilitation Centre. I am especially grateful to Marja-Kaisu Norvasuo-Heilä and Elina Okker for their guidance in the realm of clinical neuropsychology. A special thank you goes out to Dr. Carina Saarela as well, for her support, expertise and exemplary perseverance, first in the clinical trenches and later in the battlefields of research.

Additionally, I would like to thank my original alma mater, i.e., the University of Turku, and more specifically the Department of Psychology and Speech-Language Pathology as well as the psychology students' organization Fobia, for nourishing me during my bachelor's and master's studies. The department included characters such as Professor Pekka Niemi, Professor Heikki Hämäläinen and Professor Jukka Hyönä, who instilled a lasting appreciation and awe towards psychology and neuropsychology as a science. Furthermore, Docent Kätlin Peets is long overdue a thank you for supervising my master's thesis.

Various other people, groups and things have contributed to the sanity and wellbeing of the author and thus to the completion of this thesis. In no particular order I give my thanks and a shout-out to: The whiskey distilleries in Islay Island; The wonderful and crazy gentlemen that trace their origin to the Lahti region (i.e., Riku Mikkonen, Aaro Noponen; Joonas Niilola, Markus Iivonen, Joonas Teurokoski, Teemu Laine); Finnish-Swedish dictionaries; The "Game-group" (i.e., Satu

Östman, Lauri Östman, Suvi Holm & Janne-Matti Holm); Atlus USA and pre-EA Bioware; Municipal day-care in Turku; The Cock!tail-aficionados (i.e., Antti Riipinen & Antti Saloranta); The forests and beaches of Ruissalo island; The Baby Madness Support Group (i.e., Antti Tuominen, Pilvi Lehtilä, Minna Takku, Matti Rautiainen); Professor Andy Field and his bible on statistics; The finno-ugric/poro-language expert Liliana Listus; The Psychological Association of Southwest Finland (Tupsy) and the awesome people in it; Ella Kahila and her work on the cover page as well as sage advice on plants, tequila and other topics; Santeri Heinonen and all the beers that have been drunk as well as those waiting their turn.

I also wish to thank my mother Anne as well as my parent-in-laws Tiina and Kimmo for their continued support (and help in child-rearing). Finally, the greatest gratitude I offer to you, Tanja and Aatos. You guys make life meaningful. No mere words can do justice for that.

Turku, spring of 2021

LIST OF ORIGINAL PUBLICATIONS

The present thesis is based on the following original peer-reviewed publications.

I. Kaskikallio, A., Karrasch, M., Rinne, J. O., Tuokkola, T., Parkkola, R., Grönholm-Nyman, P. (2019). Cognitive Effects of White Matter Pathology in Normal and Pathological Aging. *Journal of Alzheimer's Disease*, 67(2), 489-493. DOI: https://doi.org/10.3233/jad-180554 [a]

II. Kaskikallio, A., Karrasch, M., Rinne, J. O., Tuokkola, T., Parkkola, R., Grönholm-Nyman, P. (2020). Domain-specific cognitive effects of white matter pathology in old age, mild cognitive impairment and Alzheimer's disease. *Journal of Aging, Neuropsychology and Cognition*, 27(3), 453-470. DOI: https://doi.org/10.1080/13825585.2019.1628916 [b]

III. Kaskikallio, A., Karrasch, M., Koikkalainen, J., Lötjönen, J., Rinne, J. O., Tuokkola, T., Parkkola, R., Grönholm-Nyman, P. (2019). White Matter Hyperintensities and Cognitive Impairment in Healthy and Pathological Aging: A Quantified Brain MRI Study. *Dementia and Geriatric Cognitive Disorders*, 48(5-6), 297-307. DOI: https://doi.org/10.1159/000506124 [c]

IV. Kaskikallio, A., Karrasch, M., Koikkalainen, J., Lötjönen, J., Rinne, J. O., Tuokkola, T., Parkkola, R., Grönholm-Nyman, P. (2021). Effects of White Matter Hyperintensities on Verbal Fluency in Healthy Older Adults and MCI/AD. *Frontiers in Aging Neuroscience, 13,* 194. DOI: https://doi.org/10.3389/fnagi.2021.614809 [d]

[a] Reprinted under the terms of the Creative Commons Attribution Non-Commercial License (CC BY-NC 4.0).
[b] Reprinted under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License (CC NC-ND-BY 4.0).
[c] Reprinted with permission from copyright holders.
[d] Reprinted under the terms of the Creative Commons Attribution License (CC BY 4.0).

ABSTRACT

Aging is associated with an increased risk for developing vascular pathology in cerebral white matter (WM). These brain changes can have a variety of cognitive repercussions, ranging from insignificant to mild cognitive impairment to dementia. Concomitant WM pathology is also frequently found in patients with mild cognitive impairment (MCI) and Alzheimer's disease (AD). Previous research generally supports the notion that WM pathology and AD-related pathology would have a cumulative impairing effect on cognition, but relatively few studies have focused on studying these effects. Thus, the aim of this thesis was to investigate the effects of WM pathology on cognitive function in cognitively healthy older adults and patients with MCI or AD.

Study I investigated the effects of WM pathology on general cognitive functioning as measured by the CERAD-NB and utilized visual ratings of magnetic resonance imaging (MRI) data. Here, AD patients with severe frontal WM pathology had markedly lower performances than AD patients with milder pathology.

Study II utilized the same sample as Study I but expanded the scope of analysis to include four specific cognitive domains. Frontal WM pathology was associated with lower cognitive performance in processing speed and visual memory, and parieto-occipital WM pathology solely with processing speed, in all groups. Furthermore, notably slower processing speed performance was seen in AD patients with moderate or severe left frontal WM pathology than in AD patients with less cerebrovascular pathology in that region.

Study III included the same four cognitive domains as Study II but utilized quantitative volumetric measurements of WM pathology. A portion of the sample used in Study II had to be excluded due to inadequate MRI resolution, which resulted in combining the MCI and AD groups into a single patient group. Overall, temporal and parieto-occital WM pathology were associated with lower processing speed, and parieto-occipital WM pathology with lower verbal memory. Furthermore, a group-specific effect was seen in the follow-up analyses: Here WM pathology in the left temporal lobe was associated with lower processing speed only in MCI or AD patients.

Study IV utilized the same sample and image analysis methods as Study III but focused solely on verbal fluency. Here, WM pathology in bilateral frontal, bilateral parieto-occipital and right temporal areas was associated with semantic fluency in right-handed participants. However, no cumulative effects on verbal fluency impairment were seen specifically in patients with MCI or AD.

The results of this thesis support the notion that WM pathology and AD-related pathologies can have cumulative effects on cognition. More specifically, AD patients who have major levels of WM pathology especially in frontal cerebral areas are likely to exhibit more cognitive impairments when compared to patients with milder levels of WM pathology. Impairments may show up as slowed information processing speed and lowered general cognitive functioning, which can be detected with general-level cognitive measures such as the Total Score of the CERAD-NB. As previous studies have shown that the prevalence of WM pathology can be lowered by minimizing modifiable risk factors and fostering physical and cognitive activity, the pre-emptive targeting of these factors is likely to yield long-term benefits in maintaining cognition in MCI and AD.

SVENSK SAMMANFATTNING

Åldrande har förknippats med en ökad risk för att utveckla vaskulär patologi i hjärnans vita vävnad. De funktionella konsekvenserna av dessa vaskulära förändringar kan variera från nästan inga konsekvenser alls till lindrig kognitiv störning eller till och med demens. Hos patienter med mild kognitiv svikt (MKS) och Alzeimers sjukdom (AS) förekommer ofta samtidig vitvävnadspatologi med annan för dessa tillstånd typisk hjärnpatologi. Tidigare forskning stöder generellt uppfattningen att vitvävnadspatologi och AS-relaterad patologi skulle ha en kumulativ försämrad effekt på kognitionen, men relativt få studier har fokuserat på att studera dessa effekter. Syftet med denna avhandling var således att undersöka vitvävnadspatologins effekt på den kognitiva funktionen hos friska äldre vuxna och patienter med MKS eller AS.

Studie I fokuserade på sambandet mellan vitvävnadspatologi och allmän kognitiv funktion, vilket mättes med CERAD-NB. Visuella uppskattningar av magnetresonansavbildningdata användes. Resultaten tydde på att AS-patienter med svår frontal vitvävnadspatologi presterade betydligt sämre än AS-patienter med mildare patologi.

Studie II inkluderade samma sampel försökspersoner som i studie I, men i denna studie undersöktes fyra specifika kognitiva domäner. En svårare grad av frontal vitvävnadspatologi var i alla grupper associerad med lägre kognitiva prestationer i processeringshastighet och visuellt minne, och därtill var parieto-occipital vitvävnadspatologi associerad med processeringshastighet. Dessutom var AS-patienter som hade måttlig eller svår vänsterfrontal vitvävnadspatologi betydligt långsammare än AS-patienter med mildare cerebrovaskulär patologi.

Studie III innefattade samma fyra kognitiva domäner som undersöktes i studie II, men i studie III användes kvantitativa volymetriska mätningar av vitvävnadspatologi i stället för visuella uppskattningar. En del av samplet som användes i studie II måste uteslutas på grund av otillräcklig spatiell upplösning, vilket resulterade i att MKS- och AS-grupperna kombinerades till en enda patientgrupp. Sammantaget var vitvävnadspatologin i de temporala och parieto-occipitala loberna förknippad med lägre prestationer i processeringshastighet och parieto-occipital patologi med lägre prestationer i verbalt minne. Dessutom var vitvävnadspatologi i temporalloben associerad med sämre informationsbearbetningshastighet specifikt i patientgruppen.

Studie IV använde samma analysmetod av hjärnavbildningsdata som studie III men studie IV fokuserade enbart på verbal ordfluens. Här var vitvävnadspatologi frontal, parieto-occipitala och temporala områden

associerad med semantisk ordfluens I högerhänt deltagare. Emellertid sågs inga kumulativa effekter på nedsatt prestation i verbal fluens hos patienter med MKS eller AS.

Resultaten i denna avhandling stöder uppfattningen om att vitvävnadspatologi och AS-relaterade patologier kan ha kumulativa effekter på kognition. Mer specifikt, AS-patienter som har en större grad av vitvävnadspatologi, särskilt i frontala hjärnområden, kommer sannolikt att uppvisa större kognitiva svårigheter jämfört med patienter med mildare nivåer av vitvävnadspatologi. Nedsättningar kan komma till synes som förlångsammad informationsbearbetningshastighet och nedsatt allmän kognitiv funktionsförmåga, vilket kan undersökas med hjälp av mått för allmän kognition, såsom CERAD-NB:s totalpoäng. Tidigare forskning har visat att prevalensen av vitvävnadspatologi kan sänkas genom att minimera modifierbara riskfaktorer och genom att främja fysisk och kognitiv aktivitet, vilket betyder att man genom förbyggande åtgärder sannolikt långsiktigt kan uppnå positiva effekter när det kommer till att upprätthålla den kognitiva funktionsförmågan i MKS och AS.

ABBREVIATIONS

AD	Alzheimer's disease
CERAD/CERAD-NB	Consortium to Establish a Registry for Alzheimer's disease Neuropsychological Battery
CERAD-TS	CERAD-NB Total Score
DTI	Diffusion tensor imaging
FLAIR	Fluid attenuated inversion recovery
GM	Grey matter
MCI	Mild cognitive impairment
MMSE	Mini-Mental State Examination
MRI	Magnetic resonance imaging
WAIS-R	Wechsler Adult Intelligence Scale Revised
WMS-R	Wechsler Memory Scale Revised
WM	White matter
WMH	White matter hyperintensities

1. INTRODUCTION

Dementia affects large numbers of aging people, and its prevalence is increasing worldwide due to population aging (Alzheimer's Disease International, 2013). The most common cause of dementia is Alzheimer's disease (AD), accounting for about 60 % of cases worldwide (Rizzi et al., 2014). This is followed by vascular dementia, that accounts for at least 15-20 % of cases (Lobo et al., 2000; Rizzi et al., 2014).

Patients with mild cognitive impairment (MCI), especially its amnestic variant, often convert to AD over time (Roberts et al., 2012). Alzheimer's disease itself has an insidious symptom progression typically beginning with mild episodic memory impairment and ending in global dementia (Förstl & Kurz, 1999). The neuropathologic developments seen in AD are primarily cortical in nature, affecting especially grey matter (GM), i.e., the cell bodies of billions of interconnected neurons in the central nervous system (Wenk, 2003). In contrast, vascular dementia is often caused by subcortical cerebral small vessel disease (Dichgans & Leys, 2017), the neuropathological hallmark of which are lesions in cerebral white matter (WM) (Smith, 2016). White matter consists mainly of myelinated axons that form fiber tracts and connect various cerebral regions (Herculano-Houzel, 2009; Kolb & Whishaw, 2003).

The risk for pathological developments in WM increases overall in old age (DeCarli et al., 2005). Furthermore, there exists substantial overlap between AD and cerebrovascular pathology, as the two pathologies share the same risk factors, are often encountered together, and predict each other (Breteler, 2000; Duron & Hanon, 2008; Prins et al., 2004; Prins & Scheltens, 2015; Salvadó et al., 2019; Smith, 2016; Wolf et al., 2000).

Previous research has generally supported the notion that WM pathology and AD-related pathology would have a cumulative effect on cognitive functioning (e.g., Bilello et al., 2015; Brickman et al., 2008; Mortimer, 2012; Petrovitch et al., 2005; Toledo et al., 2013; Tosto et al., 2014). However, the differences in how WM pathology affects cognition between cognitively healthy adults, MCI patients and AD patients has typically not been a focus in previous studies, and knowledge about the effects in specific cognitive domains is scarce.

Increasing knowledge of the cognitive repercussions that can follow from cerebrovascular pathology might be beneficial in particular to clinicians working in cognitive rehabilitation and assessment. Furthermore, as vascular risk factors can be modified by life-style choices (Brini et al., 2018), identifying the impact of cerebrovascular

pathology on cognition in geriatric populations is also important from a public health perspective.

The present thesis investigated the effects of WM pathology on cognitive function in normal aging, MCI patients and AD patients, with a focus on examining possible cumulative effects in MCI and AD patients.

1.1. The continuum of Alzheimer's disease

Alzheimer's disease is an irreversible and degenerative brain disorder that causes progressive symptoms beginning with slight episodic memory impairment and leading to loss of bodily function and death (Alzheimer's Association, 2015). In contemporary research AD has been conceptualized as a continuum that includes three overlapping stages: *Preclinical AD*, in which patients don't show cognitive or behavioural impairments but exhibit biomarker evidence of AD; *MCI due to AD*, in which patients exhibit both mild cognitive deterioration and biomarker support for AD; *Dementia due to AD*, in which patients exhibit biomarker evidence of AD and show varying degrees of dementia (Albert et al., 2011; McKhann et al., 2011; Sperling et al., 2011).

1.1.1. Preclinical Alzheimer's disease

The progression of pathology related to the AD continuum is not completely understood, but it is believed that neuropathological processes begin a decade or more before overt clinical symptoms may be seen (Morris, 2005). These include the development of neurofibrillary tangles from cellular microtubules due to the alteration of the tau protein, as well as the accumulation of amyloid-beta into extracellular areas, which interferes with intercellular communication (Samuel et al., 2002). Neuronal loss is also prevalent, and GM atrophy is seen first in areas of the temporal lobes, such as the entorhinal cortex and the hippocampus, as well as in several nuclei of the brainstem (Wenk, 2003).

Symptom progression in AD tends to be slow and subtle, with the median time span from symptom onset to death being around 8-9 years (Alzheimer's Association, 2015; Rascovsky et al., 2005). Early behavioural decline may be present years before a diagnosis is made (Jost & Grossberg, 1995), and can include inattentiveness, social withdrawal, emotional agitation or depressive dysphoria (Apostolova & Cummings, 2008; Förstl & Kurz, 1999). When cognitive deterioration is seen it often begins with impairments to episodic memory, executive functions and verbal fluency (Bäckman et al., 2004; Lezak et al., 2012).

1.1.2. Mild cognitive impairment

When patients exhibit AD-related biomarkers coupled with mild cognitive deterioration, the criteria for MCI due to AD are fulfilled (Albert et al., 2011). Mild cognitive impairment itself is traditionally regarded in many cases as a borderline condition between aging-related cognitive changes and early dementia (Petersen, 2016). It was originally characterized as a precursor to AD, but several subtypes with varying clinical presentations have been described in the last decades (Winblad et al., 2004). The amnestic MCI variant, characterized by mild memory impairment is the most prevalent, and most typically indicative of early AD (Roberts et al., 2012). Although all patients who develop dementia go through the MCI stage, it is important to note that not all patients with MCI progress to dementia (Petersen, 2016).

The risk for developing MCI is heavily age-dependent: Prevalence rates of 12-18 % have been reported for over 60 years olds (Petersen, 2016), and the annual progression rate is around 5-6 % in over 70 year olds (Roberts et al., 2012). The annual conversion rates from MCI to AD are also relatively high, averaging 6,8-8,1 % (Mitchell & Shiri-Feshki, 2009).

1.1.3. Dementia due to Alzheimer's disease

As AD progresses neuronal degenerative changes become more widespread, manifesting as cortical thinning, enlarged cerebral ventricles and GM volume loss in several cortical and subcortical areas (Zakzanis et al., 2003). With continuing cognitive deterioration, significant impairments in learning and episodic memory typically become the most prominent clinical features. Recent declarative memory incurs the greatest deterioration, whereas short-term memory, older declarative memory and implisit memory are relatively less affected (Förstl & Kurz, 1999). Complex tasks such as planning, organizing and judging become more challenging, difficulties are seen in instrumental activities of daily living and deterioration in language functions may start to affect communication (Förstl & Kurz, 1999). Patients may still be able to live somewhat independently, but they need support in organizing and handling more complex tasks (Förstl & Kurz, 1999). With disease progression cognitive impairment becomes even more broad and severe, fulfilling the requirements for moderate or severe dementia. Furthermore, the rate of decline accelerates, especially in patients with high educational attainment (Wilson et al., 2004).

1.2. White matter pathology

Most adults have some level of WM lesions (Brickman et al., 2009), and the risk for developing WM lesions increases heavily with age

(DeCarli et al., 2005). Prevalence estimations for the general population vary somewhat, but rise from a moderate 50 % of the population having them in their middle 40s (Wen et al., 2009) up to 80-95 % in over 80 year olds (de Leeuw et al., 2001; Stephan et al., 2012). White matter lesions together with lacunes are prominent manifestations of cerebral small vessel disease, which is the most common reason for developing vascular cognitive impairment and can lead to vascular dementia (Dichgans & Leys, 2017).

Contemporary research has shown a considerable amount of comorbidity and overlap between AD and cerebrovascular pathology, especially degradation in WM (Toledo et al., 2013). Both pathologies share the same risk factors, including hypertension, smoking, diabetes, hypercholesterolemia, obesity and the presence of the ε4 allele of the apolipoprotein E gene (Duron & Hanon, 2008; Salvadó et al., 2019). Additionally, the risk of AD is exacerbated by the presence of vascular diseases (Breteler, 2000) and by increased WM lesion burden (Prins et al., 2004; Wolf et al., 2000). Furthermore, comorbid vascular pathology, especially WM lesions, is often present in patients with AD (Prins & Scheltens, 2015; Smith, 2016). For example, one recent study that included 832 AD patients reported the presence of severe WM pathology in over a third of AD patients (Claus et al., 2016). Patients with MCI can also exhibit extensive WM lesions (DeCarli et al., 2001).

1.2.1. Imaging and pathophysiology

The typical method of detecting WM pathology is to analyze T2-weighted fluid attenuated inversion recovery (FLAIR) images from structural magnetic resonance imaging (MRI), where lesions appear as areas of increased signal or hyperintensities (Dichgans & Leys, 2017). White matter can also be measured by diffusion tensor imaging (DTI), a specific form of diffusion weighted MRI, measuring the diffusion of water molecules (O'Donnell & Westin, 2011). Diffusion tensor imaging is sensitive to pathological changes in the fiber microstructure (Beaulieu, 2002; Budde et al., 2011; Song et al., 2005) and can be used to map cerebral WM tractography and to measure deficits in specific WM tracts (O'Donnell & Westin, 2011).

The distribution and severity of white matter hyperintensities (WMH) are typically seen as reflecting the level of cerebrovascular pathology (Pantoni et al., 2007), but their pathophysiological origins are heterogenous and not yet completely understood (Gouw et al., 2011). Several different neuropathological processes have been proposed to contribute to the appearance of WMH, including damage or deformation of the myelin sheath (Raz et al., 2012), ischemias (Pantoni & Wallin, 2000), micro-hemorrhages (Raz et al., 2012), gliosis (Fazekas et al.,

1993), neuropil atrophy (Fazekas et al., 1998), cerebral hypoperfusion (Brant-Zawadzki, 1992), amyloid angiopathy (Gouw et al., 2011), and widened perivascular spaces (Ball, 1989).

White matter hyperintensities are most often distributed in the frontal and parietal lobes (Gootjes et al., 2004), with some studies indicating that AD patients may exhibit relatively more WMH in posterior cerebral regions specifically (Brickman, 2013; Yoshita et al., 2006). Additionally, studies utilizing DTI on AD patients have reported widespread degeneration in cerebral WM microstructure (Gold et al., 2012; Mito et al., 2018; Sexton et al., 2011); Specific tracts in the fornix, cingulum and corpus callosum have been implicated to be vulnerable already in preclinical AD (Mak et al., 2017). Interestingly, elevated WMH burden in the general population have also been shown to contribute to brain atrophy in brain regions that often show neuronal loss in AD (Habes et al., 2016).

1.2.2. Qualitative assessment: Visual rating scales

Validated visual rating scales are commonly used to assess WM pathology. These scales generally include descriptive anchors such as "focal lesions" or "beginning confluence of lesions" (Wahlund et al., 2001), that are used to assign semi-quantitative ratings of global or regional pathology according to lesion size and severity (Brickman, Sneed, et al., 2011). Scores of various WM assessment scales for both MRI and computer tomography exist (Scheltens et al., 1998). Commonly used visual rating scales include the Fazekas (1987), the Scheltens (1993) and the Wahlund (2001) scales. Although more advanced methods for quantifying imaging data have been developed in recent decades (see chapter 1.2.3.), special hardware requirements, long processing times and dependency on specific acquisition techniques among other things have effectively halted their integration into clinical work (Harper et al., 2016).

Visual rating scales have several advantages that make them well-suited for use in clinical work. They are relatively cost-effective, intuitive for radiologists to grasp without much additional training, do not require specialist software, and are ideal for analysing data that is only on radiological film, has not been collected systemically or lacks image resolution for quantitative analysis (Brickman, Sneed, et al., 2011; Harper et al., 2016). Numerous studies support the notion that visual rating scales are in many respects as valid in WMH assessment as more advanced quantitative techniques. For example, visual ratings and volumetric measurements correlate highly (Kapeller et al., 2003), show comparable associations with cognitive and physical measures (Gouw et al., 2006), and yield comparable effect sizes in meta-analysis

(Kloppenborg et al., 2014). They have also been shown to produce concordant results with DTI (Quinque et al., 2012), and often possess good inter-rater reliabilities (Fan et al., 2003; Kapeller et al., 2003). Visual rating scales naturally also have disadvantages, as they do not produce true quantitative data, require some degree of clinical background knowledge, and can be susceptible to relatively lower reliabilites with poorly trained raters (Brickman, Sneed, et al., 2011).

1.2.3. Quantitative assessment: Volumes, voxels and tracts

Various methods for quantifying WM pathology in electronic data have also been developed, allowing for the analysis of more specified regions of interest, such as specific WM tracts and even individual voxels (i.e., millimeter or submillimeter-sized image elements in 3D-space). Some of the most used quantified analysis approaches include: *Voxel-based morphometry*, which can be used to associate GM and WM tissue density with behavioural measures on a voxel-by-voxel basis (Mechelli et al., 2005); *Voxel-based symptom-lesion mapping*, which attempts to associate individual lesions containing voxels with cognitive impairments (Bates et al., 2003); *Volumetric analysis*, which may be utilized to calculate lesion volumes in specific areas, such as cerebral lobes or individual tracts, gyri or nuclei (Rorden & Karnath, 2004). Quantified analysis usually involves registering the scan of every participant to one or several 3D brain atlases, after which the data can be segmented, i.e., divided and classified into for example different tissue types and anatomical structures (Despotović et al., 2015). Finally, as WMH reflect the severe end of pathological developments in WM (Kloppenborg et al., 2014), visual rating scales or quantified MRI analysis techniques might not capture early pathological changes adequately. An imaging method which is sensitive to early pathological changes in the fiber microstructure is DTI (Beaulieu, 2002; Budde et al., 2011; Song et al., 2005).

