Brain plasticity after cognitive intervention in patients with mild cognitive impairment (MCI) evaluated by multimodal MR imaging in a randomized, controlled trial.

Haakon Ramsland Hol

Thesis for the degree of Philosophiae Doctor (PhD)
University of Bergen, Norway
2022

UNIVERSITY OF BERGEN

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Date of defense: 16.12.2022

Year: 2022

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Print: Skipnes Kommunikasjon / University of Bergen

Hjerneplasitisitet undersøkt hos individer med mild kognitiv svikt etter PC-administrert arbeidsminnetrening, evaluert med multimodal MRI teknikk, en randomisert kontroll studie.

Formål: Hovedmålet med studien var å undersøke effekten av pc-administrert arbeidsminne trening, hos personer med mild kognitive svikt(MCI), samt få kjennskap til grad av nevrokognitive funksjonstap og nevrodegenerative forandringer synlig ved MR avbildning av hjernen. Man ønsket videre å korrelere om det var en sammenheng mellom utfall i kognitive områder og visuelle scoring systemer på MR. Vi forsøkte å avklare om individer med MCI har bevart plastisitet med undersøkelser av hjernebarkens tykkelse (strukturell MR teknikk) og endringer i hvit substans (tensor basert MR teknikk). Videre ønsket vi å avklare om bærerskap av spesifikke APOE og LMX1a gener påvirket treningseffekt.

Bakgrunn: MCI er en tilstand med redusert hukommelse som ikke påvirker dagliglivets funksjoner. Tilstanden ses på som et forstadie til demens, og om lag 10-15 % av denne gruppen glir over i en demenstilstand hvert år. En teori ved MCI-tilstander er at hjernens kompensatoriske mekanismer er ikke tilstrekkelige til å håndtere bakenforliggende hjernesykdom. MCI gruppen kan deles inn i to grupper; amnestisk MCI med redusert hukommelse og ikke-amnestisk MCI hvor funksjonstapet er i ikke-hukommelses relaterte kognitive domener. Felles for begge gruppene er ofte redusert arbeidsminne. Det finnes i dag ingen behandling for denne tilstanden. Av den grunn ønsket vi å undersøke om pc-administrert arbeidsminne trening kunne bedre pasientens arbeidsminne. Arbeidsminnetrening er basert på teorier om nevroplastisitet og kognitiv motstandsdyktighet. Nevroplastisitet er hjernens evne til å tilpasse seg ytre påvirkninger ved å øke tettheten av nerveender og volumet på hjerneceller. Repetert stimulering over tid er vist å kunne igangsette nevroplastisitet og dermed kunne bidra til økte kognitive reserver. Disse mikrostrukturelle forandringene kan påvises ved endringer i hjernebarkens tykkelse eller hvit substans på MR bilder. I studier hos friske personer med normal hukommelse har arbeidsminnetrening en påvisbar effekt ved nevrokognitive tester som også gjenfinnes på MR bilder, men effekten hos eldre med kognitiv svikt er ikke undersøkt i samme grad. Det foreligger noen preliminære rapporter om positiv treningseffekt på arbeidsminne hos personer med MCI, men studiene har hatt lav statistisk styrke, og varierende resultater. Det er mange bakenforliggende sykdommer som kan føre til en MCI tilstand. Dette gir utslag i varierende grad av påvisbare endringer i hjernen.

Design: Individer med MCI ble rekruttert fra fire hukommelsesklinikker i Helse-Sør Øst. Deltagerne gjennomgikk nevrokognitive tester og MR undersøkelser ved baseline, 4 uker og 4 mnd etter trening. Ved inklusjon ble deltagerne randomisert inn i to grupper, adaptiv og aktiv kontroll. Vi brukte et PC-administrert arbeidsminnetreningsprogram med en adaptiv og en placebo arm. Gruppen med adaptiv trening fikk vanskelighetsgraden på oppgavene automatisk regulert slik at de trente dynamisk på egen maksimal vanskelighetsgrad. Den aktive kontrollgruppen brukte samme treningsprogram, men med fast lav vanskelighetsgrad uten individuell tilpasning. Videre undersøkte vi en sammenlignbar gruppe individer uten kognitiv svikt med MR undersøkelser og kognitive tester tilsvarende treningsgruppene ved baseline. Denne gruppen ble rekruttert vi media og Sørlandet sykehus sin hjemmeside. For å måle lokalisert atrofi eller hvitsubstans forandringer i hjernen, ofte er assosiert med spesifikke nevrodegenerative sykdommer eller skade på hvit substans mikrostruktur, brukte vi 4 aldersjusterte kliniske visuelle skalaer.

Resultater: Det ble rekruttert 84 deltagere i studien, hvor 62 individer hadde minst to MR undersøkelser. Genetisk profil tilgjengelig for 54 personer. Den amnestiske MCI gruppen hadde økt andel av MRI identifiserte hjerneforandringer sammenlignet med ikke-amnestisk gruppe og de

kognitivt friske. Scheltens skala for å måle medial temporal lapps atrofi, viste seg å være den beste til å skille mellom MCI og kontrollgruppen. Amnestisk-MCI gruppen hadde høyere grad av hjernesvinn i tinninglappen enn både ikke-amnestisk MCI og kontroll gruppen.

Hjernebarkens tykkelse endret seg ikke signifikant hos gruppen MCI pasientene etter arbeidsminnetrening. LMX1a-AA viste seg å ha en mulig modulerende treningseffekt uttrykt ved økning av tykkelse i hjernebarken hos pasienter med MCI. APOE genet hadde ingen signifikant modulerende effekt på hjernebarken etter arbeidsminne trening.

Endringer i hvit substans etter trening ble undersøkt ved «mean diffusivity». Denne undersøkelse gir et bilde på synaptisk tetthet, dvs antall nerveender i et område. I denne studien fant vi en økning i «mean diffusivity» i venstre sagital stratum hos den adaptive gruppen, men ikke hos non-adaptiv gruppe ved kontrollen fire måneder etter trening. Dette området rommer flere store hjernebaner og endringen er et tegn på treningseffekt bare hos den gruppen som trener på høy vanskelighetsgrad. VI fant ingen tegn til at lett trening ga økt antall nerveender. Gruppen med ikke amnestisk MCI hadde fremdeles etter fire måneder høyere andel nerveender i to områder assosiert med hukommelse og arbeidsminne sammenlignet med de som hadde amnestisk MCI. Bærerskap av undergrupper av APOE-genet og LMX1aa hadde ingen innvirkning på treningseffekten målt i hvit substans.

Konklusjon: Individer med MCI som fikk adaptiv trening hadde treningseffekt målt med MR. Dette tyder på at adaptiv arbeidsminnetrening kan bidra til å forbedre forbindelse mellom nerveceller også ved begynnende hukommelsessvikt. Videre fant vi at det var en sammenheng mellom nedsatt funksjon i forskjellige nevropsykologiske domener og funn på MR bilder. Bærere av LMX1a-AA fikk en positiv utvikling av hjernebarktykkelsen etter trening, som vedvarte etter fire måneder sammenlignet med bærere av LMX1a-GG/GA. Vi finner ingen påvirkning av bærerskap av forskjellige APOE gener på treningseffekt.

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Scientific environment

Sorlandet Hospital Trust

Research group in geriatric medicine, Dep. of Clinical Sciences, University of Bergen,

Professor Linda Chang/ABCD group/Radiology department/University of Maryland Baltimore US.

Neuroimaging Research Group at Oslo University Hospital HF.

1. Acknowledgments

Nothing would be accomplished without the help of all the people involved in this project. I would have no subjects without Marianne Møretrø Flak, who is a brilliant neuropsychologist, and the warmest human being I know. For the technical part, nothing would have been done without Knut Jørgen Bjuland and Lars Morten Rimmol. Their programming skills and knowledge of the linear mixed effect model were essential. Big thanks to Marianne Rognli and Anders Tomtestad for scanning all the participants.

Professor Linda Chang at Maryland Medical University and Professor Kenichi Oishi at John Hopkins, together with my main supervisor, Susanne Hernes, managed to drag me out of my misery when the data was going nowhere. Gro Løhaugen and Jon Skranes for agreeing to be my supervisors and being so incredibly analytical and sharp in research, getting rid of excess fillings in my writing.

My two employers Sørlandet Hospital HF and Oslo University Hospital HF, have been very supportive and let me take time off to finish this project, though Corona was a complicating factor in the finishing stages of the thesis. I am very grateful for the support from UIB and their advisement during the corona pandemic.

Without my family, nothing could have been done. Åsta and my children have been fantastic, supporting, and caring. Many weekends and late nights, I sat in front of the computer trying to fix problems or rerun analyses after correcting problems. Still, they let me travel to the US, leaving them behind for some time, with Ask being a newborn. Words cannot convey my gratitude.

All the volunteers who contributed their free time to train and be imaged for 30 minutes each time. Thank you, without your dedication, there would be no study.

Thank you too, all!

2. Summary

Aim: The main aim of this study was to investigate the effects of computer-based working memory training, measured by MRI in individuals with Mild cognitive impairment (MCI), and to investigate a possible correlation between the structural loss detectable with the radiological visual scoring systems and domain-specific function loss. Furthermore, we wanted to investigate if the neuroplasticity in MCI patients was workload-dependent or if the effect of the training was modulated by the genotypes LMX1a or APOE.

Background: Individuals with MCI have a cognitive decline above expected for normal aging, but the decline does not affect activities of daily living. A high annual transition rate from MCI to dementia of 10-15% targets this population as suitable for any delaying interventions. Currently, no treatments are available for MCI. . Depending on whether the impairment primarily affects memory, MCI is subdivided into amnestic and non-amnestic(aMCI/naMCI) groups. A common feature in both MCI groups is often the decline in working memory function. The concept behind the effect of working memory training(WMT) is based on neuroplasticity; repeated stimuli trigger a neuroplastic response in the brain resulting in increased glial volume or increased synaptic density, leading to increased connectivity. Investigating the neuroplastic process in response to WMT can be done objectively with structural or diffusion-weighted MRI imaging techniques. This is previously reported in cognitively healthy adults, but few studies with divergent results have investigated if WMT can induce brain changes detectable on MRI in MCI patients. A knowledge gap exists regarding the ability of the MCI brain to utilize neuroplasticity after stimuli.

Design: A total of 84 individuals diagnosed with MCI from four hospitals in the South-East Health Care region were included in the study. Of these, 63 had at least two MRI images harvested, and genetic results were available for 54 individuals. The participants were randomized to either adaptive working memory training or active control at inclusion. The participants participated in a computer-based WMT program for 25 sessions over five weeks and underwent cognitive testing and MRI imaging at

baseline, four weeks, and four months after training . To investigate the computerized working memory training (CMWT)effect, we utilized longitudinal multimodal MRI techniques. A group of 51 healthy controls was recruited through media and Sorlandet hospital's web page. This group underwent testing and MRI similar to baseline.

Results: The MCI group had a greater degree of brain pathology than the non-amnestic and healthy control groups, as previously reported. Age-adjusted Schelten's medial temporal atrophy (MTA) was superior to the other three visual scoring systems for measuring localized atrophy or white matter structural damage. The decline was diverse, ranging from single domain MCI to multiple domains MCI. This is in accordance with previous studies both radiologically and neurocognitively.

No significant cortical thickness changes longitudinally after CWMT were found, nor any significant differences after adaptive or non-adaptive CMWT training measured by cortical thickness. Carriers of the LMX1a-AA had a significantly greater cortical thickness trajectory than the LMX1a-GG/GA group in the right superior frontal gyrus, indicating a possible modulating effect. These findings are considered promising for further studies.

Diffusion-weighted MRI found significantly decreased mean diffusivity in the left sagittal stratum in the adaptive training group at four months compared to the non-adaptive. The sagittal stratum is a junction region for several large tracts associated with working memory. The finding indicates that some white matter changes are workload-dependent. Four months after training, significant changes were observed favoring the naMCI group compared to the aMCI group in the left posterior thalamic radiation and left hippocampal cingulum. We did not detect any modulating training effect on the white matter from APOE and LMX1a.

3. List of papers:

3.1 Cognitive Profiles and Atrophy Ratings on MRI in Senior Patients With Mild Cognitive Impairment.

Flak MM, Hol HR, Hernes SS, Chang L, Ernst T, Engvig A, Bjuland KJ, Madsen B-O, Lindland EMS, Knapskog A-B, Ulstein ID, Lona TEE, Skranes J, Løhaugen GCC.

Front. Aging Neurosci. 2018;10:384. doi: 10.3389/fnagi.2018.00384

3.2 Cortical thickness changes after computerized working memory training in patients with mild cognitive impairment.

Haakon R. Hol, Marianne M. Flak, Linda Chang, Gro Christine Christensen Løhaugen, Knut Jørgen Bjuland, Lars M. Rimol, Andreas Engvig, Jon Skranes Thomas Ernst, Bengt-Ove Madsen and Susanne S. Hernes

Front. Aging Neurosci., 04 April 2022 | https://doi.org/10.3389/fnagi.2022.796110

3.3 White matter changes after working memory training in individuals with MCI are workload-dependent.

Haakon R. Hol, Marianne M. Flak, Linda Chang, Kenichi Oishi, Gro Løhaugen, Knut Jørgen Bjuland, Lars M. Rimol, Andreas Engvig, Jon Skranes, Thomas Ernst, Ingun Ulstein, Trine Lona, Bengt-Ove Madsen, Susanne S. Hernes

Will be submitted October 2022

4. Abbreviations:

AD	Alzheimer dementia	MCI	Mild cognitive impairment
FD	Frontotemporal Dementia	aMCI	Amnestic MCI
		naMCI	Non-amnestic MCI
LBD	Lewy Body Dementia	WMT	Working memory training
PD	Parkinson's disease	FS	Freesurfer
DLB	Demenia with Lewy Bodies	SBA	Surface based analysis
		FA	Fractional anisotropy
LTP	Long term potential	MD	Mean diffusivity
LTD	Long term depression	CWMT	Computerized working memory training
BDNF	**B**rain-derived neurotrophic factor	MRI	Magnetic resonance imaging
APOE	Apolipoprotein E	DTI	Diffusion tensor imaging
LMX1-a	LIM homeobox transcription factor 1, alpha	fMRI	Functional magnetic resonance imaging
		PA	Posterior atrophy scale.
		FLAIR	Fluid Attenuation Inversion Recovery
GCA	Global cortical atrophy scale	CREB	cAMP response element-binding protein
		BOLD	Blood Oxygenation Level Dependent Contrast
MTA	Schelten's medial temporal atrophy scale	MPRAGE	Magnetization Prepared RApid Gradient Echo
		ASL	Arterial spin labeling.
WMH	White matter hyperintensities.	VBA	Voxel based analysis
		PET	Positron emition tomography
		SNR	Signal to noise ratio
lGI	Local gyrification index.	CNR	Contrast to noise ratio
		MS	Myelin sheet

5. Introduction/Background:

"Aging takes its toll" is an idiom that is true for almost all people; everyone experiences some cognitive decline during late life, except for the "superagers" (Katsumi et al. 2021). A cognitive decline outside the normal range but without impeding daily life activities constitutes the condition called mild cognitive impairment(MCI). Although some individuals remain in the MCI stage for life, this condition increases the risk of transition to dementia. Subjects with MCI also suffer a higher incidence of depression (Tsolaki et al. 2017), and patients with their caregivers report reduced quality of life (Eshkoor et al. 2015; Moon 2020; Werner 2012). MCI is the first diagnosable stage in the dementia continuum and has become at the forefront of cognitive impairment studies. This research is divided into three treatment modalities: cognitive training methods, pharmacological therapies, and transcranial stimulation. The non-pharmacological approaches base their research on the potential of neuroplasticity and the possibility of compensating for or restoring impaired function.

In neuroscience, brain plasticity is used broadly and often interchangeably between structural and functional plasticity. Structural plasticity is the brain's ability to change or adapt, such as acquiring alternative neuronal pathways or recruiting alternative brain centers in response to environmental alterations (Buchtel 2008). In neuropsychology, functional plasticity is defined as the brain's ability to regenerate or improve function in response to alterations in stimuli (Baltes et al. 1995). Direct measurement of neuroplasticity is challenging since the histopathological approach is generally incompatible with life. The development of neuroimaging has unlocked ways to investigate the microstructural responses to cognitive training. Research in this field has grown exponentially with improved imaging modalities and postprocessing techniques. Nevertheless, few studies investigate the structural responses to cognitive training in either grey or white matter in individuals with MCI. Furthermore, none have investigated whether the microstructural changes in MCI subjects depend on

workload, the allelic genotype of either LMX1a or APOE, or MCI subtype, which is what this thesis is trying to answer.

5.1 Mild cognitive impairment

5.1.1 The development of a definition of MCI

Mild cognitive impairment (MCI) was initially defined by Reisberg et al. (Reisberg et al. 1988) as a stage between dementia and age-adjusted normal cognitive function. Pettersen et al. developed in the late ’90s the first clinical criteria for MCI diagnosis, primarily for the episodic memory deficiency/impairment type (Petersen et al. 2014a; Winblad, Palmer, Kivipelto, Jelic, Fratiglioni, Wahlund, Nordberg, Backman, et al. 2004). The definition was further revised in 2003 due to international collaboration, and the subgroup of non-amnestic impairment was included in the MCI diagnostic criteria (Winblad, Palmer, Kivipelto, Jelic, Fratiglioni, Wahlund, Nordberg, Backman, et al. 2004). Furthermore, the revised classification included subgroups dependent on the number of affected domains, such as single or multiple domains, and amnestic and non-amnestic MCI (aMCI/naMCI) subgroups. Later the term neurocognitive disorder was introduced as a non-stigmatic analog to cognitive impairment. It also clarifies that it is an acquired condition due to loss of function over time in adults, not a developmental disorder. (Ganguli et al. 2011). In the US, the current criteria for mild neurocognitive disorder or MCI are based on the DSM-V(American Psychiatric Association 2013) listed in table 1.

Table 1: Criteria for MCI diagnosis adapted from DSM-V (American Psychiatric Association 2013).

Diagnostic criteria	Mild neurocognitive disorder
A	Evidence of modest cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning, and memory, language, perceptual-motor, or social cognition) based on:

	1	Concern of the individual, a knowledgeable informant, or the clinician that there has been a mild decline in cognitive function; and
	2	A modest impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.
B	The cognitive deficits do not interfere with capacity for independence in everyday activities (i.e., complex instrumental activities of daily living such as paying bills or managing medications are preserved, but greater effort, compensatory strategies, or accommodation may be required).	
C	The cognitive deficits do not occur exclusively in the context of a delirium.	
D	The cognitive deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia).	
E	Etiology: Alzheimer's disease, frontotemporal lobar degeneration, Lewy body disease, vascular disease, traumatic brain injury, substance/medication use, HIV infection, Prion disease, Parkinson's disease, Huntington's disease, another medical condition, multiple etiologies or unspecified.	

In Norway, at the time of the initiation of this thesis, the MCI classification was still based on the Mayo\Winblads MCI classification from 2004 (Winblad, Palmer, Kivipelto, Jelic, Fratiglioni, Wahlund, Nordberg, Backman, et al. 2004). While awaiting the introduction and finalization of ICD-11, the DSM-V criteria for setting the diagnosis are used in Norway, though classified as F06.7 Mild cognitive disorder in the ICD10, or sometimes F07.8 Other personality and behavioral disorders due to known physiological condition.

5.1.1 Epidemiology, etiology, and risk factors in MCI

Individuals with MCI are a heterogeneous group. The etiology forming the clinical diagnosis of MCI varies from a wide array of conditions such as neurodegeneration, depression, metabolic diseases, ischemic or traumatic pathologies (American

Psychiatric Association 2013; Petersen 2004; Winblad, Palmer, Kivipelto, Jelic, Fratiglioni, Wahlund, Nordberg, Backman, et al. 2004). Age is the primary risk factor in neurocognitive disorders (Xu et al. 2020). In MCI, additional risk factors include a family history of dementia, APOE4 gene carriage(Lambert et al. 2009; Sienski et al. 2021), or other conditions that increase cardiovascular risk, like obesity, smoking, and hypertension (Jia et al. 2020).

The incidence of MCI varies with the MCI definition, age, and population. The Trøndelag Health Study 4 (HUNT4) recently published prevalence data from their sizeable longitudinal population study, with over 9000 participants above 70 years of age. These numbers include the oldest old and people in long-term care (Gjøra et al. 2021). This data is representative for the rest of Norway since the country is relatively uniform in terms of ethnicity and socioeconomic conditions.

Table 2: MCI prevalence in Norway, Minnesota US, and China

Study:	Hunt4 (Norway)[$]	Mayo Clinic study of aging (MN-USA)[*]	Xue et al[§] (China)
70+ years	35.2% (34.3–36.4)	16% (14.4–17.5)	14.7% (14.5-14.92)
Women	33.0 (31.6-34.5)	14.1 (12.1–16.2)	12.95(12.66-13.23)

Table 2: $, HUNT4 (Gjøra et al. 2021); *,(Roberts et al. 2012)

Both Hunt4 and the Mayo Clinic study of aging(MCSA) reports a higher MCI prevalence and incidence in all MCI subtypes of men. In comparison, women have a higher prevalence in the dementia group (Gjøra et al. 2021; Roberts et al. 2012) (table 2). Women's longevity can explain part of the difference compared to males (Mielke 2018; Rocca et al. 2014), with a more abrupt transition from normal cognition to dementia than men (Gjøra et al. 2021; Nie et al. 2011; Petersen et al. 2010; Xue et al. 2018).

Challenges with MCI prevalence data

Pessoa et al. reported substantial heterogeneity prevalence variation between studies, ranging from 0.5% to 41.8% (Pessoa et al. 2019). Several other studies have

highlighted that ascertaining the prevalence of mildly afflicted people is challenging (Gillis et al. 2019; Ward et al. 2012). Commonly used diagnostic tools like the Montreal Cognitive Assessment (MoCA), Mini-Mental State Evaluation(MMSE), or Clinical Dementia Rating (CDR) have a ceiling effect, failing to detect a slight cognitive reduction in high functioning individuals or patients with no predominant memory problems like naMCI patients. The target population is an essential factor, different age groups will affect the results, and several studies do not include patients in care homes, especially outpatient studies (Gjøra et al. 2021). There is a 20% difference in the prevalence numbers between the MCSA and HUNT4; MCSA has not included 90+ years old as HUNT4 and does not report if they have included long-time care patients (Petersen et al. 2010; Roberts et al. 2012), showing the issue with target populations. Nonetheless, the populations are similar, mainly Caucasians of northern European descent. Several clinical studies also fail to report subclassifications of their MCI study population, thus reducing the transferability of the results (Ward et al. 2012).

National test battery for cognitive tests

Norwegian national guidelines for clinicians diagnosing cognitive problems recommend using the NorCog test battery. The NorCog battery is extensive, including several large scientifically validated test batteries with Norwegian validation (table 3) in addition, there are additional tests recommended for highly educated people with greater difficulty, such as the California verbal learning test-2 (CVLT2). Their respective test area with regard to cognitive function is listed in table 3.

Table 3: NORCOG test battery with functions tested. (Adapted from NORCOG)

Neurocognitive function:	Test:	Test References:
General cognition test:		
	MMSE	(Folstein et al. 1975)
	Clock drawing test	(Head 1998; Shulman et al. 1986)
Attention/psychomotor speed		
	Trail Making Test A (TMT-A)	(Llinàs-Reglà et al. 2015)
Visual and verbal memory		
	Word learning test. (CERAD)	(Morris et al. 1989)
Language function		
	Modified Boston naming test. (CERAD)	(Morris et al. 1989)
	Verbal fluency test(animals) (CERAD)	(Morris et al. 1989)
	Word List Recognition (CERAD)	(Morris et al. 1989)
Visuospatial		
	Constructional Praxis (CERAD)	(Morris et al. 1989)
Executive function		
	Trail Making Test B (TMT-B)	(Llinàs-Reglà et al. 2015)
	Verbal fluency test(animals) (CERAD)	(Morris et al. 1989)
	Word List Recognition (CERAD)	(Morris et al. 1989)

5.1.2 Subtypes of MCI

MCI is currently categorized into two main groups, amnestic (aMCI) and non-amnestic (naMCI), depending on whether memory problems are the dominant feature (figure1). The MCI subgroups are further divided into subgroups depending on which cognitive domain(s) are affected.