1.3. Functional repercussions of white matter pathology

1.3.1. General associations with cognition

Neuropathological changes in WM may have direct effects on cognitive functioning by disrupting neural transmissions in cerebral networks that subserve various processes. The degree of impairment is generally related to lesion volume and severity, as mild lesions may not cause any clinically relevant changes, whereas confluent lesions can

have major repercussions on daily functioning (Brickman, Siedlecki, et al., 2011).

Findings similar to classical frontal lobe type impairments were often reported by earlier studies that examined the cognitive effects of WMH: deficits in general cognition, processing speed, attention and executive functions were reported as cardinal symptoms (e.g., de Groot et al., 2000; Gunning-Dixon & Raz, 2000; Prins et al., 2005). As research has accumulated associations with other cognitive domains have been reported, including immediate and delayed memory both in verbal and visual modalities as well as working memory, language functions and visuospatial construction (Kloppenborg et al., 2014; Vasquez & Zakzanis, 2015). White matter hyperintensities have also been linked with various neurological and psychiatric conditions in elderly populations, including depression (Gunning-Dixon et al., 2008; Herrmann et al., 2008), migraine (Paemeleire, 2009), urinary incontinence (Ogama et al., 2016) and gait and mobility disturbance (Iseki et al., 2010; Louis et al., 2008).

1.3.2. Associations between cognitive domains and within specific regions

Individual variation in symptoms related to WM pathology can be broad and one factor contributing to this variation is lesion location. Several recent studies have indicated that degradations in strategically important parts of the WM network can lead to critical impairments in processing speed, executive functions and episodic memory, even when controlling for the global WMH burden (for a review, see: Biesbroek et al., 2017). Impairments in processing speed and executive functions have been most consistently associated with degradation in WM underlying the frontal lobes as well as with pathways connecting frontal-subcortical areas, such as the forceps minor and anterior thalamic radiation (Biesbroek et al., 2013; Biesbroek, Weaver, et al., 2016; Duering et al., 2011, 2013, 2014; Jiang et al., 2018; Lampe et al., 2019). Other associations include tracts connecting various cortical regions such as the frontal-temporal uncinatus, the inferior fronto-occipital fasciculus and the superior longitudinal fasciculus (Biesbroek et al., 2013; Biesbroek, Weaver, et al., 2016; Jiang et al., 2018; Lampe et al., 2019). As for episodic memory, preliminary associations have been reported for WMH underlying the frontal, temporo-occipital, parieto-temporal and parietal areas, as well as with the internal capsule and the corpus callosum (Biesbroek, Weaver, et al., 2016; Brugulat-Serrat et al., 2019; Duering et al., 2011; Lampe et al., 2019; Smith et al., 2011).

White matter degradation can have serious repercussion to language as well. Changes in WM underlying the posterior and middle areas of the temporal lobe has been associated with various language impairments

(Dronkers et al., 2004; Henseler et al., 2014; Pustina et al., 2016; Yourganov et al., 2016) and proposed to be a structural weak point (Griffis et al., 2017; Turken & Dronkers, 2011). This is not surprising, as both the dorsal and ventral language streams run though the area (Turken & Dronkers, 2011; for an overview on the language streams see: Hickok & Poeppel, 2007; Saur et al., 2008).

A specific language function that has been researched considerably is word generation. It is regularly measured by verbal fluency tasks that require the participant to generate words in accordance with category cues (*semantic fluency*) or letter cues (*phonological fluency*) within a time limit (Lezak et al., 2012). Verbal fluency tasks generally rely on a left-lateralized cortical network which includes the left inferior/middle frontal cortex as a focal point as well as other areas such as the fusiform gyrus, temporal cortex, superior parietal cortex, caudate and anterior cingulate (Birn et al., 2010; Schmidt et al., 2019; Wagner et al., 2014). Additionally, verbal fluency performance has been associated with degradations in various WM tracts, including the arcuate fasciculus, frontal aslant tract, inferior fronto-occipital fasciculus, superior longitudinal fasciculus and the corpus callosum (Allendorfer et al., 2016; Blecher et al., 2019; Catani et al., 2013; Kinoshita et al., 2015; Peters et al., 2012; Rodríguez-Aranda et al., 2016).

1.4. The effects of white matter pathology in MCI and AD

The effects of WMH on cognitive function in MCI and AD have received some research attention. Previous neuropathological studies have reported that WM lesions lower the threshold for dementia due to AD, in essence supporting a cumulative effect of AD pathology and WMH on cognition (Petrovitch et al., 2005; Toledo et al., 2013). In vivo studies have reported that WMH load can predict cognitive decline in MCI patients (Tosto et al., 2014) and AD patients (Brickman et al., 2008), and that lesions in the fornices and corpus callosum are associated with general cognitive decline in AD patients specifically (Bilello et al., 2015). These studies utilized relatively general-level measures of cognition, the first two using Mini-Mental State Exam (MMSE) and the third a compound score of the Consortium to Establish a Registry for Alzheimer's Disease neuropsychological battery (CERAD-NB) (see chapter 2.2.1.). Finally, Rizvi et al. (2017) used more fine-grained methods (i.e., composite scores for general cognition and specific cognitive domains) and found that the effects of WMH on general cognition and episodic memory were mediated by global and medial temporal lobe thickness. This effect was seen both in cognitively healthy and patients with MCI or AD.

Relating closely to the aim of the present thesis, studies that have focused on the effects of WMH on verbal fluency in MCI and AD have likewise been fairly limited. Associations between semantic fluency and WM microstructure measures in the the corpus callosum, right anterior periventricular and posterior periventricular regions were reported by two studies (Chen et al., 2009; Kavcic et al., 2008), though a later investigation did not confirm these findings (Serra et al., 2010). Newertheless, a relatively new DTI study reported associations in line with studies by Chen et al. (2009) and Kavcic et al (2008): Here semantic fluency was associated with a bilateral network of WM tracts, and phonological fluency with a left-lateralized WM network (Rodríguez-Aranda et al., 2016). It should be noted that a pooled group of healthy controls and early AD patients was used in data analysis in the latter study, and all four verbal fluency studies included fairly limited sample sizes ($n \leq 40$).

1.5. Aims and research questions

To summarize, the prevalence of WMH rises dramatically in old age. Pathological changes in WM tracts can lead to a variety of behavioural repercussions, including multi-domain cognitive impairments. The association between WMH and cognitive impairment seems to be modified by at least lesion volume, location, and comorbidity with other neuropathologies. Of these neuropathologies WMH have an especially strong association with AD: the two pathologies are often encountered concurrently, share the same risk factors and can predict each other. Research generally supports the notion that WMH and AD pathology would have a cumulative impairing effect on cognition and the topic has received some attention. However, comparing the effects of WMH on cognitively healthy adults, MCI patients and AD patients has typically not been a main focus. Furthermore, many studies have room for improvement in methology, as most have included fairly small sample sizes, some have pooled together healthy controls and patients for data analysis, and several have utilized only relatively general-level measurements of cognition.

The general aim of the present thesis was to investigate the effects of WM pathology on cognitive function in healthy older adults and patients with MCI or AD. The intention was to study the associations between cognition, both at a general level and in specific domains, and WMH, using both clinical and quantified volumetric measurements, between cognitively healthy adults, patients with MCI and patients with AD.

Study I

The first study investigated the effects of WMH on general cognitive functioning as measured by the Total score of the CERAD-NB. White matter pathology was assessed by expert raters utilizing the Wahlund visual rating scale. As both the CERAD-NB and the Wahlund scale are used very frequently in daily clinical practice, the aim of the study was to bring forth information that would have both theoretical and clinical relevance.

Study II

The second study continued the previous line of investigation and utilized the same sample as Study I. However, the scope of analysis was expanded to include the measurements of four specific cognitive domains: cognitive processing speed, verbal-logical memory, visual-spatial memory and verbal functions. As in Study I, WM pathology was assessed by expert raters utilizing the Wahlund rating scale.

Study III

The third study included the same four cognitive domains as Study II, but utilized quantitative volumetric measurements of WMH. A portion of the MRI data had inadequate resolution and had to be excluded from analysis. Due to a decreased sample size, the MCI and AD groups were combined into a single patient group. Of particular interest here was to see if automated quantitative methods would result in findings similar to Study II, where visual ratings where used instead.

Study IV

The final study focused on the effects of WMH on verbal fluency, which begins to typically deteriorate in the early stages of AD. The study utilized the same sample and quantitative imaging analysis methods as Study III.

2. METHOD

2.1. Participants and data collection

The data for the studies was originally collected as part of the DEMPET and TWINPIB research projects (Kemppainen et al., 2006; Koivunen et al., 2011; Scheinin et al., 2011), that were conducted at the National PET-Centre in Turku, Finland over many years. Both studies were approved by the Joint Ethical Committee of the University of Turku and Turku University City Hospital and performed in accordance with the 1964 Declaration of Helsinki. The subjects received oral and written information about the study and gave informed consent prior to their inclusion.

Data collection included the recruitment of cognitively healthy controls, patients with MCI and patients with AD. The recruited participants underwent extensive neurological and neuropsychological assessments. Control subjects were volunteers who had no history of neurological or psychiatric disease and performed within age-adjusted Finnish norms in neuropsychological testing. Mild cognitive impairment was diagnosed according to the Petersen et al. criteria (Petersen et al., 2001), whereas the DSM-IV criteria for dementia as well as the NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association) criteria were used to diagnose probable AD (McKhann et al., 1984).

A minimum score of 25/30 in the MMSE test was required for inclusion in the cognitively healthy adult control group utilized in the studies. Additionally, two 24-point exceptions were admitted in light of their otherwise adequate level of cognitive performance.

2.1.1. Studies I & II

The sample in Study I originally consisted of 57 cognitively healthy adults, 40 patients with MCI and 52 patients with AD (n = 149). However, in late stages of the analysis we chose to remove an extreme outlier from the control group, bringing the final sample size to 148 participants (see Table 1). The same sample was utilized in Study II.

The three subgroups exhibited some differences regarding demographic characteristics: The controls were significantly younger than MCI patients and patients with AD, and also more educated than AD patients. Age and education were controlled for in all analyses due to these group differences. Gender distributions were equal in all three groups.

Table 1.

Demographic Characteristics of Participants in Studies I & II

	All	*Controls*	*MCI*	*AD*
n	148	56	40	52
Women %	47.3%	44.6%	45.0%	51.9 %
Age M (SD), years	72.8 (5.2)	71.4 (5.4)	74.0 (5.4)	73.5 (4.6)
Handedness:				
Right-handed	137	51	38	48
Left-handed	4	1	1	2
Ambidextreous	7	4	1	2
Education level:				
Primary school	73	22	19	32
Vocational school	57	25	13	19
Upper secondary	2	2	0	0
Academic degree	16	7	8	1

M = Mean; SD = Standard deviation; MCI = Mild cognitive impairment; AD = Alzheimer's disease.

Table 2.

Demographic Characteristics of Participants in Studies III & IV

	All	*Controls*	*MCI+AD*	*MCI*	*AD*
n	86	42	44	14	30
Women %	41.9 %	45.2 %	38.6 %	40.0 %	43.3 %
Age M (SD), years	71.8 (4.7)	71.5 (5.2)	71.0 (4.4)	71.6 (4.7)	72.2 (4.2)
Handedness:					
Right-handed	79	38	41	13	28
Left-handed	3	1	2	1	1
Ambidextreous	4	3	1	0	1
Education level:					
Primary school	43	20	23	6	17
Vocational school	32	15	17	5	12
Upper secondary	2	2	0	0	0
Academic degree	9	5	4	3	1

M = Mean; SD = Standard deviation; MCI = Mild cognitive impairment; AD = Alzheimer's disease.

2.1.2. Studies III-IV

Studies III and IV utilized a portion of the same sample as Studies I and II, but used quantified MRI data instead (see chapter 2.3.2.). Study III used the same cognitive variables as Study II, whereas new cognitive variables measuring verbal fluency were used for Study IV. A number of participants had to be excluded due to inadequate image resolution, resulting in a sample of 42 cognitively healthy adults, 14 patients with MCI and 32 patients with AD, with a total sample of 86 participants (see Table 2).

Since the individual group sizes of the MCI and AD groups were relatively small, the groups were pooled together into one patient group. No statistically significant differences were found between the groups regarding age, education or gender. However, since age and education typically have strong connections with cognitive performance, they were set as covariates in the analyses to control against possible confounding effects.

2.2. Cognitive measurements

2.2.1. Study I: General cognitive performance

The Consortium to Establish a Registry for the Alzheimer's Disease neuropsychological battery (CERAD-NB) (Morris et al., 1989) is a relatively brief assessment battery that measures several of the primary cognitive impairments typically seen in AD. The battery was originally developed in the United States in 1988, and has since become the most utilized cognitive testing battery in use with the elderly worldwide, being translated to at least 18 languages. During data gathering, the Finnish version of the CERAD-NB was administered to the participants.

The original CERAD-NB included five short subtests, measuring various cognitive functions. First, *MMSE* (Folstein et al., 1975) is a brief general measure of cognitive performance, containing varying tasks of orientation, attention, memory, language and visual-spatial skills. Verbal functions are measured by *Verbal Fluency* (Isaacs & Kennie, 1973), requiring the participant to verbally produce as many animals as possible during 60 seconds, as well as *Naming*, a 15-item shortened version of the Boston Naming Test (Kaplan et al., 1983), involving the naming of various items from pictures. Episodic verbal memory is measured by: *Word List Memory Learning*, requiring the participant to learn by rote a 10-item word list presented three times; *Word List Delayed Recall*, involving the recall of the previously learned word list from memory after a small delay; *Word List Recognition*, requiring the participant to recognize the original words from a set containing both

familiar and new items (Atkinson & Shiffrin, 1971). Finally, visuospatial functions are measured by the *Constructional Praxis* test (Rosen et al., 1984), requiring the participant to copy four increasingly complex figures by hand. Later, a sixth test was added: In *Constructional Praxis Recall* the participant is required to draw the previous figures from memory after a small delay. This modification was done to add a measure of visuospatial memory to the battery and in order to balance the uneven load between verbal and visual tests (Spangenberg et al., 1997). Finally, the Finnish version of CERAD-NB also contains the *Clock Drawing test*, in which the participant is asked to draw a clockface according to specific instructions (Brodaty & Moore, 1997).

In a clinical context the results of CERAD-NB are typically interpreted by using population-based and subtest-specific cutoff values. When specific subtests are considered, the Word List Delayed Recall is sensitive in detecting mild AD (Karrasch et al., 2005; Künig et al., 2006), and the Word List Immediate Recall and Verbal Fluency in detecting cognitive decline in MCI (Gavett et al., 2010). However, interpreting several separate subtests can be problematic since the probability of getting low scores in a portion of cognitive tests increases when several tests are performed (for examples, see: Brooks et al., 2010; Mistridis et al., 2015).

As the CERAD-NB originally lacked a validated global score, these have been developed after the battery's initial conception. One such compound score was described by Chandler and colleagues (2005): The CERAD-NB Total Score (CERAD-TS) is a measure of general cognitive performance calculated by summing the scores of all subtests except Constructional Recall, MMSE and Clock Drawing (total score range 0-100). An expanded version, which added Constructional Recall (score range 0-111), was later described by Seo and colleagues (2010). Both CERAD-TS versions have shown high test-retest and interrater reliability (Seo et al., 2010), and validity in detecting both MCI (Paajanen et al., 2010; Seo et al., 2010) and AD (Paajanen et al., 2014; Seo et al., 2010). The expanded version of CERAD-TS was chosen as the method of computing the CERAD-NB scores in Study I.

2.2.2. Studies II & III: Specific cognitive domains

Studies II and III utilized several neuropsychological tests for assessing performance in specific cognitive domains. Nine neuropsychological tests were originally used to form the four composite variables measuring *cognitive processing speed, verbal-logical memory, visuo-spatial memory and verbal functions*. The tests are globally validated instruments that have been utilized often in WM

Table 3.
Factor Loadings for Exploratory Factor Analysis of Cognitive Tests

Cognitive domain	*Variable*	*Factor*			
		1	2	3	4
Processing speed	Trail Making Test A	-.02	-.01	.02	**.79**
	WAIS-R Coding	.01	.01	.05	**.79**
Verbal-logical memory	WMS-R Logical memory 1	**.79**	-.10	.16	-.03
	WMS-R Logical memory 2	**.99**	.03	-.03	.06
Visual-spatial memory	WMS-R Visual reproduction 1	-.01	**-.98**	.11	-.02
	WMS-R Visual reproduction 2	.26	**-.49**	-.17	.29
Verbal functions	WAIS-R Similarities	.22	.04	**.58**	.06
	CERAD Naming	-.06	-.12	**.90**	.09

Note: Bold indicates the greatest loadings of each factor per variable.

pathology and dementia research (for examples, see: Au et al., 2006; Gunning-Dixon & Raz, 2000; Vasquez & Zakzanis, 2015).

In order to guarantee the internal consistency of the composites a factor analysis was performed on the nine tests. Eight tests loaded on four factors as expected. The exception was CERAD-NB's Verbal Fluency, which was included in the verbal functions compound, but in fact shared little variation with the extracted verbal functions factor. Thus Verbal fluency was removed in order to strengthen the internal consistency of the verbal functions compound. When factor analysis was re-run with the remaining eight tests, factor extraction resulted in a four-factor model that supported the formation of four composite variables (Table 3). More details about the factor analysis are provided in the supplementary material of Study II.

The final composite variables were computed by calculating the mean of z-transformed test scores for each domain. The *processing speed* composite was calculated from the Trail Making Test A (Poutiainen et al., 2010) and the Digit Symbol Coding of the Finnish WAIS-R (Wechsler, 1992), both tests being classic measurements of visuomotor processing speed. The *verbal-logical memory* composite was calculated from Logical memory 1 and 2 of the Finnish Wechsler Memory Scale Revised (WMS-R) (Wechsler, 1996). The Logical memory tests measure the ability to memorize, store and recall auditive verbal material in episodic memory. The *visuo-spatial memory* composite was computed from the Visual reproduction 1 and 2 of the Finnish WMS-R (Wechsler, 1996), which in

turn measure the ability to memorize, store and recall visual and spatial material in episodic memory. Finally, the *verbal function* composite was computed from the Similarities subtest of the Finnish WAIS-R (Wechsler, 1992), as well as the Naming subtest of the Finnish CERAD-NB (Pulliainen et al., 1999). Similarities measures verbal concept formation and reasoning, whereas Naming is a shortened version of the Boston Naming Test (Kaplan et al., 1983) requiring recognition of visually presented items, word activation and retrieval as well as the encoding and articulation of that word. More details about compound score calculation as well as test content is provided in the Method section of Study II.

2.2.3. Study IV: Verbal fluency

Study IV utilized measures of semantic fluency and phonological fluency. These tasks measure the ability to generate words according to a semantic or phonological rule, but also require the utilization of various executive control features (e.g., focusing on the task, updating working memory, inhibiting responses), which is why they are also seen as measurements of executive functioning (Henry & Crawford, 2004). In the semantic fluency task the participants were asked to verbally produce different animals, and in the phonemic fluency task different words beginning with the letter 'S'. Both tasks utilized a 60 second time limit, and the total number of correct responses was reported as the final score for each task. As is the case with CERAD-NB's Naming test, the data for semantic fluency was one of the measures included in the CERAD-TS in Study I.

2.3. Magnetic resonance imaging

2.3.1. Studies I & II: Visual ratings

Magnetic resonance imaging of the subjects was performed with 1.5T Philips Intera (Best, the Netherlands). White matter hyperintensities were analyzed using two-dimensional (2D) T2 TSE transaxial (TR/TE 4850/100 ms, slice thickness 5 mm, matrix 512 x 512) and 2D FLAIR coronal (fluid attenuated inversion recovery, TR/TE: 11000/140 ms, slice thickness 5 mm, matrix 512 x 512) images. The same sequence was applied to the whole sample.

Visual ratings of imaging data were utilized in Studies I and II: The MRI sequences were analyzed independently by two radiologists, who used the Wahlund/Age-related white matter changes scale (Wahlund et al., 2001). The Wahlund scale is a modified and more detailed version of the Fazekas scale (Fazekas et al., 1987), which itself has been used

extensively in WM research (Wahlund et al., 2017). The Wahlund scale uses a semi-quantitative rating system for visually assessing WMH in specific brain regions, with ratings from 0 to 3 points given to each area (0 - no lesions; 1 - focal lesions; 2 - beginning confluence of lesions; 3 - diffuse involvement of the entire region). As visual ratings of WM pathology in the frontal and parieto-occipital areas have shown the highest interrater reliabilities (Wahlund et al., 2001), Studies I and II focused on these areas. Inter-rater reliability between the two raters, as assessed by Cohen's weighted Kappa, showed good agreement for the right-parieto-occipital area and moderate agreement for the other areas. The final rating scores were obtained by calculating a mean of the two ratings and rounding it up to whole numbers. In cases of disagreement between the raters the higher one of the two scores was assigned as the final score.

Ratings were given for the frontal and parieto-occipital lobes in the left and right hemispheres separately. These hemispheric scores were stratified into three groups: *none/focal changes* (0-1 points), *beginning confluent changes* (2 points) and *diffuse changes* (3 points). Additionally, summary scores for the frontal and occipito-parietal regions were computed by combining the left and right hemispheric scores for each area. Next, these were stratified similarly into three groups: *none/focal changes* (0-2 points in the hemispheric summary score), *beginning confluent changes* (3-4 points) and *diffuse changes* (5-6 points). Summary scores of WM pathology in the frontal and parieto-occipital regions in the total sample and subgroups are presented in Table 4.

Table 4.
Visual Assessments of White Matter Pathology for Studies I-II

Level of pathology	*All*	*Controls*	*MCI*	*AD*
Frontal:				
none/focal	98	41	25	32
beginning confluent	39	15	10	14
diffuse	10	0	5	5
Parieto-occipital:				
none/focal	100	46	24	30
beginning confluent	37	8	12	17
diffuse	11	3	3	5

Note: Frontal MRI data is missing for one participant, and parieto-occipital data for another.
MCI = Mild cognitive impairment; AD = Alzheimer's disease.

Table 5.
Quantitative Assessments of White Matter Hyperintensity Volumes for Studies III-IV

Anatomical area	*All*	*Controls*	*MCI+AD*	*MCI*	*AD*
Total WMH Burden[1]	6.87 (8.80)	5.29 (5.06)	8.39 (11.13)	6.91 (9.02)	9.09 (12.07)
Frontal Left WMH	1.45 (1.51)	1.18 (0.97)	1.71 (1.86)	1.39 (1.54)	1.87 (2.00)
Frontal Right WMH	1.72 (2.12)	1.39 (1.15)	2.04 (2.73)	1.84 (2.36)	2.13 (2.92)
Frontal WMH	3.17 (3.57)	2.56 (1.99)	3.75 (4.55)	3.23 (3.88)	4.00 (4.87)
Temporal Left WMH	0.45 (0.75)	0.34 (0.58)	0.55 (0.88)	0.45 (0.91)	0.59 (0.89)
Temporal Right WMH	0.51 (0.88)	0.45 (0.71)	0.57 (1.03)	0.43 (0.68)	0.64 (1.16)
Temporal WMH	0.96 (1.54)	0.79 (1.17)	1.12 (1.83)	0.88 (1.56)	1.23 (1.96)
Parieto-occipital Left WMH	1.26 (1.95)	0.85 (0.95)	1.65 (2.52)	1.38 (2.25)	1.78 (2.66)
Parieto-occipital Right WMH	1.49 (2.38)	1.09 (1.71)	1.87 (2.85)	1.42 (2.14)	2.08 (3.14)
Parieto-occipital WMH	2.75 (4.22)	1.93 (2.43)	3.53 (5.32)	2.80 (4.37)	3.87 (5.75)

WMH = White Matter Hyperintensity; MCI = Mild cognitive impairment; AD = Alzheimer's disease. Means and standard deviations of segmented WMH volumes are reported. WMH values are in millilitres.
[1] The summed value of WMH volumes in frontal, temporal and parieto-occipital areas.

2.3.2. Studies III & IV: Quantitative assessment

For the portion of data that was used in Studies III and IV, the T1 image was segmented into 133 regions using an automated multi-atlas segmentation method (Lötjönen et al., 2011; Lötjönen et al., 2010). First, from the original 79 manually segmented atlases 28 best-matching atlases were chosen. The selected atlases were non-rigidly registered with the T1 image. Then, the T1 image was registered with the FLAIR image, and the segmentation result was propagated to the FLAIR image to provide spatial information for the segmentation of WMH and for computing regional WMH measures.

The method for the segmentation of WMH is based on the method presented by Wang and colleagues (2012), and presented in full detail by Koikkalainen and colleagues (2016). The WMH are segmented using the EM algorithm in a stepwise way. First, WM is segmented into two classes from the T1 image representing hypointense WM regions in the T1 image and normal bright WM regions. Second, using the results of the previous step as an initialization, the FLAIR image is segmented to three classes: cerebrospinal fluid, normal brain tissue, and hyperintense voxels. Finally, using the results of the previous step as an initialization, WM and subcortical regions from the FLAIR image are segmented into two classes. The class with higher intensities is then regarded as the final segmentation of WMH.

Means and standard deviations of WMH volumes in various brain regions in the total sample and subgroups are presented in Table 5. The mean WMH volumes were systematically higher in the patient groups when compared to the controls, with AD patients having the highest values. However, no statistically significant differences in WMH volumes were found between the groups, though the difference in the left parieto-occipital area was on the threshold of being significant.

2.4. Statistical analysis

2.4.1 Study I

For testing the main research questions, separate univariate ANOVAs were conducted for the frontal and parieto-occipital regions respectively. Age and level of education were set as covariates and the CERAD-TS score (Seo et al., 2010) as the dependent variable.

2.4.2. Study II

A series of separate univariate ANCOVAs were conducted for testing the main research questions. Separate analyses were conducted for each of the six anatomical regions of interest (left frontal, right frontal, left

parieto-occipital, right parieto-occipital, bilateral frontal, bilateral parieto-occipital), and for each of the four cognitive composites (processing speed, verbal memory, visual memory, verbal functions). The level of WM pathology in each anatomical region and group (Control, MCI, AD) were set as independents, age and level of education as covariates, and one of the cognitive composite scores (processing speed, verbal memory, visual memory, verbal functions) as the dependent (WMH x group x cognitive composite). Two sets of analyses were run: One set containing both left and right hemispheric scores in the same model as independent variables, and another set containing the regional summary score as the independent.

2.4.3. Study III

Several multiple linear regression analyses were conducted for testing the main research questions. In each regression model age and level of education were entered as covariates in step 1, after which a measure for WMH in each anatomical region of interest was added as a dependent in step 2. One of the four cognitive composites (processing speed, verbal memory, visual memory, verbal functions) was set as the independent variable. Separate analyses were conducted for the eight anatomical regions (left frontal, right frontal, left parieto-occipital, right parieto-occipital, left temporal, right temporal, bilateral frontal, bilateral parieto-occipital), and for each of the four cognitive composites. Analyses including the whole sample (Controls, MCI & AD) were run first. For those regression models that achieved significance, further subgroup analyses were performed, i.e., the models were re-run separately for the controls group and the patient group (MCI+AD).

2.4.4. Study IV

Several multiple linear regression analyses were performed for testing the main research questions. In each regression model age and level of education were entered as covariates in step 1, after which a measure for WMH in each anatomical region of interest was added as a dependent in step 2. Following this, semantic fluency or phonological fluency was set as the independent for each analysis. Separate analyses were conducted for the eight anatomical regions (left frontal, right frontal, left parieto-occipital, right parieto-occipital, left temporal, right temporal, bilateral frontal, bilateral parieto-occipital). Analyses including the whole sample (Controls, MCI & AD) were run first. This was followed with analyses that contained only right-handed participants.

As several independent tests were run, Type I errors were controlled with the Benjamini-Hochberg procedure (Benjamini & Hochberg, 1995). The original *p*-values of the main predictor variables were compared

against adjusted *p*-values, which were produced by using a false discovery error rate of 0.05. The correction was perfomed on all nine predictor variables for both hypothesis families (semantic fluency / phonological fluency), and separately for both the total sample and the sample that contained only right-handed participants.

For those regression models that remained significant after multiple testing correction, further subgroup analyses were performed separately for the controls group and the patient group (MCI+AD).

3. RESULTS

3.1. Study I

First, as would be expected, significant differences in cognitive function were seen between all three groups. The highest performances were found in the cognitively healthy controls, intermediate performances in MCI patients and the lowest performances in patients with AD (Table 6). Separate univariate ANOVAs were conducted for testing the main research questions. Age and education were controlled for. In the initial analyses no significant main effects of WM pathology on cognitive performances were seen, but a significant interaction effect was discovered between group and the level of frontal WM pathology.

Table 6.
CERAD Total Scores in Study I

	All	*Controls*	*MCI*	*AD*
CERAD Total Score	79.23 (15.27)	87.75 (10.48)	80.82 (11.68)	68.92 (16.28)

Score range 0-111. Means are reported first, followed by standard deviations in brackets. MCI = Mild cognitive impairment; AD = Alzheimer's disease.

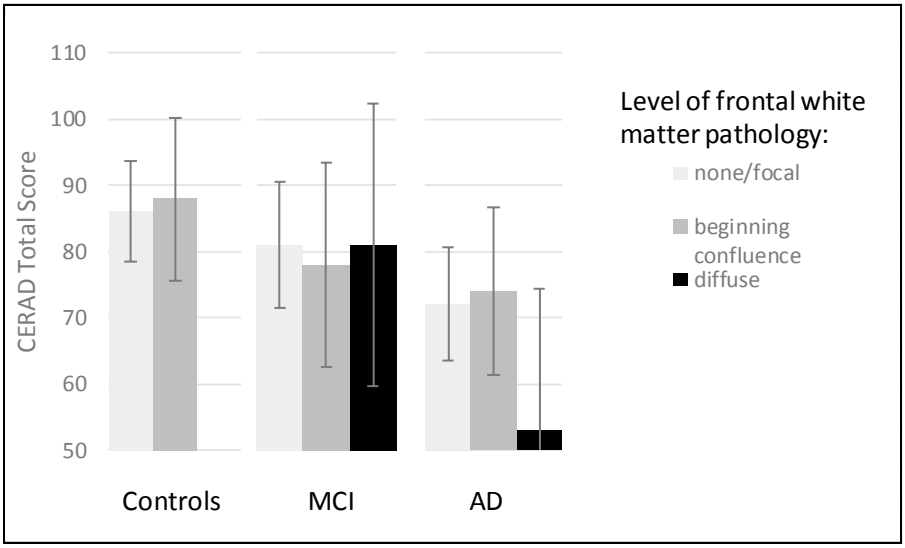

Figure 1. Cognitive performance (CERAD-TS, range 0-111 points; Seo et al., 2010) in the three groups as a function of frontal WM pathology. Estimated marginal means with 95 % CIs reported.

However, as mentioned previously, the control group contained an outlier: a participant with major WM pathology, who also had unusually high cognitive performance. In order to examine whether this single participant may have affected the results, the participant was removed and the analyses performed again. After this, the interaction term between group and level of frontal WM pathology fell slightly below the .05 alpha threshold, but only marginally. Moreover, the effect size stayed at a near moderate level, indicating that the interaction still explained a considerable amount of variation. This trend level interaction indicated that AD patients with major levels of frontal WM pathology seemed to perform worse than AD patients with lesser levels of WMH (Fig 1).

3.2. Study II

As expected, significant differences in cognitive performances were found between the three groups in almost all of the composite cognitive measures, with controls having the highest performances, MCI patients intermediate performances and AD patients the lowest performances (Table 7). Separate univariate ANCOVAs were conducted for testing the main research questions.

Table 7.
Cognitive Composite Scores in Study II

Domain/Composite	*All*	*Controls*	*MCI*	*AD*
Processing speed	0.00 (0.91)	0.47 (0.60)	0.01 (0.87)	-0.52 (0.95)
Verbal-logical memory	0.00 (0.88)	0.59 (0.55)	-0.05 (0.79)	-0.60 (0.81)
Visual-spatial memory	0.00 (0.94)	0.49 (0.72)	-0.11 (0.95)	-0.45 (0.90)
Verbal functions	0.00 (0.92)	0.46 (0.53)	0.10 (0.84)	-0.58 (1.01)

The composites were calculated by converting individual test scores into z-scores and obtaining the mean of the tests for each domain. Means are reported first, followed by standard deviations in brackets. MCI = Mild cognitive impairment; AD = Alzheimer's disease.

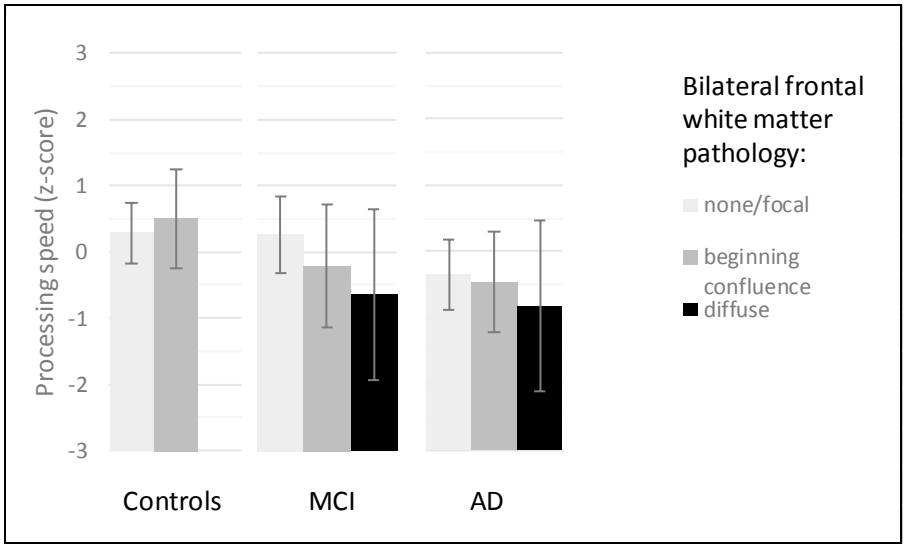

Figure 2. Cognitive processing speed in the three groups as a function of bilateral frontal WM pathology. Estimated marginal means of z-scores with 95 % CIs are reported. A lower z-score represents decreased processing speed.

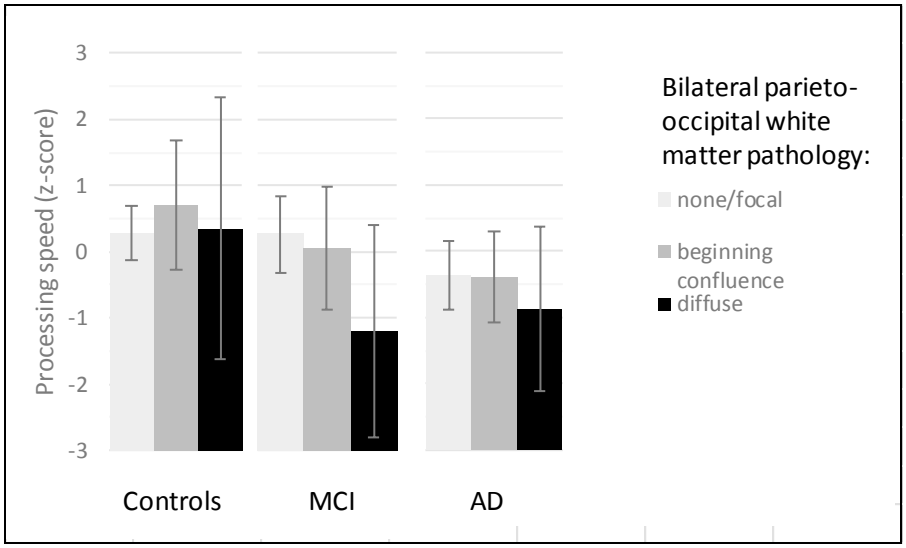

Figure 3. Cognitive processing speed in the three groups as a function of bilateral parieto-occipital WM pathology. Estimated marginal means of z-scores with 95 % CIs are reported. A lower z-score represents decreased processing speed.

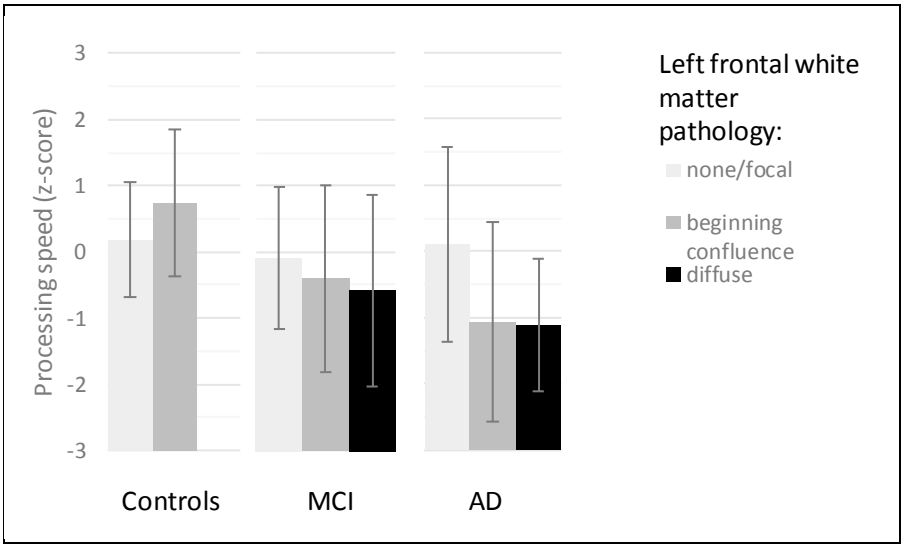

Figure 4. Cognitive processing speed in the three groups as a function of left frontal WM pathology. Estimated marginal means of z-scores with 95 % CIs are reported. A lower z-score represents decreased processing speed.

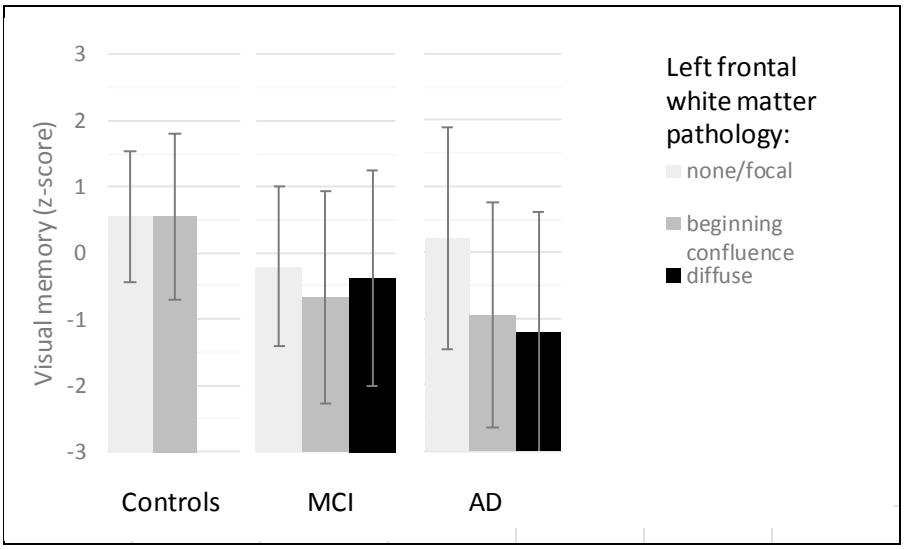

Figure 5. Visual memory performance in the three groups as a function of left frontal WM pathology. Estimated marginal means of z-scores with 95 % CIs are reported. A lower z-score represents decreased visual memory.

Age and education were controlled for. Here, WM pathology had the most robust effects on processing speed: the level of WMH had a main effect on processing speed in both bilateral frontal and parieto-occipital areas (Figs 2-3). Furthermore, a significant interaction between group and left frontal WM pathology on processing speed was seen (Fig 4). This interaction stemmed from the fact that AD patients with moderate or severe levels of WM pathology in the left frontal lobe had considerably slower processing speed performances than AD patients with milder levels of pathology in the corresponding area. The analyses also indicated that left frontal WM pathology had a main effect on visual memory (Fig 5). No significant effects of WM pathology on verbal-logical memory or verbal functions were observed.

3.3. Study III

Cognitive performances of the total sample and subgroups are shown in Table 8. Several multiple linear regression analyses were conducted for testing the main research questions (see Study III for regression tables). Age and education were controlled for. Regression analyses involving the whole sample (Controls, MCI, AD) showed two main findings: (1) WMH in the left and right parieto-occipital areas, as well as in the left temporal lobe were associated with impairments in processing speed; (2) WMH in the left parieto-occipital areas were associated with impaired performance in verbal memory. Following this, for those regression models that achieved significance, the models were re-run separately for the controls and patient groups. Here, the volume of WMH

Table 8.
Cognitive Composite Scores in Study III

Domain/Composite	*All*	*Controls*	*MCI+AD*	*MCI*	*AD*
Processing speed	0.00	0.33	-0.31	-0.03	-0.44
	(0.91)	(0.67)	(1.00)	(0.85)	(1.05)
Verbal-logical memory	0.00	0.47	-0.45	-0.08	-0.61
	(0.98)	(0.76)	(0.96)	(0.96)	(0.93)
Visual-spatial memory	0.00	0.29	-0.28	-0.55	-0.38
	(0.93)	(0.84)	(0.95)	(0.89)	(0.97)
Verbal functions	0.00	0.21	-0.20	0.14	-0.36
	(0.80)	(0.52)	(0.97)	(0.64)	(1.06)

Means are reported first, followed by standard deviations in brackets. MCI = Mild cognitive impairment; AD = Alzheimer's disease.

in the left temporal lobe was significantly associated with impaired processing speed specifically in patients with MCI or AD.

3.4. Study IV

Several multiple linear regression analyses were conducted for testing the main research questions. Analyses were first performed on the total sample, which included right-handed, ambidextreous and left-handed participants (n = 86). After this, identical analyses followed on solely right-handed participants (n = 79). Age and education were controlled for in each analysis. Verbal fluency performances are presented in Table 9 (see Study IV for regression tables).

In the whole sample WMH volumes in both bilateral frontal and parieto-occipital areas were associated with decreases in semantic fluency. However, these associations did not remain significant after multiple testing correction. The analyses containing only right-handed participants produced similar results: White matter hyperintensity volumes in bilateral frontal and parieto-occipital areas were associated with decreased semantic fluency. However, a new significant association was seen between increased WMH volumes in the right temporal area and lowered semantic fluency solely in right-handed participants. Analyses that contained only right-handed participants remained significant after multiple testing correction, excluding the association between left parieto-occipital WMH and semantic fluency (the association regarding bilateral parieto-occipital remained significant, however).

Since only the models that contained solely right-handed participants remained significant after correction for multiple testing, additional subgroup analyses were performed only with right-handed participants.

Table 9.
Verbal Fluency Scores in Study IV

	All	*Controls*	*MCI+AD*	*MCI*	*AD*
Semantic fluency	21.55 (6.62)	22.36 (5.39)	20.77 (7.59)	19.93 (5.51)	21.17 (8.44)
Phonological fluency	13.37 (6.51)	14.43 (6.03)	12.36 (6.86)	13.79 (5.44)	11.70 (7.42)

Means are reported first, followed by standard deviations in brackets.
MCI = Mild cognitive impairment; AD = Alzheimer's disease.

The follow-up analyses concerned the areas significantly associated with semantic fluency in the total sample (left and right frontal, left and right parieto-occipital areas) and were performed separately for the cognitively healthy and patient (MCI+AD) subgroups. No significant associations were seen here.

4. DISCUSSION

This thesis set out to investigate the possible effects of WM pathology on cognitive function in cognitively healthy adults, patients with MCI and patients with AD. **Study I** investigated the effects of WMH on general cognitive functioning in controls, MCI patients and AD patients, as measured by the Total Score of the CERAD-NB. **Studies II-III** continued the previous line of investigation and expanded the scope to include four specific cognitive domains. Finally, **Study IV** investigated the effects of WMH on verbal fluency. Studies I and II utilized visual ratings of WM pathology, whereas Studies III and IV used quantitative volumetric assessments of WMH. The main findings can be summarized as follows:

1) *General effects of WM pathology on cognition*
   White matter pathology has robust associations with impaired processing speed in all three groups. Other associations are seen with impairments in visual and verbal episodic memory and semantic fluency.

2) *Additive effects of WM pathology on cognition*
   a) Frontal WM pathology seems to have an additive negative effect on cognition in AD: Patients with AD who also had severe frontal WM pathology exhibited clearly lower performances in both general cognitive functioning and processing speed than AD patients with milder levels of frontal WM pathology.
   b) Temporal WM pathology may have a similar additive negative effect on processing speed in MCI or AD patients, although this association should be considered preliminary.

3) *Frontal white matter*
   White matter pathology in the frontal lobes, especially in the left hemisphere, appears to have multi-domain effects on cognitive functions in cognitively healthy controls, patients with MCI and patients with AD.

4.1. General effects of white matter pathology

A number of general (i.e., not group-specific) effects between WMH and processing speed, visual and verbal episodic memory as well as semantic fluency were seen in Studies II-IV.

4.1.1. Processing speed (Studies II-III)

Overall, the most robust association that was seen between WMH and cognition was in the domain of processing speed. General (i.e., not group-specific) associations with decreased processing speed were seen for frontal WMH and parieto-occipital WMH in Study II with visual assessment of WM pathology. Furthermore, decreased processing speed was associated with parieto-occipital WMH in Study III, when quantitative assessment of WMH was used. Additionally, two group-specific associations were found concerning left frontal WMH in AD patients in Study II, and left temporal WMH in AD or MCI patients in Study III. These group-specific findings are discussed in chapter 4.2.2., and possible reasons for the differences in the results between Studies II and III in chapter 4.3.1.

The overall finding that WMH is associated with decreased processing speed is clearly in line with previous literature, as processing speed impairments have often been described as the most cardinal or classic symptom of WM pathology (Gunning-Dixon & Raz, 2000; Kloppenborg et al., 2014; Vasquez & Zakzanis, 2015).

The association between processing speed and frontal WMH specifically, as seen in study II, has been reported previously in a number of studies, and similar associations have been found for frontal GM volumes as well (e.g., Bartzokis et al., 2010; Kochunov et al., 2010; Quinque et al., 2012; Righart et al., 2013). Unsurprisingly, processing speed impairments have also been associated with specific frontal-subcortical WM pathways, including the forceps minor and the anterior thalamic radiation (Biesbroek, Weaver, et al., 2016; Duering et al., 2011, 2013, 2014; Jiang et al., 2018). Both of these tracts have been described as strategic pathways that have major contributions to processing speed and executive functioning (Biesbroek et al., 2017). The anterior thalamic radiation might be especially important, as it runs through the anterior internal capsule and has connections with several nuclei in the thalamus, which in turn have been associated with cognitive impairments in several case studies (Fisher, 1982; L. Pantoni et al., 2001; Tatemichi et al., 1992; Van der Werf et al., 2003).

The associations between parieto-occipital WMH and decreased processing speed seen in Study III are likewise consistent with the literature, though previous findings are relatively sparse. At least a few studies have reported associations between decreased processing speed and lesions in parietal WM (Quinque et al., 2012; Turken et al., 2008), with at least one similar association being reported for parietal GM as well (Peers et al., 2005). Furthermore, a few studies have reported associations specifically for the superior longitudinal fasciculus, which integrates frontal and parietal cerebral regions (Jiang et al., 2018; Turken et al., 2008).

In summary, the findings from Studies II-III concerning general (not-group-specific) associations of WMH with decreased processing speed are in line with previous reports. These have indicated that impairments to processing speed often follow from the disruption of frontal and/or parieto-occipital WM as well as the WM tracts connecting these areas.

4.1.2. Episodic memory (Studies II-III)

General (i.e., not group-specific) associations were also found for visual and verbal episodic memory: visually assessed left frontal WMH was associated with performance in visual memory in Study II, and quantitatively assessed left parieto-occipital WMH with verbal memory in Study III. No group-specific associations were seen for episodic memory.

At a general level, these findings are consistent with previous reports, as associations between increased WMH and impairments in episodic memory have been reported fairly often (Kloppenborg et al., 2014; Vasquez & Zakzanis, 2015). Findings about verbal memory are generally more common, though associations regarding visuospatial memory have been reported as well (e.g. (Au et al., 2006; Chin et al., 2012; Villeneuve et al., 2011). Furthermore, a number of studies that have linked episodic memory impairments to WMH in specific regions have been published during the last decade: associations have been reported between verbal episodic memory and WMH in temporal, occipital and parietal areas (Brugulat-Serrat et al., 2019; Burton et al., 2004b; Fujishima et al., 2014; Green et al., 2016).