Figure 1. MCI subtypes

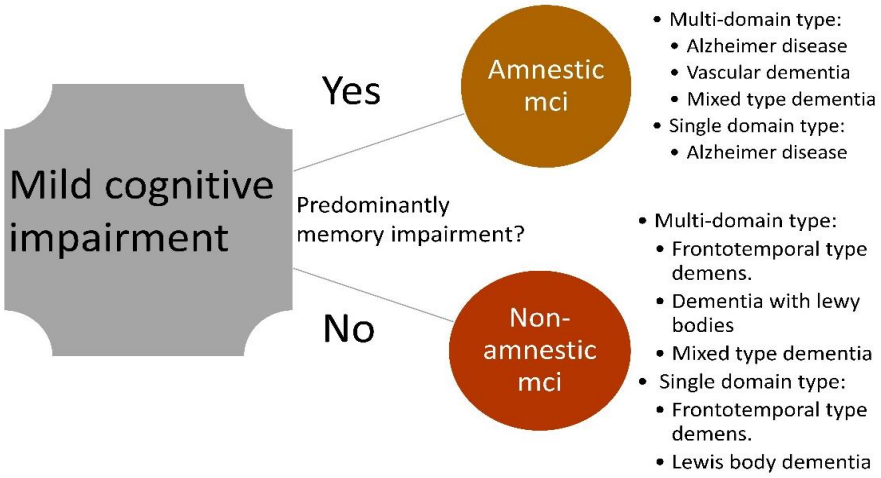

Figure 1: The four subcategories of MCI types and their most common neuropathological substrate. Based on Petersen et al. 2017.

The domains are explored through neurocognitive testing. There is no unanimous division of cognitive function into cognitive domains. (Fields et al. 2011; Harvey 2019; Sachdev et al. 2014). In 2013 the DSM-V introduced a six-key cognitive domain model, which is the framework for diagnosis and subcategories (figure 2).

Figure 2. Six-key neurocognitive domain model for classification

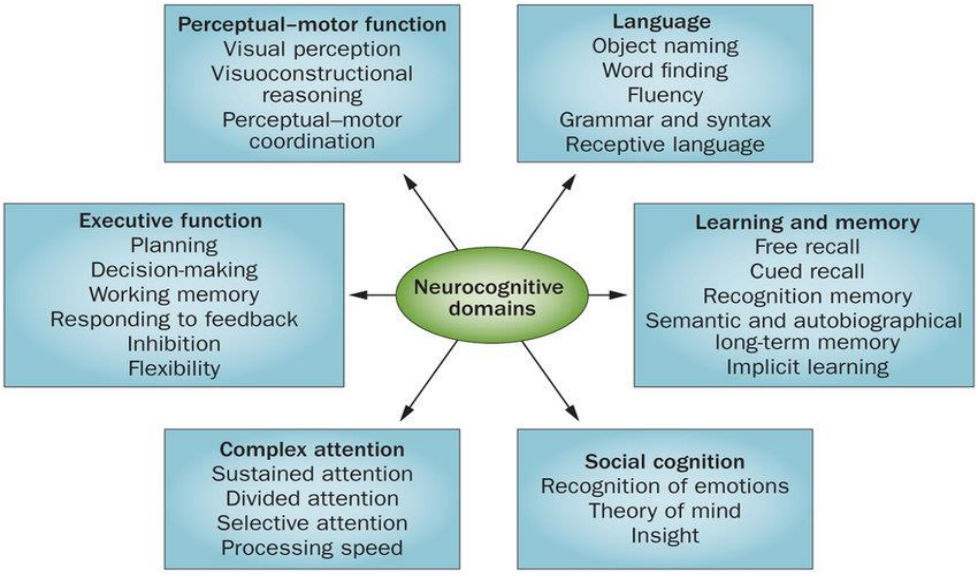

Figure 2: DSM-V neurocognitive domain model, with subdomains. From Sachdev et al., 2014, Reproduced with permission from publisher Springer Nature

There are several testing regimes for establishing a neuropsychological cognitive profile on an individual; some of the most recognized are the Wechsler Adult intelligence scale 4. Ed. (WAIS-IV), Wechsler Memory scale III/IV, Delis-Kaplan Executive Function Tes(D-KEFS), Reys Complex Figure Test(RCFT). and California Verbal Learning Test (CVLT). These tests enable investigations of the different key cognitive domains with age- and education-adjusted scores. Commonly, a score below 1-1.5 standard deviations of the mean on two tests in one or more cognitive domains constitutes a cognitive impairment.

In amnestic MCI, impairments are found within the verbal and/or visual episodic memory domains. In naMCI, domains such as working memory and/or executive function, attention, or processing speed, are impaired (Petersen 2009; Petersen et al. 2014b; Petersen et al. 1997; Petersen et al. 1999; Winblad, Palmer, Kivipelto, Jelic, Fratiglioni, Wahlund, Nordberg, Backman, et al. 2004), but the subjects have less affected/normal scores in the memory domains. The MCI subtypes correlate with different neurodegenerative pathologies. Single domain aMCI is commonly classified as a prodromal stage of AD/MCI with AD, while multidomain aMCI is associated with AD, vascular or mixed pathology, or severe depression. Single domain naMCI might indicate tauopathy or α-synuclein-disease, such as frontal-temporal dementia or dementia with Lewis bodies or focal infarction (Petersen et al. 2018).

Etiology-based MCI classification

Another common approach is to use etiology as a classification criterion, defining the different types of MCI dependent on the causative etiology, such as MCI from Alzheimer's disease (MCI-AD), MCI from vascular dementia (VAD-MCI), MCI from Lewy body dementia (MCI-LBD), Traumatic brain injury associated-MCI or other diseases-MCI has been proposed as categories(Winblad, Palmer, Kivipelto, Jelic, Fratiglioni, Wahlund, Nordberg, Backman, et al. 2004). This approach resulted in an

update to the minor cognitive disorder chapter in DSM-V in 2015 (Association 2015), which now includes etiology specifiers.

5.1.3 Outcome of MCI

Figure 3. Annual conversion of MCI.

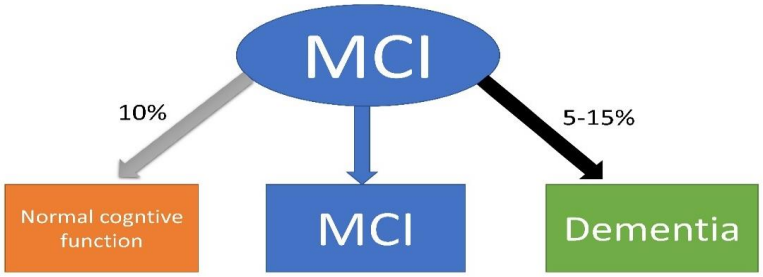

Figure 3: Depiction of annual conversions within an MCI population

Conversion from MCI to dementia is divergent depending on the population in question (Petersen et al. 2014). Studies report an annual conversion rate of 10-15% in a clinical setting while 5-10 % in a community setting (Chen et al. 2017; Farias et al. 2009; Michaud et al. 2017; Mitchell and Shiri-Feshki 2009; Roh et al. 2016). The higher incidence in women with dementia compared to men in the 70+ age group indicates a faster conversion rate in women. However, this appears later in women compared to men (Petersen et al. 2010)(Gjøra et al. 2021). Interestingly, approximately 10% revert to a non-cognitive impaired state annually (Figure 4) (Robertson et al. 2019; Roh et al. 2016).

5.2 Dementia

Dementia is defined as a permanent loss of function more severe than MCI. DSM-V describes dementia as a Major Neurocognitive Disorder. The impairment must be sufficient to interfere with independence in everyday activities and fulfill specific criteria listed in table 4. According to WHO, "*dementia is a syndrome in which there is a deterioration in cognitive function beyond what might be expected from the usual consequences of biological aging*" (https://www.who.int/news-room/fact-

sheets/detail/dementia). The ICD10 defines dementia as *"A syndrome due to disease of the brain, usually of a chronic or progressive nature, in which there is disturbance of multiple higher cortical functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgment. Consciousness is not clouded. Cognitive function impairments are commonly accompanied, and occasionally preceded, by deterioration in emotional control, social behavior, or motivation."* (https://icd.who.int/browse10/2019/en#/F00-F09)

The memory loss/cognitive reduction in dementia is caused by loss of function in neurons/neuronal networks due to loss of cells/cell function or their connections (axons and synapses).

Table 4. Adapted from DSM-V (American Psychiatric Association 2013).

Diagnostic criteria:	Major neurocognitive disorder	
A	Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning, and memory, language, perceptual-motor, or social cognition) based on:	
0	1	Concern of the individual, a knowledgeable informant, or the clinician that there has been a significant decline in cognitive function; and
	2	A substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.
B	The cognitive deficits interfere with independence in everyday activities (i.e., at a minimum, requiring assistance with complex instrumental activities of daily living such as paying bills or managing medications).	
C	The cognitive deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia).	
D	The cognitive deficits do not occur exclusively in the context of a delirium.	
E	Etiology behind dementia: Alzheimer's disease, frontotemporal lobar degeneration, Lewy body disease, vascular disease, traumatic brain	

	injury, substance/medication use, HIV infection, Prion disease, Parkinson's disease, Huntington's disease, another medical condition, multiple etiologies or unspecified.

Dementia is divided into five main types, based on their pathological or clinical commonality; Alzheimer's dementia(AD), vascular type dementia(VaD), mixed type dementia(MTD), frontotemporal dementia(FTD), Lewy body dementia(LBD). The prevalence of the different dementias differs from region to region (Norway and western countries are listed in table 5); in Asia, VaD tends to have a higher percentage; it used to be a 2:1 VAD/AD ratio, especially in Japan (Grant 1999). However, with the increased western lifestyle and older age, there has been an increase in the incidence of AD than previously; the VaD/AD ratio is now reportedly 1:1 (Grant 1999).

Table 5. Prevalence of the main types of dementia:

Type of dementia:	Prevalence in Norway (95% CI)†	Prevalence in Western countries[1]
Alzheimer dementia	8.4% (7.8–9.0)	8% (4-10)
Vascular dementia	1.4% (1.2–1.7)	1.3%(0.7-3)
Mixed type dementia:	1.4% (1.1–1.7)	1.9%(0.9-3.8)
Lewy Body dementias	0.6% (0.4–0.8)	0.8%(0.4-1.6)
Frontotemporal dementia	0.6% (0.4–0.8)	0.9%(0.3-1.4)
Unspecified dementia	2.5% (2.2–2.8)	-
Total:	14.6% (13.9-15.4)	13.9% (11.5-16.2)

†Data from HUNT4, [1](Averaged > 70y from: Dementia UK, Spanish foundation of the Brain, US: (Plassman et al. 2007) and Alzheimer foundation 2020.)

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5.2.1 Alzheimer dementia

Alzheimer's dementia (AD) is the most common type of neurodegenerative dementia. It was first described in 1901 by Alois Alzheimer. Alzheimer's disease is a slow

progressive neurocognitive disease. In most cases, the disease starts 20 years before symptoms arise (Braak et al. 2011; Jack et al. 2009), resulting in severe dementia or death(Figure 4).

Figure 4: Cognitive decline described in stages during Alzheimer's disease progression.

Figure 4: adapted form Jack et al 2009, Braak et al 2011.

Clinical features:

Memory loss is considered one of the key features of AD, with a progressive loss of memory function, forgetting conversations, appointments or events and not recollecting them later. The patients are afflicted with reduced problem-solving abilities and difficulties planning ahead, misplacing things, or getting lost in familiar environments. With disease progression, difficulties in orientation for time and place become apparent. Later symptoms include impaired communication, disorientation, confusion, poor judgment, and behavioral changes. Ultimately, difficulty speaking, swallowing and walking occurs ('2020 Alzheimer's disease facts and figures' 2020). The degree of dementia reflects the ability to perform everyday activities such as washing, getting dressed, and other daily activities(Nadler et al. 1993).

Neuropathological

Classical Alzheimer's disease-induced dementia has a neuroanatomical picture characterized by the accumulation of neurofibrial tangles (NFT) inside the neurons and deposition of amyloid-beta plaques between the neurons. The accumulation of amyloid-beta between the cells may interfere with neuron-to-neuron communication at the synaptic level. In comparison, the Tau tangles might interfere with intracellular transport function, leading to cell death and reduced glucose metabolism. These two molecules are toxic and are believed to activate the microglia for clearance (Neumann et al. 2009). When the clearance rate is not sufficient, the release of the toxins induces

a chronic inflammatory response. Atrophy occurs due to cell death, and normal brain function is compromised.

Despite a clear neuroanatomical picture, the etiology behind the disease is not entirely understood. To complicate things further, Post-mortem studies combined with clinical data show that the clinical syndrome expression can be found with or without neuropathological changes (Jack et al. 2018). Following the characterization of the trajectories from normal cognition through Alzheimer's disease to AD, a shift towards a more biological approach has occurred due to a lack of cohesion between symptoms and neuropathological correlations. To explain the underlying mechanisms and provide further understanding of the AD's varying degrees of clinical manifestations, the National Institute on aging spearheaded the development of the AT(N) (β amyloid deposition, pathologic tau, and neurodegeneration) framework. The intention is to group different biomarkers associated with AD to make it easier to understand the disease continuum. The initial release did not include imaging for evaluating neurodegeneration. However, in 2018, the guidelines were revised, adding the neurodegenerative variable as a biomarker. This variable is determined by rating the hippocampal or parietal atrophy, either by MRI or CT. Metabolic hypoactivity measured by PETCT-FDG or total TAU in CSF can also be seen as an expression for neurodegeneration in addition to or instead of atrophy (table 6). According to Norwegian guidelines for dementia diagnosis, spinal fluid (CSF) examinations are performed in cases where the dementia diagnosis is complicated. The most common CSF finding in AD is decreased β amyloid and increased tau proteins.

Table 6: ATN framework.

AT(N) biomarkers:

A: Aggregated Aβ or associated pathologic state	T: Aggregated tau (neurofibrillary tangles) or associated pathologic state	(N): Neurodegeneration or neuronal injury
CSF $A\beta_{42}$, or $A\beta_{42}/A\beta_{40}$ ratio	CSF phosphorylated tau Tau PET	Brain MRI
Amyloid PET	CSF phosphorylated tau Tau PET	FDG PET
		CSF total tau

The ATN biomarkers framework, adapted from Jack et al. 2018.

Risk factors

Although the etiology of AD is not completely understood, some risk factors have been identified, such as age, obesity, and the carriage of the *APOE*-ε4 gene. The carriage of two apolipoprotein ε4 alleles is currently the most important risk factor for Alzheimer's disease, even carrying a single allele ε3/ε4 or ε2/ε4 increases the risk by 513% and 168% respectively, compared to ε3/ε3 (Reiman et al. 2020). In the general population, the frequency of apolipoprotein ε4 carriage is 20-30% (Rajan et al. 2017), whereas 40-65% of the AD cases (Crean et al. 2011). AD has regional variances, with a higher prevalence in Northern Europe and North America than in Asia and the Mediterranean (Crean et al. 2011), which does not entirely follow the APOE4 prevalence showing that other factors also affect disease development.

5.2.2 Vascular type dementia

Stroke or subclinical brain injury of vascular origin causing cognitive impairment is considered a separate entity within dementia illnesses. Vascular type dementia (VAD) accounts for 10-20% of the dementia types (Akhter et al. 2021; Korczyn et al. 2012; Thal et al. 2012). There are significant regional variations; Asia has a higher prevalence than North America and Europe.

Table 7. Diagnostic criteria for the diagnosis of vascular type dementia.

Diagnostic criteria	Major or mild vascular Neurocognitive disorder:	
A	The criteria are met for major or mild neurocognitive disorder.	
B	The clinical features are consistent with a vascular etiology, as suggested by either of the following:	
	1	Onset of the cognitive deficits is temporally related to one or more cerebrovascular events.
	2	Evidence for decline is prominent in complex attention (including processing speed) and frontal-executive function.
C	There is evidence of the presence of cerebrovascular disease from history, physical examination, and/or neuroimaging considered sufficient to account for the neurocognitive deficit	
D	The symptoms are not better explained by another brain disease or systemic disorder.	

Adapted from DSM-V (American psychiatric association 2011)

Clinical features

The clinical picture in VaD will depend on the vascular etiology described in table 8.

Table 8. Vascular dementia etiology and clinical features.

	Vascular pathology causing vascular dementia:			Clinical picture:
1	Non-hereditary (Most common):			
	A	Subcortical vascular encephalopathy (Confluent WMH).		Slow progressive decline, often affecting processing speed initially.
	B	Strategic infarct. (Basal ganglia, Thalamus or Cortical infarct.)		Abrupt cognitive change, followed by sometimes cognitive improvement.
	C	Multi-infarct encephalopathy.		Stepwise progression of impairment.
2.	Degenerative vessel disorders (less common):			
	A	Atherosclerosis (Large, medium sized vessels)		Slow progressive impairment, often followed by sudden infarcts/stepwise progressive decrease in cognitive function.
	B	Small vessel disease (SVD):		
		I	Small vessel arteriosclerosis,	Often considered primarily affecting processing speed and executive function, though other cognitive domains are also affected.
		II	Arteriolosclerosis	
		III	Cerebral amyloid angiopathy (CAA).	
3	Hereditary (rare):			
	A	Cadasil: Cerebral Autosomal Dominant Arteriopathy with		Cognitive impairment initially manifests through mild executive

		Subcortical Infarcts and Leukoencephalopathy	and visuospatial deficits, psychomotor slowing, and apathy.

Adapted from DSM-V, Caeiro and Ferro 2006 and Hamilton et al. 2021.

DSM-V states, "Structural neuroimaging, using MRI or CT, has an important role in the diagnostic process. There are no other established biomarkers of major or mild vascular NCD". The VaD diagnosis is determined by excluding neurodegenerative diseases like AD as the leading cause of dementia and by using imaging techniques to verify vascular pathologies. CT and MRI can discover most types of vascular pathologies causing VaD. However, MRI using dedicated vascular pathology sequences increases the sensitivity and specificity; FLAIR, Diffusion, T2*, or SWI, in addition to anatomical T1 images (Vernooij et al. 2019). VaD is one of the few dementia types(except for CADASIL) where preventive measures are effective, such as regulating blood pressure in case of hypertension, stroke prevention, LDL-reduction, and lifestyle interventions (Livingston et al. 2020). More commonly in older people, vascular pathology coexists with a neurodegenerative disease.

5.2.3 Mixed type dementia

For those over 75 years, the mixed type of dementia (MTD) is more common than the vascular dementia entity. Older people commonly have both vascular components and Alzheimer's disease since age is a risk factor for both. Mixed-type dementia is characterized by overlapping clinical features and more than one pathological diagnosis. Often a combination of a neurodegenerative disease associated with aging (AD, LBD, FTD, PD+) together with a vascular component causing impairment (such as stroke, subcortical vascular encephalopathy, or small vessel disease.). In DSM-V, MTD is named "*Major Neurocognitive Disorder Due to Multiple Etiologies.*" (Table 9.)

Table 9. The diagnostic criteria for the diagnosis of Mixed type dementia.

Diagnostic criteria	*Major Neurocognitive Disorder Due to Multiple Etiologies*
A	The criteria are met for major neurocognitive disorder.
B	There is evidence from the history, physical examination, or laboratory findings that the neurocognitive disorder is the pathophysiological consequence of more than one etiological process, excluding substances (e.g., neurocognitive disorder due to Alzheimer's disease with subsequent development of vascular neurocognitive disorder)
C	The cognitive deficits are not better explained by another mental disorder and do not occur exclusively during the course of a delirium

Adapted from DSM-V (American psychological association 2015)

The clinical difficulties with diagnosing MTD are illustrated by the noncoherent requirement for the diagnosis or the exclusion in the diagnostic classification system. Custiodioe et al. showed this in their review of MTD and its diagnostic challenges. They list three international organizations and their requirements; The Alzheimer's disease diagnostic and treatment centers organization have proposed that the diagnosis of MTD requires the existence of typical AD and closely dementia-related cardiovascular disease. The Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences have different proposed criteria: 1. Evidence of memory impairment and more than two other domains. 2. Focal neurological findings together with detection of WML in the brain. 3. Dementia onset during the three first months after a cerebral stroke. Concurrently a third organization, the Consortium to Establish a Registry for Alzheimer's Disease, has

not considered mixed-type dementia in its diagnostic classification system (Custodio et al. 2017).

5.2.4 Fronto-temporal dementia

Fronto-temporal dementia (FTD) comprises several syndromic variants, occurring between 40-65(21-81) years of age. They present with early progressive changes in language, personality, and behavior. Prevalence is around 2-10% of dementia cases or 15 to 22 per 100,000 person-year (Knopman and Roberts 2011). FTD is divided into several sub-categories dependent on symptoms such as behavioral FTD (bvFTD), primary progressive aphasia (PPA), semantic variant of PPA, nonfluent variant of PPA, the logopenic variant of PPA, three types that also include movement disorders, motor neuron disease, progressive supranuclear palsy(PSP) and corticobasal syndrome. The

Figure 5. Certainty of diagnostic criteria in Dementia with Lewis bodies and Frontotemporal dementia,

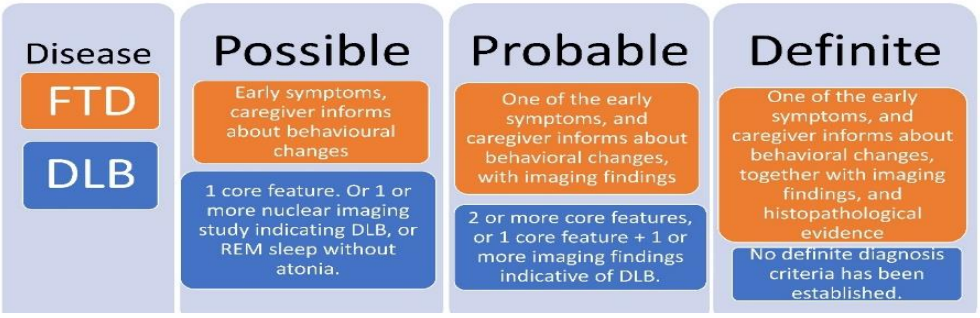

Figure 5: Adapted from DSM-V

most common type of FTD is the bvFTD, characterized by changes in behavior, especially the emotional presentation. Often unnoticed by the individual affected, but evident to those around, by being disinhibited and impulsive, presenting as childish, lacking empathy, and having a cold, self-centered demeanor. In contrast, the PPA's are characterized by progressive loss of oral and written language skills. The average median survival after onset of the disease is about 8.7 years for patients with FTD, with a mean duration from onset to diagnosis is 2.6 years (Ljubenkov and Miller

2016). A diagnostic framework has been established for both FTD and dementia with Lewy bodies, with three categories based on disease certainty (figure 5). Both diseases are difficult to diagnose in the early stages, with often intact memory function, resulting in a non-amnestic cognitive impairment, and this framework is an attempt to reduce the time from symptoms onset to diagnosis.

Pathological features

Common for all the non-movement disorders is pathological atrophy, observable with imaging techniques, in the anterior part of the temporal lobes and frontal cortex. Histopathologically it presents as degenerative neurons with intracellular pathological protein accumulations. This accumulation forms inclusion bodies (neuronal cytoplasmic inclusions and neuronal intranuclear inclusions) or dystrophic neurites in the cerebral cortex, hippocampus, and subcortex (Halliday et al. 2012). Four different types of proteins are accumulating in the inclusions: TAU, 43-TDP, Fused in Sarcoma (FUS), and Ubiquitin/protease system (UPS) (FTD-TAU/FTD-TDP,/FTD-UPS/FTD-FUS). The ratio of different inclusion types varies among the different kinds of FTDs (Bahia et al. 2013; Dickson et al. 2010; Jo et al. 2020). With SD being a mainly FTD-TDP inclusion disease, bvFTD is more diverse, with 50% of cases associated with FTD-TDP, 40% with FTD-TAU, and the remainder mainly with FTD-FUS (Bahia et al. 2013). The different inclusion bodies responsible for the same disease expression can explain why so many genes are connected with FTD. Several of these genes are autosomal dominant with low penetration, such as PPA, with only a 12% family history, compared to bvFTD, with 48% (Greaves and Rohrer 2019).