Studies using measures that pool verbal and visual memory scores together have shown associations with WMH in the frontal forceps minor (Biesbroek et al., 2017; Biesbroek, Weaver, et al., 2016) and the left superior longitudinal fasciculus (Sasson et al., 2013b), as well as WMH in parietal, parieto-occipital and parieto-temporal areas (Lampe et al., 2019; Smith et al., 2011). However, to the best of the Author's knowledge no studies have reported associations between left frontal WM and a episodic memory score with a measure that would contain *only* visual memory tasks (i.e., not a pooled score that mixes both visual and verbal memory tasks). Thus, the association regarding visual memory in Study II seems to be somewhat novel. When discussing this finding, it would be prudent to take into account the apparent underusage of visual memory tasks in WMH research: most studies examining episodic memory seem to focus on verbal memory specifically, and those that do utilize measures of visual memory seem to often pool verbal and visual memory scores together into a compound score. Generally speaking, the notion that left-hemisphere pathology would be associated with visuo-spatial processing is not unprecedented,

as for example preliminary associations have been reported between left-sided WM lesions and visuo-spatial working memory (Paulraj et al., 2018). Regardless, it is likely that the left frontal WMH measured from the current sample reflects pathological changes in certain WM pathways that have been previously associated with episodic memory, such as the forceps minor or the left superior longitudinal fasciculus (Biesbroek et al., 2017; Biesbroek, Weaver, et al., 2016; Sasson et al., 2013a). Another possible explanation is that the disintegration of frontal WM tracts often leads to impairments in executive functions (e.g., Biesbroek et al., 2016; Sasson et al., 2013), which in turn can have negative effects on episodic memory processes as well (Lezak et al., 2012). This is not, however, consistent with the fact that left-frontal WMH was not associated with verbal episodic memory. In summary, the association regarding visual memory should be treated as preliminary and investigated further in future studies.

The associations regarding left parieto-occipital WMH and verbal memory, as seen in Study III, are in line with previous studies showing similar associations (Brugulat-Serrat et al., 2019; Lampe et al., 2019; Smith et al., 2011). These reports on posterior WMH are also consistent with previous cortical studies, which indicate that the posterior parietal cortex has a significant contribution to memory retrieval (A. D. Wagner et al., 2005), and that parietal lesions can impair attention during memory retrieval (Cabeza et al., 2008). White matter hyperintensities in parieto-occipital areas might reflect damage to specific WM pathways traversing the area. For example, the inferior longitudinal fasciculus connects the posterior parietal cortex to the middle temporal lobe, and WMH in it is associated with episodic memory impairments (Lockhart et al., 2012; Palacios et al., 2013).

A null finding that should be addressed concerns the lack of associations between episodic memory and temporal WM in Study III. As episodic memory is supported by frontal, temporal and parietal WM tracts (Cabeza et al., 2008; Fletcher & Henson, 2001; Simons & Spiers, 2003), the integrity of temporal WM would be expected to correlate with episodic memory performance. Indeed, preliminary associations have been reported between episodic memory and WMH in specific tracts traversing the temporal regions, such as the fornix, the frontal-temporal uncinatus and the temporal-parietal inferior longitudinal fasciculus (Lockhart et al., 2012; Metzler-Baddeley et al., 2011; Sasson et al., 2012). However, many of these tracts are not isolated to the temporal lobes and some of them might be related to specific memory processes. Indeed, studies that have assessed WMH specifically in the temporal lobes have produced more varied results: Some studies have produced significant associations between episodic memory and temporal WMH (e.g., (Burton et al., 2004a; J. Huang et al., 2007)), whereas others have

reported null findings (Biesbroek, Weaver, et al., 2016; Firbank et al., 2007; Meier & Manly, 2012). Thus, significant associations might be found if tract-specific analyses were used instead of lobar WMH assessments.

These null findings should be considered preliminary and tested in future studies, which should ideally: (1) utilize specified measures for different memory processes (e.g. immediate free recall, delayed free recall, recognition); (2) utilize measures of different sense modalities separately without pooling scores; (3) target more delineated parts of the WM network or specific WM tracts; (4) combine different imaging methods (e.g. DTI and volumetric analysis of WMH).

In summary, no group-specific effects were seen regarding visual or verbal episodic memory impairment; I.e., the results do not give support to the notion that WM pathology would have cumulative effects on episodic memory in MCI or AD patients. The association concerning left frontal WMH and visual memory in Study II is novel and requires further validation. The association concerning left parieto-occipital WMH and verbal memory in Study III is consistent with the previous literature and supports the notion that parietal cerebral structures are involved in memory functions.

4.1.3. Verbal functions (Studies II-III)

No associations were found between the verbal function composite and any measure of WM pathology in Studies II-III. The verbal function compound was calculated from two different verbal tests: the CERAD Naming (picture naming) and the WAIS-R Similarities (verbal comprehension/reasoning). Decreased naming performance has been associated with reduced WM volume and increased WMH volumes in the temporal lobes (Baldo et al., 2013; Meier & Manly, 2012; Meyer et al., 2013); The uncinatus and temporal regions of the arcuate fasciculus, inferior longitudinal fasciculus and the inferior fronto-occipital fasciculus have been implicated specifically (Agosta et al., 2010; Griffis et al., 2017; Sarah et al., 2011). As for Similarities, though it is often used as a part of neuropsychological assessment in studies (e.g., Vasquez & Zakzanis, 2015), findings about its association with specific WM regions are scarce. One study has found associations between Similarities and global WMH load (Brugulat-Serrat et al., 2019), whereas others have reported null findings (e.g. Au et al., 2006; Hidese et al., 2020). As naming tasks have been previously linked with temporal WMH, one would expect to see a similar association in the current sample as well. However, as the evidence about the regional associations of the Similarities task is unconfirmed, it is possible that its presence in the

compound could have cancelled any possible associations that might be seen otherwise regarding the Naming subtest.

4.1.4. Verbal fluency (Study IV)

General (not group-specific) associations were found regarding semantic fluency in Study IV. Initial analyses were run on both the total sample (i.e., right-handed, left-handed and ambidextrous participants) and only on right-handed participants. After correcting for multiple comparisons, only the associations in the right-handed group remained significant (See Study IV for specifics). Here, WMH in bilateral frontal and bilateral parieto-occipital areas were associated with decreases in semantic fluency. No group-specific effects were seen for MCI or AD patients in the pooled patient group. Furthermore, no significant associations were seen for phonological fluency.

The findings concerning semantic fluency in Study IV also fit in with previous research: fluency tasks seem to depend on a network of frontal-parietal cortical regions, the temporal lobes and subcortical structures that include the anterior cingulate, left hippocampus, thalamus and cerebellum (Abrahams et al., 2003; Biesbroek, van Zandvoort, et al., 2016; Costafreda et al., 2006; Gourovitch et al., 2000; Phelps et al., 1997; Robinson et al., 2012). Though previous studies have shown a preference for left hemispheric lateralization, the right hemisphere, especially the frontal lobe, has been implicated in verbal fluency tasks as well (Loring et al., 1994; Martin et al., 1990; Perret, 1974; Robinson et al., 2012), with the right inferior frontal gyurs specifically being identified as important to semantic fluency (Biesbroek, van Zandvoort, et al., 2016). Indeed, a number of researchers have advocated the view that the right hemisphere could be relatively more involved with semantic fluency over phonological fluency (Donnelly et al., 2011; Glikmann-Johnston et al., 2015; Schlösser et al., 1998). Additionally, bilateral associations between WM tract integrity and verbal fluency performance have been reported at least for the inferior fronto-occipital fasciculus and the superior longitudinal fasciculus (Blecher et al., 2019; Rodríguez-Aranda et al., 2016).

The degree of right-hemispheric associations with semantic fluency seen in Study IV might also be affected by two other phenomena. First, as the sample utilized in the studies was relatively elderly, it is possible that the degree of hemispheric lateralization was affected by age. Neuroimaging studies have indicated that hemispheric specialization lessens with advancing age: this happens due to the recruitment of additional cortical areas in order to preserve performance, which leads to relative increases in bilateral activation (Cabeza, 2002; Reuter-Lorenz et al., 2000). This effect has been reported with language functions such

as fluency and naming (La et al., 2016; Meinzer et al., 2012; Wierenga et al., 2008), but also with other functions such as the motor system and the ventral visual system (Carp et al., 2011; Park et al., 2004). Second, the right-hemispheric involvement in semantic fluency might to some degree be the result of applying visual imaging strategies while performing fluency tasks (Biesbroek, van Zandvoort, et al., 2016; Gordon et al., 2018).

As for why only analyses on solely right-handed participants remained significant after correction, it is likely that the removal of left-handed/ambidextrous participants nullified any confounding effects related to language lateralization. This in turn resulted in slightly stronger effects in the regression models.

Finally, as no group-specific results concerning the MCI or AD patients were seen regarding verbal fluency, the results do not support the notion that WM pathology would have cumulative effects with AD-related pathology on fluency. This differs from a few earlier findings (Chen et al., 2009; Kavcic et al., 2008), though these studies utilized fairly small sample sizes and analyzed specific WM tracts.

4.2. Additive effects of white matter pathology

In addition to the general (not group-specific) effects discussed in chapter 4.1., a number of group-specific effects were seen with MCI and AD patients in Studies I-III.

4.2.1. Effects on general cognition (Study I)

In Study I, a significant group-specific effect was seen between frontal WMH and general cognition as measured by the CERAD-TS. Patients with AD who had severe frontal WMH had the lowest cognitive performances, and performed clearly worse when compared to AD patients with milder levels of frontal WM pathology. No significant associations were seen for the parieto-occipital area, which might be due to CERAD-NB tests placing a relatively higher emphasis on verbal functions over visuospatial ones.

Previous studies have indicated that WMH increase the risk for dementia in AD (Mortimer, 2012; Petrovitch et al., 2005; Toledo et al., 2013), as well as accelerate the rate of cognitive decline in MCI and AD patients (Brickman et al., 2008; Tosto et al., 2014). Furthermore, WMH in the corpus callosum and the fornices have been reported to correlate with CERAD-TS in AD patients specifically (Bilello et al., 2015). However, no associations have been reported in AD patients concerning frontal WMH. Overall, the effect seen in Study I indicates that comorbid frontal WMH in AD patients may be associated with cumulative decline in general cognitive functioning.

4.2.2. Effects on processing speed (Studies II-III)

Group-specific effects concerning processing speed were seen in Studies II-III. In Study II, patients with AD that had severe left-frontal WMH had the lowest performances in processing speed. In Study III, a similar effect was found for left-temporal WMH in the pooled patient group.

These results are in line with previous reports (Bilello et al., 2015; Brickman et al., 2008; Mortimer, 2012; Petrovitch et al., 2005; Toledo et al., 2013; Tosto et al., 2014), as well as the finding from Study I, and indicate that concomitant frontal and temporal WMH in AD patients may lead to additive decline in processing speed. The findings are not unexpected when one considers that processing speed impairment is usually described as a cardinal cognitive symptom of WMH (de Groot et al., 2000; Gunning-Dixon & Raz, 2000) and cerebrovascular diseases in general (Duering et al., 2014; Jacobs et al., 2013; Righart et al., 2013b; Rösler et al., 2005). Furthermore, though processing speed deficits are not a classic symptom in AD-related neuropathology, slowed processing speed has been reported consistently in amnestic MCI and AD (Amieva et al., 2000; Haworth et al., 2016; Kochan et al., 2016; Phillips et al., 2013; van Deursen et al., 2009; Warkentin et al., 2008). Thus, it is very probable that the cause for these findings is the concurrent proliferation of both cerebrovascular pathology (i.e., WMH) and primary AD-related neuropathology. To the best of the Author's knowledge, neither of these group-specific findings have been reported previously in the literature.

4.3. Considerations and implications

Results from Studies I-III indicate that AD patients suffering from major levels of comorbid WMH especially in the frontal areas are likely to have increased cognitive impairments when compared to patients with milder WM pathology. Impairments may show up as lowered general cognitive functioning and slowing of information processing speed. A number of implications concerning the interplay between pathologies, clinical assessment and targets for interventions can be drawn from the results. However, first the differences in results obtained by different MRI data analysis methods as well as the possible role of cortical atrophy will be considered.

4.3.1. Different results from visually rated vs quantitative MRI data?

As stated previously, the results differed somewhat between Studies II and III, which utilized visually rated and quantified MRI data, respectively. First, Study III could replicate neither the general nor the

group-specific effects concerning frontal WMH and processing speed seen in Study II. Second, the association between left frontal WMH and decreased visual memory was seen only in Study II, whereas the association between left parieto-occipital WMH and decreased verbal memory was seen only in Study III.

There are a number of reasons between the two studies that most likely explain the differences in the results. First, Study III used a portion of the same sample as Studies I-II, but utilized quantitative volumetric analysis for assessing WMH, and also included temporal WMH as a region in the analyses. Second, as the sample size decreased from Study II to Study III, this weakened the power to detect smaller effects. Third, the participants excluded from Study III were more likely to be older and had lower cognitive performances than those included. Finally and most importantly, the move from categorical to continual data required changing statistical methods, which likely affected the results. Overall, due to the limited sample size and relatively small effect size, the finding concerning temporal WMH should be considered preliminary.

4.3.2. Taking grey matter into consideration

As GM measurements were not included in the models, cortical atrophy was not controlled for. Thus we cannot exclude the possibility that cortical atrophy would have a mediating effect on the relationship between WMH and cognitive performance, as reported by Rizvi and colleagues (2017). Regardless, we concurrently assume that cortical atrophy would be inherently to a degree intertwined in the group classifications utilized in the models (C vs. MCI vs. AD, C vs. MCI/AD), and that adding GM measurements in the analysis could in the worst case act as a "secondary control" and diminish statistical power.

Post hoc analyses of quantified GM volumes (including 94 % of the sample used in Studies I-II) showed that the AD patient group indeed had the smallest mean cortical and hippocampal volumes of the three groups. However, contrary to expectations, the mean global cortical volume of the MCI group surpassed that of the cognitively healthy control group, and no significant differences between the groups could be seen regarding hippocampal atrophy either. However, it should be mentioned that this might be due to the fact that compared to the control and AD groups, the MCI group had the most missing data (15 % vs. 2-4 %).

4.3.3. Explaining additive effects

As discussed previously, the group-specific effects found in Studies I-III are most likely caused by the concomitant accumulation of cerebrovascular pathology and primary AD pathology. The

neuropathological processes seen in AD involve the accumulation of amyloid plaques and neurofibrillary tangles, which leads to widespread neuronal loss and global cognitive impairment. Alzheimer's disease patients also often exhibit comorbid vascular pathology including WMH (Claus et al., 2016; Prins & Scheltens, 2015; Smith, 2016), and when these changes become prominent enough, these two pathologies seem to have cumulative effects on certain cognitive functions (Bilello et al., 2015; Brickman et al., 2008; Kaskikallio et al., 2020; Kaskikallio, Karrasch, Koikkalainen, et al., 2019; Kaskikallio, Karrasch, Rinne, et al., 2019; Mortimer, 2012; Petrovitch et al., 2005; Toledo et al., 2013; Tosto et al., 2014). Judging from the findings presented in this thesis, major pathological changes especially in frontal WM might lead to these cumulative effects. This is not unexpected when considering previous findings that highlight the importance of frontal-subcortical, frontal-temporal and frontal-parietal tracts in processing speed, executive functions and episodic memory (Biesbroek et al., 2013; Biesbroek, Weaver, et al., 2016; Duering et al., 2011, 2013, 2014; Jiang et al., 2018; Lampe et al., 2019; Smith et al., 2011).

As to the question of how AD-related pathology and WMH are associated with each other, several non-mutually exclusive explanations can be formulated (Brickman, 2013): First, WMH might be indicative of independent pathological processes that contribute cumulatively to the overall clinical symptomology. In this case, WMH might reflect cerebrovascular abnormarmalities, which do not influence AD pathology *per se.* Second, WMH might reflect a heterogeneous underlying etiology, which might interact with or reflect AD-related neuropathological processes. Third, it is also possible to focus on shared associations with a third set of factors, such as risk factors, between the two pathologies.

Discussion about the validity of these scenarios is ongoing. For example, in a study by Marchant and colleagues (2013) the global WMH burden was not in fact associated with β-Amyloid depositions, which are classic markers for AD-related neuropathology. WMH and Aβ deposition were not significantly correlated in a study by Hughes and colleagues (2013) either, but they co-occurred especially in patients who also had high arterial stiffness, implying that both independent processes and interactions between various pathologies might exist. Several studies have given support to the second explanation (e.g., Brickman et al., 2008; McAleese et al., 2017; Rizvi et al., 2017). For example, McAleese and colleagues (2017) reported that posterior WMH in AD patients might be associated with AD-typical Wallerian degeneration, instead of having a vascular origin. Nonetheless, until any conclusive evidence is presented, it seems sensible to consider a mix of all three explanations. In other words, though WMH and AD share mutual risk factors (explanation #3), and WMH in certain cerebral regions might reflect and interact with AD-

pathology (explanation #2), WMH can also exist independent of AD (explanation #1).

4.3.4. Clinical assessment

Concerning clinical assessment, an important finding is that the impairments in general cognitive functioning may be detected even with a relatively rough general-level cognitive measure such as the Total Score of the CERAD-NB. The CERAD-NB itself is already very commonly used in basic clinical screening and assessment by several healthcare professions. Most commonly the results are interpreted by using subtest-based cutoff scores as per the original administration procedure (Pulliainen et al., 1999). However, the results in Study I support the notion that a compound score representing the performance of several subtests might be a useful addition to clinical settings (for studies on compound scores of CERAD-NB see: Chandler et al., 2005; Paajanen et al., 2010, 2014; Seo et al., 2010).

Processing speed on the other hand is not often investigated in basic clinical screening, but rather as part of a larger neuropsychological assessment performed by a clinical neuropsychologist (Lezak et al., 2012). However, some researchers have suggested that the original CERAD-NB could be expanded by inlcuding tests that assess processing speed and executive functions, such as the Trail Making Test A and B (for example, see: Schmid et al., 2014). Regardless, as markedly slowed processing speed can be a specific symptom in AD patients suffering from major comorbid cerebrovascular pathology, care should be taken to assess this domain of cognitive functioning properly.

4.3.5. Clinical interventions

As AD patients with comorbid cerebrovascular pathology can suffer from increased cognitive impairment, preventing and treating said vascular pathology could have major impacts on the functioning of amnestic MCI patients and AD patients in earlier stages of disease progression. The main targets of risk factor prevention include hypertension, obesity, diabetes and hypercholesterolaemia in addition to smoking and heavy alcohol consumption (Farooq & Gorelick, 2013; Prins & Scheltens, 2015). High blood pressure and hypertension especially are risk factors associated with the development and progression of WMH (Goldstein et al., 2005; Gottesman et al., 2010).

Regarding long-term health promotion, higher educational attainment and increased physical activity have been generally described to provide benefits to maintaining cognition in old age (Brini et al., 2018; Lautenschlager et al., 2008). Both can be seen as critical factors that strengthen the neurocognitive reserve in adolescence

(Arenaza-Urquijo et al., 2017; Prakash et al., 2015). The neurocognitive reserve in turn helps our brains to maintain cerebral networks and cognitive functions in the case of age-related or pathological changes (Cabeza et al., 2018; C.-M. Huang & Huang, 2019). Several studies have reported that higher education has benefits on cognitive functioning and cerebral health during old age. For example, higher education has been reported to slow age-related cognitive decline (Stern, 2006), to be negatively associated with WMH volumes (Habes et al., 2016), to mitigate the negative effects of WMH on cognition (Brickman, Siedlecki, et al., 2011; Dufouil et al., 2003; Jokinen et al., 2016), and to lower the risk for developing dementia and AD (Stern et al., 1994; Xu et al., 2016). However, though education has clear associations with cognition, the exact specifics and mechanisms behind this association are still debated. For instance, a number of recent studies have challenged the association between education and cognitive decline (e.g., Berggren et al., 2018; Nyberg et al., 2021; Seblova et al., 2021), with a recent comprehensive review concluding that education does not seem to slow down cognitive decline in old age (Lövdén et al., 2020). Overall, these recent studies can be seen as supporting the concept of a passive neurocognitive reserve (Barulli & Stern, 2013): Instead of slowing decline, education may in fact bestow individuals with a life-long advantage that persist throughout adulthood and helps to offset any decline in old age.

Long-term physical activity is also associated with better cognitive functioning and a slower decline in cognition (Cotman & Berchtold, 2002; Soumaré et al., 2009; Sturman et al., 2005; Weuve et al., 2004), as well as a decrease in vascular risk factors (Uemura et al., 2012). Physical activity has also been associated with reduced WMH volume in many studies (e.g., Burzynska et al., 2014; Gow et al., 2012; Rovio et al., 2010; Wirth et al., 2014), though others have found no such effects (A. J. Ho et al., 2011; Rosano et al., 2010; Zheng et al., 2012). In addition to physical activity, cognitive stimulation seems to have benefits as well, as participation in cognitively stimulating activities is associated with slower cognitive decline (Verghese et al., 2003; Wilson et al., 2003; Wilson, Mendes de Leon, et al., 2002) and a decreased risk for developing AD (H.-X. Wang et al., 2002; Wilson, Bennett, et al., 2002; Wilson, Mendes de Leon, et al., 2002).

Findings about the effectiveness of clinical interventions are scarce. A number of findings have been published concerning GM, with a few studies reporting increases in hippocampal volumes after physical activity interventions (Erickson et al., 2011; Rosano et al., 2017), and similar findings being reported in decade-long observational studies as well (Bugg & Head, 2011; Tan et al., 2017). To the best of the Author's knowledge, no findings have been reported showing decreases in WMH volumes due to physical activity or cognitive stimulation interventions.

However, a recent randomized controlled trial that was carried out as part of the Finnish Geriatric Intervention Study to prevent Cognitive Impairment and Disability (Kivipelto et al., 2013) did report positive effects following a two-year multi-domain intervention (Stephen et al., 2020). Following the intervention that included diet, exercise, cognitive training, and vascular risk management, more positive changes in WM microstructure and an increase in cognitive functioning were found in the intervention group over the control group. Though these findings should be considered preliminary, they indicate that WM pathology may be modulated by multi-domain lifestyle interventions even in old age.

The current thesis did not include any measures for physical activity, but a rough measure for educational attainment was included, and a number of effects regarding it were seen in additional analyses. In the sample used in Studies I-II the cognitively healthy group was significantly more educated when compared to AD patients. Unsurprisingly, education was also by itself a significant predictor of cognitive performance for almost every cognitive domain, with the highest coefficients being seen for the CERAD-TS as well as for verbal functions.

4.3.6. The role of age

Age is a strong predictor for increased WMH burden *per se* (DeCarli et al., 2005), but the specific effects of WMH on cognition may also in fact vary with age (Mortamais et al., 2013). One view states that WMH might have more severe effects on cognition with increased age, since elderly populations often have less neurocognitive reserve available due to cerebral aging, and could thus be more vulnerable to developing impairments (Kloppenborg et al., 2014). However, the empirical evidence for this hypothesis is somewhat mixed and needs further confirmation (for differing accounts, see: Kloppenborg et al., 2014; Vasquez & Zakzanis, 2015). An alternate hypothesis states that WMH might in fact have *a lesser* impact on cognition in older cohorts (Mortamais et al., 2013). This theory has received some empirical support, as the few studies that have examined WMH on very old cohorts (+80 years) have reported *non-significant* associations for cognitive measures (Firbank et al., 2007, 2012; Piguet et al., 2003; Zamboni et al., 2019). These findings might be explained by the diverse etiologies underlying WMH (see chapter 1.2.1.); Some WMH might reflect processes that have strong associations with dementia and increased mortality rate (i.e., leading to the dementia and/or death of these patients by the age of 80), whereas the WMH found in these very old cohorts might not be related to neurodegeneration to such a degree (Zamboni et al., 2019). Overall, these two hypotheses need not be

mutually non-exclusive. Elderly cohorts might be at risk of developing more severe impairments from WMH due to lowered neurocognitive reserve, but concurrently these associations might become weaker in very old cohorts (+80 years) due to mortality and increasingly diverse etiologies.

In this thesis age was used as a covariate in each analysis to guard against possible confounding effects. In the sample used in Studies I-II, cognitively healthy participants were younger than MCI patients or AD patients. However, the age of the participants was not associated with any measure of WM pathology used in Studies I-II or in Studies III-IV. Interestingly, age did correlate negatively with every cognitive measure used in Studies I-IV. As might be expected, the largest correlation coefficients were seen with processing speed. Overall, further research utilizing large community-dwelling samples and including various age groups is needed to help elucidate the issue of how age affects the relationship between WMH and cognition.

4.4. Strengths and limitations

A clear strength of the present thesis is that cognitive functioning was measured by several validated neuropsychological tests, and compound scores were calculated for several domains. Furthermore, factor analysis was utilized to check the internal consistency of the compounds. Additionally, the thesis utilized both visually rated and quantified measures for MRI analysis, and applied more specific topographic divisions than what has been seen in many studies, where either global measures of pathology or larger areas of interest have been examined (de Groot et al., 2000; Debette et al., 2007; Söderlund et al., 2006).

As for limitations, it should be noted that other studies have assessed more specific regions with higher resolution magnetic imaging. Furthermore, as the MRI data was obtained with a 1.5 T set-up, the resolution in a number of images was unadequate for quantification. This lead to the exclusion of a portion of participants for Studies III-IV, which resulted in a somewhat unideal sample size and also necessated the merging of the MCI and AD groups. The reduced sample size might have had an effect on the statistical power to detect smaller effects in Studies III-IV and might also explain the null findings in Study IV. This change also complicated the comparison of results between visually rated and quantified data, and most likely contributed to the differences in results between Studies II and III. Furthermore, since GM volumes were not controlled for, we cannot exclude the possibility that cortical atrophy would have effects on the relationship between WMH and cognitive performance. Nonetheless, we also assumed that cortical atrophy is inherently to a degree intertwined in the group classifications

utilized in the models (see chapter 4.3.2.). Regarding the covariates, as there were small group-wise differences concerning age and education, the effects of these variables were controlled for in all the models. Nonetheless, it is not possible to verify with complete confidence that these variables would not have any confounding effects. Other limitations include the cross-sectional design, which does not allow to specify clear causal relationships, as well as the utilization of one sample or portions of it in all four studies.

Finally, as each study has included several alternative models testing for several hypotheses, this naturally increases the risk for Type I errors (i.e., detecting false positives). However, utilizing for example Bonferroni adjustments to account for this would in practice nullify any significant findings and clearly inflate the risk for Type II error instead (i.e., detecting false negatives) (Perneger, 1998). Regarding the findings presented in studies I-III the Author is of the opinion that the risk for Type II errors is higher than the risk for Type I errors. The main arguments for this are: the novel nature of the findings; the unevenness in group sizes in Studies I-II, i.e., participants with low levels of WMH being overrepresented; the relatively small sample size in Study III, which hinders the statistical power to detect effects. Further support for the validity of these results comes from the alternative set of multivariate analyses that were performed in Study II to check for Type I errors. Here, every independent variable was included in the same statistical models, which produced mainly similar results when compared with univariate models used otherwise (see details in Discussion of Study II). Finally, it should be noted that Study IV utilized multiple testing correction: Here the Benjamini–Hochberg procedure, a fairly less conservative correction method than the Bonferroni adjustment, was utilized to guard against false positives (Benjamini & Hochberg, 1995).

4.5. Future suggestions

It would first of all be advisable to attempt to replicate the findings with larger samples and with relatively even sample sizes in any included subgroups, with preferably effects being compared between cognitively healthy participants and patients with MCI/AD. Furthermore, the focus should generally move from measuring WMH in larger areas to looking at pathological development in specific WM tracts (see for example: Jiang et al., 2018; Lampe et al., 2019).

Concerning measurements, short neuropsychological tests such as the MMSE or the Montreal cognitive assessment are often used in studies to assess general cognitive performance (e.g., Gouw et al., 2006; Stephan et al., 2012). However, these tests have originally been developed for

clinical screening, and can be used to obtain only a rough general-level assessment. Thus, it would be recommended that studies utilize a wide array of neuropsychological tests for measuring cognition, preferably including at least two different tests per function/domain and differentiating between different sense modalities (e.g., verbal and visual episodic memory).

As for brain imaing, though it requires more resources, multimodal imaging methods should be utilized for measuring WM; An example would be to employ both volumetric analysis of WMH and diffusion-weighted imaging of specific WM tracts (see for example: Zamboni et al., 2019). Possible interactions with AD-related cortical atrophy should be accounted for either by controlling the effects, or investigating any possible mediating relationships (see for example: Rizvi et al., 2017).

Regarding language lateralization, it might be recommended to include solely right-handed participants in studies that measure verbal functions in order to guard against possible confounding effects with left-handed/ambidextrous participants (as seen in Study IV).

Finally, as discussed in chapters 4.3.5.-4.3.6., it would be recommended for future studies to more fully ascertain the possible modifying effects that age and the neurocognitive reserve can have on the relationship between WMH, AD and cognition.

4.6. Conclusions

White matter hyperintensities reflect underlying cerebrovascular pathology and are by themselves associated with impairments in various cognitive domains. There exists a great deal of overlap between WMH and AD, and the results presented in this thesis support the notion that the two pathologies seem to have cumulative effects on certain cognitive functions. More specifically, AD patients suffering from major levels of comorbid WM pathology especially in frontal cerebral areas are likely to have increased cognitive impairments when compared to patients with milder levels of WM pathology. Impairments may show up as lowered general cognitive functioning and slowed information processing speed.

Regarding clinical assessment, it is noteworthy that impairments in general cognitive functioning can be detected even with general-level cognitive measures such as the Total Score of the CERAD-NB. Furthermore, as AD patients with major comorbid cerebrovascular pathology can exhibit markedly slowed processing speed, care should be taken to assess this domain properly in addition to traditional targets of investigation, such as episodic memory.

Previous studies have shown that the prevalence of WMH can be lowered by minimizing risk factors such as hypertension, obesity, diabetes and hypercholesterolaemia, as well as through fostering

physical and cognitive activity throughout the lifespan. The preemptive targeting of these modifiable risk factors and good health likely yields long-term benefits in maintaining cognition in amnestic MCI and AD.

Overall, more research is required to elucidate the relationships between WMH and AD, and to fully explain the overlaps and interactions between the two pathologies.

References

Abrahams, S., Goldstein, L. H., Simmons, A., Brammer, M. J., Williams, S. C. R., Giampietro, V. P., Andrew, C. M., & Leigh, P. N. (2003). Functional magnetic resonance imaging of verbal fluency and confrontation naming using compressed image acquisition to permit overt responses. *Human Brain Mapping*, *20*(1), 29–40. https://doi.org/10.1002/hbm.10126

Agosta, F., Henry, R. G., Migliaccio, R., Neuhaus, J., Miller, B. L., Dronkers, N. F., Brambati, S. M., Filippi, M., Ogar, J. M., Wilson, S. M., & Gorno-Tempini, M. L. (2010). Language networks in semantic dementia. *Brain*, *133*(1), 286–299. https://doi.org/10.1093/brain/awp233

Albert, M. S., DeKosky, S. T., Dickson, D., Dubois, B., Feldman, H. H., Fox, N. C., Gamst, A., Holtzman, D. M., Jagust, W. J., Petersen, R. C., Snyder, P. J., Carrillo, M. C., Thies, B., & Phelps, C. H. (2011). The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia : The Journal of the Alzheimer's Association*, *7*(3), 270–279. https://doi.org/https://doi.org/10.1016/j.jalz.2011.03.008

Allendorfer, J. B., Hernando, K. A., Hossain, S., Nenert, R., Holland, S. K., & Szaflarski, J. P. (2016). Arcuate fasciculus asymmetry has a hand in language function but not handedness. *Human Brain Mapping*, *37*(9), 3297–3309. https://doi.org/10.1002/hbm.23241

Alzheimer's Association. (2015). 2015 Alzheimer's disease facts and figures. *Alzheimer's & Dementia : The Journal of the Alzheimer's Association*, *11*(3), 332–384. https://doi.org/https://doi.org/10.1016/j.jalz.2015.02.003

Alzheimer's Disease International. (2013). *Alzheimer's Disease International. Policy Brief for G8 Heads of Government. The Global Impact of Dementia 2013-2050.*

Amieva, H., Rouch-Leroyer, I., Fabrigoule, C., & Dartigues, J.-F. (2000). Deterioration of Controlled Processes in the Preclinical Phase of Dementia: A Confirmatory Analysis. *Dementia and Geriatric Cognitive Disorders*, *11*(1), 46–52. https://doi.org/10.1159/000017213

Apostolova, L. G., & Cummings, J. L. (2008). Neuropsychiatric Manifestations in Mild Cognitive Impairment: A Systematic Review of the Literature. *Dementia and Geriatric Cognitive Disorders*, *25*(2), 115–126. https://doi.org/10.1159/000112509

Arenaza-Urquijo, E. M., Bejanin, A., Gonneaud, J., Wirth, M., La Joie, R., Mutlu, J., Gaubert, M., Landeau, B., de la Sayette, V., Eustache, F., & Chételat, G. (2017). Association between educational attainment and amyloid deposition across the spectrum from normal cognition to dementia: neuroimaging evidence

for protection and compensation. *Neurobiology of Aging*, *59*, 72–79. https://doi.org/https://doi.org/10.1016/j.neurobiolaging.2017.06.016

Atkinson, R. C., & Shiffrin, R. M. (1971). The control of short-term memory. *Scientific American*, *225*(2), 82–90. https://doi.org/10.1038/scientificamerican0871-82

Au, R., Massaro, J. M., Wolf, P. A., Young, M. E., Beiser, A., Seshadri, S., D'Agostino, R. B., & DeCarli, C. (2006). Association of white matter hyperintensity volume with decreased cognitive functioning: The framingham heart study. *Archives of Neurology*, *63*(2), 246–250. https://doi.org/10.1001/archneur.63.2.246

Bäckman, L., Jones, S., Berger, A.-K., Laukka, E. J., & Small, B. J. (2004). Multiple cognitive deficits during the transition to Alzheimer's disease. *Journal of Internal Medicine*, *256*(3), 195–204. https://doi.org/https://doi.org/10.1111/j.1365-2796.2004.01386.x

Baldo, J. V., Arévalo, A., Patterson, J. P., & Dronkers, N. F. (2013). Grey and white matter correlates of picture naming: Evidence from a voxel-based lesion analysis of the Boston Naming Test. *Cortex*, *49*(3), 658–667. https://doi.org/10.1016/J.CORTEX.2012.03.001

Ball, M. J. (1989). "Leukoaraiosis" explained. *The Lancet*, *18*, 612–613. https://doi.org/https://doi.org/10.1016/S0140-6736(89)91633-4

Bartzokis, G., Lu, P. H., Tingus, K., Mendez, M. F., Richard, A., Peters, D. G., Oluwadara, B., Barrall, K. A., Finn, J. P., Villablanca, P., Thompson, P. M., & Mintz, J. (2010). Lifespan trajectory of myelin integrity and maximum motor speed. *Neurobiology of Aging*, *31*(9), 1554–1562. https://doi.org/https://doi.org/10.1016/j.neurobiolaging.2008.08.015

Barulli, D., & Stern, Y. (2013). Efficiency, capacity, compensation, maintenance, plasticity: emerging concepts in cognitive reserve. *Trends in Cognitive Sciences*, *17*(10), 502–509. https://doi.org/10.1016/j.tics.2013.08.012

Bates, E., Wilson, S. M., Saygin, A. P., Dick, F., Sereno, M. I., Knight, R. T., & Dronkers, N. F. (2003). Voxel-based lesion–symptom mapping. *Nature Neuroscience*, *6*(5), 448–450. https://doi.org/10.1038/nn1050

Beaulieu, C. (2002). The basis of anisotropic water diffusion in the nervous system – a technical review. *NMR in Biomedicine*, *15*(7-8), 435–455. https://doi.org/10.1002/nbm.782

Benjamini, Y., & Hochberg, Y. (1995). Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *Journal of the Royal Statistical Society. Series B (Methodological)*, *57*(1), 289–300. http://www.jstor.org/stable/2346101

Berggren, R., Nilsson, J., & Lövdén, M. (2018). Education Does Not Affect Cognitive Decline in Aging: A Bayesian Assessment of the Association Between Education and Change in Cognitive Performance . In *Frontiers in Psychology* (Vol. 9, p. 1138). https://www.frontiersin.org/article

/10.3389/fpsyg.2018.01138

Biesbroek, J. M., Kuijf, H. J., van der Graaf, Y., Vincken, K. L., Postma, A., Mali, W. P. T. M., Biessels, G. J., Geerlings, M. I., & Group, on behalf of the S. S. (2013). Association between Subcortical Vascular Lesion Location and Cognition: A Voxel-Based and Tract-Based Lesion-Symptom Mapping Study. The SMART-MR Study. *PLOS ONE*, *8*(4), e60541. https://doi.org/10.1371/journal.pone.0060541

Biesbroek, J. M., van Zandvoort, M. J. E., Kappelle, L. J., Velthuis, B. K., Biessels, G. J., & Postma, A. (2016). Shared and distinct anatomical correlates of semantic and phonemic fluency revealed by lesion-symptom mapping in patients with ischemic stroke. *Brain Structure & Function*, *221*(4), 2123–2134. https://doi.org/10.1007/s00429-015-1033-8

Biesbroek, J. M., Weaver, N. A., & Biessels, G. J. (2017). Lesion location and cognitive impact of cerebral small vessel disease. *Clinical Science*, *131*(8), 715–728. https://doi.org/10.1042/CS20160452

Biesbroek, J. M., Weaver, N. A., Hilal, S., Kuijf, H. J., Ikram, M. K., Xu, X., Tan, B. Y., Venketasubramanian, N., Postma, A., Biessels, G. J., & Chen, C. P. L. H. (2016). Impact of Strategically Located White Matter Hyperintensities on Cognition in Memory Clinic Patients with Small Vessel Disease. *PLOS ONE*, *11*(11), e0166261. https://doi.org/10.1371/journal.pone.0166261

Bilello, M., Doshi, J., Nabavizadeh, S. A., Toledo, J. B., Erus, G., Xie, S. X., Trojanowski, J. Q., Han, X., & Davatzikos, C. (2015). Correlating Cognitive Decline with White Matter Lesion and Brain Atrophy MRI Measurements in Alzheimer's Disease. *Journal of Alzheimer's Disease : JAD*, *48*(4), 987–994. https://doi.org/10.3233/JAD-150400

Birn, R. M., Kenworthy, L., Case, L., Caravella, R., Jones, T. B., Bandettini, P. A., & Martin, A. (2010). Neural systems supporting lexical search guided by letter and semantic category cues: A self-paced overt response fMRI study of verbal fluency. *NeuroImage*, *49*(1), 1099–1107. https://doi.org/10.1016/J.NEUROIMAGE.2009.07.036

Blecher, T., Miron, S., Schneider, G. G., Achiron, A., & Ben-Shachar, M. (2019). Association Between White Matter Microstructure and Verbal Fluency in Patients With Multiple Sclerosis. *Frontiers in Psychology*, *10*, 1607. https://doi.org/10.3389/fpsyg.2019.01607

Brant-Zawadzki, M. (1992). Interpreting abnormal foci in MRI of the aging brain. *Diagnostic Imaging*, *5*, 114–116.

Breteler, M. M. B. (2000). Vascular risk factors for Alzheimer's disease. *Neurobiology of Aging*, *21*(2), 153–160. https://doi.org/10.1016/S0197-4580(99)00110-4

Brickman, A. M. (2013). Contemplating Alzheimer's Disease and the Contribution of White Matter Hyperintensities. *Curr Neurol Neurosci Rep*, *25*(8), 713–724. https://doi.org/10.1097/MCA.0000000000000178.Endothelial

Brickman, A. M., Honig, L. S., Scarmeas, N., Tatarina, O., Sanders, L., Albert, M. S., Brandt, J., Blacker, D., & Stern, Y. (2008). Measuring cerebral atrophy and white matter hyperintensity burden to predict the rate of cognitive decline in Alzheimer disease. *Archives of Neurology*, *65*(9), 1202–1208. https://doi.org/10.1001/archneur.65.9.1202

Brickman, A. M., Muraskin, J., & Zimmerman, M. E. (2009). Structural neuroimaging in Alzheimer's disease: Do white matter hyperintensities matter? *Dialogues in Clinical Neuroscience*, *11*(2), 181–190. https://doi.org/10.1016/j.bbi.2008.05.010

Brickman, A. M., Siedlecki, K. L., Muraskin, J., Manly, J. J., Luchsinger, J. A., Yeung, L. K., Brown, T. R., DeCarli, C., & Stern, Y. (2011). White matter hyperintensities and cognition: Testing the reserve hypothesis. *Neurobiology of Aging*, *32*(9), 1588–1598. https://doi.org/10.1016/j.neurobiolaging.2009.10.013

Brickman, A. M., Sneed, J. R., Provenzano, F. A., Garcon, E., Johnert, L., Muraskin, J., Yeung, L.-K., Zimmerman, M. E., & Roose, S. P. (2011). Quantitative approaches for assessment of white matter hyperintensities in elderly populations. *Psychiatry Research: Neuroimaging*, *193*(2), 101–106. https://doi.org/10.1016/J.PSCYCHRESNS.2011.03.007

Brini, S., Sohrabi, H. R., Peiffer, J. J., Karrasch, M., Hämäläinen, H., Martins, R. N., & Fairchild, T. J. (2018). Physical Activity in Preventing Alzheimer's Disease and Cognitive Decline: A Narrative Review. *Sports Medicine*, *48*(1), 29–44. https://doi.org/10.1007/s40279-017-0787-y

Brodaty, H., & Moore, C. M. (1997). The Clock Drawing Test for dementia of the Alzheimer's type: A comparison of three scoring methods in a memory disorders clinic. *International Journal of Geriatric Psychiatry*, *12*(6), 619–627.

Brooks, B. L., Holdnack, J. A., & Iverson, G. L. (2010). Advanced Clinical Interpretation of the WAIS-IV and WMS-IV: Prevalence of Low Scores Varies by Level of Intelligence and Years of Education. *Assessment*, *18*(2), 156–167. https://doi.org/10.1177/1073191110385316

Brugulat-Serrat, A., Salvadó, G., Sudre, C. H., Grau-Rivera, O., Suárez-Calvet, M., Falcon, C., Sánchez-Benavides, G., Gramunt, N., Fauria, K., Cardoso, M. J., Barkhof, F., Molinuevo, J. L., Gispert, J. D., Camí, J., Cacciaglia, R., Operto, G., Skouras, S., Minguillón, C., Polo, A., … Study, for the A. (2019). Patterns of white matter hyperintensities associated with cognition in middle-aged cognitively healthy individuals. *Brain Imaging and Behavior*. https://doi.org/10.1007/s11682-019-00151-2

Budde, M. D., Janes, L., Gold, E., Turtzo, L. C., & Frank, J. A. (2011). The contribution of gliosis to diffusion tensor anisotropy and tractography following traumatic brain injury: validation in the rat using Fourier analysis of stained

tissue sections. *Brain*, *134*(8), 2248–2260. https://doi.org/10.1093/brain/awr161

Bugg, J. M., & Head, D. (2011). Exercise moderates age-related atrophy of the medial temporal lobe. *Neurobiology of Aging*, *32*(3), 506–514. https://doi.org/https://doi.org/10.1016/j.neurobiolaging.2009.03.008

Burton, E. J., Kenny, R. A., O'Brien, J., Stephens, S., Bradbury, M., Rowan, E., Kalaria, R., Firbank, M., Wesnes, K., & Ballard, C. (2004a). White Matter Hyperintensities Are Associated With Impairment of Memory, Attention, and Global Cognitive Performance in Older Stroke Patients. *Stroke*, *35*(6), 1270–1275. https://doi.org/10.1161/01.STR.0000126041.99024.86

Burton, E. J., Kenny, R. A., O'Brien, J., Stephens, S., Bradbury, M., Rowan, E., Kalaria, R., Firbank, M., Wesnes, K., & Ballard, C. (2004b). White Matter Hyperintensities Are Associated With Impairment of Memory, Attention, and Global Cognitive Performance in Older Stroke Patients. *Stroke*, *35*(6), 1270–1275. https://doi.org/10.1161/01.STR.0000126041.99024.86

Burzynska, A. Z., Chaddock-Heyman, L., Voss, M. W., Wong, C. N., Gothe, N. P., Olson, E. A., Knecht, A., Lewis, A., Monti, J. M., Cooke, G. E., Wojcicki, T. R., Fanning, J., Chung, H. D., Awick, E., McAuley, E., & Kramer, A. F. (2014). Physical Activity and Cardiorespiratory Fitness Are Beneficial for White Matter in Low-Fit Older Adults. *PLOS ONE*, *9*(9), e107413. https://doi.org/10.1371/journal.pone.0107413

Cabeza, R. (2002). Hemispheric asymmetry reduction in older adults: The HAROLD model. *Psychology and Aging*, *17*(1), 85–100. https://doi.org/https://doi.org/10.1037/0882-7974.17.1.85

Cabeza, R., Albert, M., Belleville, S., Craik, F. I. M., Duarte, A., Grady, C. L., Lindenberger, U., Nyberg, L., Park, D. C., Reuter-Lorenz, P. A., Rugg, M. D., Steffener, J., & Rajah, M. N. (2018). Maintenance, reserve and compensation: the cognitive neuroscience of healthy ageing. *Nature Reviews Neuroscience*, *19*(11), 701–710. https://doi.org/10.1038/s41583-018-0068-2

Cabeza, R., Ciaramelli, E., Olson, I. R., & Moscovitch, M. (2008). The parietal cortex and episodic memory: an attentional account. *Nature Reviews Neuroscience*, *9*, 613. https://doi.org/10.1038/nrn2459

Carp, J., Park, J., Hebrank, A., Park, D. C., & Polk, T. A. (2011). Age-Related Neural Dedifferentiation in the Motor System. *PLOS ONE*, *6*(12), e29411. https://doi.org/https://doi.org/10.1371/journal.pone.0029411

Catani, M., Mesulam, M. M., Jakobsen, E., Malik, F., Martersteck, A., Wieneke, C., Thompson, C. K., Thiebaut de Schotten, M., Dell'Acqua, F., Weintraub, S., & Rogalski, E. (2013). A novel frontal pathway underlies verbal fluency in primary progressive aphasia. *Brain*, *136*(8), 2619–2628. https://doi.org/10.1093/brain/awt163

Chandler, M. J., Lacritz, L. H., Hynan, L.

S., Barnard, H. D., Allen, G., Deschner, M., Weiner, M. F., & Cullum, C. M. (2005). A total score for the CERAD neuropsychological battery. *Neurology*, *65*(1), 102–106. https://doi.org/10.1212/01.wnl.0000167607.63000.38

Chen, T.-F., Chen, Y.-F., Cheng, T.-W., Hua, M.-S., Liu, H.-M., & Chiu, M.-J. (2009). Executive dysfunction and periventricular diffusion tensor changes in amnesic mild cognitive impairment and early Alzheimer's disease. *Human Brain Mapping*, *30*(11), 3826–3836. https://doi.org/10.1002/hbm.20810

Chin, J., Seo, S. W., Kim, S. H., Park, A., Ahn, H. J., Lee, B. H., Kang, S. J., & Na, D. L. (2012). Neurobehavioral dysfunction in patients with subcortical vascular mild cognitive impairment and subcortical vascular dementia. *Clinical Neuropsychologist*, *26*(2), 224–238. https://doi.org/10.1080/13854046.2012.658865

Claus, J. J., Staekenborg, S. S., Roorda, J. J., Stevens, M., Herderschee, D., Van Maarschalkerweerd, W., Schuurmans, L., Tielkes, C. E. M., Koster, P., Bavinck, C., & Scheltens, P. (2016). Low Prevalence of Mixed Dementia in a Cohort of 2,000 Elderly Patients in a Memory Clinic Setting. In *Journal of Alzheimer's Disease* (Vol. 50, Issue 3). https://doi.org/10.3233/JAD-150796

Costafreda, S. G., Fu, C. H. Y., Lee, L., Everitt, B., Brammer, M. J., & David, A. S. (2006). A systematic review and quantitative appraisal of fMRI studies of verbal fluency: Role of the left inferior frontal gyrus. *Human Brain Mapping*, *27*(10), 799–810. https://doi.org/10.1002/hbm.20221

Cotman, C. W., & Berchtold, N. C. (2002). Exercise: a behavioral intervention to enhance brain health and plasticity. *Trends in Neurosciences*, *25*(6), 295–301. https://doi.org/https://doi.org/10.1016/S0166-2236(02)02143-4

de Groot, J. C., Oudkerk, M., Gijn, J., Hofman, A., Jolles, J., & Breteler, M. M. (2000). Cerebral white matter lesions and cognitive function: the Rotterdam Scan Study. *Annals of Neurology*, *47*(2), 145–151. https://doi.org/10.1002/1531-8249(200002)47:2<145::AID-ANA3>3.0.CO;2-P

de Leeuw, F. E., de Groot, J. C., Achten, E., Oudkerk, M., Ramos, L. M., Heijboer, R., Hofman, A., Jolles, J., van Gijn, J., & Breteler, M. M. (2001). Prevalence of cerebral white matter lesions in elderly people: a population based magnetic resonance imaging study. The Rotterdam Scan Study. *Journal of Neurology, Neurosurgery, and Psychiatry*, *70*(1), 9—14. https://doi.org/10.1136/jnnp.70.1.9

Debette, S., Bombois, S., Bruandet, A., Delbeuck, X., Lepoittevin, S., Delmaire, C., Leys, D., & Pasquier, F. (2007). Subcortical hyperintensities are associated with cognitive decline in patients with mild cognitive impairment. *Stroke*, *38*(11), 2924–2930.