5.2.5 Lewy body dementia (LBD)

Researchers and clinicians use the terms Lewy body dementia (LBD) and dementia with Lewy bodies (DLB) interchangeably. Lewy body dementia includes dementia in Parkinson's in addition to DLB (Arnaoutoglou et al. 2019; McKeith et al. 2017).

Clinical features

LBD accounts for around 3.2-15% of all dementia cases (Arnaoutoglou et al. 2019; Hogan et al. 2016). The average age at diagnosis for LBD is 76 years (Yang et al. 2018); more men tend to have Parkinson's disease with dementia than women, the opposite for DLB (Mouton et al. 2018). Disease features are categorized into a central feature, dementia (deficits on tests of attention, executive function, and visuospatial ability may be especially prominent), and primary and secondary clinical features (Yamada et al. 2020). See table 9.

Table 10: Clinical features of Lewy body dementia.

Features:	Core/primary:	Secondary:
	Fluctuation in cognition and attention	Increased sensitivity to antipsychotic drugs.
	Recurrent visual hallucinations	Psychological disturbances: hallucinations in other modalities, systematized delusions, apathy, anxiety, and depression
	Rapid eye movement (REM) sleep behavior disorder.	Severe autonomic dysfunction.
		Postural instability

Adapted from the 2017 revised consensus criteria for the clinical diagnosis of dementia with Lewy bodies (DLB)

Pathological features

The pathology behind the LBD is an accumulation of intracellular inclusions consisting of α-synuclein, ubiquitin, neurofilaments, and α-crystallin. These components form the Lewy Bodies, which, when accumulating, cause degraded cell structures/functions, leading to functional loss and eventually neuronal death. The Lewy body composition is anatomical/disease dependent, with cortical cells affected in DLB showing a halo when stained with eosinophilic histological staining, while the brainstem cells affected in PD have no such halo. The difference in affected cell distribution can also explain the deficit difference in neuropsychological testing. DLB usually presents with amnestic features, deficits in attention, deficits in visuoconstruction, and executive function(Metzler-Baddeley 2007). In PD, the motor

and visuospatial and executive functions show deficits initially, while memory deficits often occur later (Parker et al. 2013).

5.2.6 Treatment for MCI

Currently, no known medical treatment exists for MCI; however, extensive pharmacological research is ongoing for disease prevention and symptomatic treatment. Cholinesterase inhibitors were one of the first investigated pharmacological treatments for MCI, but there were no significant benefits for the pharmacologically treated groups compared to the control groups (Petersen et al. 2005). Other studies of cholinesterase inhibitors were discontinued for methodological or safety reasons (Karakaya et al. 2013a). The reported side-effects of these drugs are substantial, with headache, diarrhea, and nausea being the most predominant. Furthermore, there is an absence of research documenting favorable long-term effects; some institutions still use these drugs in MCI patients as off-label (Petersen et al. 2018), mainly in patients with prodromal AD (Karakaya et al. 2013b).

NSAID, Statins, Ginko Biloba, and other pharmacological substances have been investigated, but no drug or compound has produced any significant benefit compared to a placebo (Karakaya et al. 2013a). Vortioxetine, an SSRI/SSMD, has in one study shown promising results with significantly improved cognitive performance in an adult Chinese population. However, it is a small pilot study with 111 MCI subjects and a very short follow-up of only six months; thus, the long-term efficacy is unknown. However, fewer adverse events and adverse drug reactions were registered than with acetylcholinesterase inhibitors, reportedly only 9.9% (n = 11) and 2.7% (n = 3) of the subjects in the Vortioxetine trial vs. 20% and 5 % with acetylcholinesterase inhibitors, respectively (Tan and Tan 2021)

5.3 Genes associated with dementia

Most genes are diploid; each individual receives one of two haploid gametes from each parent. The allele is one version of the genetic code for a specific protein; in most

cases, both variants of genes are expressed. However, the transcription of the different alleles varies, due to the different affinity of transcription factors to the different gene variants (Xia et al. 2020), or the promoter regions of the genes might be different even though the DNA encoding(allele) of the end product (protein) are identical(Xiao et al. 2017).

Apolipoprotein E (APOE) is one of the most researched genes correlated with dementia. The gene is biallelic, and the allelic frequency of the gene in the Norwegian population is previously reported; APOE ε2/2 (0.4 %), APOE ε2/3(8.5%), APOE ε3/3(55%), APOE ε2/4(2.4%), APOE ε3/4(29%) or APOE ε4/4 (4%) (Kumar et al. 2002). However, the reports from Saami populations are scarce, with reported APOE-ε4 frequency up to 30% (Corbo and Scacchi 1999). Details about APOE effects and influences are detailed in the next page.

Early-onset AD has been associated with the Val66Met substitution variant of brain-derived neurotrophic factor (*BDNF*) (Boots et al. 2017; Lim et al. 2022). Egan et al. reported the same mutation lead to decreased actvity-induced BDNF secretion and memory impairment (Pruunsild et al. 2007). The protein level of peripheral BDNF is also reportedly decreased in MCI and AD compared to HC (Qin et al. 2017; Xie et al. 2020). BDNF is a growth factor essential for stem cell development into neurons, synaptic plasticity, and neuronal survival and is vital in long-term memory formation (Bekinschtein et al. 2008; Song et al. 2015).

Presenilin 1 and presenilin 2 are strongly associated with hereditary AD (Goate et al. 1991; Levy-Lahad et al. 1995; Rogaev et al. 1995). Glucosylceramidase beta and synuclein alpha (PARK1 or SNCA) genes are associated with LBD development (Orme et al. 2018). These are outside the scope of this thesis and will not be discussed further.

5.3.1 Apolipoprotein Epsilon

The Apolipoprotein epsilon gene (APOE, also known as AD2; LPG; APO-E; ApoE4; LDLCQ5) is situated on chromosome 19q13,31. There are three common allele variants with variations of amino acids in positions 112 and 158 (Rall et al. 1982). The atomic weight of the protein is 34 kDa, transcribing into a glycoprotein consisting of 299 amino acids. Its primary functions are cholesterol metabolism and synaptogenesis; current research has mapped APOE involvement in over 100 functions (https://www.ncbi.nlm.nih.gov/gene/348). Intracerebrally, the astrocytes, microglia, and the choroid plexus are the main manufacturing sites for APOE. Extracerebrally, APOE is produced in pancreatic beta cells, regulating (Li et al. 2020) lipoproteins such as Cholesterol and triglycerides (Kr. 2000).

The APOE- ε2 is an isoform with two CYS amino acids at position 112 and 158 (Weisgraber et al. 1981); the ε3 allele have an Arg instead of ε2's CYS at the 158 positions. The ε4 allele has Arg at both localizations (Rall et al. 1982). The different isoforms show different affinities for lipoproteins in blood and Aβ in the brain.

The ε2 allele is not associated with an increased risk of AD; recent research suggests that APOE- ε2 might protect against AD by acting through both an Amyloid-β (Aβ) dependent and independent mechanisms (Li et al. 2020). Several studies report a higher incidence of super-agers among APOE- ε2 carriers than among APOE- ε4 carriers (Berlau et al., 2009; Deelen et al. 2014). The mechanism behind this protective effect is not well understood; it is postulated that a higher affinity binding towards binding Aβ when in lapidated/lipid-linked form compared to ε3 and ε4 variants (Li et al 2020), thus reducing the direct toxic effect of Aβ. Reiman et al. did 5000 neuropathological examinations and found that ε2/ ε2 is protective against AD, and homozygotic ε2 rarely develops AD. The risk of developing AD depends on the alleles with ε4 attributed with the highest risk, APOE ε2/2 < APOE ε2/3 < APOE ε3/3 < APOE ε2/4 < APOE ε3/4 << APOE ε4/4(Reiman et al. 2020).

Few studies investigate the APOE effect on Tau, primarily in mice, with diverging results. One author report that APOE- ε2 protects against tau pathogenesis through an

unknown Aβ-mediated reaction (Farfel et al. 2016), while *APOE-ε4* seems associated with neurofibrillary tau deposition. Gotz et al. report no difference between the APOE variants and TAU deposition (Götz et al. 2018), while Zhao et al. found increased TAU-associated neurofibrillary tangles with the *APOE- ε2* alleles, suggesting increased primary tauopathy risk with *APOE ε2* (Li et al. 2020; Zhao et al. 2018). *APOE ε2* is suggested to influence neuronal survival and synaptic functions during AD pathogenesis through APOE2-mediated neuroprotective signaling pathways (Huang et al. 2019). However, there is evidence of an increased risk of CAA and stroke with the ε2 compared to ε3 (Kokubo et al. 2000; Love et al. 2014).The *ε3* allele APOE protein is the most frequent and is not associated with an increased risk of AD or tauopathies.

While the APOE ε4 allele shows an increased risk of developing AD, it is also associated with an increased risk of vascular dementia (Sun et al. 2015), DLB, PD, and CAA (Yamazaki et al. 2019). In addition, the APOE ε4 genotype increases disease severity in DLB as measured by time to death (Keogh et al. 2016). Compared to AD, the DLB median time from onset of symptoms to death is 3.3 y. for men and 4.4y for women, while reported as 6 and 8 years in AD. (Price et al. 2017).

Albeit each allele's function is determined by its amino acid composition, the allele's expression and binding of the APOE are individually affected by other genes/mechanisms. Gene expression in eukaryotes is generally regulated by transcription factors (TF) that initiate or block, thereby regulating the transcription (Latchman 1997). The APOE gene contains a working TATA box, a binding site for the TATA-binding protein; it is a general TF. However, other TF factors are needed to initiate transcription. C/EBPβ is one such TF for the APOE genes; Xia et al. report that C/EBPβ selectively promotes more ApoE4 expression versus ApoE3 in human neurons, correlating with higher activation of C/EBPβ in human AD brains with *ApoE ε4/4* compared to *APOE ε3/3*, which can explain the increased effect of APOE ε4 in *ε4/ ε3* combinations compared to the 50-50 expression (Xia et al. 2020). However, there are other mechanisms; One such repressor mechanism is CGI methylation–modulated transcription, which blocks the transcription factor (TF) site for APOE, thus silencing the specific allele (Foraker et al. 2015). Foraker et al. found that AD patients

had completely un-methylated TF sites in the hippocampus while anatomical areas not associated with AD were methylated, while Lee et al. found lower methylation levels in the frontal lobe of AD patients compared to healthy controls (Lee et al. 2020). RNA alternative splicing is also a factor in AD; Mills et al. found that variants with exon five excluded from the APOE RNA lead to increased beta-amyloid deposition (Mills et al. 2013). Post-translational modified oligomeric amyloid-β (Aβ) also plays a role in developing AD by disrupting synaptic function. Multiple post-translational modifications (PTM) of Aβ have been identified, among which N-terminally truncated forms are the most abundant (Grochowska et al. 2017).

Further investigations are needed to map all the interactions of different genes and their regulatory mechanisms that lead to Alzheimer's dementia because the penetrance for dementia in ApoE *ε4* homozygotes is 50% in men, and 60% in women, indicating a significant effect from the other factors involved (Louwersheimer et al. 2017).

The Apolipoprotein E antagonistic pleiotropy hypothesis

Though APOE4 seems detrimental in old age, it might be beneficial in young people. Research on young females shows that *APOE-ε4* carriers have higher IQ than ε2 and ε3 carriers (Yu et al. 2000). Noé et al. found that young patients with traumatic brain injury (TBI) and *APOE-ε4* carriage had steeper working memory improvement over time than non-carriers (Noé et al. 2010). Studies have also shown a distinct difference in neural correlates of episodic memory and working memory (Filbey et al. 2010; Shu et al. 2019). Hernes et al. found significant longitudinal training effects in naMCI *APOE-ε4* carriers, showing that these patients still have neuroplasticity potential. Gharbi-Meliani et al. followed 5561 individuals for 20 years and studied the effect of E4 on trajectories. They reported better than average cognitive performance in the younger *ε4* heterozygotes, primarily attributable to executive function (Gharbi-Meliani et al. 2021). However, around 67 years of age, they had a lower cognitive performance than non-E4. Despite some positive reinforcing reports, the pleiotropy theory is disputed, and Henson et al. found no such evidence in a recently published cohort study of healthy adults (18-88 years)(Henson et al. 2020). They only found a linear interaction between age and *APOE-ε4* carriers on fluid intelligence.

5.4 Neuroplasticity

The brain's ability to adapt to internal or external stimuli is accomplished through regulating its activity. It adapts by up or down-regulating functions, connections, or the nervous system's structure. Changing the connections or synapses is referred to as synaptic plasticity. The concept of neuroplasticity arose with the discovery of synapses and their chemical nature by Cajal, Lugaro, and Foster in the late 1890s (Mateos-Aparicio and Rodríguez-Moreno 2019), while William James described behavioral plasticity in the same period (Blanco 2014). A similar classification is used in neuropsychology, describing cognitive plasticity as the ability to acquire cognitive skills. Confirmation of structural plasticity came about from experiments on rhesus monkeys in the early 1920s by Karl Lashley and rat experiments in the 1960s by Marian Diamond (Bennett et al. 1964; Diamond et al. 1964); by exposing rats to different levels of stimuli she found that rats that had the thickest cortex were those that were stimulated the most.

The impact of neuroplasticity is seen every day, learning new skills and improving cognitive or motor functions. Powerful emotional stresses or psychoactive substances may create strong connections through neuroplasticity detrimental to the individual. Thus, the nature of neuroplasticity can be good or bad; it is a response to stimuli and is the foundation behind the concept of cognitive training.

5.4.1 Gene effect on neuroplasticity

Genes affect the brain's adaptability on several levels. The basic level is the presence of the genes. Allele polymorphism is the second level, where the different alleles have alterations in their nucleotide composition, which might influence the gene's phenotype. The third level is gene expression, which can be divided into several sub-regulatory stages; transcription, RNA splicing, translation, and post-translational modification (PTM) (Grochowska et al. 2017; Whiteheart et al. 1989) Transcription factors tightly control transcription, responding to internal and external cell stimulation, causing modifications to transcription factors, enabling strict regulation of

DNA binding, nuclear import, or allowing binding to essential cofactors (McClung and Nestler 2008). Several TFs are also essential for programmed cell death, e.g., P53 and NFkB (Barkett and Gilmore 1999). Alternative splicing is involved in neuroplasticity by affecting the development of neuronal cell type-specific properties, growth, self-recognition, synapse specification, and neuronal network function (Furlanis and Scheiffele 2018). PTM's are involved in neuroplasticity; one researched example is the modification of voltage-gated sodium channels (VGSC) in chronic pain patients' peripheral sensory nervous system, where inflammatory molecules affect the dorsal root ganglia sensory neurons leading to abnormal activation of enzymes that induce PTM of the VGSCs. The PTM-modified VGSC can have a lower activation threshold for pain signals from the periphery (Laedermann et al. 2015). Less is known about the mechanisms of plasticity involved in cognitive processes.

Neuronal synaptic plasticity

The primary mechanism for neuronal cell adaptation to stimuli is synaptic plasticity. NMDA-receptor-dependent long-term dependent potentiation(LTP) and depression (LTD) of excitatory synaptic transmission in the neocortex and hippocampus are two mechanisms heavily involved in neuronal synaptic plasticity (Malenka and Bear 2004) and synaptic maintenance for memory stability (Bliss and Collingridge 1993). The modulatory genetic effect of neuroplasticity is often quite complex and tightly regulated mechanisms; BDNF and APOE are some of the most researched.

APOE gene affects the regulation of LTP and LTD; Loizzo et al. investigated this correlation by investigating the effect of the APOE-E4 gene on LTP and LTD performance compared to that of APOE- E3. By injecting E.coli toxin CNF1 intrathecally, which produces a modulation in the Rho and Rac1 activity, they decreased the beta-amyloid accumulation and interleukin-1beta expression in the neurons of the hippocampus of the ApoE-E4 Rats. The manipulated APOE4 cells had similar LTP and LTD performance to the ApoE- E3 cells (Loizzo et al. 2013). Qiao et al. found that *APOE- ε4* reduced the phosphorylation of CREB and CAMKIIA, impairing hippocampal LTP function. They suggest ApoE4-induced suppression of hippocampal long-term synaptic plasticity may contribute to the cognitive impairments

in genetic AD (Qiao et al. 2014). Lane-Donovan et al. studied APOE knockout mice and found that these mice had a severe synaptic loss and cognitive impairment independent of plasma levels of APOE. Others report involvement of APOE in the synaptic pruning process via the astrocytes, with APOE-E4 reportedly limiting the astrocytes' ability to prune synapses (Lane-Donovan and Herz 2017). Since synaptic plasticity is linked to the formation or maintenance of memory in short-term or working memory, APOE seems, directly and indirectly, involved in synaptic neuroplasticity in cognition.

BDNF, or abrineurin, is the brain's most common growth factor/ neurotrophin. Its function is reportedly pleiotropic on neuronal morphology (De Vincenti et al. 2019), and it is involved in synaptic plasticity, with both short- and long-term influences (Pearson-Fuhrhop et al. 2009). The regulatory mechanisms of BDNF are not entirely understood, but alternative splicing is one of the mechanisms involved. The BNDF has nine different promoters connected to the same number of different exons. All these have a common coding exon, enabling nine distinct exons with varying lengths on the mRNA. These variants have an affinity for different locations within a neuron, creating several response pathways within a cell stemming from one gene (Laedermann et al. 2015). Selectively responding to stimuli, it being postsynaptic (through interactions with NR2B subunits) or presynaptic, whether it be upregulating receptors (NMDA receptor) or stabilizing synapses (upregulating AMPA receptors), permitting pleiotropic mechanisms, essential for maintaining and forming new synapsis as a response to stimuli, e.g., memory formation(De Vincenti et al. 2019).

5.4.2 LIM homeobox transcription factor 1 alpha protein

LIM homeobox transcription factor 1 alpha protein (LMX1a) is also known as LMX1, DFNA7, and LMX1.1. The LMX1a gene is located on Chromosome 1 q22–q23, and the transcribed protein contains 382-amino acids with a mass of 42,747 Daltons. It has a critical role in dopaminergic progenitor cell differentiation during the embryonic stage of the midbrain (Friling et al. 2009) and forebrain development of GABAergic neurons (Nefzger et al. 2012). In mice, Doucet-Beaupre reported a significant effect on

adult midbrain dopaminergic neurons; inactivation of *Lmx1a* and *Lmx1b* recreated Parkinson's disease/DLB-like features, including progressive loss of dopaminergic neurons, due to α-synuclein aggregation and subsequent cell death (Doucet-Beaupré et al. 2016). Previous reports support the increased risk of developing Parkinson's disease, linked to the polymorphism of LMX1a (Bergman et al. 2009).

The GABAergic neurons in the forebrain have a critical role via inhibitory circuits in prefrontal cortex-dependent working memory, theorized to affect via the LTD mechanism(Murray et al. 2015). Thus, the LMX1a gene polymorphism may hypothetically influence working memory development and working memory network function by synaptic dopaminergic neuroplasticity. Hernes et al. reported that LMX1a AA allele naMCI carriers had a more significant working memory training effect than GA/GG carriers (Hernes et al. 2021). Similarly, Chang et al. discovered that LMX1a AA-carriers in HIV patients had a greater working memory training effect than GA/GG carriers.

LMX1a is also present in the pancreas, liver, kidneys, and testis and is central to insulin regulation (Makarev and Gorivodsky 2014). Downregulation of LMX1a has been linked to increased tumor aggressivity in various cancer cells (Feng et al. 2016; Tsai et al. 2012; Wang et al. 2014; Zhang et al. 2018).

5.5 Working memory

The working memory (WM) is a theoretical construct describing the individual's ability to remember information while actively using and responding to it. Individuals with impaired WM function struggle with keeping track of the tasks at hand, often reporting problems with everyday tasks such as retrieving items, stopping in the middle of a procedure, etc. (Baddeley 1992; Baddeley and Wilson 2002). The individual WM capacity was previously understood as a constant factor, whereas research has identified this core function as modifiable by external stimuli (Wilhelm et al. 2013)

Figure 6. The multi-component working memory model.

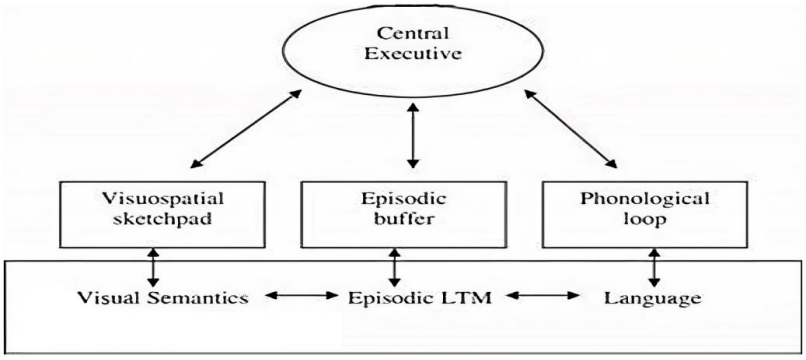

Figure 6: The multi-component working memory model. Baddeley et al 2000. Reproduced with permission from the publisher Elsevier.

The concept of WM was introduced in 1974 by Baddely et al. as a theoretical psychological construct. The working memory is considered a core cognitive function, with an ability to manipulate the data without "overwriting" memories, unlike short-term memory or other linear memory categories. Initially, a model with three quite different interconnected components, "visuospatial sketchpad," "central executive," and "the phonological loops," were proposed to constitute the working memory (Baddeley 1992; Baddeley and Hitch 1974). Later, Baddeley et al., expanded and revised the model, due to the close correlation with episodic memory, an episodic buffer was added (figure 6). This buffer handles information not covered by the other two subsystems("visuospatial sketchpad" and "the phonological loops") and recodes information into a unitary episodic representation/multidimensional code. Furthermore, the buffer links the episodic long-term memory with the working memory (Baddeley 2000). It is believed to be controlled by the central executive, which combines information from several input sources into retrievable coherent episodes, being an important stage, though separate from episodic long-term memory.

Reduced WM function is prevalent in both aMCI and naMCI subtypes (Salthouse & Meinz, 1995, Salthouse, 1991a). Both WM and Executive function share a common relationship with episodic memory, via the episodic buffer. Together with processing

speed, all three have a common trait: aging takes its toll, but the accelerated decline is the defining factor of MCI. (McCabe et al. 2010)

5.6 Cognitive interventions

Substantial resources have been allocated to developing interventional treatments for age-associated neurocognitive decline. One of the focus areas of cognitive impairment research has been on MCI, with its 5-10% annual conversion rate to dementia. Delaying or preventing this conversion or improving the cognitive and daily life function of the MCI patient would benefit the individual with impairment and society as a whole (Clement and Belleville 2010, 2012; Clement et al. 2013). However, the commercial focus has been to "prevent" dementia and "delay" the average age-associated decline and make a profit from people's fear of aging (Underwood 2016). Furthermore, the improved understanding and advancement in the cognitive domain theories have seen the emergence of three main branches; cognitive stimulations, cognitive rehabilitation, and cognitive training (Bahar-Fuchs et al. 2013; Chandler et al. 2016; Mowszowski et al. 2016; Smith et al. 2009).

5.6.1 Main branches of cognitive interventions

Cognitive rehabilitation

Focused on restoring and increasing cognitive functions or compensating for the function that has been impaired—commonly applied in stroke patients. The therapy uses skill training or strategies individualized to target the affected cognitive function, typically tasks that the individual needs for mastering activities of daily living (Cicerone et al. 2019; Zhao et al. 2021). The therapy is not necessarily domain-specific, and the assumption is that the improvement of a task is task-specific and does not necessarily transfer to other tasks.

Cognitive stimulation

The therapy is frequently employed in mild/moderate dementia/MCI settings and is social, relaxing, and group-oriented. Activities can be discussing the current news, singing together, and doing practical activities like baking or woodworking. The treatment is not domain-specific but rather activation of the brain in general. Trials have found the method effective in dementia cases and can easily be applied to patients with dementia in care homes (Aguirre et al. 2013; Cafferata et al. 2021; Woods et al. 2012). Gomez-Soria et al. found a favorable effect on cognition in a randomized trial with MCI patients; however, the cognitive stimulation failed to improve the performance of instrumental ADLs, depression, or anxiety levels (Gomez-Soria et al. 2020).