DeCarli, C., Massaro, J., Harvey, D., Hald, J., Tullberg, M., Au, R., Beiser, A., D'Agostino, R., & Wolf, P. A. (2005). Measures of brain morphology and infarction in the framingham heart study:

establishing what is normal. *Neurobiology of Aging*, *26*(4), 491–510. https://doi.org/10.1016/J.NEUROBIOLAGING.2004.05.004

DeCarli, C., Miller, B., Swan, G., Reed, T., Wolf, P., & Carmelli, D. (2001). Cerebrovascular and brain morphologic correlates of mild cognitive impairment in the national heart, lung, and blood institute twin study. *Archives of Neurology*, *58*(4), 643–647. https://doi.org/doi:10.1001/archneur.58.4.643

Despotović, I., Goossens, B., & Philips, W. (2015). MRI Segmentation of the Human Brain: Challenges, Methods, and Applications. *Computational and Mathematical Methods in Medicine*, *2015*, 23. https://doi.org/10.1155/2015/450341

Dichgans, M., & Leys, D. (2017). Vascular Cognitive Impairment. *Circulation Research*, *120*(3), 573–591. https://doi.org/10.1161/CIRCRESAHA.116.308426

Donnelly, K. M., Allendorfer, J. B., & Szaflarski, J. P. (2011). Right hemispheric participation in semantic decision improves performance. *Brain Research*, *1419*, 105–116. https://doi.org/10.1016/j.brainres.2011.08.065

Dronkers, N. F., Wilkins, D. P., Van Valin, R. D., Redfern, B. B., & Jaeger, J. J. (2004). Lesion analysis of the brain areas involved in language comprehension. *Cognition*, *92*(1–2), 145–177. https://doi.org/10.1016/J.COGNITION.2003.11.002

Duering, M., Gesierich, B., Seiler, S., Pirpamer, L., Gonik, M., Hofer, E., Jouvent, E., Duchesnay, E., Chabriat, H., Ropele, S., Schmidt, R., & Dichgans, M. (2014). Strategic white matter tracts for processing speed deficits in age-related small vessel disease. *Neurology*, *82*(22), 1946–1950. https://doi.org/10.1212/WNL.0000000000000475

Duering, M., Gonik, M., Malik, R., Zieren, N., Reyes, S., Jouvent, E., Hervé, D., Gschwendtner, A., Opherk, C., Chabriat, H., & Dichgans, M. (2013). Identification of a strategic brain network underlying processing speed deficits in vascular cognitive impairment. *NeuroImage*, *66*, 177–183. https://doi.org/10.1016/J.NEUROIMAGE.2012.10.084

Duering, M., Zieren, N., Hervé, D., Jouvent, E., Reyes, S., Peters, N., Pachai, C., Opherk, C., Chabriat, H., & Dichgans, M. (2011). Strategic role of frontal white matter tracts in vascular cognitive impairment: a voxel-based lesion-symptom mapping study in CADASIL. *Brain*, *134*(8), 2366–2375. https://doi.org/10.1093/brain/awr169

Dufouil, C., Alpérovitch, A., & Tzourio, C. (2003). Influence of education on the relationship between white matter lesions and cognition. *Neurology*, *60*(5), 831 LP – 836. https://doi.org/10.1212/01.WNL.0000049456.33231.96

Duron, E., & Hanon, O. (2008). Vascular risk factors, cognitive decline, and dementia. *Vascular Health and Risk Management*, *4*(2), 363–381. https://doi.org/10.2147/VHRM.S1839

Erickson, K. I., Voss, M. W., Prakash, R. S., Basak, C., Szabo, A., Chaddock, L., Kim, J. S., Heo, S., Alves, H., White, S. M., Wojcicki, T. R., Mailey, E., Vieira, V. J., Martin, S. A., Pence, B. D., Woods, J. A., McAuley, E., & Kramer, A. F. (2011). Exercise training increases size of hippocampus and improves memory. *Proceedings of the National Academy of Sciences*, *108*(7), 3017 LP – 3022. https://doi.org/10.1073/pnas.1015950108

Fan, Y. H., Lam, W. W. M., Mok, V. C. T., Huang, R. X., & Wong, K. S. (2003). Variability and Validity of a Simple Visual Rating Scale in Grading White Matter Changes on Magnetic Resonance Imaging. *Journal of Neuroimaging*, *13*(3), 255–258. https://doi.org/10.1111/j.1552-6569.2003.tb00187.x

Farooq, M. U., & Gorelick, P. B. (2013). Vascular Cognitive Impairment. *Current Atherosclerosis Reports*, *15*(6), 330. https://doi.org/10.1007/s11883-013-0330-z

Fazekas, F., Chawluk, J., Alavi, A., Hurtig, H., & Zimmerman, R. (1987). MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. *AJR. American Journal of Roentgenology*, *149*(2), 351–356. https://doi.org/10.2214/ajr.149.2.351

Fazekas, F., Kleinert, R., Offenbacher, H., Schmidt, R., Kleinert, G., Payer, F., Radner, H., & Lechner, H. (1993). Pathologic correlates of incidental MRI white matter signal hyperintensities. *Neurology*, *43*(9), 1683–1689. https://doi.org/10.1212/wnl.43.9.1683

Fazekas, F., Schmidt, R., & Scheltens, P. (1998). Pathophysiologic Mechanisms in the Development of Age-Related White Matter Changes of the Brain. *Dementia and Geriatric Cognitive Disorders*, *9*(Suppl. 1), 2–5. https://doi.org/10.1159/000051182

Firbank, M. J., Allan, L. M., Burton, E. J., Barber, R., O'Brien, J. T., & Kalaria, R. N. (2012). Neuroimaging predictors of death and dementia in a cohort of older stroke survivors. *Journal of Neurology, Neurosurgery, and Psychiatry*, *83*(3), 263—267. https://doi.org/10.1136/jnnp-2011-300873

Firbank, M. J., Burton, E. J., Barber, R., Stephens, S., Kenny, R. A., Ballard, C., Kalaria, R. N., & O'Brien, J. T. (2007). Medial temporal atrophy rather than white matter hyperintensities predict cognitive decline in stroke survivors. *Neurobiology of Aging*, *28*(11), 1664–1669. https://doi.org/https://doi.org/10.1016/j.neurobiolaging.2006.07.009

Fisher, C. M. (1982). Lacunar strokes and infarcts. *Neurology*, *32*(8), 871 LP – 871. https://doi.org/10.1212/WNL.32.8.871

Fletcher, P. C., & Henson, R. N. A. (2001). Frontal lobes and human memory: Insights from functional neuroimaging. *Brain*, *124*(5), 849–881. https://doi.org/10.1093/brain/124.5.849

Folstein, M. F., Folstein, S. E. S., & 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*(3), 189–198. https://doi.org/10.1016/0022-3956(75)90026-6

Förstl, H., & Kurz, A. (1999). Clinical features of Alzheimer's disease. *European Archives of Psychiatry and Clinical Neuroscience*, *249*(6), 288–290. https://doi.org/10.1007/s004060050101

Fujishima, M., Maikusa, N., Nakamura, K., Nakatsuka, M., Matsuda, H., & Meguro, K. (2014). Mild cognitive impairment, poor episodic memory, and late-life depression are associated with cerebral cortical thinning and increased white matter hyperintensities. In *Frontiers in Aging Neuroscience* (Vol. 6, p. 306). https://www.frontiersin.org/article/10.3389/fnagi.2014.00306

Gavett, B. E., Ozonoff, A., Doktor, V., Palmisano, J., Nair, A. K., Green, R. C., Jefferson, A. L., & Stern, R. A. (2010). Predicting cognitive decline and conversion to Alzheimer's disease in older adults using the NAB List Learning test. *Journal of the International Neuropsychological Society*, *16*(4), 651–660. https://doi.org/10.1017/S1355617710000421

Glikmann-Johnston, Y., Oren, N., Hendler, T., & Shapira-Lichter, I. (2015). Distinct functional connectivity of the hippocampus during semantic and phonemic fluency. *Neuropsychologia*, *69*, 39–49. https://doi.org/10.1016/j.neuropsychologia.2015.01.031

Gold, B. T., Johnson, N. F., Powell, D. K., & Smith, C. D. (2012). White matter integrity and vulnerability to Alzheimer's disease: Preliminary findings and future directions. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease*, *1822*(3), 416–422. https://doi.org/https://doi.org/10.1016/j.bbadis.2011.07.009

Goldstein, I. B., Bartzokis, G., Guthrie, D., & Shapiro, D. (2005). Ambulatory blood pressure and the brain: a 5-year follow-up. *Neurology*, *64*(11), 1846—1852. https://doi.org/10.1212/01.wnl.0000164712.24389.bb

Gootjes, L., Teipel, S. J., Zebuhr, Y., Schwarz, R., Leinsinger, G., Scheltens, P., Möller, H.-J., & Hampel, H. (2004). Regional Distribution of White Matter Hyperintensities in Vascular Dementia, Alzheimer's Disease and Healthy Aging. *Dementia and Geriatric Cognitive Disorders*, *18*(2), 180–188. https://doi.org/10.1159/000079199

Gordon, J. K., Young, M., & Garcia, C. (2018). Why do older adults have difficulty with semantic fluency? *Aging, Neuropsychology, and Cognition*, *25*(6), 803–828. https://doi.org/10.1080/13825585.2017.1374328

Gottesman, R. F., Coresh, J., Catellier, D. J., Sharrett, R. A., Rose, K. M., Coker, L. H., Shibata, D. K., Knopman, D. S., Jack, C. R., & Mosley, T. H. (2010). Blood Pressure and White-Matter Disease Progression in a Biethnic Cohort. *Stroke*, *41*(1), 3–8. https://doi.org/10.1161/STROKEAHA.109.566992

Gourovitch, M. L., Kirkby, B. S.,

Goldberg, Terry E. Weinberger, D. R., Gold, J. M., Esposito, G., Van Horn, J. D., & Berman, K. F. (2000). A comparison of rCBF patterns during letter and semantic fluency. *Neuropsychology*, *14*(3), 353–360. https://doi.org/10.1037/0894-4105.14.3.353

Gouw, A. A., der Flier, W. M., van Straaten, E. C. W., Barkhof, F., Ferro, J. M., Baezner, H., Pantoni, L., Inzitari, D., Erkinjuntti, T., Wahlund, L. O., Waldemar, G., Schmidt, R., Fazekas, F., & Scheltens, P. (2006). Simple versus complex assessment of white matter hyperintensities in relation to physical performance and cognition: the LADIS study. *Journal of Neurology*, *253*(9), 1189–1196. https://doi.org/10.1007/s00415-006-0193-5

Gouw, A. A., Seewann, A., van der Flier, W. M., Barkhof, F., Rozemuller, A. M., Scheltens, P., & Geurts, J. J. G. (2011). Heterogeneity of small vessel disease: a systematic review of MRI and histopathology correlations. *Journal of Neurology, Neurosurgery &Amp; Psychiatry*, *82*(2), 126 LP – 135. https://doi.org/10.1136/jnnp.2009.204685

Gow, A. J., Bastin, M. E., Maniega, S. M., Hernández, M. C. V., Morris, Z., Murray, C., Royle, N. A., Starr, J. M., Deary, I. J., & Wardlaw, J. M. (2012). Neuroprotective lifestyles and the aging brain: Activity, atrophy, and white matter integrity. *Neurology*, *79*(17), 1802–1808. https://doi.org/10.1212/WNL.0b013e3182703fd2

Green, A. E., Croft, R. J., Maller, J. J., & Fitzgerald, P. B. (2016). White matter correlates of episodic memory encoding and retrieval in schizophrenia. *Psychiatry Research: Neuroimaging*, *254*, 188–198. https://doi.org/10.1016/J.PSCYCHRESNS.2016.07.002

Griffis, J. C., Nenert, R., Allendorfer, J. B., & Szaflarski, J. P. (2017). Damage to white matter bottlenecks contributes to language impairments after left hemispheric stroke. *NeuroImage. Clinical*, *14*, 552–565. https://doi.org/10.1016/j.nicl.2017.02.019

Gunning-Dixon, F. M., & Raz, N. (2000). The cognitive correlates of white matter abnormalities in normal aging: a quantitative review. *Neuropsych.*, *14*(2), 224–232. https://doi.org/10.1037//0894-4105.14.2.224

Gunning-Dixon, F. M., Brickman, A. M., Cheng, J. C., & Alexopoulos, G. C. (2008). Aging of cerebral white matter: a review of MRI findings. *International Journal of Geriatric Psychiatry*, *24*(2), 109–117. https://doi.org/10.1002/gps.2087

Habes, M., Erus, G., Toledo, J. B., Zhang, T., Bryan, N., Launer, L. J., Rosseel, Y., Janowitz, D., Doshi, J., Van der Auwera, S., von Sarnowski, B., Hegenscheid, K., Hosten, N., Homuth, G., Völzke, H., Schminke, U., Hoffmann, W., Grabe, H. J., & Davatzikos, C. (2016). White matter hyperintensities and imaging patterns of brain ageing in the general population. *Brain : A Journal of Neurology*, *139*(Pt 4), 1164–1179. https://doi.org/10.1093/brain/aww008

Harper, L., Fumagalli, G. G., Barkhof, F.,

Scheltens, P., O'Brien, J. T., Bouwman, F., Burton, E. J., Rohrer, J. D., Fox, N. C., Ridgway, G. R., & Schott, J. M. (2016). MRI visual rating scales in the diagnosis of dementia: Evaluation in 184 post-mortem confirmed cases. *Brain*, *139*(4), 1211–1225. https://doi.org/10.1093/brain/aww005

Haworth, J., Phillips, M., Newson, M., Rogers, P. J., Torrens-Burton, A., & Tales, A. (2016). Measuring Information Processing Speed in Mild Cognitive Impairment: Clinical Versus Research Dichotomy. *Journal of Alzheimer's Disease : JAD*, *51*(1), 263–275. https://doi.org/10.3233/JAD-150791

Henry, J. D., & Crawford, J. R. (2004). A meta-analytic review of verbal fluency performance following focal cortical lesions. *Neuropsychology*, *18*(2), 284–295. https://doi.org/10.1037/0894-4105.18.2.284

Henseler, I., Regenbrecht, F., & Obrig, H. (2014). Lesion correlates of patholinguistic profiles in chronic aphasia: comparisons of syndrome-, modality- and symptom-level assessment. *Brain*, *137*(3), 918–930. https://doi.org/10.1093/brain/awt374

Herculano-Houzel, S. (2009). The human brain in numbers: a linearly scaled-up primate brain . In *Frontiers in Human Neuroscience* (Vol. 3, p. 31). https://www.frontiersin.org/article/10.3389/neuro.09.031.2009

Herrmann, L. L., Le Masurier, M., & Ebmeier, K. P. (2008). White matter hyperintensities in late life depression: a systematic review. *Journal of Neurology, Neurosurgery &Amp; Psychiatry*, *79*(6), 619–624. https://doi.org/10.1136/jnnp.2007.124651

Hickok, G., & Poeppel, D. (2007). The cortical organization of speech processing. *Nature Reviews Neuroscience*, *8*(5), 393–402. https://doi.org/10.1038/nrn2113

Hidese, S., Ota, M., Matsuo, J., Ishida, I., Hiraishi, M., Yokota, Y., Hattori, K., Yomogida, Y., & Kunugi, H. (2020). Correlation Between the Wechsler Adult Intelligence Scale-3rd Edition Metrics and Brain Structure in Healthy Individuals: A Whole-Brain Magnetic Resonance Imaging Study . In *Frontiers in Human Neuroscience* (Vol. 14, p. 211). https://www.frontiersin.org/article/10.3389/fnhum.2020.00211

Ho, A. J., Raji, C. A., Becker, J. T., Lopez, O. L., Kuller, L. H., Hua, X., Dinov, I. D., Stein, J. L., Rosano, C., Toga, A. W., Toga, A. W., & Thompson, P. M. (2011). The effects of physical activity, education, and body mass index on the aging brain. *Human Brain Mapping*, *32*(9), 1371–1382. https://doi.org/10.1002/hbm.21113

Huang, C.-M., & Huang, H.-W. (2019). *Chapter Six - Aging, neurocognitive reserve, and the healthy brain* (K. D. B. T.-P. of L. and M. Federmeier (Ed.); Vol. 71, pp. 175–213). Academic Press. https://doi.org/https://doi.org/10.1016/bs.plm.2019.07.006

Huang, J., Friedland, R. P., & Auchus, A. P. (2007). Diffusion Tensor Imaging of Normal-Appearing White Matter in Mild Cognitive Impairment and Early Alzheimer

Disease: Preliminary Evidence of Axonal Degeneration in the Temporal Lobe. *American Journal of Neuroradiology*, *28*(10), 1943–1948. https://doi.org/10.3174/ajnr.A0700

Isaacs, B., & Kennie, A. T. (1973). The set test as an aid to the detection of dementia in old people. *The British Journal of Psychiatry: The Journal of Mental Science*, *123*(575), 467–470. https://doi.org/10.1192/bjp.123.4.467

Iseki, K., Hanakawa, T., Hashikawa, K., Tomimoto, H., Nankaku, M., Yamauchi, H., Hallett, M., & Fukuyama, H. (2010). Gait disturbance associated with white matter changes: A gait analysis and blood flow study. *NeuroImage*, *49*(2), 1659–1666. https://doi.org/10.1016/J.NEUROIMAGE.2009.09.023

Jacobs, H. I., Leritz, E. C., Williams, V. J., Van Boxtel, M. P., van der Elst, W., Jolles, J., Verhey, F. R., McGlinchey, R. E., Milberg, W. P., & Salat, D. H. (2013). Association between white matter microstructure, executive functions, and processing speed in older adults: the impact of vascular health. *Human Brain Mapping*, *34*(1), 77–95. https://doi.org/https://doi.org/10.1002/hbm.21412

Jiang, J., Paradise, M., Liu, T., Armstrong, N. J., Zhu, W., Kochan, N. A., Brodaty, H., Sachdev, P. S., & Wen, W. (2018). The association of regional white matter lesions with cognition in a community-based cohort of older individuals. *NeuroImage: Clinical*, *19*, 14–21. https://doi.org/10.1016/J.NICL.2018.03.035

Jokinen, H., Melkas, S., Madureira, S., Verdelho, A., Ferro, J. M., Fazekas, F., Schmidt, R., Scheltens, P., Barkhof, F., Wardlaw, J. M., Inzitari, D., Pantoni, L., & Erkinjuntti, T. (2016). Cognitive reserve moderates long-term cognitive and functional outcome in cerebral small vessel disease. *Journal of Neurology, Neurosurgery &Amp; Psychiatry*, *87*(12), 1296 LP – 1302. https://doi.org/10.1136/jnnp-2016-313914

Jost, B. C., & Grossberg, G. T. (1995). The Natural History of Alzheimer's Disease: A Brain Bank Study. *Journal of the American Geriatrics Society*, *43*(11), 1248–1255. https://doi.org/10.1111/j.1532-5415.1995.tb07401.x

Kapeller, P., Barber, R., Vermeulen, R. J., Adèr, H., Scheltens, P., Freidl, W., Almkvist, O., Moretti, M., del Ser, T., Vaghfeldt, P., Enzinger, C., Barkhof, F., Inzitari, D., Erkinjunti, T., Schmidt, R., & Fazekas, F. (2003). Visual Rating of Age-Related White Matter Changes on Magnetic Resonance Imaging. *Stroke*, *34*(2), 441–445. https://doi.org/10.1161/01.STR.0000049766.26453.E9

Kaplan, E., Goodglass, H., & Weintraub, S. (1983). *Boston Naming Test*. Lea & Febiger.

Karrasch, M., Sinerva, E., Gronholm, P., Rinne, J., & Laine, M. (2005). CERAD test performances in amnestic mild cognitive impairment and Alzheimer's disease. *Acta Neurologica Scandinavica*, *111*(3), 172–179. https://doi.org/10.1111/j.1600-0404.2005.00380.x

Kaskikallio, A., Karrasch, M., Koikkalainen, J., Lötjönen, J., Rinne, J. O., Tuokkola, T., Parkkola, R., & Grönholm-Nyman, P. (2019). White matter hyperintensities and cognitive impairment in healthy and pathological aging – A Quantified Brain MRI Study. *Dementia and Geriatric Cognitive Disorders*, *48*(5–6), 297–307. https://doi.org/10.1159/000506124

Kaskikallio, A., Karrasch, M., Rinne, J. O., Tuokkola, T., Parkkola, R., & Grönholm-Nyman, P. (2019). Cognitive effects of white matter pathology in normal and pathological aging. *Journal of Alzheimer's Disease*, *67*(2), 489–493. https://doi.org/10.3233/JAD-180554

Kaskikallio, A., Karrasch, M., Rinne, J. O., Tuokkola, T., Parkkola, R., & Grönholm-Nyman, P. (2020). Domain-specific Cognitive Effects of White Matter Pathology in Old Age, Mild Cognitive Impairment and Alzheimer's Disease. *Journal of Aging, Neuropsychology and Cognition*, *27*(3), 453–470. https://doi.org/10.1080/13825585.2019.1628916

Kavcic, V., Ni, H., Zhu, T., Zhong, J., & Duffy, C. J. (2008). White matter integrity linked to functional impairments in aging and early Alzheimer's disease. *Alzheimer's & Dementia*, *4*(6), 381–389. https://doi.org/10.1016/J.JALZ.2008.07.001

Kemppainen, N. M., Aalto, S., Wilson, I. A., Någren, K., Helin, S., Brück, A., Oikonen, V., Kailajärvi, M., Scheinin, M., Viitanen, M., Parkkola, R., & Rinne, J. O. (2006). Voxel-based analysis of PET amyloid ligand [11C] PIB uptake in Alzheimer disease. *Neurology*, *67*(9), 1575–1580. https://doi.org/10.1212/01.wnl.0000240117.55680.0a

Kinoshita, M., de Champfleur, N. M., Deverdun, J., Moritz-Gasser, S., Herbet, G., & Duffau, H. (2015). Role of fronto-striatal tract and frontal aslant tract in movement and speech: an axonal mapping study. *Brain Structure & Function*, *220*(6), 3399–3412. https://doi.org/10.1007/s00429-014-0863-0

Kivipelto, M., Solomon, A., Ahtiluoto, S., Ngandu, T., Lehtisalo, J., Antikainen, R., Bäckman, L., Hänninen, T., Jula, A., Laatikainen, T., Lindström, J., Mangialasche, F., Nissinen, A., Paajanen, T., Pajala, S., Peltonen, M., Rauramaa, R., Stigsdotter-Neely, A., Strandberg, T., … Soininen, H. (2013). The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER): Study design and progress. *Alzheimer's & Dementia*, *9*(6), 657–665. https://doi.org/https://doi.org/10.1016/j.jalz.2012.09.012

Kloppenborg, R. P., Nederkoorn, P. J., Geerlings, M. I., & van den Berg, E. (2014). Presence and progression of white matter hyperintensities and cognition. *Neurology*, *82*(23), 2127 LP – 2138. https://doi.org/10.1212/WNL.0000000000000505

Kochan, N. A., Bunce, D., Pont, S., Crawford, J. D., Brodaty, H., & Sachdev, P. S. (2016). Reaction Time Measures Predict Incident Dementia in Community-Living Older Adults: The Sydney Memory and Ageing Study. *The*

American Journal of Geriatric Psychiatry, *24*(3), 221–231. https://doi.org/https://doi.org/10.1016/j.jagp.2015.12.005

Kochunov, P., Coyle, T., Lancaster, J., Robin, D. A., Hardies, J., Kochunov, V., Bartzokis, G., Stanley, J., Royall, D., Schlosser, A. E., Null, M., & Fox, P. T. (2010). Processing speed is correlated with cerebral health markers in the frontal lobes as quantified by neuroimaging. *NeuroImage*, *49*(2), 1190–1199. https://doi.org/10.1016/J.NEUROIMAGE.2009.09.052

Koikkalainen, J., Rhodius-Meester, H., Tolonen, A., Barkhof, F., Tijms, B., Lemstra, A. W., Tong, T., Guerrero, R., Schuh, A., Ledig, C., Rueckert, D., Soininen, H., Remes, A. M., Waldemar, G., Hasselbalch, S., Mecocci, P., Van Der Flier, W., & Lötjönen, J. (2016). Differential diagnosis of neurodegenerative diseases using structural MRI data. *NeuroImage: Clinical*, *11*, 435–449. https://doi.org/10.1016/j.nicl.2016.02.019

Koivunen, J., Scheinin, N., Virta, J. R., Aalto, S., Vahlberg, T., Någren, K., Helin, S., Parkkola, R., Viitanen, M., & Rinne, J. O. (2011). Amyloid PET imaging in patients with mild cognitive impairment. *Neurology*, *76*(12), 1085–1090. https://doi.org/https://doi.org/10.1212/WNL.0b013e318212015e

Kolb, B., & Whishaw, I. (2003). *Fundamentals of human neuropsychology* (5th ed.). Worth Publishing.

Künig, G., Jäger, M., Stief, V., Kaldune, A., Urbaniok, F., & Endrass, J. (2006). The impact of the CERAD-NP on diagnosis of cognitive deficiencies in late onset depression and Alzheimer's disease. *International Journal of Geriatric Psychiatry*, *21*(10), 911–916. https://doi.org/10.1002/gps.1579

La, C., Garcia-Ramos, C., Nair, V. A., Meier, T. B., Farrar-Edwards, D., Birn, R., Meyerand, M. E., & Prabhakaran, V. (2016). Age-Related Changes in BOLD Activation Pattern in Phonemic Fluency Paradigm: An Investigation of Activation, Functional Connectivity and Psychophysiological Interactions. *Frontiers in Aging Neuroscience*, *8*, 110. https://doi.org/https://doi.org/10.3389/fnagi.2016.00110

Lampe, L., Kharabian-Masouleh, S., Kynast, J., Arelin, K., Steele, C. J., Löffler, M., Witte, A. V., Schroeter, M. L., Villringer, A., & Bazin, P.-L. (2019). Lesion location matters: The relationships between white matter hyperintensities on cognition in the healthy elderly. *Journal of Cerebral Blood Flow & Metabolism*, *39*(1), 36–43. https://doi.org/10.1177/0271678X17740501

Lautenschlager, N. T., Cox, K. L., Flicker, L., Foster, J. K., van Bockxmeer, F. M., Xiao, J., Greenop, K. R., & Almeida, O. P. (2008). Effect of Physical Activity on Cognitive Function in Older Adults at Risk for Alzheimer Disease: A Randomized Trial. *JAMA*, *300*(9), 1027–1037. https://doi.org/10.1001/jama.300.9.1027

Lezak, M. D., Howieson, D. B., & Bigler, E. D. (2012). *Neuropsychological*

Assessment (5th ed.). Oxford University Press.

Lobo, A., Launer, L., Fratiglioni, L., Andersen, K., Di Carlo, A., Breteler, M., Copeland, J., Dartigues, J., Jagger, C., Martinez-Lage, J., Soininen, H., & Hofman, A. (2000). Prevalence of dementia and major subtypes in Europe: A collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. *Neurology*, *54*(11 Suppl 5), S4-9.

Lockhart, S. N., Mayda, A. B. V., Roach, A. E., Fletcher, E., Carmichael, O., Maillard, P., Schwarz, C. G., Yonelinas, A. P., Ranganath, C., & DeCarli, C. (2012). Episodic memory function is associated with multiple measures of white matter integrity in cognitive aging. *Frontiers in Human Neuroscience*, *6*(March), 1–12. https://doi.org/10.3389/fnhum.2012.00056

Loring, D. W., Meador, K. J., & Lee, G. P. (1994). Effects of temporal lobectomy on generative fluency and other language functions. *Arch Clin Neuropsychol*, *9*(3), 229–238. https://doi.org/https://doi.org/10.1016/0887-6177(94)90028-0

Lötjönen, J. M., Wolz, R., Koikkalainen, J. R., Thurfjell, L., Waldemar, G., Soininen, H., & Rueckert, D. (2010). Fast and robust multi-atlas segmentation of brain magnetic resonance images. *NeuroImage*, *49*(3), 2352–2365. https://doi.org/10.1016/j.neuroimage.2009.10.026

Lötjönen, J., Wolz, R., Koikkalainen, J., Julkunen, V., Thurfjell, L., Lundqvist, R., Waldemar, G., Soininen, H., & Rueckert, D. (2011). Fast and robust extraction of hippocampus from MR images for diagnostics of Alzheimer's disease. *NeuroImage*, *56*(1), 185–196. https://doi.org/10.1016/j.neuroimage.2011.01.062

Louis, E. D., Brickman, A. M., DeCarli, C., Small, S. A., Marder, K., Schupf, N., & Brown, T. R. (2008). Quantitative Brain Measurements in Community-Dwelling Elderly Persons With Mild Parkinsonian Signs. *Archives of Neurology*, *65*(12), 1649–1654. https://doi.org/10.1001/archneurol.2008.504

Lövdén, M., Fratiglioni, L., Glymour, M. M., Lindenberger, U., & Tucker-Drob, E. M. (2020). Education and Cognitive Functioning Across the Life Span. *Psychological Science in the Public Interest*, *21*(1), 6–41. https://doi.org/10.1177/1529100620920576

Mak, E., Gabel, S., Mirette, H., Su, L., Williams, G. B., Waldman, A., Wells, K., Ritchie, K., Ritchie, C., & O'Brien, J. (2017). Structural neuroimaging in preclinical dementia: From microstructural deficits and grey matter atrophy to macroscale connectomic changes. *Ageing Research Reviews*, *35*, 250–264. https://doi.org/https://doi.org/10.1016/j.arr.2016.10.001

Marchant, N. L., Reed, B. R., Sanossian, N., Madison, C. M., Kriger, S., Dhada, R., Mack, W. J., DeCarli, C., Weiner, M. W., Mungas, D. M., Chui, H. C., & Jagust, W. J. (2013). The Aging Brain and Cognition: Contribution of Vascular Injury and Aβ to Mild Cognitive

Dysfunction. *JAMA Neurology*, *70*(4), 488–495. https://doi.org/10.1001/2013.jamaneurol.405

Martin, R. C., Loring, D. W., Meador, K. J., & Lee, G. P. (1990). The effects of lateralized temporal lobe dysfunction on formal and semantic word fluency. *Neuropsychologia*, *28*(8), 823–829. https://doi.org/10.1016/0028-3932(90)90006-a

McAleese, K. E., Walker, L., Graham, S., Moya, E. L. J., Johnson, M., Erskine, D., Colloby, S. J., Dey, M., Martin-Ruiz, C., Taylor, J.-P., Thomas, A. J., McKeith, I. G., De Carli, C., & Attems, J. (2017). Parietal white matter lesions in Alzheimer's disease are associated with cortical neurodegenerative pathology, but not with small vessel disease. *Acta Neuropathologica*, *134*(3), 459–473. https://doi.org/10.1007/s00401-017-1738-2

McKhann, G. M., Drachman, D., Folstein, M., Katzman, R., Price, D., & Stadlan, E. M. (1984). Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*, *34*(7), 939–944. https://doi.org/10.1212/wnl.34.7.939

McKhann, G. M., Knopman, D. S., Chertkow, H., Hyman, B. T., Jack Jr., C. R., Kawas, C. H., Klunk, W. E., Koroshetz, W. J., Manly, J. J., Mayeux, R., Mohs, R. C., Morris, J. C., Rossor, M. N., Scheltens, P., Carrillo, M. C., Thies, B., Weintraub, S., & Phelps, C. H. (2011). The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia*, *7*(3), 263–269. https://doi.org/10.1016/j.jalz.2011.03.005

Mechelli, A., Price, C. J., Friston, K. J., & Ashburner, J. (2005). Voxel-Based Morphometry of the Human Brain: Methods and Applications. *Current Medical Imaging Reviews*, *1*(1), 1–9. https://doi.org/10.2174/1573405054038726

Meier, I., & Manly, J. (2012). White matter predictors of cognitive functioning in older adults. *J Int Neuropsychol Soc*, *18*(3), 414–427. https://doi.org/10.1017/S1355617712000227.White

Meinzer, M., Seeds, L., Flaisch, T., Harnish, S., Cohen, M. L., McGregor, K., Conway, T., Benjamin, M., & Crosson, B. (2012). Impact of changed positive and negative task-related brain activity on word-retrieval in aging. *Neurobiology of Aging*, *33*(4), 656–669. https://doi.org/10.1016/J.NEUROBIOLAGING.2010.06.020

Metzler-Baddeley, C., Jones, D. K., Belaroussi, B., Aggleton, J. P., & O'Sullivan, M. J. (2011). Frontotemporal Connections in Episodic Memory and Aging: A Diffusion MRI Tractography Study. *Journal of Neuroscience*, *31*(37), 13236–13245. https://doi.org/10.1523/JNEUROSCI.2317-11.2011

Meyer, P., Feldkamp, H., Hoppstädter, M., King, A., Frölich, L., Wessa, M., & Flor, H. (2013). Using Voxel-Based Morphometry to Examine the Relationship between Regional Brain Volumes and Memory Performance in Amnestic Mild Cognitive Impairment. In *Frontiers in Behavioral Neuroscience* (Vol. 7, p. 89). https://www.frontiersin.org/article/10.3389/fnbeh.2013.00089

Mistridis, P., Egli, S. C., Iverson, G. L., Berres, M., Willmes, K., Welsh-Bohmer, K. A., & Monsch, A. U. (2015). Considering the base rates of low performance in cognitively healthy older adults improves the accuracy to identify neurocognitive impairment with the Consortium to Establish a Registry for Alzheimer's Disease-Neuropsychological Assessment Battery (CERAD-. *European Archives of Psychiatry and Clinical Neuroscience*, *265*(5), 407–417. https://doi.org/10.1007/s00406-014-0571-z

Mitchell, A. J., & Shiri-Feshki, M. (2009). Rate of progression of mild cognitive impairment to dementia – meta-analysis of 41 robust inception cohort studies. *Acta Psychiatrica Scandinavica*, *119*(4), 252–265. https://doi.org/10.1111/j.1600-0447.2008.01326.x

Mito, R., Raffelt, D., Dhollander, T., Vaughan, D. N., Tournier, J. D., Salvado, O., Brodtmann, A., Rowe, C. C., Villemagne, V. L., & Connelly, A. (2018). Fibre-specific white matter reductions in Alzheimer's disease and mild cognitive impairment. *Brain*, *141*(3), 888–902. https://doi.org/10.1093/brain/awx355.

Morris, J. C. (2005). Early-Stage and Preclinical Alzheimer Disease. *Alzheimer Disease & Associated Disorders*, *19*(3), 163–165. https://doi.org/doi: 10.1097/01.wad.0000184005.22611.cc

Morris, J. C., Heyman, A., Mohs, R. C., Hughes, J. P., Vanbelle, G., Fillenbaum, G., Mellits, E. D., & Clark, C. (1989). The consortium to establish a registry for Alzheimers-disease (CERAD). Clinical and neuropsychological assessment of Alzheimers-disease. *Neurology*, *39*(9), 1159–1165.

Mortamais, M., Artero, S., & Ritchie, K. (2013). Cerebral white matter hyperintensities in the prediction of cognitive decline and incident dementia. *International Review of Psychiatry*, *25*(6), 686–698. https://doi.org/10.3109/09540261.2013.838151

Mortimer, J. A. (2012). The Nun Study: Risk Factors for Pathology and Clinical-Pathologic Correlations. In *Current Alzheimer Research* (Vol. 9, Issue 6, pp. 621–627). https://doi.org/10.2174/156720512801322546

Nyberg, L., Magnussen, F., Lundquist, A., Baaré, W., Bartrés-Faz, D., Bertram, L., Boraxbekk, C. J., Brandmaier, A. M., Drevon, C. A., Ebmeier, K., Ghisletta, P., Henson, R. N., Junqué, C., Kievit, R., Kleemeyer, M., Knights, E., Kühn, S., Lindenberger, U., Penninx, B. W. J. H., … Fjell, A. M. (2021). Educational attainment does not influence brain aging. *Proceedings of the National Academy of Sciences*,

118(18), e2101644118. https://doi.org/10.1073/pnas.2101644118

O'Donnell, L. J., & Westin, C.-F. (2011). An introduction to diffusion tensor image analysis. *Neurosurgery Clinics of North America*, *22*(2), 185–viii. https://doi.org/10.1016/j.nec.2010.12.004

Ogama, N., Yoshida, M., Nakai, T., Niida, S., Toba, K., & Sakurai, T. (2016). Frontal white matter hyperintensity predicts lower urinary tract dysfunction in older adults with amnestic mild cognitive impairment and Alzheimer's disease. *Geriatrics & Gerontology International*, *16*(2), 167–174. https://doi.org/10.1111/ggi.12447

Paajanen, T., Hänninen, T., Tunnard, C., Hallikainen, M., Mecocci, P., Sobow, T., Tsolaki, M., Vellas, B., Lovestone, S., & Soininen, H. (2014). CERAD neuropsychological compound scores are accurate in detecting prodromal Alzheimer's disease: a prospective AddNeuroMed study. *Journal of Alzheimer's Disease*, *39*, 679–690. https://doi.org/10.3233/JAD-122110

Paajanen, T., Hänninen, T., Tunnard, C., Mecocci, P., Sobow, T., Tsolaki, M., Vellas, B., Lovestone, S., Soininen, H., & AddNeuroMed Consortium. (2010). CERAD neuropsychological battery total score in multinational mild cognitive impairment and control populations: the AddNeuroMed study. *Journal of Alzheimer's Disease*, *22*, 1089–1097. https://doi.org/10.3233/JAD-2010-100459.

Paemeleire, K. (2009). Brain lesions and cerebral functional impairment in migraine patients. *Journal of the Neurological Sciences*, *283*, 134–136. https://doi.org/https://doi.org/10.1016/j.jns.2009.02.050

Palacios, E. M., Sala-Llonch, R., Junque, C., Fernandez-Espejo, D., Roig, T., Tormos, J. M., Bargallo, N., & Vendrell, P. (2013). Long-term declarative memory deficits in diffuse TBI: Correlations with cortical thickness, white matter integrity and hippocampal volume. *Cortex*, *49*(3), 646–657. https://doi.org/10.1016/J.CORTEX.2012.02.011

Pantoni, I. D., & Wallin, A. (Eds.). (2000). *The matter of white matter. Clinical and pathophysiological aspects of white matter disease related to cognitive decline and vascular dementia.* Academic Pharmaceutical Productions.

Pantoni, L., Basile, A. M., Romanelli, M., Piccini, C., Sarti, C., Nencini, P., & Inzitari, D. (2001). Abulia and cognitive impairment in two patients with capsular genu infarct. *Acta Neurologica Scandinavica*, *104*(3), 185–190. https://doi.org/10.1034/j.1600-0404.2001.00370.x

Pantoni, L., Poggesi, A., & Inzitari, D. (2007). The relation between white-matter lesions and cognition. *Current Opinion in Neurology*, *20*(4), 390–397. https://doi.org/10.1097/WCO.0b013e328172d661

Park, D. C., Polk, T. A., Park, R., Minear, M., Savage, A., & Smith, M. R. (2004). Aging reduces neural specialization in ventral visual cortex. *Proceedings of the National*

Academy of Sciences of the United States of America, *101*(35), 13091–13095. https://doi.org/10.1073/pnas.0405148101

Paulraj, S. R., Schendel, K., Curran, B., Dronkers, N. F., & Baldo, J. V. (2018). Role of the left hemisphere in visuospatial working memory. *Journal of Neurolinguistics*, *48*, 133–141. https://doi.org/https://doi.org/10.1016/j.jneuroling.2018.04.006

Peers, P. V, Ludwig, C. J. H., Rorden, C., Cusack, R., Bonfiglioli, C., Bundesen, C., Driver, J., Antoun, N., & Duncan, J. (2005). Attentional Functions of Parietal and Frontal Cortex. *Cerebral Cortex*, *15*(10), 1469–1484. http://dx.doi.org/10.1093/cercor/bhi029

Perneger, T. V. (1998). What's wrong with Bonferroni adjustments. *BMJ (Clinical Research Ed.)*, *316*(7139), 1236–1238. https://www.ncbi.nlm.nih.gov/pubmed/9553006

Perret, E. (1974). The left frontal lobe of man and the suppression of habitual responses in verbal categorical behaviour. *Neuropsychologia*, *12*(3), 323–330. https://doi.org/10.1016/0028-3932(74)90047-5

Peters, B. D., Szeszko, P. R., Radua, J., Ikuta, T., Gruner, P., DeRosse, P., Zhang, J.-P., Giorgio, A., Qiu, D., Tapert, S. F., Brauer, J., Asato, M. R., Khong, P. L., James, A. C., Gallego, J. A., & Malhotra, A. K. (2012). White Matter Development in Adolescence: Diffusion Tensor Imaging and Meta-Analytic Results. *Schizophrenia Bulletin*, *38*(6), 1308–1317. https://doi.org/10.1093/schbul/sbs054

Petersen, R. C. (2016). Mild Cognitive Impairment. *Continuum: Lifelong Learning in Neurology*, *22*(2 Dementia), 404–418. https://doi.org/10.1212/CON.0000000000000313

Petersen, R. C., Stevens, J. C., Ganguli, M., Tangalos, E. G., Cummings, J. L., & DeKosky, S. T. (2001). Practice parameter: Early detection of dementia: Mild cognitive impairment (an evidence-based review). *Neurology*, *56*(9), 1133–1142. https://doi.org/10.1212/WNL.56.9.1133

Petrovitch, H., Ross, G. W., Steinhorn, S. C., Abbott, R. D., Markesbery, W., Davis, D., Nelson, J., Hardman, J., Masaki, K., Vogt, M. R., Launer, L., & White, L. R. (2005). AD lesions and infarcts in demented and non-demented Japanese-American men. *Annals of Neurology*, *57*(1), 98–103. https://doi.org/10.1002/ana.20318

Phelps, E. A., Hyder, F., Blamire, A. M., & Shulman, R. G. (1997). FMRI of the prefrontal cortex during overt verbal fluency. *NeuroReport*, *8*(2), 561–565. https://doi.org/10.1097/00001756-199701200-00036

Phillips, M., Rogers, P., Haworth, J., Bayer, A., & Tales, A. (2013). Intra-Individual Reaction Time Variability in Mild Cognitive Impairment and Alzheimer's Disease: Gender, Processing Load and Speed Factors. *PLOS ONE*, *8*(6), e65712. https://doi.org/10.1371/journal.pon

e.0065712

Piguet, O., Ridley, L., Grayson, D. A., Bennett, H. P., Creasey, H., Lye, T. C., & Broe, G. A. (2003). Are MRI White Matter Lesions Clinically Significant in the 'Old-Old'? Evidence from the Sydney Older Persons Study. *Dementia and Geriatric Cognitive Disorders*, *15*(3), 143–150. https://doi.org/10.1159/000068482

Poutiainen, E., Kalska, H., Laasonen, M., Närhi, V., & Räsänen, P. (2010). *Trail making -testi [Finnish manual for the Trail Making Test]*. Psykologien Kustannus Oy.

Prakash, R. S., Voss, M. W., Erickson, K. I., & Kramer, A. F. (2015). Physical Activity and Cognitive Vitality. *Annual Review of Psychology*, *66*(1), 769–797. https://doi.org/10.1146/annurev-psych-010814-015249

Prins, N. D., & Scheltens, P. (2015). White matter hyperintensities, cognitive impairment and dementia: an update. *Nature Reviews Neurology*, *11*(3), 157–165. https://doi.org/10.1038/nrneurol.2015.10

Prins, N. D., van Dijk, E., & den Heijer, T. (2004). Cerebral white matter lesions and the risk of dementia. *Archives of Neurology*, *61*(10), 1531–1534. https://doi.org/10.1001/archneur.61.10.1531

Prins, N. D., Van Dijk, E. J., Den Heijer, T., Vermeer, S. E., Jolles, J., Koudstaal, P. J., Hofman, A., & Breteler, M. M. B. (2005). Cerebral small-vessel disease and decline in information processing speed, executive function and memory. *Brain*, *128*(9), 2034–2041. https://doi.org/10.1093/brain/awh553

Pulliainen, V., Hokkanen, L., Salo, J., & Hänninen, T. (1999). *CERAD-kognitiivinen tehtäväsarja. Käsikirja. [Manual of the Finnish version of CERAD]*. Suomen Alzheimer-tutkimusseura r.y.

Pustina, D., Coslett, H. B., Turkeltaub, P. E., Tustison, N., Schwartz, M. F., & Avants, B. (2016). Automated segmentation of chronic stroke lesions using LINDA: Lesion identification with neighborhood data analysis. *Human Brain Mapping*, *37*(4), 1405–1421. https://doi.org/10.1002/hbm.23110

Quinque, E. M., Arélin, K., Dukart, J., Roggenhofer, E., Streitbuerger, D.-P., Villringer, A., Frisch, S., Mueller, K., & Schroeter, M. L. (2012). Identifying the neural correlates of executive functions in early cerebral microangiopathy: a combined VBM and DTI study. *Journal of Cerebral Blood Flow & Metabolism*, *32*(10), 1869–1878. https://doi.org/10.1038/jcbfm.2012.96

Rascovsky, K., Salmon, D. P., Lipton, A. M., Leverenz, J. B., DeCarli, C., Jagust, W. J., Clark, C. M., Mendez, M. F., Tang-Wai, D. F., Graff-Radford, N. R., & Galasko, D. (2005). Rate of progression differs in frontotemporal dementia and Alzheimer disease. *Neurology*, *65*(3), 397 LP – 403. https://doi.org/10.1212/01.wnl.0000171343.43314.6e

Raz, N., Yang, Y., Dahle, C. L., & Land, S. (2012). Volume of white matter hyperintensities in healthy adults: contribution of age, vascular risk factors, and inflammation-related

genetic variants. *Biochimica et Biophysica Acta*, *1822*(3), 361–369. https://doi.org/10.1016/j.bbadis.2011.08.007

Reuter-Lorenz, P. A., Jonides, J., Smith, E. E., Hartley, A., Miller, A., Marshuetz, C., & Koeppe, R. A. (2000). Age Differences in the Frontal Lateralization of Verbal and Spatial Working Memory Revealed by PET. *Journal of Cognitive Neuroscience*, *12*(1), 174–187. https://doi.org/10.1162/089892900561814

Righart, R., Duering, M., Gonik, M., Jouvent, E., Reyes, S., Hervé, D., Chabriat, H., & Dichgans, M. (2013a). Impact of regional cortical and subcortical changes on processing speed in cerebral small vessel disease. *NeuroImage: Clinical*, *2*, 854–861. https://doi.org/10.1016/J.NICL.2013.06.006

Righart, R., Duering, M., Gonik, M., Jouvent, E., Reyes, S., Hervé, D., Chabriat, H., & Dichgans, M. (2013b). Impact of regional cortical and subcortical changes on processing speed in cerebral small vessel disease. *NeuroImage: Clinical*, *2*, 854–861. https://doi.org/https://doi.org/10.1016/j.nicl.2013.06.006

Rizvi, B., Narkhede, A., Last, B. S., Budge, M., Tosto, G., Manly, J. J., Schupf, N., Mayeux, R., & Brickman, A. M. (2017). The effect of white matter hyperintensities on cognition is mediated by cortical atrophy. *Neurobiology of Aging*, *64*, 25–32. https://doi.org/10.1016/j.neurobiolaging.2017.12.006

Rizzi, L., Rosset, I., & Roriz-Cruz, M. (2014). Global Epidemiology of Dementia: Alzheimer's and Vascular Types. In L. Ho (Ed.), *BioMed Research International* (Vol. 2014). Hindawi Publishing Corporation. https://doi.org/10.1155/2014/908915

Roberts, R. O., Geda, Y. E., Knopman, D. S., Cha, R. H., Pankratz, V. S., Boeve, B. F., Tangalos, E. G., Ivnik, R. J., Rocca, W. A., & Petersen, R. C. (2012). The incidence of MCI differs by subtype and is higher in men. *Neurology*, *78*(5), 342 LP – 351. https://doi.org/10.1212/WNL.0b013e3182452862

Robinson, G., Shallice, T., Bozzali, M., & Cipolotti, L. (2012). The differing roles of the frontal cortex in fluency tests. *Brain*, *135*(7), 2202–2214. https://doi.org/10.1093/brain/aws142

Rodríguez-Aranda, C., Waterloo, K., Johnsen, S. H., Eldevik, P., Sparr, S., Wikran, G. C., Herder, M., & Vangberg, T. R. (2016). Neuroanatomical correlates of verbal fluency in early Alzheimer's disease and normal aging. *Brain and Language*, *155–156*, 24–35. https://doi.org/10.1016/J.BANDL.2016.03.001

Rorden, C., & Karnath, H.-O. (2004). Using human brain lesions to infer function: a relic from a past era in the fMRI age? *Nature Reviews Neuroscience*, *5*(10), 812–819. https://doi.org/10.1038/nrn1521

Rosano, C., Guralnik, J., Pahor, M., Glynn, N. W., Newman, A. B., Ibrahim, T. S., Erickson, K., Cohen, R., Shaaban, C. E., MacCloud, R.