Cognitive training

Cognitive training aims to improve cognitive functioning through structured guided practice and intentional instruction individually or in a group (Bahar-Fuchs et al. 2019). The training commonly focuses on one or more cognitive domains to improve or maintain cognitive abilities. Many different training regimes aims to enhance functions such as attention, working memory, memory, or processing speed (Zhang, Huntley, et al. 2019).

One of the most cited cognitive training studies and often upheld as a gold-standard example for RCT design in cognitive training is the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) trial. The ACTIVE trial consisted of four training arms, randomizing healthy older participants into four different training regimes; cognitive reasoning, processing speed training, memory training, and a non-training group (figure 7). The subgroups received training for different periods, including a training boost after the two-year follow-up. All training groups showed training effects in their trained cognitive area; however, the processing speed trained group had the highest gain. In addition, all the trained groups found transfer effects on daily function (Willis et al. 2006). Furthermore, in 2006, Salthouse et al. reported that the processing speed trained group in the ACTIVE trial had a steeper decline in

cognitive function than the control group. However, further investigation into the results showed that even though the processing speed trained group appeared to be experiencing a more significant than age-related decline, they scored much better than the control group in the 5-year control and even in 10-years control (Tennstedt and Unverzagt 2013).

Figure 7. Long-term effect of the different training regimes after 5 years.

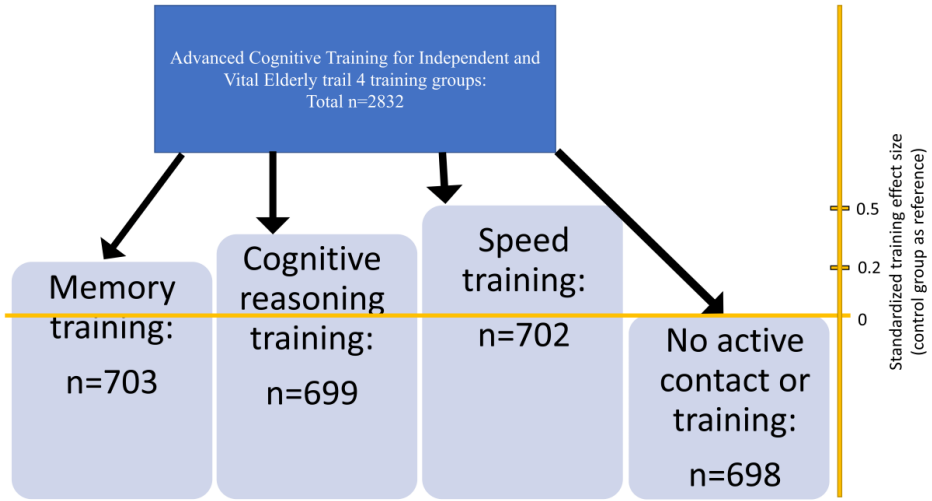

Figure 7. Long-term effect of the different training regimes after five years in the ACTIVE trial. Based on Willis et al. 2006.

Working memory training

Working memory training (WMT) is a subgroup of cognitive training targeting one or more facets within the working memory domain. Some of the premises for using working memory training is that it is a core function and is closely connected with attention, memory, and executive function.

5.6.2 Outcome measures of cognitive interventions

How to measure the effectiveness of the training varies from study to study; some studies use general cognitive measures like MOCA or MMSE, while others focus on the domain trained, with some including likely transfer effects measures/non-trained

domains. (Ward et al. 2022; Zhang, Huntley, et al. 2019). Some of the critiques of the early studies were directed at the methodological limitation due to the use of a single measure of effect or transfer measure or lack of defined outcome measures before study initiation (Au et al. 2015; Baniqued et al. 2013; Soveri et al. 2017). In N-back studies, some researchers only report the accuracy, differentiating between omission and commission errors, and do not report the reaction time. Since it has been pointed out that N-back training lacks clear associations with other working memory tasks, it might be more useful with a higher granularity level of reporting when using N-back in studies, including accuracy, reaction time, and types of errors committed by the participant (Meule 2017).

Transfer effects in cognitive training refer to the transfer of trained skills across domains or increasing performance in a non-trained subdomain. Commonly the transfer effects are divided into near and far transfer effects; this mainly relies on whether the trained domain has shared subdomains with the non-trained domain with transfer effect. Working memory has shared subdomains with executive function, and a meta-review found that WM training had a small transfer effect to the executive function (Weng et al. 2019). Furthermore, fluid intelligence received transfer effects from multicomponent working memory training programs (Linares et al. 2019). Most WM training programs have tasks targeting different subgroups of WM, such as auditory and visual WM, to increase the reliability and effect of the training, including possible transfer effects (Schwaighofer et al. 2015).

5.6.3 Training in MCI patients

Since people with cognitive impairment have a loss of function, two parallel but different views on the best approach have developed; Compensatory training is based on the individual's goal to adapt/compensate for the cognitive impairment (Smith 2016). Strategic interventions are among the typical methods employed, such as memorization techniques or electronic devices, to circumvent and compensate for cognitive deficits. While restitutional training was popular in the 70-80ies, little evidence of any generalized effect made it less popular than the compensatory method

(Willis et al. 2006; Wilson 1996). However, with the introduction of computer-based cognitive training, the restitutional approach had a resurgence. The old method with repetition, which generally showed little to no effect on cognition, was swapped with programs that have novelty, multidomain training, and are often adaptive (Zhang, Huntley, et al. 2019). The adaptive method with continuous adjustment of the difficulty level maximizes the hypothesized training effect (Constantinidis and Klingberg 2016).

MCI patients reportedly need a closer follow-up than healthy adults; Gigler et al. found that in their feasibility study, the MCI patients were somewhat less likely to adhere to the protocol (Gigler et al. 2013).

5.6.4 Computer-based working memory training

Computers' increased availability and familiarity enable computer-based working memory training (CWMT). As with regular working memory training, the training targets the working memory. The computerized standardization of the training can reduce unwanted variation and make the training accessible to everyone, independent of geographic location, and socioeconomic status, at a presumed low cost. The most recent programs tend to be platform-independent and can be used on iPad, pc, or even smartphones.

There are two categories of CWMT research; research-developed training programs and game-centered cognitive research. The first was developed as a tool to enhance training, reduce the cost of doing WM training, standardize the method, and enable easy monitoring, often developed as a game or game-like to make the program fun and interesting. The latter is research into habitual gaming effects on cognition, and together with many commercial brain training programs, their effects are questionable (Allaire et al. 2014; Cicerone et al. 2019). The number of computer-based cognitive training programs dramatically increased in the early 2000s, many claiming memory enhancement without any scientific results or theoretical approach. It became such a problem that the Federal trade commission (FTC) fined several brain training games/programs providers for false advertising (Underwood 2016). FTC demanded

that future providers needed a valid study design and reliably conducted studies as a bare minimum to utilize a commercial product in an effort to tame the brain training industry.

Most reportedly, the training program is a variant of the N-back or dual N-back; some programs have adaptive functions, increasing the difficulty for the user to ensure training at individual maximal difficulty level(Course-Choi et al. 2017; Lawlor-Savage and Goghari 2016; Li et al. 2021; Vartanian et al. 2021).

N-back training involves serial presentation of an image, shape, number or word spaced a short period apart. The n is a variable number of stimuli the participant is subjected to after the initial stimulus, and the participant has to decide if the current stimuli match the one displayed n stimuli ago. The variable n be increased or decreased respectively to change the cognitive load (Au et al. 2015). Dual-N back is an N-back modification proposed in 2003 by Susanne Jaeggi, with the simultaneous presentation of two independent sequences, such as one auditory and one visual (Jaeggi et al. 2003). The training effect of Dual N-back in digital working memory training programs is still controversial, with reports ranging from no effect to some effect. Although some studies report improvement in untrained cognitive function after WM training (transfer effects) (Dahlin et al. 2008; Klingberg et al. 2005; Klingberg et al. 2002), others have disputed this (Melby-Lervåg et al. 2016). The controversy within the academic community became visible in 2015-2016, when several large research collaborations published meta-analyses with opposite results (Au et al. 2015; Chandler et al. 2016; Melby-Lervåg et al. 2016; Mueller 2016; Schwaighofer et al. 2015). Even later, the meta-analysis reviews still report different results (Bahar-Fuchs et al. 2019; Butler et al. 2017; Lintern and Boot 2019; Nousia et al. 2020; Ophey et al. 2020; Soveri et al. 2017; Teixeira-Santos et al. 2019; Zhang, Huntley, et al. 2019). Some of the differences can be to different measures of outcome. Some choose global fluid intelligence, while others choose executive function or memory. The most recent metareview with findings are listed below in table 11.

Table 11: Meta-analysis and reviews on computer-based working memory training from 2015-2020					
Type of review	Author	Year	Patient type	# of studies	Conclusion
Metanalysis	Lintern and Boot	2019	HC	9	No significant transfer effect from the CCT to real life. Methodological limitations compromise the credibility of the studies reviewed.
Metanalysis	Nousia et al	2020	PD	7*	Multidomain CCT leads to improvement in all domains associated with affliction in PD.
Metanalysis	Bahar-Fuchs	2019	MCI/mild dementia	33*	Small to moderate effect on global cognition and verbal semantic fluency at the end of treatment.
Metanalysis	Butler et al	2017	HC + MCI	5 HC*, 6 MCI.	Healthy older adults improved cognitive performance in the domain trained but no transfer effect. MCI suggested no effect of training on performance. Evidence for the prevention of cognitive decline or dementia was insufficient.
Metanalysis	Melby-Lervåg	2016	Healthy cognitively	87	Effect on WM, no significant transfer effect from WMT
Metanalysis	Au et al	2015	Healthy cognitively	20	Effect on WM and transfer effect on fluid intelligence.
Metanalysis	Zhang et al.	2019	MCI	18	CCT improves cognitive function; however, long-term transfer remains unclear.
Metanalysis	Chandler et al.	2016	MCI	30	Positive WM effect from training, transfer effect: positive effect on daily living.
Metanalysis	Soveri et al	2017	HC	33	moderate effect of task-specific transfer to untrained n-back tasks and minimal transfer effects to other untrained WM measures, cognitive control
Metanalysis	Ophey	2020	HC	16	Methodological shortcomings in the included studies, no clear conclusions could be drawn.
Metanalysis	Teixeira-Santos	2019	HC	24	Effect of WMT to near transfer tasks. Far-transfer effects were not verified.

The Association for Psychological Science (APS) published recommended guidelines/framework for computerized cognitive training (CCT) trials in 2016 in an effort to increase the scientific value and standards of CCT trials (Simons et al. 2016). A central recommendation from this framework is the preference for an active control group. The framework states that the effect of a repetitive task such as an interaction with a computer over several weeks might be sufficient to inflict changes in the brain, regardless of the type of training intervention. Designing trials with an active control group reduces the risk of misinterpreting the cognitive effects of the training intervention from the cognitive effects of the shift in habit alone. Furthermore, only a few studies have been conducted on adaptive cognitive working memory training, and the number of studies with RCTs remains low for MCI patients, and the studies are small and underpowered.

5.6.5 Common examples of computer-based cognitive training programs

COGMED

Pearson's Cogmed Working Memory Training (COGMED); HTTPS://WWW.COGMED.COM) is one of the most publicized computer-based working memory training programs (Aksayli et al. 2019; Simons et al. 2016). The program was developed by professor Klingberg during the late 1990s and acquired by Pearson in 2010. As of 2020, the ownership returned to Klingberg and the group Neural Assembly AB. Initially, COGMED used separate user interfaces for children and adults, and the current thesis is based on the COGMED RoboMemo interface. Lately, the program has been redesigned to a general interface for all age groups. The Cogmed training program consists of 25 separate 45-minute sessions over five weeks, aided by weekly coaching, either in person or digitally (Simons et al. 2016). The program consists of verbal and visuospatial WM tasks that require participants to work at their maximum individual levels. The program changes adaptively as the participant improves (Simons et al. 2016). During our study, COGMED offered researchers a

non-adaptive training arm fixed at three repetitions per task to serve as an active training control group. The results published by researchers using COGMED have been meta-analyzed, reportedly a general near transfer effects for both adults and children, but no significant far-transfer effects, though methodological shortcomings in the studies limit the value of the conclusions on far-transfer and longitudinal effects (Aksayli et al. 2019; Chacko et al. 2013; Shinaver et al. 2014).

COGPACK

Cogpack is a multidomain online cognitive training program primarily used in schizophrenia research; it has domain-specific exercises such as verbal memory, verbal fluency, motor coordination, sustained attention, selective attention, working memory, and executive functions. It also includes non-domain-specific exercises. Combining cognitive remediation therapy with a standard treatment of metacognitive training in schizophrenic patients significantly improved the global neurocognitive functioning and strengthened verbal and working memory, selective and sustained attention (Caponnetto et al. 2018).

BRAINHQ

BrainHQ - Former Brain Fitness (www.brainhq.com) is an online subscription-based training platform; it includes attention, working memory, and executive function training. Its initial development was for the ACTIVE trial by Posit Science, but further development continued after that, becoming a commercial entity. Besides its effect in healthy adults seen in the ACTIVE trial, its effectiveness in various disease states, including Schizophrenia and MCI, has also been investigated (Shah et al. 2017). Significant delay in general cognition decline(MMSE) was reported in a trained MCI group compared to an active control MCI group (Gooding et al. 2016). Furthermore, those trained with the program scored significantly better at one measure of verbal learning and one measure of verbal memory after training than an active control group (Gooding et al. 2016). Edwards et al. have done secondary analysis of the ACTIVE trial data and found that using the speed training application reduced the risk for

dementia by 29% compared to the control group when comparing the groups after ten years (Edwards et al. 2017).

COGNIFIT

Cognifit – (www.cognifit.com), an online subscription-based training platform, has games for various cognitive domains, like working memory and short-term memory, including visual and phonological memory and naming. It has several publications on different patient groups, including old adults and MCI. Significant improvements in global cognitive performance, memory, and non-memory domains were reported in trials with old adult patients with diabetes and MCI patients (Bahar-Fuchs et al. 2020; Bahar-Fuchs et al. 2017).

NEURONATION

Neuronation is an online cognitive training program claiming the ability to prevent cognitive decline leading to impairment. It targets several cognitive functions in 30 different programs, including working memory. Its scientific validation is based on one completed study and several ongoing (Hill et al. 2017; Strobach and Huestegge 2017). Strobach found significant gains in cognitive performance not limited to the near transfer, but also slight far transfer effects, but no change in daily activities (Strobach and Huestegge 2017).

BRAINGYMMER

Braingymmer is an online cognitive training program with “applications” for several cognitive domains. According to trials.gov, there are several ongoing studies but currently no publications.

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5.6.6 Neuroimaging as a pseudo marker for working memory training effect

The increasing resolution and development of specialized sequences within the field of MRI imaging of the brain have opened the possibility of showing in a spatial fashion where the effect of training occurs and acquiring quantifiable data. There are some studies with working memory training correlating with MRI imaging. However, they utilize different training programs, reporting different areas with significant changes, complicated by using different MRI parameters that measure different brain characteristics, such as oxygenation levels in BOLD, volumetric or thickness in morphometric studies, or diffusion in DTI studies. Furthermore, many different methods are employed with different setups (Haeger et al. 2019). Some of the parameters affecting the results are listed in table 12.

Table 12. Some of the parameters affecting reported results with working memory training correlated with longitudinal MRI changes.

Parameter:	Influencing factors:
MRI	Type of MRI examination: BOLD, morphometric, diffusion-based, or other. The time between acquisitions, immediate after training cessation or long term. Statistical setup; a priori, whole brain vertex. Statistical analysis; algorithmic or AI-driven.
WM training:	Adaptive – non-adaptive – training Single WM subdomain, or multidomain. E.g., visual and auditory wm training. Amount of training, both duration per session and # of sessions
Type of participants	HC, MCI or dementia, or other special groups: Cognitive impairment, secondary centers, or stroke patients. Age; increased age increases the recruitment of secondary centers.

Comparing studies is inherently difficult, as opposed to regular working memory training; there are only a few review articles on the correlation between MRI

detectable longitudinal changes and WMT. The few published report a general effect on the frontoparietal and striatal networks (Brooks et al. 2020), but the studies are generally underpowered.

5.7 Magnetic resonance imaging:

Hydrogen, the most abundant substance in the universe and yet the simplest atom, enables imaging with unrivaled tissue contrast by applying a magnetic field and manipulating the nuclear spin with RF waves. Going through the detailed physics behind MRI imaging is beyond the scope of this thesis, but a simplified version is provided below.

5.7.1 Generating an MRI image

When placed in a strong magnetic field, the "mobile" protons in the body start to orient themselves parallel or anti-parallel to the magnetic field. Net Magnetization is created due to a lack of equilibrium between the parallel and anti-parallel protons, with a small surplus in the parallel state. The protons spin/orbit around their axis, and the speed of this precession is known as the precession frequency. The precession frequency is determined by the magnetic field strength in a proportional manner. The Larmor equation calculates this frequency if the field strength is known.

Equation 1: Larmor's precessional frequency equation:

$$\omega = \gamma B$$

ω = Larmor frequency in MHz, y=gyromagnetic ratio in MHz/tesla, B= Field strength in Tesla.

The gyromagnetic ratio for hydrogen is 42.58 MHz/T; for a 1.5T machine, the precession frequency of hydrogen protons is 63.87 MHz. This frequency enables the interaction with the protons causing the net magnetization by introducing electromagnetic waves at an identical frequency. However, for creating spatial differentiation, a gradient magnetic field is applied in addition to the main magnetic

field; the typical gradient field strength applied is in the 30-45mT/m range. Typically, three gradients are applied in each direction of the XYZ axis. Enabling a frequency variation of protons precession as a function of position along the direction of the gradient creates spatial encoding, called frequency encoding, creating the axes of the spatial data needed for an image stack or 3d image.

When measuring the signal, the signal intensity depends on the number of hydrogen protons in the tissue that emit energy. T1 times rely on the ability of the tissue/material of energy conduction from the hydrogen protons to the environment (longitudinal relaxation time). The T1 time of a tissue is defined as when the longitudinal magnetization reaches 63% of its maximal intensity, Figure 8. It is considered a constant time, the time for the protons to return to equilibrium, the state prior to sending the radio signal. The RF pulse also synchronizes the presession of the protons. The time it takes for the protons to "lose" this synchronized presession is called transverse relaxation, called T2 time figure 9. Also known as transverse decay, the affected protons lose their synchronized precession. The T2 time is considered at 37% of the maximum signal intensity. The precessing proton interaction gives different intensities for

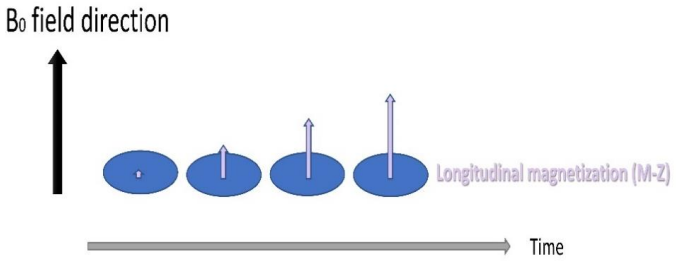

Figure 8: T1 - longitudinal relaxation

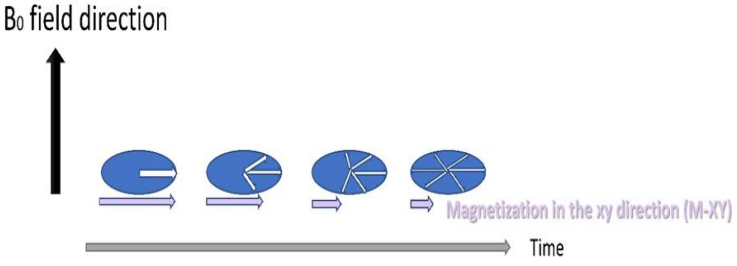

Figure 9: Phase cohesion loss is the factor behind T2 - transverse relaxation.

tissues, see table 13 for examples.

Table 13. Average T1 and T2 times for different tissue seen at MRI of the head at B0 @ 1.5T.

Tissue:	T1 (msec):	T2 (msec):
CSF	4000	2000
Gray matter	900	90
White matter	780	75
Muscle	900	50

The raw MRI image, which we call the *k*-space, contains spatial frequency information in two or three dimensions of an object. The k-space is a coordinate system with two or three axes, kx, ky, and or kz; they correspond to the image's X-Y-Z axes. However, they do not represent positions but spatial frequencies. Every K-space coordinate contains phase and frequency encoding data for every pixel in the final image. Conversely, each pixel in the image maps to every point in the k-space. However, there is some order to K-space. Contrast is located centrally, while details are in the periphery. Fourier transform(FT) is the mathematical procedure enabling image generation from a complicated MRI signal. It decomposes the signal and is transferred into K-space(Fourier space), transforming the signal into a sum of sine waves consisting of spatial frequency and amplitude information (Gallagher et al. 2008). The

inverse FT is then used to reconstruct the data into an image or volume. See figure 10.

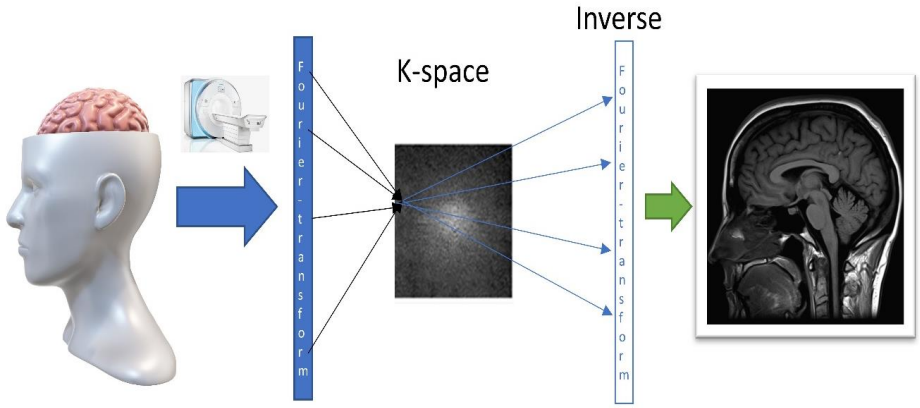

Figure 10: Simplification of the image creation in an MRI through K-space.

5.7.2 Parameters affecting the image quality

There are two main categories of factors affecting the scan: firstly, scanner properties, including the sequence properties, the scanner itself, and scanner coils used, and secondly, physiological factors. The sequence properties are essential for the scan quality. The relationship between scan time, sequence properties, and signal-to-noise ratio(SNR) is strong, and increasing scan time will yield increased SNR/contrast to noise ratio(CNR). Still, there is a drawback, the risk of motion artifact increases, and it will decrease the SNR and CNR. The radiographer/physicist can modify sequence parameters affecting the spatial and temporal resolution, the FOW, the CNR, scan time, and the influence of various types of artifacts. The physiological factors, however, are patient-dependent. It can be motion artifacts from respiration, swallowing, cardiac cycle, essential tremor, or metal objects in the body like a prosthesis. Ways to minimize these physiological artifacts are often to reduce the scan time, prepare the subject/patients for the MRI machine with premedication and good information, and reminders to lie still during the scan. Some sequences are more sensitive to motion artifact while others are less, but with less motion-sensitive, the trade-off is often reduced CNR like with propeller sampling sequences.

5.8 Brain atrophy and radiological visual biomarkers

As a person ages, the brain ages at an individualized rate. Age-related neurodegenerative diseases often cause disease-specific localized atrophy patterns, such as hippocampal atrophy in classic Alzheimer's disease or precuneal atrophy in early-onset AD. Using scientifically validated radiological scoring systems to categorize brain atrophy or other brain pathology by either MRI or CT comparisons between groups or individuals is possible. The definition of a scoring system is any of various methods in which a predetermined numerical scale is used to estimate the degree of a clinical situation (Martin and Press 2010). In the radiological dementia setting, the degree of localized atrophy or visual pathology is commonly used as a basis for scoring. Clinical scoring systems need to be efficient in routine imaging assessment of dementia and may improve the accuracy of diagnosis (Wahlund et al., 2017). Many early scoring systems were developed for research to increase the reliability and reproducibility of findings and enable visual quantification of the atrophy. One of the earliest developed and most commonly reported is Schelten's medial temporal lobe atrophy score. However, more than 15 visual scores are published for Dementia/stroke alone(Enkirch et al. 2018; Ferreira, Cavallin, Granberg, Lindberg, Aguilar, Mecocci, Vellas, Tsolaki, Kloszewska, et al. 2016; Harper et al. 2015; Harper et al. 2016; Persson et al. 2017; Rhodius-Meester et al. 2017; Scheltens et al. 1997; Wahlund et al. 2017; Wardlaw et al. 2015). Furthermore, these scoring systems are not static; several are tweaked with modified age cut-offs to increase the usefulness in the diagnostic workup of dementia and adapt them to new use cases such as MCI patients(Ten Kate et al. 2017).

5.8.1 Scheltens medial temporal lobe atrophy score

Scheltens developed this method in the early ’90s, first published in 1992, for evaluating hippocampal atrophy in AD patients(Scheltens et al. 1992). The method entails CT or MRI images in an oblique coronal plane, where both the medial temporal lobe and the anterior part of the pons are visible, see figure 11.

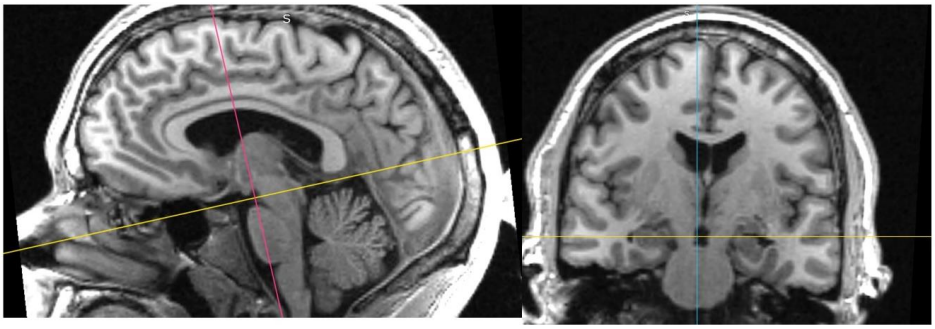

Figure 11: Correct positioning for scoring medial temporal lobe atrophy according to the original paper.

This part of the hippocampus/ medial part of the temporal lobe was the most significantly atrophied region in AD patients. The method was validated on a small sample, only 21 AD vs. 21 healthy cognitive adults, with a sensitivity of 81% and a specificity of 67%. The initial study highlighted the problem they experienced with age-related hippocampal atrophy; it decreased the sensitivity. Van der Pol et al. later described the spread of hippocampal volume in both AD and normal cognitive controls at the different age groups; this gave credence to the need for an age-appropriate cut-off value. Initially, the age cut-off was placed for the > 75-year group; an average score of 3 or above was considered abnormal; this increased the sensitivity to 85% for diagnosing AD in a mixed study population (van de Pol et al. 2006). Though the original method is sensitive to hippocampal atrophy related to late-onset AD, alterations associated with early AD are often visible as subtle hippocampal changes. Several papers have refined the age cut-off to remedy this weakness in the method, most notably from a research group at Karolinska’s university hospital in Sweden. The first paper by Pereira et al. suggested a new cut-off, with the mean of the two halves and a cut-off at 1.5 for those under 75 years of age and 2.0 for those above 75 years of

age; resulting in higher sensitivity for identifying patients with AD (84.5%) and MCI subjects who converted to dementia (75.8%) (Pereira et al. 2014). However, clinical factors, genetic variations(APOE), and demographics can affect the correct classification. The research group investigated these factors, and it resulted in a revised recommended age cut-offs for what is normal age-related atrophy and what is to be considered pathological for the age group in patients suspected of having AD or MCI, in addition to adjusting for APOE status, the adjusted cut-off values are listed in table 23(Ferreira, Cavallin, Larsson, Muehlboeck, Mecocci, Vellas, Tsolaki, Kloszewska, et al. 2015).

Table 13: Age cut-off for pathological hippocampal atrophy in different age groups and APOE status, according to Ferriera et al. 2015.

Patient group:	Age group	MTA - Score cut-off.
Heterogenous	45–64 years	≥1.5
	65–74 years	≥1.5
	75–84 years	≥2
	85–94 years	≥2.5
Early-onset ApoE e4 non-carriers	45–64 years	≥2
	65–74 years	≥2
	75–84 years	≥3
	85–94 years	≥3

The radiological scale is the most utilized dementia-specific radiology scoring system and has been used in numerous research papers (Hakansson et al. 2021; Molinder et al. 2021; Park et al. 2021; Roh et al. 2020; Sheng et al. 2020; Thomas et al. 2021; Wang et al. 2021). It is also one of the recommended dementia scoring systems used in everyday clinical practice when evaluating senior citizens' brain CT or MRI scans (Ten Kate et al. 2017; Wahlund et al. 2017), and is used in the A/T/N evaluation of atrophy on MRI scans (Ebenau et al. 2020).

5.8.2 Koedam's Posterior cerebral atrophy score

While Schelten's MTA is a reliable score for the medial temporal lobe atrophy, some AD patients do not have the same degree of atrophy of the hippocampus as the level of cognitive impairment should suggest. Especially the early onset-AD patients show minor initial hippocampal atrophy and develop atypical atrophy in the parietal lobe, particularly the precuneal region and posterior cingulate (Lehmann et al. 2012). These regions are heavily involved in the working memory. Koedam et al. developed a visual scale for evaluating this parietal lobe atrophy; they found that the widening of the posterior cingulate sulci and parieto-occipital sulci, together with parietal atrophy, was possible to score. By evaluating the parietal atrophy assessed in the sagittal, coronal, and transversal planes, using a 0-3 grade scale, the highest atrophy grade of any side at any plane determining the score, the method provided valuable independent information useful in discrimination AD from other dementias (Koedam et al. 2011). Mean PA scores were higher in AD compared to controls (1.6±0.9 and 0.6±0.7, $p<0.01$) and other dementias (0.8±0.8, $p<0.01$) (Koedam et al. 2011).

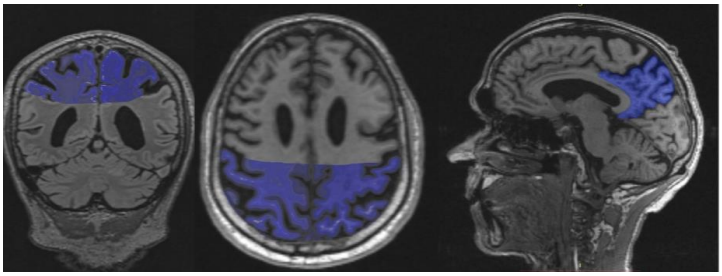

Figure 12: Regions evaluated for atrophy in the three different planes in the PA-scale.

The rating system was validated for use in clinical practice in 2012 by an article from Lehman et al. They concluded that the presence of posterior atrophy might be a helpful additional marker for AD, especially in younger patients. The method reportedly improves the diagnostic accuracy for distinguishing early-onset AD from healthy subjects in younger subjects and AD from FTLD (Lehmann et al. 2012). The original pathological cut-off was ≥2 for all ages. However, this rating score was also adjusted to optimize specificity and sensitivity in later publications (Ferreira, Cavallin, Larsson, Muehlboeck, Mecocci, Vellas, Tsolaki, Kloszewska, et al. 2015). They found that

considering the score ≥1 as pathological for all age groups was optimal for classifying AD patients and MCI-converters in a heterogeneous group.

5.8.3 Global cortical atrophy score

Pasquier et al. published the Global cortical atrophy score in 1996 for assessing cerebral atrophy in patients with post-stroke dementia (Pasquier et al. 1996). It was performed on 50 stroke patients, with four radiologists scoring the images. The score consists of 13 subscores per hemisphere; each subscore, a region to be evaluated, and the sum gave the final cortical atrophy score (0-39). The initial study had a moderate interobserver agreement (mean overall kappa: 0.48), while the intraobserver agreement was good for all raters (mean overall kappa: 0.68) (Pasquier et al. 1996). A later publication from the same research group on non-stroke participants concluded that the rating scale in an aged population had a poor reproducibility among raters. However, it provided a regional atrophy assessment (Scheltens et al. 1997). The total score has not seen wide clinical use, but it has been used in research, though not to the extent of Scheltens MTA. However, GCA is recommended in standard dementia workups; it ensures complete evaluation of the brain concerning atrophy (Wahlund et al. 2017). In addition, the frontal subscore, a newer construct from GCA, where only the mean score of the frontal subscores is reported, is commonly referred to as GCA-F. With a range from 0-3, it has seen greater implementation than GCA, both in clinical usage and research; Ferriera et al. have validated the score on 1036 participants, consisting of 329 healthy controls, 421 mild cognitive impairment patients, and 286 Alzheimer's disease (AD) patients (Ferreira, Cavallin, Granberg, Lindberg, Aguilar, Mecocci, Vellas, Tsolaki, Kloszewska, et al. 2016). Executive function has been linked closely to the frontal brain regions (Stuss 2011); the score can be a tool in diagnosing AD with more executive presentation or FTD cases. It is also used in memory clinic cohort studies, establishing it as a valuable marker in everyday memory clinical use (Persson et al. 2017; Ramusino et al. 2021).

5.8.4 Fazekas – a white matter hyperintensity scale

The Fazekas score was introduced in 1987 by Fazekas et al. It is not an atrophy scale, but a scale that rates the white matter hyperintensities(WMH) identified on T2 weighted images or preferably on fluid-attenuated inversion recovery sequence images. The score has been validated through many articles (Inzitari et al. 2009) and has been cited at least 1244 times according to the Pubmed database. Originally a composite scale consisting of two parts, deep/subcortical white substance hyperintensities as one part and the periventricular white matter hyperintensities as the second part. Subsequent publications mainly report the deep white matter changes.

WMH is an umbrella term for many different conditions, including ischemia, micro-hemorrhages, gliosis, damage to small blood vessel walls, breaches of the blood-brain barrier, or loss of/damage to the myelin sheath(MS). The scale ranges from 0 to 3 (picture 8), and scores 2 and 3 are considered pathological in the elderly.

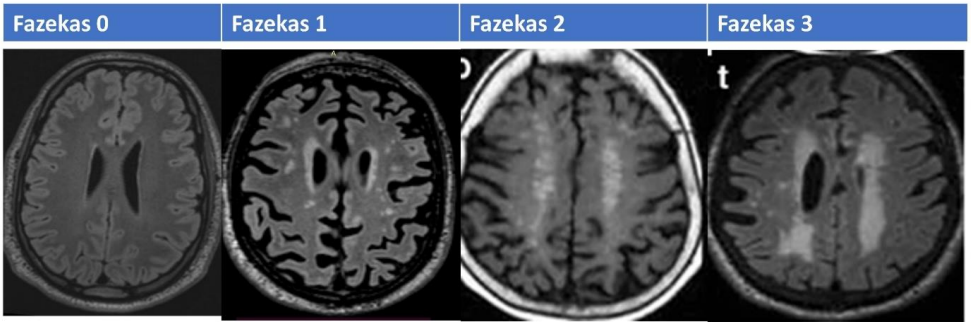

Figure 13: White matter intensities scores according to Fazekas et al. 1992. Images for scores 2 and 3 were used under the creative commons license from Wahlund et al. 2017.

The original study investigated a previously reported correlation of AD patients having increased white matter changes compared to normal cognitive controls at the same age. Fazekas et al. did not find this the case, with no significant difference between AD and HC (Fazekas et al. 1987). However, it seems to be suitable for selecting SVD patients. The LADIS study found a higher risk of disability in the Fazekas 2 and 3 score, at 14 and 25%, respectively, and independently predicted global functional

decline seen after three years; the same patients also had a significantly higher incidence of hypertension(Inzitari et al. 2009).

Since the method quantifies white matter lesions, it has been adapted to more diseases and uses cases, from vascular dementia to MS to neuroborreliosis (Andreassen et al. 2021; Fazekas et al. 1999; Wahlund et al. 2017). However, the scale has several challenges, especially not regionalizing the white matter changes nor differentiating between the different types of white matter hyperintensities. In addition, some publications use T2 instead of FLAIR images; evaluating WMH on T2 alone is a source of misinterpretation of perivascular rooms or subcortical lacunes as WMH. On FLAIR images, perivascular rooms will be dark, while true WMH will be hyperintense. Wardlaw et al. extensively reviewed the pitfall associated with both T2 and FLAIR images regarding WMH to decrease errors in reporting non-WMH as WMH. (Wardlaw et al. 2015).

5.8.5 Visual rating systems and their reliability and effectiveness in MCI patients

While the scoring systems were developed as tools for aiding in diagnosing dementia, they may also play a role in MCI diagnostics. The initial studies with MCI patients showed mixed results, with low sensitivity compared to healthy controls. MCI patients are a mixed group of patients, consisting of both naMCI and amnestic MCI patients, with numerous etiologies behind a spectrum of cognitive decline, which might explain some of the poor performance of the visual rating systems. In addition, an MCI population might vary depending on the clinical setting, memory clinics vs. population-based studies. An out-patient population might see a higher incidence than the general population of neurodegenerative brain changes (Petersen et al. 2014b), indicating that it is more useful in a memory clinic setting.

It is common to use a visual scoring system in most memory clinics since it gives crucial information on the level and position of neuropathology, enabling the use of the ATN framework. The ATN framework enables diagnosing MCI patients as prodromal AD patients below is a table of the different scoring systems with the different age adjustments published(table 14) .

Table 14. Sumarized scales and published age-cutoffs for the recommended visual rating/scoring scales.

Schelten's Medial lobe atrophy scale	Koedams Posterior atrohpy scale	Global Cortical atrophy – frontal subscore	Fazekas White matter hyperintensities scale.
Scale: 0: No atrophy. 1: Widened choroid fissure. 2: Increased ch. Fissure and temporal horn, opening of surrounding sulci. 3. Pronounced volume/height loss of hippocampus. 4. Pronounced atrophy.	Scale: 0: No atrophy. 1: mild atrophy, opening of sulci. 2: Moderate atrophy, volume loss of gyri. 3. Severe atrophy, knife blade gyri.	Scale: 0: No atrophy 1: Mild atrophy, opening of sulci. 2: Moderate atrophy, volume loss of gyri. 3. Severe atrophy, knife blade gyri.	Scale: 0: none or single (max 3) punctuate lesions. 1: > 3 punctuate lesions. 2: Beginning of confluent lesions. 3: Large confluent lesions.
Age cut offs; Schelten et al 1992: Sens: 0.81, Spec: 0.67 > 1 Below 75 years > 1.5 Above 75 years Periera et al 2014: Sens: 0.82, spec: 0.75 > 1.5 below 75 years > 2.0 Above 75 years Ferrieira et al 2015: Sens: 0.60, spec: 0.88 Rhodius-Meester et al 2017: Sens: 0.72, spec 0.88 ≥1.0 for persons under 65, ≥1.5 for persons between 66 and 74 years ≥2 for those ≥ 75 years	Age cutoffs: Koedam et al 2010: >2 independent of age. Ferrieira:et al 2015: > 1 independent of age.	No age cut-offs	No age cut-offs:

5.9 Quantitative brain morphometry

The brain is continuously changing, from the early development during intrauterine life through childhood to the neurodegenerative phase associated with aging. Correlating diseases with developmental patterns or neurodegenerative changes in the brain requires detailed measurements of the brain and its substructures. Often initial changes can be small and require precise measurements; while the visual rating systems might be helpful in some use cases, they lack granularity and specificity and have a high degree of inter-rater variability needed for morphometric investigations (Mäntylä et al. 1997).

To measure any characteristics of different tissues, they need to be classified/identified from each other; image segmentation is assigning classifiers to the voxels/pixels in a volume/image to separate different tissues. The main classifiers for brain imaging segmentation with MRI are white matter, gray matter, and cerebrospinal fluid. Some algorithms have added additional classifiers like white matter hyperintensities or tumor mass, infarcted tissue, etc. These are often secondary, involving information from the first classification, like white matter or gray matter.

5.9.1 Manual Delineation/segmentation

The initial method of obtaining "objective" volumetric data from brain MRI scans was manually tracing the region of interest (ROI). Volume was calculated from 2D scans with manually traced ROIs and combining the area from each slice times the slice thickness for volume. C R Jack et al. from the Mayo Clinic at Rochester, Minnesota, published one of the first manual segmentation articles, measuring the temporal lobe and hippocampus and finding the normative volumes of these structures in young adults (C R Jack et al. 1989). Manual segmentation is still in use, but more commonly in other organs than the brain, though it is still considered the gold standard (Shen et al. 2009). The method's benefits are the flexibility of using a human mind to determine the border, while complex algorithms are always limited to the parameters of the algorithm, much stricter, and often unable to handle issues outside a specific norm for which the algorithm was developed. Commonly, noise negatively affects the automated method more than an experienced rater (Hsu et al. 2002). The negative side of manual delineation, even by an experienced rater, is that it is very time-consuming and labor-intensive, and there are still several precision-related issues with inter, intra-rater, and even inter-measurement variability since it involves a human mind determining the delineation of structures (Wu et al. 2016). Subsegmentation of the hippocampus takes 2-3 hours per brain (Schmidt et al. 2018). The brain's gray-white matter interface is more challenging to delineate than many other structures due to a blurred cortical boundary; this is also seen in histology, where Von Economo et al. reported even in 1925 that the inter-measurement variability could be as high as 0.5 mm on cortical thickness (Economo 1925). In hippocampus morphometry, defining

the border of different structures is difficult if the contrast difference between structures is low; similar to the gray-white interface, the hippocampus blends over into other structures, and a survey done by Boccardi et al. illustrates the difficulties, with 53 segmentation protocols for the hippocampus, with providing up to 2.5-fold volume differences (Boccardi et al. 2011).

5.9.2 Computer-based image segmentation

The development of automatic segmentation methods leads to an increase in brain morphometric studies, as the method is faster, cheaper, and more accurate than manual delineation, leading to the method being the primary choice for brain morphometry. Furthermore, the search for more reliable and comparable data and the need to overcome individual variability in brain size, shape, and composition led to the development of techniques to correct for differences in brain size and gyrification between people. These automated segmentation techniques have different methodologies for the segmentation, some use Voxel-based morphometry, and others use other methods that will be detailed in the later segments.

5.9.3 A common space

When using computer-based techniques, the “3d digital brain” must be in the same coordinate systems as a reference atlas enabling the labeling of structures. One of the critical and challenging steps is registering the brain towards a common space/coordination system; this involves several essential steps.

Image conversion

The MRI machine natively uses the Digital Imaging and Communications in Medicine (DICOM), a standard for digital medical imaging. Each DICOM file is a 2D image, one file per image for conventional Xray. MRI or CT images are preserved/stored in a stack, where the image number in the stack is used to describe the Z (axial plane) axis, thus enabling the volumetric data. The definition of the coordinate system in the MRI scanner is the center of the gradient coil/magnet. The X increases from right to left, the

Y-axis increases from anterior to posterior, and the Z-axis increases from inferior to superior (bottom to the top of the head). Each axis goes from 1 to 128-1024 depending on the sequence scanner's matrix size, the sequence scanner, or the reformatting algorithm of the scanner. Together with the field of view, this sets the resolution (voxel size). FOV/Matrix size: 384/384 equals voxel/pixels size of 1 mm.

There are some challenges when converting this data from DICOM to a Neuroimaging standard; there are some challenges. Information such as height, weight, sequence data, or other personal data is stored in the header as DICOM tags; these tags are two-number code/id, defining the meaning of the following data, such as the subject's weight (0010,1030) followed by a value which is the actual weight value. The different MRI manufacturers extend extra data into the DICOM headers, in a non-standardized way, by using "private" tags. The main issue is that the private tag codes may be used for different purposes depending on the vendor. This data can be lost unless the converting program is programmed to handle the non-standard data. In addition, every MRI vendor has its own file format for the images, e.g., Siemens uses a 2d mosaic to store 3d images from DTI and fMRI (Li et al. 2016). The NiFTI format is an open image format based on the ANALYSE 7.5 data format developed to ease the interoperability of images between imaging software (Cox et al. 2004). In addition, the format allows more spatial data to be saved, reducing the risk of left to right errors. There are several different programs for converting DICOM to NiFTI, DCM2NIIX (https://github.com/rordenlab/dcm2niix) is one such converting program, still in active development and continuously being updated to handle new private DICOM tags.

Registration

After the conversion, the next step is registration (also known as spatial normalization) of the images into the image space used by the anatomical atlas intended to analyze the images. This step will also correct any misalignments towards the center, e.g. if the patient was not aligned with the head-neck coil's midline. To make inferences/to find patterns at a group level in the data, we need the brains to be lined up to measure structures across the subjects in a common space, enabling vertex/ voxel-wise examinations.

The Talairach atlas is based on gross pathology cuts from a single woman, with hand-drawn tracings from photographs of the slices, created in a stereotactic rectangular coordinate system, with the anterior commissure-posterior commissure(AC-PC) as a reference. Later anatomical atlases based on group averages from MRI scans of several different persons have become the norm. The most widely used is the Montreal Neurologic Institute (MNI) atlas. It is based on several brain scans from healthy adults. The actual number in the name refers to the number of brains used to create the template, e.g., mni152 refers to 152 brains, while MNI305 refers to 305 brains. These atlases are based on the group average and better represent an average brain than the original Talairach atlas. These atlases are based on normal adults; however, special atlases are based on different neurodegenerative or developmental stage cases. E.g., an atlas based on children or older adults. Both Talairach and MNI atlases are stereotactic atlases. The AC-PC defines the origin of the coordinates, and all brain locations can be defined as [x, y, z] coordinates. The registration towards an atlas is most commonly done by nonlinear registration algorithms, though linear algorithms and other registration methods, like large deformation diffeomorphic metric mapping (LDDMM). Both LDDMM and nonlinear registration methods will allow local areas to stretch and compress in respect of each other when registering an image towards a group/atlas template, producing a deformation field map/target parameters.

5.9.4 Smoothing:

Smoothing or blurring of images is essential to minimize false positives while still retaining maximum statistical power. In MRI imaging, this can also be seen as increasing SNR; however, much as the smoothing increases statistical power, it is at the cost of spatial resolution. It can also counteract some of the anatomical differences between the subjects that the registration process did not adapt perfectly and decreases inter-subject variability (Lerch and Evans 2005; Stelzer et al. 2014; Zeighami and Evans 2021).

There are different methods to smooth image data; the most common is a form of the gaussian kernel. The kernel in this context means the shape of the function for getting

the average of the neighboring voxels/vertices. Square wave and convolution are other kernels/methods utilized in neuroimaging. The Gaussian kernel used in neuroimaging is often called the full-width half-maximum (FWHM) kernel. The benefits of surface-based analysis for cortical thickness are that it enables larger smoothing kernels than volumetric-based analyses since there is no risk of smoothing across gyri. Publications of cortical thickness vary with smoothing values between 10-30 mm FWHM. However, for local gyrification index (lGI) analysis, there is a practical limit of around 7 mm FWHM since cortical *l*GI maps are already relatively smooth (Schaer et al. 2012).

5.9.5 Voxel-based morphometry

Wright et al were the first to publish an article using a voxel-based method (VBM) for the statistical analysis of gray and white matter density, derived from some similar applications created for fMRI. The initial study involved automatic scalp-editing of images followed by segmentation, smoothing, and spatial normalization to a symmetrical template brain in stereotactic Talairach space. They used a statistical parametric mapping technique to connect the image findings and symptoms in 15 schizophrenic patients (Wright et al. 1995).VBMs create a voxel-by-voxel correspondence across subjects. The VBM creates a deformation map during the registration step and a modulated jacobian VBM map, showing the amount of stretching/compressing done during registration(Ashburner and Friston 2000). VBM analysis gives two parameters, volume, and concentration. Volume is the number of voxels from gray matter or white matter in an ROI, while concentration is a more complex measurement where the jacobian map and smoothing affect the calculation of an ROI's volume divided by the neighboring structure's volume. Often it is easier to use volume and adjust for intracranial volume(ICV). The most commonly used VBM software are the FMRIB software library (FSL)(https://fsl.fmrib.ox.ac.uk/fsl/fslwiki) and Statistical parametric mapping (SPM)(https://www.fil.ion.ucl.ac.uk/spm/).