L., & Aizenstein, H. J. (2017). Hippocampal Response to a 24-Month Physical Activity Intervention in Sedentary Older Adults. *The American Journal of Geriatric Psychiatry*, *25*(3), 209–217. https://doi.org/https://doi.org/10.1016/j.jagp.2016.11.007

Rosano, C., Venkatraman, V. K., Guralnik, J., Newman, A. B., Glynn, N. W., Launer, L., Taylor, C. A., Williamson, J., Studenski, S., Pahor, M., & Aizenstein, H. (2010). Psychomotor Speed and Functional Brain MRI 2 Years After Completing a Physical Activity Treatment. *The Journals of Gerontology: Series A*, *65A*(6), 639–647. https://doi.org/10.1093/gerona/glq038

Rosen, W. G., Mohs, R. C., & Davis, K. L. (1984). A new rating scale for Alzheimer's disease. *The Maerican Journal of Psychiatry*, *141*(11), 1356–1364. https://doi.org/10.1176/ajp.141.11.1356

Rösler, A., Billino, J., Müller, N. G., Weidauer, S., Steinmetz, H., & Kleinschmidt, A. (2005). Visual Search in Patients with Subcortical Vascular Dementia: Short Fixations but Long Reaction Times. *Dementia and Geriatric Cognitive Disorders*, *20*(6), 375–380. https://doi.org/10.1159/000089104

Rovio, S., Spulber, G., Nieminen, L. J., Niskanen, E., Winblad, B., Tuomilehto, J., Nissinen, A., Soininen, H., & Kivipelto, M. (2010). The effect of midlife physical activity on structural brain changes in the elderly. *Neurobiology of Aging*, *31*(11), 1927–1936. https://doi.org/10.1016/j.neurobiolaging.2008.10.007

Salvadó, G., Brugulat-Serrat, A., Sudre, C. H., Grau-Rivera, O., Suárez-Calvet, M., Falcon, C., Fauria, K., Cardoso, M. J., Barkhof, F., Molinuevo, J. L., Gispert, J. D., Camí, J., Polo, A., Mustata, C., Tenas, L., Marne, P., Gotsens, X., Menchón, T., Soteras, A., … Study, for the A. (2019). Spatial patterns of white matter hyperintensities associated with Alzheimer's disease risk factors in a cognitively healthy middle-aged cohort. *Alzheimer's Research & Therapy*, *11*(1), 12. https://doi.org/10.1186/s13195-018-0460-1

Samuel, W., Galasko, D., & Tal, L. J. (2002). Alzheimer disease: Biochemical and pharmacologic aspects. In T. E. Feinberg & M. J. Farah (Eds.), *Behavioral neurology and neuropsychology* (2nd ed.). McGraw-Hill.

Sarah, M., L., Z. L., Andrea, N., Lauryn, Z., Y., W. C., & Gottfried, S. (2011). Impairment of Speech Production Predicted by Lesion Load of the Left Arcuate Fasciculus. *Stroke*, *42*(8), 2251–2256. https://doi.org/10.1161/STROKEAHA.110.606103

Sasson, E., Doniger, G. M., Pasternak, O., Tarrasch, R., & Assaf, Y. (2012). Structural correlates of cognitive domains in normal aging with diffusion tensor imaging. *Brain Structure and Function*, *217*(2), 503–515. https://doi.org/10.1007/s00429-011-0344-7

Sasson, E., Doniger, G. M., Pasternak, O., Tarrasch, R., & Assaf, Y. (2013a). White matter correlates of

cognitive domains in normal aging with diffusion tensor imaging. *Frontiers in Neuroscience*, *7*, 32. https://doi.org/10.3389/fnins.2013.00032

Sasson, E., Doniger, G. M., Pasternak, O., Tarrasch, R., & Assaf, Y. (2013b). White matter correlates of cognitive domains in normal aging with diffusion tensor imaging. *Frontiers in Neuroscience*, *7*, 32. https://doi.org/10.3389/fnins.2013.00032

Saur, D., Kreher, B. W., Schnell, S., Kümmerer, D., Kellmeyer, P., Vry, M.-S., Umarova, R., Musso, M., Glauche, V., Abel, S., Huber, W., Rijntjes, M., Hennig, J., & Weiller, C. (2008). Ventral and dorsal pathways for language. *Proceedings of the National Academy of Sciences*, *105*(46), 18035–18040. https://doi.org/https://doi.org/10.1073/pnas.0805234105

Scheinin, N. M., Aalto, S., Kaprio, J., Koskenvuo, M., Räihä, I., Rokka, J., Hinkka-Yli-Salomäki, S., & Rinne, J. O. (2011). Early detection of Alzheimer disease. *Neurology*, *77*(5), 453–460. https://doi.org/https://doi.org/10.1212/WNL.0b013e318225118e

Scheltens, P., Barkhof, F., Leys, D., Pruvo, J. ., Nauta, J. J. P., Vermersch, P., Steinling, M., & Valk, J. (1993). A semiquantative rating scale for the assessment of signal hyperintensities on magnetic resonance imaging. *Journal of the Neurological Sciences*, *114*(1), 7–12. https://doi.org/10.1016/0022-510X(93)90041-V

Scheltens, P., Erkinjunti, T., Leys, D., Wahlund, L.-O., Inzitari, D., del Ser, T., Pasquier, F., Barkhof, F., Mäntylä, R., Bowler, J., Wallin, A., Ghika, J., Fazekas, F., & Pantoni, L. (1998). White Matter Changes on CT and MRI: An Overview of Visual Rating Scales. *European Neurology*, *39*(2), 80–89. https://doi.org/10.1159/000007921

Schlösser, R., Hutchinson, M., Joseffer, S., Rusinek, H., Saarimaki, A., Stevenson, J., Dewey, S. L., & Brodie, J. D. (1998). Functional magnetic resonance imaging of human brain activity in a verbal fluency task. *Journal of Neurology, Neurosurgery &Amp; Psychiatry*, *64*(4), 492 LP – 498. https://doi.org/10.1136/jnnp.64.4.492

Schmid, N. S., Ehrensperger, M. M., Berres, M., Beck, I. R., & Monsch, A. U. (2014). The Extension of the German CERAD Neuropsychological Assessment Battery with Tests Assessing Subcortical, Executive and Frontal Functions Improves Accuracy in Dementia Diagnosis. *Dementia and Geriatric Cognitive Disorders Extra*, *4*(2), 322–334. https://doi.org/https://doi.org/10.1159/000357774

Schmidt, C. S. M., Nitschke, K., Bormann, T., Römer, P., Kümmerer, D., Martin, M., Umarova, R. M., Leonhart, R., Egger, K., Dressing, A., Musso, M., Willmes, K., Weiller, C., & Kaller, C. P. (2019). Dissociating frontal and temporal correlates of phonological and semantic fluency in a large sample of left hemisphere stroke patients. *NeuroImage: Clinical*, *23*, 101840. https://doi.org/10.1016/J.NICL.2019.101840

Seblova, D., Fischer, M., Fors, S., Johnell, K., Karlsson, M., Nilsson, T., Svensson, A. C., Lövdén, M., & Lager, A. (2021). Does Prolonged Education Causally Affect Dementia Risk When Adult Socioeconomic Status Is Not Altered? A Swedish Natural Experiment in 1.3 Million Individuals. *American Journal of Epidemiology*, *190*(5), 817–826. https://doi.org/10.1093/aje/kwaa255

Seo, E. H., Lee, D. Y., Lee, J. H., Choo, I. H., Kim, J. W., Kim, S. G., Park, S. Y., Shin, J. H., Do, Y. J., Yoon, J. C., Jhoo, J. H., Kim, K. W., & Woo, J. I. (2010). Total scores of the CERAD neuropsychological assessment battery: Validation for mild cognitive impairment and dementia patients with diverse etiologies. *American Journal of Geriatric Psychiatry*, *18*(9), 801–809. https://doi.org/10.1097/JGP.0b013e3181cab764

Serra, L., Cercignani, M., Lenzi, D., Perri, R., Fadda, L., Caltagirone, C., MacAluso, E., & Bozzali, M. (2010). Grey and white matter changes at different stages of Alzheimer's disease. *Journal of Alzheimer's Disease*, *19*(1), 147–159. https://doi.org/10.3233/JAD-2010-1223

Sexton, C. E., Kalu, U. G., Filippini, N., Mackay, C. E., & Ebmeier, K. P. (2011). A meta-analysis of diffusion tensor imaging in mild cognitive impairment and Alzheimer's disease. *Neurobiology of Aging*, *32*(12), 2322.e5-2322.e18. https://doi.org/https://doi.org/10.1016/j.neurobiolaging.2010.05.019

Simons, J. S., & Spiers, H. J. (2003). Prefrontal and medial temporal lobe interactions in long-term memory. *Nature Reviews Neuroscience*, *4*(8), 637–648. https://doi.org/10.1038/nrn1178

Smith, E. (2016). Vascular Cognitive Impairment. *CONTINUUM: Lifelong Learning in Neurology*, *22*(2, Dementia), 490–509. https://doi.org/10.1212/CON.0000000000000304

Smith, E., Jeng, J., Fischl, B., & Blacker, D. (2011). Correlations between MRI white matter lesion location and executive function and episodic memory. *Neurology*, *76*, 1492–1499. https://doi.org/https://doi.org/10.1212/WNL.0b013e318217e7c8

Söderlund, H., Nilsson, L.-G. G., Berger, K., Breteler, M. M., Dufouil, C., Fuhrer, R., Giampaoli, S., Hofman, A., Pajak, A., Ridder, M. De, Sans, S., Schmidt, R., & Launer, L. J. (2006). Cerebral changes on MRI and cognitive function: The CASCADE study. *Neurobiology of Aging*, *27*(1), 16–23. https://doi.org/10.1016/j.neurobiolaging.2004.12.008

Song, S.-K., Yoshino, J., Le, T. Q., Lin, S.-J., Sun, S.-W., Cross, A. H., & Armstrong, R. C. (2005). Demyelination increases radial diffusivity in corpus callosum of mouse brain. *NeuroImage*, *26*(1), 132–140. https://doi.org/https://doi.org/10.1016/j.neuroimage.2005.01.028

Soumaré, A., Tavernier, B., Alpérovitch, A., Tzourio, C., & Elbaz, A. (2009). A Cross-Sectional and Longitudinal Study of the Relationship Between Walking Speed and Cognitive Function in Community-Dwelling Elderly

People. *The Journals of Gerontology: Series A*, *64A*(10), 1058–1065. https://doi.org/10.1093/gerona/glp077

Spangenberg, K. B., Henderson, S., & Wagner, M. T. (1997). Validity of a recall and recognition condition to assess visual memory in the CERAD battery. *Applied Neuropsychology*, *4*(3), 154–159. https://doi.org/10.1207/s15324826an0403_2

Sperling, R. A., Aisen, P. S., Beckett, L. A., Bennett, D. A., Craft, S., Fagan, A. M., Iwatsubo, T., Jack Jr., C. R., Kaye, J., Montine, T. J., Park, D. C., Reiman, E. M., Rowe, C. C., Siemers, E., Stern, Y., Yaffe, K., Carrillo, M. C., Thies, B., Morrison-Bogorad, M., … Phelps, C. H. (2011). Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia*, *7*(3), 280–292. https://doi.org/10.1016/j.jalz.2011.03.003

Stephan, B. C. M., Matthews, F. E., Ma, B., Muniz, G., Hunter, S., Davis, D., McKeith, I. G., Forster, G., Ince, P. G., Brayne, C., & Study, T. M. R. C. C. F. and A. N. (2012). Alzheimer and Vascular Neuropathological Changes Associated with Different Cognitive States in a Non-Demented Sample. *Journal of Alzheimer's Disease : JAD*, *29*(2), 309–318. https://doi.org/10.3233/JAD-2011-110518

Stephen, R., Solomon, A., Ngandu, T., Levälahti, E., Rinne, J. O., Kemppainen, N., Parkkola, R., Antikainen, R., Strandberg, T., Kivipelto, M., Soininen, H., Liu, Y., & group, for the F. study. (2020). White Matter Changes on Diffusion Tensor Imaging in the FINGER Randomized Controlled Trial. *Journal of Alzheimer's Disease*, *78*, 75–86. https://doi.org/10.3233/JAD-200423

Stern, Y. (2006). Cognitive reserve and Alzheimer disease. *Alzheimer Dis Assoc Disord*, *20*(2), 112–117. https://doi.org/10.1097/01.wad.0000213815.20177.19

Stern, Y., Gurland, B., Tatemichi, T. K., Tang, M. X., Wilder, D., & Mayeux, R. (1994). Influence of Education and Occupation on the Incidence of Alzheimer's Disease. *JAMA*, *271*(13), 1004–1010. https://doi.org/10.1001/jama.1994.03510370056032

Sturman, M. T., Morris, M. C., Mendes de Leon, C. F., Bienias, J. L., Wilson, R. S., & Evans, D. A. (2005). Physical Activity, Cognitive Activity, and Cognitive Decline in a Biracial Community Population. *Archives of Neurology*, *62*(11), 1750–1754. https://doi.org/10.1001/archneur.62.11.1750

Tan, Z. S., Spartano, N. L., Beiser, A. S., DeCarli, C., Auerbach, S. H., Vasan, R. S., & Seshadri, S. (2017). Physical Activity, Brain Volume, and Dementia Risk: The Framingham Study. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *72*(6), 789–795. https://doi.org/10.1093/gerona/glw130

Tatemichi, T. K., Desmond, D. W., Prohovnik, I., Cross, D. T., Gropen, T. I., Mohr, J. P., & Stern, Y. (1992). Confusion and memory loss from capsular genu infarction. *Neurology*, *42*(10), 1966 LP – 1966. https://doi.org/10.1212/WNL.42.10.1966

Toledo, J. B., Arnold, S. E., Raible, K., Brettschneider, J., Xie, S. X., Grossman, M., Monsell, S. E., Kukull, W. A., & Trojanowski, J. Q. (2013). Contribution of cerebrovascular disease in autopsy confirmed neurodegenerative disease cases in the National Alzheimer's Coordinating Centre. *Brain*, *136*(9), 2697–2706. https://doi.org/https://doi.org/10.1093/brain/awt188

Tosto, G., Zimmerman, M. E., Carmichael, O. T., Brickman, A. M., & Initiative, for the A. D. N. (2014). Predicting Aggressive Decline in Mild Cognitive Impairment: The Importance of White Matter Hyperintensities. *JAMA Neurology*, *71*(7), 872–877. https://doi.org/10.1001/jamaneurol.2014.667

Turken, A. U., & Dronkers, N. F. (2011). The neural architecture of the language comprehension network: converging evidence from lesion and connectivity analyses. *Frontiers in Systems Neuroscience*, *5*, 1. https://doi.org/10.3389/fnsys.2011.00001

Turken, A. U., Whitfield-Gabrieli, S., Bammer, R., Baldo, J., Dronkers, N. F., & Gabrieli, J. D. E. (2008). Cognitive processing speed and the structure of white matter pathways: Convergent evidence from normal variation and lesion studies. *NeuroImage*, *42*(2), 1032–1044. https://doi.org/10.1016/j.neuroimage.2008.03.057

Uemura, K., Doi, T., Shimada, H., Makizako, H., Yoshida, D., Tsutsumimoto, K., Anan, Y., & Suzuki, T. (2012). Effects of Exercise Intervention on Vascular Risk Factors in Older Adults with Mild Cognitive Impairment: A Randomized Controlled Trial. *Dementia and Geriatric Cognitive Disorders Extra*, *2*(1), 445–455. https://doi.org/10.1159/000343486

Van der Werf, Y. D., Scheltens, P., Lindeboom, J., Witter, M. P., Uylings, H. B. M., & Jolles, J. (2003). Deficits of memory, executive functioning and attention following infarction in the thalamus; a study of 22 cases with localised lesions. *Neuropsychologia*, *41*(10), 1330–1344. https://doi.org/https://doi.org/10.1016/S0028-3932(03)00059-9

van Deursen, J. A., Vuurman, E. F. P. M., Smits, L. L., Verhey, F. R. J., & Riedel, W. J. (2009). Response speed, contingent negative variation and P300 in Alzheimer's disease and MCI. *Brain and Cognition*, *69*(3), 592–599. https://doi.org/https://doi.org/10.1016/j.bandc.2008.12.007

Vasquez, B. P., & Zakzanis, K. K. (2015). The neuropsychological profile of vascular cognitive impairment not demented: A meta-analysis. *Journal of Neuropsychology*, *9*(1), 109–136. https://doi.org/10.1111/jnp.12039

Verghese, J., Lipton, R. B., Katz, M. J., Hall, C. B., Derby, C. A., Kuslansky, G., Ambrose, A. F.,

Sliwinski, M., & Buschke, H. (2003). Leisure Activities and the Risk of Dementia in the Elderly. *New England Journal of Medicine*, *348*(25), 2508–2516. https://doi.org/10.1056/NEJMoa022252

Villeneuve, S., Massoud, F., Bocti, C., Gauthier, S., & Belleville, S. (2011). The nature of episodic memory deficits in MCI with and without vascular burden. *Neuropsychologia*, *49*(11), 3027–3035. https://doi.org/10.1016/J.NEUROPSYCHOLOGIA.2011.07.001

Wagner, A. D., Shannon, B. J., Kahn, I., & Buckner, R. L. (2005). Parietal lobe contributions to episodic memory retrieval. *Trends in Cognitive Sciences*, *9*(9), 445–453. https://doi.org/10.1016/J.TICS.2005.07.001

Wagner, S., Sebastian, A., Lieb, K., Tüscher, O., & Tadić, A. (2014). A coordinate-based ALE functional MRI meta-analysis of brain activation during verbal fluency tasks in healthy control subjects. *BMC Neuroscience*, *15*(1), 19. https://doi.org/10.1186/1471-2202-15-19

Wahlund, L.-O. O., Barkhof, F., Fazekas, F., Bronge, L., Augustin, M., Sjögren, M., Wallin, A., Ader, H., Leys, D., Pantoni, L., Pasquier, F., Erkinjuntti, T., & Scheltens, P. (2001). EuropeanTask Force on Age-Related White Matter Changes.A new rating scale for age-related white matter changes applicable to MRI and CT. *Stroke*, *32*(6), 1318–1322. https://doi.org/10.1161/01.str.32.6.1318.

Wahlund, L.-O. O., Westman, E., Westen, D. Van, Wallin, A., Shams, S., Cavallin, L., Larsson, E., & Imaging, F. (2017). Imaging biomarkers of dementia : recommended visual rating scales with teaching cases. *Insights into Imaging*, *8*(1), 79–90. https://doi.org/10.1007/s13244-016-0521-6

Wang, H.-X., Karp, A., Winblad, B., & Fratiglioni, L. (2002). Late-Life Engagement in Social and Leisure Activities Is Associated with a Decreased Risk of Dementia: A Longitudinal Study from the Kungsholmen Project. *American Journal of Epidemiology*, *155*(12), 1081–1087. https://doi.org/10.1093/aje/155.12.1081

Wang, Y., Catindig, J. A., Hilal, S., Soon, H. W., Ting, E., Wong, T. Y. Venketasubramanian, N. Chen, C., & Qiu, A. (2012). Multi-stage segmentation of white matter hyperintensity, cortical and lacunar infarcts. *NeuroImage*, *60*(4), 2379–2388. https://doi.org/10.1016/j.neuroimage.2012.02.034

Warkentin, S., Erikson, C., & Janciauskiene, S. (2008). rCBF pathology in Alzheimer's disease is associated with slow processing speed. *Neuropsychologia*, *46*(5), 1193–1200. https://doi.org/https://doi.org/10.1016/j.neuropsychologia.2007.08.029

Wechsler, D. (1992). *WAIS-R käsikirja [Manual of the Finnish version of WAIS-R]*. Psykologien Kustannus Oy.

Wechsler, D. (1996). *WMS-R käsikirja [Manual of the Finnish version of WMS-R]*. Psykologien Kustannus

Oy.

Wen, W., Sachdev, P. S., Li, J. J., Chen, X., & Anstey, K. J. (2009). White matter hyperintensities in the forties: Their prevalence and topography in an epidemiological sample aged 44–48. *Human Brain Mapping*, *30*(4), 1155–1167. https://doi.org/10.1002/hbm.20586

Wenk, G. L. (2003). Neuropathologic changes in Alzheimer's disease. *The Journal of Clinical Psychiatry*, *64*(Suppl 9), 7–10.

Weuve, J., Kang, J. H., Manson, J. E., Breteler, M. M. B., Ware, J. H., & Grodstein, F. (2004). Physical Activity, Including Walking, and Cognitive Function in Older Women. *JAMA*, *292*(12), 1454–1461. https://doi.org/10.1001/jama.292.12.1454

Wierenga, C. E., Benjamin, M., Gopinath, K., Perlstein, W. M., Leonard, C. M., Rothi, L. J. G., Conway, T., Cato, M. A., Briggs, R., & Crosson, B. (2008). Age-related changes in word retrieval: Role of bilateral frontal and subcortical networks. *Neurobiology of Aging*, *29*(3), 436–451. https://doi.org/10.1016/J.NEUROBIOLAGING.2006.10.024

Wilson, R. S., Bennett, D. A., Bienias, J. L., Aggarwal, N. T., Mendes de Leon, C. F., Morris, M. C., Schneider, J. A., & Evans, D. A. (2002). Cognitive activity and incident AD in a population-based sample of older persons. *Neurology*, *59*(12), 1910 LP – 1914. https://doi.org/10.1212/01.WNL.0000036905.59156.A1

Wilson, R. S., Bennett, D. A., Bienias, J. L., Mendes de Leon, C. F., Morris, M. C., & Evans, D. A. (2003). Cognitive activity and cognitive decline in a biracial community population. *Neurology*, *61*(6), 812 LP – 816. https://doi.org/10.1212/01.WNL.0000083989.44027.05

Wilson, R. S., Li, Y., Aggarwal, N. T., Barnes, L. L., McCann, J. J., Gilley, D. W., & Evans, D. A. (2004). Education and the course of cognitive decline in Alzheimer disease. *Neurology*, *63*(7), 1198 LP – 1202. https://doi.org/10.1212/01.WNL.0000140488.65299.53

Wilson, R. S., Mendes de Leon, C. F., Barnes, L. L., Schneider, J. A., Bienias, J. L., Evans, D. A., & Bennett, D. A. (2002). Participation in Cognitively Stimulating Activities and Risk of Incident Alzheimer Disease. *JAMA*, *287*(6), 742–748. https://doi.org/10.1001/jama.287.6.742

Winblad, B., Palmer, K., Kivipelto, M., Jelic, V., Fratiglioni, L., Wahlund, L.-O., Nordberg, A., Bäckman, L., Albert, M., Almkvist, O., Arai, H., Basun, H., Blennow, K., De Leon, M., DeCarli, C., Erkinjuntti, T., Giacobini, E., Graff, C., Hardy, J., … Petersen, R. C. (2004). Mild cognitive impairment – beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. *Journal of Internal Medicine*, *256*(3), 240–246. https://doi.org/10.1111/j.1365-2796.2004.01380.x

Wirth, M., Haase, C. M., Villeneuve, S., Vogel, J., & Jagust, W. J. (2014). Neuroprotective pathways:

lifestyle activity, brain pathology, and cognition in cognitively normal older adults. *Neurobiology of Aging*, *35*(8), 1873–1882. https://doi.org/https://doi.org/10.1016/j.neurobiolaging.2014.02.015

Wolf, H., Ecke, G., Bettin, S., Dietrich, J., & Gertz, H. (2000). Do white matter changes contribute to the subsequent development of dementia in patients with mild cognitive impairment? A longitudinal study. *International Journal of Geriatric Psychiatry*, *15*(9), 803–812. https://doi.org/10.1002/1099-1166(200009)15:9<803::aid-gps190>3.0.co;2-w.

Xu, W., Tan, L., Wang, H.-F., Tan, M.-S., Tan, L., Li, J.-Q., Zhao, Q.-F., & Yu, J.-T. (2016). Education and Risk of Dementia: Dose-Response Meta-Analysis of Prospective Cohort Studies. *Molecular Neurobiology*, *53*(5), 3113–3123. https://doi.org/10.1007/s12035-015-9211-5

Yoshita, M., Fletcher, E., Harvey, D., Ortega, M., Martinez, O., Mungas, D. M., Reed, B. R., & DeCarli, C. S. (2006). Extent and distribution of white matter hyperintensities in normal aging, MCI, and AD. *Neurology*, *67*(12), 2192–2198. https://doi.org/10.1212/01.wnl.0000249119.95747.1f

Yourganov, G., Fridriksson, J., Rorden, C., Gleichgerrcht, E., & Bonilha, L. (2016). Multivariate Connectome-Based Symptom Mapping in Post-Stroke Patients: Networks Supporting Language and Speech. *The Journal of Neuroscience*, *36*(25), 6668–6679. https://doi.org/10.1523/JNEUROSCI.4396-15.2016

Zakzanis, K. K., Graham, S. J., & Campbell, Z. (2003). A meta-analysis of structural and functional brain imaging in dementia of the Alzheimer's type: a neuroimaging profile. *Neuropsychology Review*, *13*(1), 1–18. https://doi.org/https://doi.org/10.1023/a:1022318921994

Zamboni, G., Griffanti, L., Mazzucco, S., Pendlebury, S. T., & Rothwell, P. M. (2019). Age-dependent association of white matter abnormality with cognition after TIA or minor stroke. *Neurology*, *93*(3), e272 LP-e282. https://doi.org/10.1212/WNL.0000000000007772

Zheng, J. J. J., Delbaere, K., Close, J. C. T., Sachdev, P., Wen, W., Brodaty, H., & Lord, S. R. (2012). White matter hyperintensities are an independent predictor of physical decline in community-dwelling older people. *Gerontology*, *58*(5), 398–406. https://doi.org/10.1159/000337815

ISBN 978-952-12-4078-2