5.9.6 Surface-based analysis

Geometric models of the cortical surface are the basis for Surface-based analysis (SBA) and have a different pipeline order than VBM. The most widely used SBA program is Freesurfer (FS), which will be the basis for this SBA explanation. FS is based on surface models research to solve the EEG/MEG inverse problem, done by Anders Dahle and Marty Sereno at Martinos Center, Massachusetts Gen. Hosp/Harvard Med. School. At the time, surface-based models were afflicted by improperly rendered sulci due to the limited resolution in MRI (~ 1 mm), which reduces the ability to resolve the pial surface since sulci gaps can be less than 1 mm. However, Dahle and Sereno found that using the gray/white boundary instead of the pial surface bypassed the topological defects problem afflicting other surface-based models. Since the width of the gray matter was within the resolution gray/white surface could be resolved directly (Fischl 2012).

FS starts with surface extraction instead of the registration step performed in VBM. The surface extraction gives both pial and white matter surfaces. The surface model of the cortex consists of a mesh of triangles, the junction where triangles meet is called a vertex. Each vertice has its own set of XYZ coordinates assigned during the extraction process. After the surface extraction, the surface is inflated in an unfolding process, in which no folds are hidden, like opening an umbrella. The image data are further converted into a sphere registered towards the group template, creating a deformation field. This field is further applied to the data, and after smoothing, group analysis is performed, creating statistical maps.

Freesurfer provides many different morphometric parameters; cortical thickness, volume, area, local gyrification index of the cortices, and volume of the subcortical grey structures, compared to VBM. Cortical thickness has been reported to be the most reliable morphometric unit from Freesurfer; however, local gyrification was not included in that study (Winkler et al. 2018).

5.9.7 Whole-brain structural segmentation

Whole-brain structural segmentation is an alternative approach to vertex/voxel-wise analysis. The method utilizes a priori anatomical knowledge of the brain structures, defined in an atlas; the different voxels of a structure should be joined as one structure, dependent on their location. It uses voxels as the VBA method but has a much lower granularity level; in the segmentation-based approach, the information from more than 10^6 voxels in the VBA method is significantly reduced to the 200-300 structures in the structural segmentation approach(Mori et al. 2013). There are limitations associated with the method; the accuracy depends on the accuracy of the boundaries defined in the atlas used and the registration method applied to the data.

5.9.8 Diffusion tensor imaging (DTI)

The development of DTI allowed researchers and physicians to connect the “dots” or centers in the brain and assess these connections. Basser et al. developed in 1994 an MRI method to estimate effective diffusion tensors within voxels and derive useful quantitative DTI data for the voxels (Basser et al. 1994).

The method uses the concept of Brownian motion, where intra- and extracellular water molecules are in continuous thermal motion and measure this motion. The diffusion is isotropic or spheric ellipsoid in fluid volumes with no walls. While if there are cell walls or obstructions for the water molecules, the diffusion is in unrestricted directions; this will give a non-spheric ellipsoid diffusion(anisotropic). The diffusion imaging technique introduces two gradient pulses, one dephasing, and one rephasing, making the resultant image sensitive to motional processes such as flow or diffusion. The amount of diffusional signal loss by the gradient application depends on several factors; the time between the gradients, gradient strength, or length of gradient application; these factors make up the b-value. The higher the b-value, the more diffusion influence the image, but at a cost, mainly SNR. Furthermore, the extent of the signal decay depends on the diffusion constants of tissue water (Mori and Barker 1999).

In white matter, diffusion is mainly anisotropic, while in GM and especially in CSF, it is more isotropic. DTI values are more indicative of intercellular rather than intracellular diffusion due to the micron range of cellular structures, while diffusion measurements are made in the mm. range (Sen and Basser 2005).

By combining and varying the individual XYZ gradient's strengths, different diffusion directions are created; by adding them together, the strength and directional accuracy of the diffusion vector in each voxel can be increased. These diffusion vectors, called tensors, describe the motion of water molecules within a voxel. This technique has revolutionized the neuroimaging field. According to PUBMED, more than 1540 brain articles use the DTI method. The DTI method provides several diffusion parameters; Fractional anisotropy (FA), Mean diffusivity (MD), Radial diffusivity (RD), and Axial diffusivity (AD) Table 15.

Table 15: Diffusion parameters, with explanations and general interpretation.

Diffusion parameter:	Description	Interpretations:	Limitations:	# of sampling direct. needed:
Fractional Anisotropy	Scalar value describing how ellipsoid the tensor of the water diffusion is	↓ FA: axonal inj., vasogenic edema, or demyelination. ↑ FA: Cytotoxic edema. Neuroplasticity.	Crossing fibers with high integrity can have low fractional anisotropy	➢ 20
Mean diffusivity	The average free diffusion from the three eigenvectors combined shows the diff's strength.	↓ MD: Axonal inj, Cytotoxic edema, necrosis. Neuroplasticity ↑ MD: Vasogenic edema, demyelination, aging	Crossing fibers.	➢ 30
Radial diffusivity	Average of the diffusivities in the two minor directions of the diffusion axis.	↓ RD: Cytotoxic edema, necrosis. Neuroplasticity ↑ RD: Demyelination, aging	Crossing fibers will increase RD.	➢ 30
Axial diffusivity	Diffusivity in the primary diffusion direction in the voxel.	↓ AD: Axonal injury		➢ 30

DTI reliability:

The number of directions in the acquisition of DTI is essential; a study from 2004 by Jones showed that at least 20 unique sampling directions are necessary for a robust estimation of FA, whereas at least 30 unique sampling directions are required for the individual tensors and MD (Jones 2004). These directions are usually scanned with a high identical b-value, which is a factor that reflects the strength and timing of the gradients used to generate diffusion-weighted images. The DTI series are phase-encoded in either anterior-posterior (AP), posterior-anterior (PA), or left-to-right directions. The rapid changes in gradient magnetic fields induce eddy current effects on the rapid echo-planar imaging (EPI) sequences. The effects are influenced by many factors, such as gradient strength, speed of change, coil designs, current flux, and more. Several of these factors will create a large number of coexisting eddy current effects with different time constants; however, the most influential ones in the EPI sequences will distort the image in the direction of phase encoding, e.g., PA, AP or LR, or image sharing effects (frequency-encode directions based). EPI enables a single slice in < 100 msec, enabling diffusion sampling with high sensitivity to diffusional changes, and the phase encoding directional eddy current effects can be handled in the postprocessing of the data of one of the most used DTI sequences in research and clinical use.

The reliability or reproducibility of the DTI method has been proven; two studies have investigated the reliability of the different DTI parameters, and found intra-site variation around 5-7% for FA, while 1.7-6% for MD(Cercignani et al. 2003; Pagani et al. 2010). The influencing factors are commonly different strength gradient systems, main magnetic field strength (B0), and different manufacturers using different DTI sequences; Single Shot EPI sequence vs. Fast Spin Echo (FSE) or other sequences.

Different preprocessing methods of DTI data

After the images are acquired and converted to Nifti format, the processing of the images is the next procedural step. Many DTI software methods exist; the most

important ones are listed in table 16.

Table 16. Some of the research or commercial DTI software available

Different DTI software available:
3D Slicer https://www.slicer.org/
AFNI https://afni.nimh.nih.gov/afni
BrainVoyager QX https://www.brainvoyager.com
Camino https://web4.cs.ucl.ac.uk/research/medic/camino/pmwiki/pmwiki.php?
Dipy https://dipy.org
DoDTI https://neuroimage.yonsei.ac.kr/dodti/
DTI-Query https://graphics.stanford.edu/projects/dti/software/
DTI-TK https://dti-tk.sourceforge.net/pmwiki/pmwiki.php
DTIStudio https://www.mristudio.org/wiki/DtiStudioV2
ExploreDTI https://www.exploredti.com/
Freesurfer/tracula https://surfer.nmr.mgh.harvard.edu/
FSL https://www.fmrib.ox.ac.uk/fsl/fdt/index.html
JIST https://www.nitrc.org/projects/jist/
MedINRIA https://wwwsop.inria.fr/asclepios/software/MedINRIA/
MrDiffusion https://white.stanford.edu/mrdiff
MRICloud https://www.mricloud.org/
MRtrix https://www.brain.org.au/software/mrtrix/
SATURN https://www.lpi.tel.uva.es/saturn/
SPM and toolboxes https://www.fil.ion.ucl.ac.uk/spm/ext/
TrackVis https://trackvis.org/
TORTOISE https://science.nichd.nih.gov/confluence/display/nihpd/

Only three methods are briefly described here, FSL's TBSS, Freesurfer's Tracula, and MRI-Clouds DTI atlas-based segmentation technique; the rest are outside the scope of this thesis. Common features for all three are related to quality control, pre-processing, and data processing see figure 13.

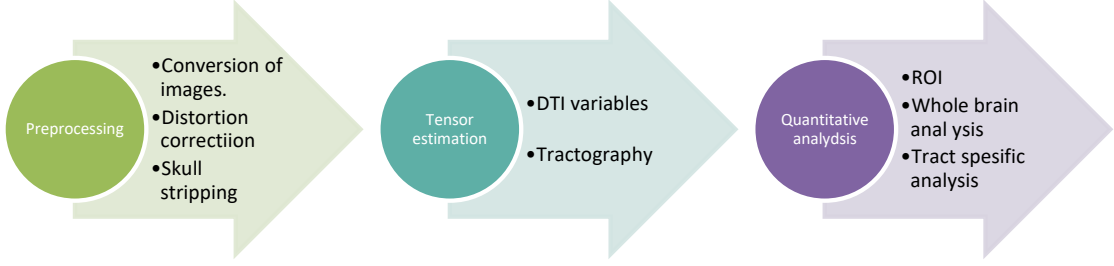

Figure 13: DTI pipeline commonalities

Preprocessing steps in DTI

FSL (The Analysis group: https://fsl.fmrib.ox.ac.uk) is a free software tools package for brain imaging research. The FSL package includes tools for preprocessing, diffusion modeling, and tractography. The same preprocessing tools are also used in Freesurfer's Tracula, providing a robust pipeline for DTI with motion and eddy current corrections. As with T1 morphometry, some of the differences in the preprocessing stage are the spatial registration method utilized, eddy current, and motion correction. The FSL and Freesurfer correct for these two common artifacts with eddy, a program that corrects for motion eddy-currents and models how the susceptibility-induced field changes occur with patients' movement during the scan (Andersson and Sotiropoulos 2016).

MRI-Cloud's preprocessing step for eddy current correction involves a nine-mode affine linear registration process, in which both six-mode rigid motion and three-mode gradient-dependent Eddy-current distortion are simultaneously fitted and estimated using the normalized mutual information as the cost function. In addition, the images are fitted with the LDDMM registration method, which has been validated to work effectively in countering B0 inhomogeneity and eddy currents distortion effects (Huang et al. 2008).

Tensor estimation

Data processing is the next step, and here the program/method estimates the tensors. There are several methods for tensor estimation; the most commonly used is the ordinary least squares(OLS), a linear regression model like in FSL or Freesurfer (Behrens et al. 2007). Moreover, MRI-Cloud uses multivariate linear fitting, an extension of the OLS method (Mori et al. 2008).

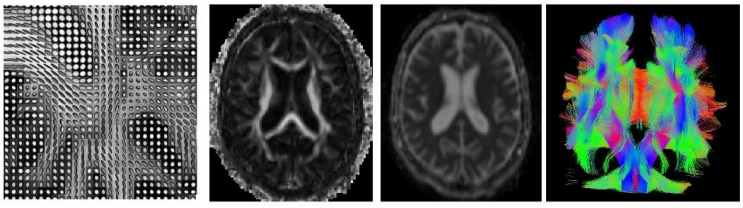

Figure 14: Examples of tensor data visualization: Ellipsoid glyphs, FA map, MD map, and Tractography

The tensor is a 3x3 matrix describing diffusion directions in a Cartesian coordinate system. The diffusion tensor can be described by the eigenvector and eigenvalues for one voxel. Visualizing the tensor is done in different ways, either as a value reduced from the multidimensional to one- or two-dimension value (FA or MD map) / with or as a graphical glyph presentation (containing size, shape, location, and color) or Tractography, see figure 14.

FSL has two different methods: FSL TBSS and FSL FDT. Tract-Based Spatial Statistics (TBSS) solve alignment problems using alignment-invariant features, enabling comparison of FA across subjects. The method uses skeletonization to get average FA from tracts, which are then compared, giving less spurious results than the VBM method. TBSS enables whole-brain comparisons between groups, resulting in many studies in different neurodegenerative or neurocognitive fields. However, the tract-specific method requires an a priori hypothesis for which brain regions and tracts are to be studied. However, its one of the most utilized (Table 16).

Table 16: Overview of TBSS articles available for search at Pubmed

Disease	# of studies:
AD	223
MCI	23
PD	105
ADHD	20
Total TBSS studies	664

AD: Alzheimer's disease, MCI: Mild Cognitive impairment, PD: Parkinson’s Disease, ADHD: Attention deficit hyperactivity disorder.

FDT and Tracula are collections of tools for creating tractography. The tractography gives information about the large tracts non-invasively for the whole brain, enabling

white matter connectivity evaluation and evaluating dysconnectivity associated with neurological and psychiatric disorders. However, it is error-prone, especially in areas with crossing fibers, and the low resolution of the method will mainly map the large bundles accurately. Furthermore, it is difficult to interpret the results quantitatively. Both Tracula and FDT use a probabilistic tractography approach (Soares et al. 2013) to compensate for the limitations caused by multiple fiber orientations in a voxel. Each voxel's fiber orientations are estimated along with the probability distribution that a fiber would run along these directions; this technique was developed to compensate for the fact that each voxel can contain many thousands of fibers going in different directions with is below the resolutions of the voxels (Mori et al. 1999; Wiegell et al. 2000).

MRI-Cloud builds on previous work done by Mori et al., DTI-studio (Jiang et al. 2006), and progressed into a cloud-based system (MRI-cloud.org). It differs from the FSL and Tracula, being an atlas-based DTI registration method, utilizing a powerful LDDMM registration method towards a range of age-related atlases. The results contain several layers of granularity; max granularity contains 168 ROIs. The MRI-Cloud program also includes computational power; the uploaded images are processed at a supercomputer in the US. MRI-cloud/DTI cloud has fewer publications than that of TBSS, only 40, spread over a wide field of brain research, including intrauterine DTI.

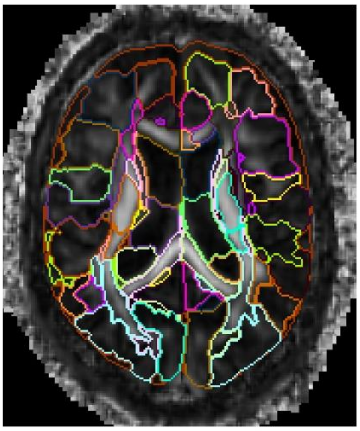

Figure 15: Highest level of granularity from FA map in MRI-cloud, 168 ROIs

5.9.9 Challenges with longitudinal analysis in radiology

Longitudinal studies are always complicated, not only practically but also statistically. This is likewise true for statistics in neuroimaging. Proper longitudinal studies have multiple image sets of the same patients separated by time. Cross-sectional studies are sometimes used in neuroscientific research as a foundation of longitudinal inferences

on the progression of diseases and neurodegenerative processes (Kraemer et al. 2000), but this is outside the scope of this thesis.

In longitudinal studies, there are always dropouts or missing data. Using statistical models that can handle dropouts/missing data reduces the significance of this problem. Some examples of such models are the modified WGEE model (Liu and Zhao 2021), linear mixed effect models (Bernal-Rusiel, Greve, Reuter, Fischl and Sabuncu 2013), and GLM with inference methods (Ibrahim et al. 2005). In neuroimaging, acquisition and processing are essential for securing consistent data of intra-subject measurements, and maintaining predictive power is necessary due to the high amount of data if the granularity is high. Preventing processing bias is an essential aspect of longitudinal image analysis. Processing bias can occur accidentally when follow-up images are registered and mapped to a baseline. The follow-up images might be affected by interpolation artifacts, creating a usually spurious volume loss due to blurry edges and create bias. Different solutions are available, like the SIENA (Structural Image Evaluation, using Normalization of Atrophy) framework provided by FSL (Smith et al. 2002). This method segments the brain from non-brain tissue in the head, estimates the outer skull surface (for both time points), and uses these results to register the two images while correcting (normalizing) imaging geometry changes. Then the registered segmented brain images are used to find local atrophy, measured based on the movement of image edges (Smith et al. 2002). However, later works showed a significant risk of interpolation-related artifacts due to the registration step and measuring the last image towards an average (Yushkevich et al. 2010). The group behind FS learned from this approach and solved it differently. Their framework registers all timepoints together in a common average. The images are then registered towards this group average to treat all the timepoints equally. Information such as preliminary surfaces is transferred only from the common within-subject template but not directly across time points, minimizing the bias (Reuter et al. 2012). Other applications like Advanced Normalization Tools (Tustison et al. 2017) use variations of the LME approach from FS.

5.10 Table 16. Computerbased working memory training in MCI with imaging as pseudo-biomarker:

Img	#	Author Yr	Year	Age	Female	Subjects	Training	Time	/wk	Sess	Imaging after training	Results
DTI	1	Engvig et al.	2012	61.7+-9.4	11	Train(n=21)	Intensive Memory Training	25 min	5	40	immediately	↑ FA whole brain (frontal, occipital, CR)
		Human Brain Mapp		60.3+-9.1	11	Contr(n=20)						↑ MD, ↓ RD whole brain (front, occip, CR)
	2	Lovden et al.	2010	25.1±2.8	11	Young Train(n=20)	spatial, numeric, verbal WM tasks episod	60 min		101	immediately	↑FA↓MD Genu CorpC no ΔAD
		Neuropsychologia		25.6±2.6	4	Young Control(n=10)	memory, percep speed					↑ area of Genu CorpC using sMRI
	3	Takeuchi et al.		21.7±1.4	3	Healthy (n=11)	VSWM, N-back, dual N-back (3compWMtask)	25min	7	50-60	immediately	↑FA IPS-adjacent/bodyACorpC
		J Neurosci	2010									↑FA WM Frontal/Parietal border
	4	Takeuchi et al.		21.0±1.6	13	Young Adult	WM Tasks (Takeuchi et al 2013)	20-60min	7	27	immediately	↑ MD B-Caud, R-Putam, L-DLPFC

	Brain Struct Funct 2015	2015				passive control					R-ACingC, R-SN, and V-tegmental
5	Nichols et al	2021	25.2±5.09	19	Double trouble(8) Self-ordered search (8)	Cambrigde brain science	30 min	4	12 to 20	Pre->3 times during training->immediately	↓ FA L-ILF, L-LOFF L-DLPFC
6	Na et al JCN 2018	2018	60.6±5.3 62.2±4.0 65.3±4.0	9 4 8	HC (n= 10) SCI (n= 6) MCI (n= 10)	Custom developed korean SCI and HC are the control	40min	12	24	immediately	↑FA Ant + Post. Cingulate, MCI only.
7	Dziemian et al. Frontiers in Human Neuroscience	2021	69+-3.57 Old (n=20) 23+-3.34 Young (n= 34)	8 19	WMT(n=16young, 10 old) Active control (n=16 young, 10 old)	Custom WMT	30 min 30min	4	20 20		↓MD R-ILF only old(WMT),R-SLF both young and old(WMT),
8	Metzler-Baddeley et al. Journal of neuroscience	2017	26±6.2 27±6.8	11 10	Adapt.WMT(n=20) NonAdapt (n=20)	Cogmed®	30-45min	5	40	immediately	↑FA + RD Right Dorsolat. SLF, Left parahippocampal cingulum.
9	Salminen et al	2016	24+-3.9	14	WMT(n=18)	dual N-back (Buschkuehl) adaptive	30min	4	16		↑FA L-SFL, L-IFL,L-IFOF, FM and corticospinal tract

				24.1+-3.1	14	Active control(n=18)		30 min			No MD change.
		NeuroImage		25+-4.0	11	Passive control(n=18)		0 min			
GA-DM	9	Caeyenberghs et al.		26.0±6.2	11	Train (n=20)	Cogmed® adaptive	45min	5	40	↑ connectivity R-ACinG, R-IVLPFC ↑ efficiency&strength of F-P network
		J Neurosci 2016	2016	27.0±6.8	10	Contr(n=20)	Cogmed® non-adaptive				
VBM / sMRI	10	Takeuchi et al.		21.9±1.5	5	IATWMMC(n=18)	mental multiplication Placebo: non-adaptive	240min	5	5	immediately ↓rGMV in B-DLPFC, B-PC, L-STG
		PLoS One 2011	2011	21.7±1.3	2	No Interv(n=19)	training				(only in IATWMMC)
				21.6±1.6	6	Placebo(n=18)					
	11	Lampit et al.		70.2±6.7	0	Train(n=7)	COGPACK®	60min	3	36	wk 3 of training ↑GM R-PCG; ↑ROTC L-FFG,R-Parietal
		Front Aging Neurosci 2015	2015	72.3±8	6	Active control(n=5)					&immediately
	12	Metzler-Baddeley et al.		**26±6.2**	11	Adaptive (n=20)	Cogmed® adaptive	45 min	5	40	immediately ↑Cortical thick RCMFC; ↑Vol L-Pallidum ↓R-insula thick correl w/ back digitspan
		Data Brief 2016	2016	**27±6.8**	10	Active Contr (n=20)					
	13	Na et al	2018	60.6±5.3	9	HC	Custom developed korean	40min	12	24	immediately Cortical thinckess increase in rostral ant. Cingulate
		JCN 2018		62.2±4.0	4	SCI	SCI and HC are the control				
				65.3±4.0	8	MCI					

14	Metzler-Baddeley et al. Neuroimage 2016	2016	26±6.2 27±6.8	11 10	Adapt.WMT(n=20) NonAdapt (n=20)	Cogmed®	30-45min	5	40	immediately	↑cortical thick RCMFC; ↑Vol L-Pallidum ↑ thick pars triangularis & opercularis ↓R-insula thick correl w/ back digitspan
15	Roman et al. Brain Strcut Func 2016	2016			adapt train (n=28F) passive control(n=28F)	vis n-back, aud n-back	30min	12	24	pre/immediatly	↓cortical thickness/surface area control group included right ventral frontal cortex (CT), right pars opercularis (CSA), right middle temporal cortex (CT and CSA), and
16	Hervais-Adelmen Neuropsychologia 2017		26±4.3 25.7±5.27	19 19	Trainee interpreters (n=34) multilingual passive controls (n=33)	Master's program in conference interpreting Control post graduate studies	10hrs/week	42	*	interscan interval 1.11yr(.11) interscan interval 1.13yr(.06)	↑cortical thick Left PSTG, anterior SMG, and PT; right AG and DPMC
17	Ghio et al.		22.96±2.57	2	Proximal Group(n=10)	PsychoPy software :action verbs	20min	3	15	wk 3 of training	↑volume in LDPCG of proximal group

		Neuropsychologia 2018		22.96±2.75	4	Distal Group (n=10)	referring to proximal and distal musculature				&immediately	↑volume in right cerebellar lobule VIIa
	18	Zhang et al.	2019	74+-3.6	8	Training group (n=12)	MDCT intervention, Neowave	3*20 min	12	24	Immediately	
	19	Tsukasa et al.	2018	20.7±5	18	Time compressed speech in a second language(TCSSL) (n= 30)	TCSSL 6 auditory files/day playing speed modulated	30-60min	4 (27d)	27	day 1,[train 2-28]	↓rGMV in the left STG in the TCSSL group relative to active control
		Hindawi Neural Plasticity		20.8±1.7	14	active control(n=30)	active control: 3 auditory files/day pitch modulated				day 29	
TBM	20	Colom et al.	2016	`?	?	Adapt Train (n=26)	vis n-back, aud n-back	30min	2	24	pre/post (avg interval 117d)	↓Volume in temporal lobe of Controls neg correlation with improved performance
		Neuropsychologia		?	?	Passive Control (n=26)						

The latest reference search was performed 29.06.2022

6. Objectives:

The objectives of the thesis were mainly to

1. Investigate the degree of atrophy quantified with three commonly used visual radiological rating scales and white matter hyperintensities together with a neuropsychological cognitive profile in MCI patients compared to a closely matched healthy control. Paper 1.
2. Investigate the gray matter changes as a response to the different types of WMT training used in the study by MRI morphometry. Paper 2.
3. Investigate the effects of *LMX*1A and APOE4 genes on working memory training, "visualized by" the cortical gray matter. Paper 2
4. Investigate if the microstructural changes after WMT training are different in adaptive or non-adaptive training. Paper 3.

6.1 Knowledge at study initiation:

At the start of the study in 2013, the knowledge was incomplete on the effects of adaptive computerized working memory training in patients with MCI. No studies had used MRI imaging as a quantitative measure for ACCWT training effect/plasticity in MCI patients. Our motivation for implementing the study was the possible insight into the status of plasticity in MCI patients as a future intervention for our patients. At study initiation in 2013, no publications combined extensive neuropsychological testing and four qualitative and semi-quantitative neuroradiological visual rating scales. Furthermore, no published studies examined the correlation between the different regions' atrophy states, expressed by the visual rating scales and the cognitive domains.

At the time of the study initiation, no study had investigated working memory plasticity in MCI patients. Some studies had explored the difference between cognitively normal brains and MCI brains in response to challenging stimuli with

fMRI. However, this research was impaired by the lack of correction for multiple comparisons(Yetkin et al. 2006), as was much of the early fMRI studies. Furthermore, at study initiation, it was the first to study the effect of LMX1a and APOE4 on cortical thickness and diffusion changes after CCWT training. We also believed that the study, with its objective biomarker for working memory training in MCI patients, could increase the knowledge about the effects of CCWT in MCI patients.

7. Methods

7.1 Study design

The basis for this thesis is the imaging part of the Memory aid Study, a multicenter randomized controlled, double-blind trial (Flak et al. 2014). The baseline paper investigated baseline visual rating scales for brain atrophy and neuropsychological profiles differences between MCI and a cognitive unimpaired control group. The second article is a randomized control study, investigating the longitudinal differences between computerized adaptive and non-adaptive training's effect on the cortical structures in MCI patients. The last article investigates the longitudinal effect of computerized adaptive and non-adaptive training on a microstructural level in the brain, and MCI subtypes and genes an in observational cohort study.

7.2 Population

Individuals with MCI were recruited from the memory clinics at four hospitals in the South-Eastern Health Region of Norway.

County	Hospital:	Catchment population for each hospital in 2014:	Recruitment period:	# Eligible for inclusion:
Aust-Agder	Sørlandet Sykehus HF – Arendal	114 779	August 2013-Desember 2017	148
Telemark	Sykehuset Telemark – HF	171 971	August 2013-Desember 2017	81
Oslo	Oslo university hospital -HF.	464 293	August 2013-Desember 2017	145
Oslo	Diakonhjemmet Sykehus.	132 704	Jun 2016 - Desember 2017	87

Table 17. Study population as reported by Statistics Norway(SSB) and recruitment period for the individual hospitals.

In 2014 approximately 23% of Norway's population was above the age of 60, and 15% were above the age of 67 (Ref: SSB). The mean individual annual income in Norway was NOK 503 800 before tax in 2014. The average life span for women was 83.5 years and 79.6 for men in 2014(SSB).

Inclusion criteria

Patients who meet the Peterson diagnostic criteria of MCI: 1) memory problems, preferably confirmed by an informant, 2) memory impairment with respect to age and education, 3) preserved general cognitive function, 4) intact activities of daily living and (5) absence of dementia (per the ICD-10/DMS-IV criteria). Patients who have had head trauma with post-traumatic loss of consciousness for at least 30 minutes during their lifespan, or who have a loss of senses (blindness, deafness) or photosensitive epilepsy, or who are unsuitable for magnetic resonance imaging because of implanted metal foreign bodies or severe claustrophobia will be excluded from the study.

Participants

A total of 461 patients were diagnosed with MCI during the study period at the four hospitals, diagnosis of MCI was made in accordance with the Petersen/Winblad criteria for MCI (Petersen 2004; Petersen et al. 2014b; Winblad, Palmer, Kivipelto, Jelic, Fratiglioni, Wahlund, Nordberg, Backman, et al. 2004). The participants were assessed in accordance with the Norwegian national guidelines established by the Norwegian register of persons assessed for cognitive symptoms (NorCog), undergoing neuropsychological tests, questionnaires for risk factors ascertainment, spinal biomarkers, and MRI of the brain.

A total of 85 individuals accepted the invitation to participate. Of the 85 recruited and enrolled, one declined due to MRI incompatibility, and two were unwilling to travel for the MRI examinations. Eighty-two were then randomized for the study; from these participants, 15 dropped out after the initial MRI and before training initiation. Three discontinued the training. Sixty-four completed the training, and 62 had MRI images from at least two-time points. Four participants declined to participate in the study's genetic part, and an additional four samples yielded inconclusive genetic results.

To gain more knowledge about the neurocognitive and radiological changes present at baseline in the MCI group, we selected 51 of the recruited MCI patients. We included a control group of 51 closely matched normal cognitive individuals for baseline comparison of the neuropsychological and neuroimaging results of the study. The control group was matched to the MCI group by sex, age, and socioeconomic status (SES). These healthy controls were recruited through Sørlandet hospital's website, and a recruitment ad was put in the local newspapers and an interview on the local radio. The participants underwent MRI with a visual rating and neurocognitive tests identical to the MCI patients; the images were also evaluated clinically. The results are described in the paper I

Levels of education

Level of education	Share:	Years – average:
Below upper secondary education	26.9	< 10 years
Upper secondary education	40.9	11-13 years
Higher education	32.2	> 14 years

Table 18. Level of education 2015 reported by Statistics Norway.

The average years of education in the study cohort was 13.2 years, which is similar to the Norwegian national average from 2015(see table 22).

7.3 Socioeconomic status (SES)

Hollingshead's education and occupational position index were used to calculate the study participants' SES. The index scales from 1 (low) to 5 (high) (Hollingshead and Redlich 2007). The average level of SES among the participants was 3.4.

7.4 Neuropsychological assessment

The following cognitive domains: working memory, executive functions, intelligence, attention, verbal episodic learning/short delay recall, verbal episodic memory/long delay recall, visual episodic learning/short delay recall, visual episodic memory/long delay recall, and processing speed were tested in the neuropsychological test battery. Standardized, internationally accepted neuropsychological tests were selected (Wechsler Adult Intelligence Scale 4.ed, Wechsler Memory Scale 3.ed, Delis-Kaplan Executive Function System, Reys Complex Figure Test, California Verbal Learning Test 2.ed.). The same neuropsychologist administered the test battery in a fixed order to all study participants at each time point. The test battery included sufficient tests for assessing the general cognitive function and the performing subclassification of the MCI condition.

Table 19. List of domains with corresponding neurocognitive tests.

Domain:	Tests:
Working memory	WMS-IV Digit Span backward, WMS-III Spatial Span backward, WMS-III Letter-Number Sequencing
Attention:	WAIS-IV Digit Span forward, WMS-III Spatial Span forward, CVLT-II Trial 1, CVLT-II Trial B
Processing speed:	WAIS-IV Coding, WAIS-IV Symbol search, D-KEFS Color Word Interference Test 1 color naming, D-KEFS Color Word Interference Test 2 Word reading
Visual and Verbal learning:	RCFT Immediate recall, WMS-III Faces I, WMS-III Logical Memory I, CVLT-II Total learning, CVLT-II Short Delay Free Recall
Visual and Verbal memory:	RCFT Delayed Recall, WMS-III Faces II Delayed recall, Logical memory II Delayed recall, CVLT-II Long delay free recall, CVLT Total hits
Executive functions	RCFT, D-KEFS Color Word Interference Test 3 Inhibition, D-KEFS Color Word Interference test 4 Inhibit/Switching, D-KEFS

	Verbal Fluency Test Letter fluency, D-KEFS Verbal Fluency Test Category fluency, D-KEFS Verbal Fluency Test Category switching
Intelligence (IQ)	WAIS-IV (General Ability Index/GAI)

The WAIS-IV is considered a robust battery for intelligence testing in adults. When a complete test is performed, it gives two general cognitive function measures: full-scale IQ and GAI (Sattler 2009). GAI was chosen as the measure of intelligence in our study.

MCI subclassification

MCI subtypes classification is mainly used in research and not routinely performed in Norwegian memory clinics. The subclassification was performed during the initial neurocognitive testing after inclusion in the study. If the individual with MCI scored > −1.5 SD from the mean on the tasks within the verbal and/or visual episodic memory domain, the individual was classified as amnestic MCI. Less than -1.5 SD from the mean in memory domains and combined with scores > −1.5 standard deviation from the mean in one or more non-memory domains, the individual would be classified as non-amnestic MCI.

Estimation of z-scores Paper 1:

The median scores divided by the standard deviation from the neuropsychological test scores of the control group were set as a reference point for calculating the Z-scores; each participant got an individual z-score for each domain to reduce the number of variables for the structure-function correlation analyses. The Z-scores enabled comparison of cognitive performance across groups, and in the different domains.

Genotyping/DNA collection

Participants' saliva was collected in the Oragene Self collection Kit (DAN Genoteck, Inc. Ottawa, Ontario, Canada), and the samples were subjected to Restriction Fragment Length Polymorphism analyses (RFLP-PCR) for genotype analyses of APOEε (rs429358 and rs7412) and LMX1A (rs4657412). Amplification of approximately three ng of genomic DNA by PCR was performed using the primers

LMX-5':5'-CTCGCCTCCAGGAA TGGGTGTTGTA-3' and LMX-3': 5'-GCCACGAGGAACTTGTGAGAGGGTT-3' for LMX1A and APO-5' and APO-3' for APOEε (Andres et al., 2011) with the following conditions: denaturation at 94 °C for 5 minutes, followed by 30 cycles at 94 °C for 30 seconds, annealing at 64 °C for 30 seconds and extending at 72 °C for 30 seconds. 15 µl Amplificated PCR products were digested directly by 2.5 U of restriction enzymes MslI (R0571S, New England Biolabs, Beverly, MA) for 2 hours at 37 °C and by HaeII (R0107S, New England Biolabs, Beverly, MA, USA) and AflIII (R0541S, New England Biolabs, Beverly, MA, USA) overnight at 37 °C. The digested PCR products were analyzed on 4 % agarose gel and visualized using GelGreen™ Nucleic Acid Gel Stain (89139–144, Biotium, Hayward, CA).

7.5 Intervention:

A computerized and standardized adaptive working memory training program (Cogmed RoboMemo), developed by researchers at the Karolinska Institute, Stockholm, Sweden, was used as a computer-based working memory training program. It consisted of several different "games," some required the correct order and placement of boxes and some remembering of letters, digits, etc., activating/training the visuospatial working memory, verbal, and visual working memory. At the time of the study, Cogmed offered a version with two different modes, adaptive and nonadaptive modes, set by the technician. In adaptive mode, tasks' difficulty level and complexity increase as the participant masters each level, making the participant work at his or her maximum potential at all times. The non-adaptive mode has a fixed low difficulty level, with a maximum of three items in each task. During the training period, Cogmed certified coaches from our research group called each participant at least weekly for motivational and follow-up purposes. The training groups followed the standard protocol (30–40 min of training per day, five days per week for five weeks). Seven participants had inexperience with computers and needed a closer follow-up with a higher degree of coach support. We considered the training completed if the participants finished at least 20 of 25 training sessions.

The same verbal praise rewards were given to both groups upon completion of the training. The coaches performed progress monitoring on each individual through a secure site.

7.6 Imaging:

7.6.1 MRI Scanner setup

At the initiation of the recruitment period, the available MRI machine at Sorlandet hospital Arendal HF was a new 1.5 T. Aera from Siemens. It was equipped with a 20 Ch. head-neck coil. The sequence selection for the project was made in collaboration with the Structural MRI competency center at NTNU/St. Olav directed by Asta Håberg. The initial protocol had one 3D T1 magnetization-prepared rapid gradient echo (MPRAGE) image series, one 3D fluid attenuation inversion recovery (FLAIR) series, one anterior-posterior (AP) directional diffusion tensor imaging (DTI) series, and one posterior-anterior (PA) DTI B0 image. Total scan time 25 min. After a small pilot of ten patients' scans, the protocol was changed to two T1 MPRAGE series of images to combine and get increased SNR and counter some movement artifacts. It soon became apparent that the radiographers' method to secure the patients in the head-neck coil was insufficient. Essential tremors and respiratory movements gave some artifacts, but it was partly resolved by increasing the amount of padding around the head in the head and neck coil.

The images were inspected at the scanner console before the patient could exit the MRI Scanner to detect scans that needed to be redone due to artifacts or errors. If excessive movement artifacts were detected, the sequence was redone. It was prevalent that the first sequence had to be redone; after a while, it seemed that the patients became used to the noise and environment of lying inside an MRI machine.

Image handling:

The patient images were exported directly from the console to an external hard drive and transferred to an offline Linux server via physical attachment. After an initial test, they were anonymized at the server level by exporting deidentified data directly from the scanner. The initial test revealed that anonymizing process at the scanner also removed some sequence info, creating difficulties in converting the data to NiFTI format. The anonymized NiFTI files were then stored at the offline server. The server

was part of the local Hyperion computer cluster, which added flexibility and computer power. Each patient visit was placed in a separate catalog created by the NiFTI conversion tool: MCI“assigned study number”_Run”number” detailing which visit(1-3)” In that catalog, there were the T1 MpRage images for morphometry, the FLAIR images for white matter clinical evaluation, and the DTI sequence files (AP and PA) for white matter microanalysis.

7.6.2 Radiological evaluation:

The radiological evaluation was performed by the Ph.D. candidate and by board-certified neuroradiologist Elisabeth Lindland(EL). The Ph.D. candidate had six years of clinical radiology experience at the image evaluation stage, while EL had 11 years. Both radiologists were blinded towards the group (normal cognitive and MCI) allocation in the study and viewed deidentified images labeled by a randomized number. Reference images for all the radiological scores were provided for both radiologists, as suggested by Harper et al. (Harper et al. 2015). The rated score for both hemispheres was averaged for both MTA and GCA-F. In contrast, the highest score from the two brain halves independent of the view plane for the PA score was used. For the Fazekas classification, only the subcortical score, not the periventricular score, was used as recommended. (Ferreira, Cavallin, Granberg, Lindberg, Aguilar, Mecocci, Vellas, Tsolaki, Kłoszewska, et al. 2016; Schoonenboom et al. 2008). A standardized scoring sheet was provided for each subject, where the radiologist noted the randomized number of the images viewed and each score for that subject. An example of this scoring sheet is provided in the supplemental. A consensus meeting was held if a disagreement existed between the two radiologists about a subject's score, and a final score was created for all scores. Score range and pathological age cut-offs are displayed in the table 20; scores above the set cut-off values were considered pathological.

Table 20. Age cut-offs for the different radiological scores

Radiological scoring system:	Anatomical region:	Range:	Pathological age cut off:
MTA	Medial temporal lobes	0-4	64y ≥1.0, 65-74y ≥1.5, >75y ≥ 2.0
PA	Parietal lobes	0-3	≥ 2.0 for all ages
GCA-F	Frontal lobes	0-3	≥ 1.5 for all ages
Fazekas	White matter	0-3	>1.0 for all ages

7.6.3 Cortical gray matter morphometry:

To acquire longitudinal image data, the NiFTI converted MRI images were processed in the longitudinal processing pipeline provided with the Freesurfer. It involves three processing steps; cross-sectional analysis, base template creation, and longitudinal analysis. This was done in accordance with the longitudinal Freesurfer pipeline guide published on the Freesurfer homepage: https://surfer.nmr.mgh.harvard.edu/fswiki/FsTutorial/LongitudinalTutorial

7.7 Statistics:

Prestudy:
The sample size was calculated before study initiation on the primary outcome, longitudinal differences in the cortical thickness/MD DTI trajectories. Cohen's effect size was used to calculate the number of subjects for inclusion. In order to obtain a strong medium effect with Cohens effect size of 0.6, approximately 45 patients in adaptive working memory training or "placebo training" groups were needed. Unfortunately, we did not meet the sample size of 90 patients, as only 82 were included in the study; we also had a higher dropout than expected, as 18 % dropped out before training, while the expected dropout was 10%.

Paper I:

In order to compare cognitive performance across groups and for the different domains and reduce the number of variables in the structure-function correlation analyses, a z-score was calculated for each domain in each participant. ($Z = (x - median_{controls})/sd$) This was based on the difference from the median score of the neuropsychological test scores in the control group divided by the standard deviation of the control group.

For the statistical analysis in paper I, we used IBM SPSS statistics, version 23.0. Mann-Whitney U-tests for nonparametric variables were used to explore for group differences in the demographic data. Multivariate analyses of variance within the General linear model, was used for between-group analyses (MCI patients and controls). SES and years of education are previously known for their impact on the cognitive performance of MCI patients (Fernández-Blázquez et al. 2021; Vadikolias et al. 2012). However, covarying for sex, age, SES, and years of education in the statistical model did not change the significance levels or frequency. The only covariate in the mixed model was the GAI. An alpha level <0.001 was considered statistically significant after Bonferroni-adjustment for multiple comparisons of the 31 neuropsychological outcomes. Each neuropsychological domain score was correlated with each radiological score in linear regression analysis. The linear regression analysis was performed for each radiological score separately as a part of a hierarchic regression analyses. Age and sex were added as covariates. The z-score domains were analyzed with and without GAI as a covariate in the model. For the MTA, PA, GCA-F, and Fazekas scores, two-tailed independent sample T-tests were applied to investigate possible differences in radiological scores between the MCI and the control group, and between the amnestic and nonamnestic MCI groups. For prevalence calculations, the radiological scores were dichotomized according to their pathological age cut-off. A Chi-Square test was applied to investigate associations between groups and the dichotomized scores. We used linear regressions to model the relationship between the cognitive domains and the radiological scores. Statistical significance for these analyses was set to a $p < 0.05$.

Paper 2:

Freesurfer's longitudinal design significantly reduces the confounding effect of inter-individual morphological variability. It creates a template that can be regarded as an initial starting point, unbiased concerning any time point (TP), then non-linear registering each timepoint toward the baseline. The vertex-wise longitudinal cortical data produced were analyzed in MATLAB (Mathworks, version 2018) using a spatiotemporal linear mixed-effects model (LME) included in Freesurfer. The LME model was fitted for each location (vertex) (Bernal-Rusiel, Greve, Reuter, Fischl, Sabuncu, et al. 2013). To adjust for multiple comparisons, the two p-maps from the left and right hemispheres were combined. On all statistical analyses, a threshold was applied to yield an expected false discovery rate (FDR) of 5% (Benjamini et al. 2006) across both hemispheres.

The primary analysis was to investigate whether the adaptive training or non-adaptive training groups had similar brain morphometry trajectories over time; an LME model was fitted with cortical thickness as the dependent variable and time (months since the first scan), sex, training type (adaptive or non-adaptive), age (at baseline), scanner site (1 at Arendal and 2 at Oslo), and interaction (time x training type) as independent variables. SES and years of education did not change the significance levels or frequency and were dropped from the final statistical model.

Cohen's D for effect size maps were created using a GLM model fitted for each location (vertex), creating maps of the training types effect size in a MATLAB model for each time point, with the same variables as with the LME model without interaction.

Secondary analyses of genotype effects on cortical thickness were conducted on the fifty participants with valid genotype data. Since the two training types showed no group differences, the analysis was performed by combining both training types into one group, as we had done in previous analyses (Hernes et al. 2021). To investigate a possible influence of the *LMX*1A genotype, an LME model was fitted with cortical thickness as a dependent variable and time, gender, training type, age, localization, *LMX*1A (AA vs. GG/GA variant), interaction (time x *LMX*1A genotype) as

independent variables. Since only 2 participants had the GG alleles in the *LMX*1A group, they were combined with the AG alleles group. SES and years of education did not change the significance levels or frequency and were dropped from the final statistical model.

To investigate a possible influence of the *APOE*ε gene variants on cortical thickness trajectories, an LME model was fitted with cortical thickness as a dependent variable and time, sex, training type, age, scanner site, whether they had the APOEε4 allele (ε2/ε2, ε2/ε3, or ε3/ε3 versus ε2/ε4, ε3/ε4 or ε4/ε4), and interaction (time x *APOEε* gene variants) as independent variables (Chang et al. 2017, Hernes et al. 2021). SES and years of education did not change the significance levels or frequency and were dropped from the final statistical model.

Paper III:
The longitudinal DTI data were analyzed in the LME model created in SPSS (IBM SPSS statistics), version 23.0. An LME model was fitted with the white matter segment of interest (FA or MD) as the dependent variable, training type, timepoint, and localization as fixed factors, and the white matter segment of interest (FA or MD) value at the first time point (baseline value), age, and gender as covariates. Each subject is used as their own control to reduce the confounding effect of inter-individual morphological variability. For multiple comparison correction, the Benjamini - Hochberg was used, 0.05 significance level after the correction was used.

The secondary analysis investigated APOE and LMX1a's allelic modulating effect on training in the microstructural integrity of the selected white matter regions and if the MCI-subtypes would have significantly different trajectories after training.

To investigate MCI subtypes, LMX1a, or APOE's potential modulating effect on microstructural integrity, a linear mixed model for repeated measurements with subject-specific intercept was fitted with the ROIs as dependent variables and timepoint, type of LMX1a, APOE gene or MCI, and its interaction term with timepoints as fixed factors. The regions included in this analysis were selected from previously reported regions from studies investigating the effect of working memory

training on the brain's microstructure through DTI. These regions are listed in table 1, together with the respective articles. We performed the analysis with Stata/SE 17.0 (StataCorp, College Station, TX, USA). For the multiple comparison correction, the Benjamini-Hochberg was used (Benjamini and Hochberg 1995). A corrected p- value threshold of 0.05 was selected.

Unpublished data II:

Effect of training on cortical thickness trajectories in the different MCI groups. Since the two training types showed no group differences, the analysis was performed by combining both training types into one group, as we had done in previous analyses (Hernes et al. 2021). To investigate a possible influence of the MCI subgroups, an LME model was fitted with cortical thickness as a dependent variable and time, gender, training type, age, localization, MCI subtype(aMCI vs naMCI), interaction (time x MCI subtype) as independent variables. SES and years of education did not change the significance levels or frequency and were dropped from the final statistical model.

7.8 Ethics:

The Norwegian Regional Committee for medical and health research ethics, South-Eastern Health region (no: 2013/410), and the Department of Research at each collaborating hospital approved the study registered in ClinicalTrials.gov (NCT01991405). Written informed consent was obtained from each participant when they attended the baseline examination The participants who attended the non-adaptive training groups were informed after ended training by the coaches and offered adaptive training as well. The radiologist associated with the study also offered to discuss the MRI images with the participants when wanted.

8. Main results

8.1 Main results from baseline data (Paper 1 and unpublished data)

Objective

The main aim of this study was to investigate and describe the radiological and neuropsychological differences in persons diagnosed with MCI and a healthy control group. Furthermore, we wanted to investigate if the rating scales could indicate a correlation between the cognitive domain performance and regional level of atrophy.

Results

Neuropsychological Test Results

The MCI participants in the initial paper had lower performance on 23 out of 31 cognitive outcomes than the closely matched healthy controls. Furthermore, there was a significant difference in the cognitive test performance between the amnestic MCI participants and the non-amnestic participants. A table with all the neurocognitive test results is displayed in Paper 1.

Z-score comparison

The amnestic MCI subtype results displayed reduced scores (below zero) compared to the control group on every neuropsychological measure and for all cognitive domains, and several measures were two standard deviations below the control group's mean. For the non-amnestic MCI subtype, some of the results were on the positive side of zero ranging from +0.4 to −0.9 standard deviations from the mean of the controls. These z-scores are also displayed in Paper 1.

Neuroimaging Results

Thirty-one individuals (61%) in the MCI group and 17 (33%) in the control group had at least one pathological neuroimaging score ($p = 0.010$), and 17 (33%) MCI patients and seven (14%) controls had pathological results on more than one neuroimaging

scale (p = 0.057). Hippocampal atrophy, measured by a pathological MTA score according to the age cut-off, was found in 24 of the participants, 19 (54%) in the amnestic MCI group, two (12, 5%) in the non-amnestic MCI group, and three (6%) in the control group. The MTA score differed significantly when comparing the MCI group with controls when using a two-tailed independent t-test (p <0.0001), and when comparing the amnestic MCI and non-amnestic MCI group (p = 0.006). A pathological PA score was found in 23 subjects; nine (26%) in the amnestic group, four (25%) in the non-amnestic group, and 10 (20%) in the control group (p = 0.477). Similarly, Fazekas score was rated as pathological for 23 subjects, nine (26%) in the amnestic MCI group, four (25%) in the non-amnestic MCI group, and 10 (20%) in the control group (p = 0.477). 11 participants had pathological GCA-F scores; seven (20%) in the amnestic subgroup, none in the non-amnestic subgroup and four (7%) in the control group. The mean GCA-F score was not different between MCI patients and controls, but there was a significant mean group difference (p = 0.002) between the amnestic and the non-amnestic MCI groups. These results are displayed in a table in paper 1.

Structure-Function Relationships

The MTA score showed a significant correlation with episodic memory/long delay recall domain score (R^2 = 0.100, p = 0.043). PA score significantly correlated with working memory domain scores (R^2 = 0.106, p = 0.043), while GCA-F score significantly correlated with episodic learning/short delay recall domain scores (R^2 = 0.100, p = 0.036). An increased radiological atrophy score correlated to lower performance score. Fazekas score showed no significant correlation with either of the cognitive domain scores. When looking at structure-function relationships in the control group, no correlations were found between MRI scores and domain scores, except between the GCA score and processing speed (p = 0.006). However, only four controls obtained pathological GCA scores. These results are displayed in a table in paper 1,

Unpublished data 1

We examined the different age cut-offs and how the sensitivity and specificity changed depending on the different cut-off values for the different radiological atrophy scores.

Table 21: Sensitivity and Specificity implications on the visual rating atrophy scores from the different age cut-offs

MCI vs. HC.	45-64 years		64-74		75-84	
	SN	SP	SN	SP	SN	SP
MTA 0,5	48%	62,5%	70%	72%	87,5%	33%
MTA 1:	30%	91,6%	60%	88%	62,5%	55%
MTA 1,5:	17 %	100%	45%	100	50%	72%
MTA 2	17%	100	20%	100	33%	87,5%
MTA 2,5	0	100	20%	100	14%	100%
MTA 3	0	100	0	100	0	100%
PA: 1	56%	54%	70%	33%	87,5%	11%
PA: 2	10%	95%	30%	78%	50%	33%
PA: 3	0	100	5%	100	0	100%
GCA-F: 1	48%	46%	70%	55%	100%	0
GCA-F: 2	8%	100%	20%	94%	12,5%	67%
GCA-F: 3	0%	100%	0	100	0	100%

MCI, Mild cognitive impairment; HC, Healthy control; MTA, Schelten's Medial temporal lobe atrophy score; PA, Posterior Atrophy score; GCA-F, Global Cortical Atrophy Frontal subscore.

8.2 Paper 2

Objective

The primary objective of this double-blind, randomized study was to investigate differences in longitudinal cortical thickness trajectories after adaptive and non-adaptive WM training in patients with MCI. We also investigated the genotype effects on cortical thickness trajectories after WM training combining these two training groups using longitudinal structural magnetic resonance imaging (MRI) analysis in Freesurfer.

Results

After study inclusion, the participants were randomly divided into an adaptive and non-adaptive training group—neither significant SES, years of education, age, nor gender difference between the groups. There was a significant difference in the LMX1a gene distribution between the two groups but no significant difference in the APOE gene distribution or MCI type between the two groups. By chance, significantly more participants with the *LMX1*A-AA genotype were enrolled in the adaptive training group than in the non-adaptive training group. However, for the gene results, there was a higher percentage of participants with non-valid gene results or that declined to be included in the non-adaptive group.

Table 22 Group characteristics for the intervention part of the study:

	Adaptive training n=32 Mean (SD or range)	Non-adaptive training n=30 Mean (SD or range)	Exact p-value
Age at assessment, years	66 (9)	68 (9)	0.849
Males/females	24/8	24/8	0.127
Education, years	14 (3)	13 (2.3)	0.701
Socioeconomic status	3.4 (1.2)	3.7 (1.2)	0.934
LMX1A genotype (AA or GA/GG) $\chi 2$	14 AA(46.7%) / 16 GA/GG	5 AA (20.8%) / 19 GA/GG	0.014
APOE ε ($\varepsilon 4$ or non-$\varepsilon 4$) $\chi 2$	13 $\varepsilon 4$ (43,3%) / 17 $\varepsilon 3/\varepsilon 2$	11 $\varepsilon 4$ (45,8%) / 13 $\varepsilon 3/\varepsilon 2$	0.858
MCI type (aMCI or naMCI) $\chi 2$	22 aMCI/ 10 naMCI	20 aMCI/ 10 naMCI	0.861

APOE ε Apolipoprotein e, LMX1a Lim homeobox transcription factor a. χ2 Chi-Square, † Independent T-test. aMCI, Amnestic MCI, naMCI, non-amnestic MCI.

Adaptive vs. Non-Adaptive training effects on cortical thickness

Applying a linear mixed effects model found significant differences between the adaptive and non-adaptive training groups in the longitudinal cortical thickness trajectories below the established threshold for FDR correction of 0.000084. Furthermore, no significant group differences were found when assessing the main effect of time without the interaction term when using a Groupwise comparison. Finally, combining the two training type groups found no significant cortical thickness change over time.

LMX1A genotype effect on cortical thickness after cognitive training (across all subjects)

,An LME model with the Time**LMX*1A as interaction (FDR corrected threshold of 0.00043), found significant differences between the AA and GG/GA carriers, visualized in Figure 31. Significant clusters of increased cortical thickness trajectory were found in the right superior frontal gyrus in the AA carriers compared to the GG/GA carriers. In the left hemisphere, the AA carriers showed similar trajectories as compared to GG/GA carriers. The mean cortical thickness at each timepoint, the p-values for the interaction effects for the significant clusters per region, and the size of the significant clusters in each region are included in table 2. No other brain regions showed significant interaction effects, see Figure 4.

APOEε4 genotype effect on cortical thickness after cognitive training (across all subjects)

The LME with Time**APOE*ε4 interactions did not show significant differences in cortical thickness trajectories between the *APOE*ε4 carriers and non-carriers after FDR correction (corrected threshold 0.000126).

Unpublished results II:

The LME with time*MCI subtype interactions did not show any significant differences in cortical thickness trajectories between the aMCI and NACMI groups.

8.3 Main result from paper 3:

A total of 61 participants were included in the Memory Aid study, with at least two MRI images at study timepoints. Baseline demographics for the study population are described in Table 2. No significant differences were found between the adaptive and non-adaptive training group's demographics.

White matter effect of adaptive training compared to non-adaptive training

After applying FDR correction for multiple comparisons to the linear mixed effects model results, only the left sagittal striatum remained with significantly different trajectories between the training groups in mean diffusivity after training (p=.00046). The mean MD value changed in the adaptive training groups from .8370 at baseline to .8430 at 4 weeks to .8277 at 4 months. The non-adaptive group means changed from .8370 at baseline to .8357 at 4 weeks to .8413 at 4 months.

Training-related modulating effect of LMX1a and APOE genotypes on white matter, and the effect from MCI subtypes on longitudinal

LMX1a:

The linear mixed effect model fitted with ROIs as dependent variables and timepoint, *LMX1a* gene, and its interaction term with timepoints as fixed factors. The right and left posterior thalamic regions were still significant in the *LMX1a-AA-group compared to the LMX1a-GG/AG-group at all timepoints.* after FDR correction (corrected threshold .00222). The mean MD value changed in the *LMX1a-AA* group from 0.899 to 0.893 x10^-3 four months after training cessation on the right side. The *LMX1a-GG/GA* had significantly lower MD, at 0.828 to 0.829 on the right side. On the left side, the average MD of the *LMX1a-AA* changed from 0.891 to 0.893, while *LMX1a-GG'*s average MD did not change and remained at 0.833.

APOE4:

The linear mixed effect model fitted with ROIs as dependent variables and timepoint, *APOE* gene, and its interaction term with timepoints as fixed factors. The right and left posterior thalamic radiation regions were still significant after FDR correction (corrected threshold .000222). P values are listed in table 4. The *APOE-E4 carriers* had significantly lower MD than the APOE-E3/E2 carriers at all time points for both posterior thalamic radiation regions. No significant trajectory findings were observed when comparing the different APOE carriers. After training, the mean MD value changed in the *APOE-E4* carriers from 0.828 to 0.833 x10^-3. The *APOE-E3/E2* had significantly higher MD, from 0.898 to 0.899 at 4 weeks to .895 at 4 months on the right side. On the left side, the average MD for the APOE-E4 changed from 0.830 to 0.827 at 4 weeks to 0.833 at 4 months.

MCI subtype:

In our study, the MD in aMCI and the naMCI did not significantly differ in the 24 examined brain regions at baseline. FDR thresholds were calculated and set at p=0.00208. After four weeks, the two groups differed significantly in six brain regions; the left and right posterior thalamic radiation, the right anterior corona radiata, left and right cingulum- hippocampal, and the right uncinated fasciculus. At 16 weeks after training, significant changes were observed favoring the naMCI group as compared to the aMCI group in the left posterior thalamic radiation and left hippocampal cingulum.

Table 22. Regions with significant difference in mean diffusivity at a given timepoint for MCI subtype

Region	Timepoint	Mean diffusivity		p-value*	95% confidence interval	
		aMCI	naMCI		aMCI	naMCI
Left Posterior Thalamic Radiation	Baseline	0.88712	0.84906	0.00222	0.81991-0.86004	0.83069-0.86743
Left Posterior Thalamic Radiation	4 Weeks	0.89274	0.84426	**0.00016**	0.82386-0.86471	0.82566-0.86286

Left Posterior Thalamic Radiation	4 Months	0.89371	0.84509	**0.00019**	0.81983-0.86200	0.82631-0.86387
Right Posterior Thalamic Radiation	Baseline	0.88521	0.85507	0.02194	0.86443-0.90601	0.83646-0.87368
Right Posterior Thalamic Radiation	4 Weeks	0.88937	0.84547	**0.00124**	0.86823-0.91051	0.82661-0.86434
Right Posterior Thalamic Radiation	4 Months	0.88400	0.85169	0.01959	0.86247-0.90553	0.83256-0.87081
Right Anterior Corona Radiata	Baseline	0.83998	0.80951	0.02058	0.81991-0.86004	0.79168-0.82734
Right Anterior Corona Radiata	4 Weeks	0.84429	0.80246	**0.00206**	0.82386-0.86471	0.78435-0.82056
Right Anterior Corona Radiata	4 Months	0.84094	0.81123	0.03376	0.81983-0.86200	0.79268-0.82977
Left Cingulum - Hippocampal	Baseline	0.82776	0.79322	0.00258	0.81049-0.84502	0.77790-0.80854
Left Cingulum - Hippocampal	4 Weeks	0.82886	0.78682	**0.00037**	0.81128-0.84645	0.77126-0.80239
Left Cingulum - Hippocampal	4 Months	0.82913	0.78820	**0.00086**	0.81078-0.84748	0.77212-0.80428
Right Cingulum - Hippocampal	Baseline	0.79784	0.78308	0.11728	0.78375-0.81193	0.77058-0.79558
Right Cingulum - Hippocampal	4 Weeks	0.80794	0.77533	**0.00077**	0.79359-0.82229	0.76263-0.78803
Right Cingulum – Hippocampal	4 Months	0.80663	0.77626	0.00286	0.79148-0.82177	0.76302-0.78949
Right Uncinate Fasciculus	Baseline	0.87144	0.85129	0.16461	0.85588-0.88701	0.83820-0.86438

Right Uncinate Fasciculus	4 Weeks	0.87709	0.84995	**0.00166**	0.86235-0.89183	0.83666-0.86324
Right Uncinate Fasciculus	4 Months	0.88148	0.85703	0.16461	0.86647-0.89649	0.84336-0.87069

9. Discussion:

First the methodological aspects of the study will be discussed, followed by the main findings. Finally, future aspects will be discussed.

9.1 Methodological aspects

9.1.1 Identification of the MCI population

The study population was recruited from a large regional area with three medium-sized and one large-sized hospital as recruitment centers. Since MCI is a dynamic process, some progression to dementia was expected at baseline, equally divided between the hospitals. However, all subjects recruited from one hospital had progressed to various stages of dementia when interviewed and tested by the clinical neuropsychologist at baseline. None of these patients initiated cognitive training, and most redrew from the project after the baseline test and MRI. A clear example of the difficulties with the MCI diagnosis; standardized criteria for the diagnosis are not always enough to prevent significant degrees of cognitive difference in MCI populations and are in accordance with results from previous studies of MCI incidence (Gillis et al. 2019; Pessoa et al. 2019; Xue et al. 2018). Especially the evaluation of ADL is challenging since there is no established cut-off. In Norway, NORCOG was established as a means to improve the standardization of cognitive impairment diagnosis, and the quality registry has provided national guidelines and standardized tests for cognitive evaluation. Nevertheless, the MCI diagnosis still represents a challenge, and further benchmarking efforts between centers might be applied.

The average age of our study population was 66 years, which is younger than the average reported in all 24 studies evaluated in a systematic review of technology-based cognitive and rehabilitation interventions in MCI patients (Ge et al. 2018). However, age is included as a covariate in all the statistical models, and our main aim was to compare the adaptive training group with the non-adaptive, where the average age

difference was insignificant. However, for the secondary analysis, it is a point to be considered when comparing with other studies.

9.1.2 Data acquisition

Neuropsychological testing

All of the study's neuropsychological testing was performed by the same clinical neuropsychologist, thus reducing the interpersonal variation of the tester performing the tests of the subjects. The test battery used was extensive, with 31 cognitive outcomes; nevertheless, the lack of CDR, MOCA, or MMSE inclusion reduces the ease of transferability of our patient data for comparison with other studies. Apart from this, the neuropsychological testing was optimal, with as few influencing variables as possible. If we have redone the study, these would be included to reach a larger scientific community.

MR Imaging

Acquiring images on the 1.5T B0 MRI machine is not typical for neuroscientific studies currently due to the increased availability of higher B0 MRI machines. However, it was the only machine type available for the project at the time. Both MRI machines employed were identical Siemens Area 1.5T with identical head and neck coils, scanner software, and shimming algorithms, thus minimizing potential hardware bias. Slight nuances in the B0 field will always differ between machines, but those cannot be easily removed. In addition, every patient was scanned on the same machine by the same radiographer at all time points, and the location was added as a covariate in the LME model when analyzing the data.

However, the moderate main magnetic field (1.5T) limits the options for what sequences can be reasonably performed. Availability of a 3T or 7T would have improved the possible scan resolution or reduced the scan time, resulting in less motion artifact.

The Structural MRI competency center at NTNU/St. Olav Hospital recommended using the ADNI project's standardized scan protocol. They have published their scanning protocols for many different MRI vendors and machines. Furthermore, these protocols are readily available from their project webpage. (https://adni.loni.usc.edu/methods/documents/mri-protocols/). A protocol for Siemens Aera was not among the models included, but a protocol for a Siemens Avanto was available and used as an initial template adapted to our machine. The Avanto is also a 1.5T MRI machine with similar scanner characteristics; one of the main differences is the 10 cm increased bore diameter on the Aera.

A test scan was first performed on a test phantom to evaluate the MRI machines and scanning protocol's performance. The competency center found the MRI machine and the protocol to be of adequate performance for the project.

In retrospect, as a clinical radiologist, an additional T2* or SWI for evaluating microhemorrhages from CAA and microbleed would be preferred. This would have offered improved diagnostics(Haller et al. 2021) and enabled the use of an additional visual rating system(Gregoire et al. 2009). The MRI machines were in clinical use, with allotted timeslots for research limited to 30 minutes; this did not allow for these additional sequences.

Radiological visual scoring systems

At the time of publication of the first article, only a few articles had published data on MCI compared to HC, mostly single scales, with a few exceptions(Ferreira, Cavallin, Larsson, Muehlboeck, Mecocci, Vellas, Tsolaki, Kłoszewska, et al. 2015; Pyun et al. 2017; Rhodius-Meester et al. 2017). We chose the complete set of the recommended visual rating scales for diagnostic work-up of dementia (Wahlund et al. 2017), with minor modifications to exchange the full GCA scale with the new GCA-F subscore. The full GCA scale was found to have low sensitivity. In contrast, the new GCA-F was recently introduced and validated as a frontal atrophy marker and had higher intra-rater and interrater reliability (Ferreira, Cavallin, Granberg, Lindberg, Aguilar, Mecocci, Vellas, Tsolaki, Kloszewska, et al. 2016; Ferreira, Cavallin, Larsson,

Muehlboeck, Mecocci, Vellas, Tsolaki, Kłoszewska, et al. 2015). The radiological rating systems covered the regular clinical spectrum for evaluating patients with cognitive impairment.

Establishing age adjustments for pathological scores in MCI can be a source of discussion; what is the optimal cut-off for MCI? We tested a few different age-cut-offs based on the original methods and some age-adjusted models as outlined in the unpublished data section of the results. We found the adjusted recommended age cut-off based on research from Prof. Westman's group at Karolinska in Sweden, and Scheltens/Barkhof's group from VU University Medical Centre, in the Netherlands gave the optimal sensitivity and specificity for our study as well.

Cortical segmentation pipeline

Software for brain segmentation has been an area for discussion; which imaging tool is the optimal one? Even variations or combinations of the different programs are possible. Freesurfer is one of the most utilized brain imaging software, used in over 2300 articles searchable at PUBMED, and it has a validated pipeline for minimizing bias in longitudinal studies (Reuter et al. 2012). Freesurfer uses a surface-based approach for cortical structural investigations, which results in very reliable cortical thickness estimations, unlike VBM-based approaches. However, the subcortical structures are not handled the same way. Freesurfer uses a VBM pathway for subcortical segmentation, registering the brain/object to the MNI305 space. The signal intensities in the MR images are mapped in a Gaussian classifier array, creating the basis for an initial volume labeling followed by a B1 bias field intensity correction. This method is problematic for elderly patients, especially with < 3T scanners limited to T1-weighted(T1w) images. As the brain ages, the difference between gray and white matter on T1w images decreases. In addition, especially patients suffering from hypertension develop WMH (Inzitari et al. 2007). On T1 images, the WMH will appear as dark/darker areas compared to surrounding unaffected white matter. When Freesurfer or other brain segmentation software classifies the subcortical structure, WMH can be erroneously classified as gray matter and included in a subcortical structure (Dadar et al. 2021). One method of correcting this can be a multiparametric

segmentation approach, utilizing data from the MP2RAGE or similar sequences or allowing users to perform segmentation with multiple MRI sequences. Freesurfer has the option for both but is limited to cortical structure analysis, not the subcortical structures in version 6.0 utilized in this Ph.D. The optimal way is to use multiparametric sequences, since acquiring the sequences simultaneously limits the registration steps, no head movement in between or different motion artefacts. In our study, we included the FLAIR images in the segmentation process for improved delineation between gray and white matter to optimize our results.

Hence, we conclude that Freesurfer is an adequate software suite for evaluating cortical structures. For subcortical structures, due to the WMH being incorrectly registered as grey matter, at least in the software version 6.0 we used in the study, we were reluctant to publish these results, particularly with the few subjects included. Nevertheless, it is widely used, and the results will be easily transferable to other studies.

Before study initiation, extensive research/literature reviews were performed on how to avoid/minimize asymmetry-induced bias in longitudinal image processing. Analyzing the images sequentially will create a bias towards the initial image since that is used as the reference point. However, Freesurfer's longitudinal pipeline creates an initial template based on all images and transfers data via the template to minimize selection. This method has been validated and accepted as the optimal method for longitudinal image analysis. We conclude that the longitudinal pipeline included in Freesurfer was adequate for our study.

DTI longitudinal pipeline:

Several options were available for the DTI software suite: Tracula from Freesurfer and TBSS from FSL. However, due to our collaboration with Prof. Chang's group, we got invited to use John Hopkins MRICLOUD system. The MRICLOUD pipeline provided us with several advantages; it provided an easy-to-use interface for achieving the results and included supercomputer time from the National Institute of Biomedical Imaging and Bioengineering. It utilizes age-adjusted atlases to reduce the amount of

stretching during the registration process, which is important due to the generalized atrophy associated with aging, particularly in individuals with MCI.

The age-adjusted atlases used with the LDDMM have previously been validated in both normal elderly and Alzheimer's patients (Oishi et al. 2009), making it a suitable method for our atlas parcellation in the DTI study.

9.2 Main findings:

9.2.1 Working memory effect measurable by MRI

The cortical thickness trajectory analysis found no difference between the adaptive and non-adaptive training groups. Our initial hypothesis was not proven that there would be different cortical trajectories between the groups. Nevertheless, after publishing the neuropsychological results(Hernes et al. 2021) that showed no clear benefit of the adaptive part of the training compared with the non-adaptive, we assumed the structural findings would be similar, so this did not come as an unexpected result. However, a difference was found when the secondary analysis was performed; the *LMX1A-AA* carrier group had significant cortical changes in two regions. This difference will be discussed in detail in a subsequent chapter in this discussion.

Cortical grey matter

Several studies report cortical grey matter changes after computer-based cognitive training (Ghio et al. 2018; Hervais-Adelman et al. 2017; Lampit et al. 2015; Maruyama et al. 2018; Metzler-Baddeley et al. 2016b; Roman-Urrestarazu et al. 2016; Takeuchi et al. 2011; Zhang, Wang, et al. 2019). Only one research paper has published results of not finding a significant change in the cortical gray matter after computer-based cognitive training (Lawlor-Savage et al. 2019). However, in addition to the initial cortical paper that found significant changes, Meltzer-Baddeley also published a paper, with the longitudinal data of the whole brain vertex-wise, with no significant longitudinal cortical trajectory difference between the two training groups (Metzler-Baddeley et al. 2016a). There are several methodological design differences

in the previous research compared to our study; only one of the previous studies used the same computer-based training program like ours and had a similar group set up with an active control group (Metzler-Baddeley et al. 2016b). Meltzer-Baddeley et al. had a younger subject group, the average age of the subjects in their study were 26 years and cognitively unimpaired, while ours were 66 years and MCI patients. One possible factor for the non-difference between our two training groups could be the non-adaptive program being at a sufficient training level for this cognitively impaired subject group.

The number of sessions was also different; they trained for five weeks with 40 sessions, while our subjects trained for 25 sessions during five weeks, and our coaches considered the training completed if the participants finished 20 or more of 25 training sessions.

We considered that the MCI subject group had heterogeneous pathologies/etiologies as underlying causes of the impairment. Training in cognitively normal older adults activates more secondary brain centers than younger people (Cook et al. 2007). For individuals with MCI, even greater secondary recruitment as a compensatory mechanism is expected (Hohenfeld et al. 2020). However, MCI research into secondary brain regions/centers recruitment when using the working memory is not extensive (Farras-Permanyer et al. 2015), and potential regions recruited not seen in cognitively normal subjects could be missed if using an ROI-based approach. This is a concern for the prefrontal cortex (PFC), which is heavily involved in working memory function. Subdivisions of PFC have been suggested in the literature (Taren et al. 2011), but currently, no consensus on the details of the functional organization of the PFC exists (Eriksson et al. 2015).

We decided to use the whole-brain vertex-wise approach to the cortical data to exclude averaging (ROI based) out any subregional changes due to the training effect. However, the whole-brain approach necessitated an FDR approach to minimize the effect of the extensive multiple comparisons, and it is a distinct possibility that some training effect is left undiscovered with this approach, type II errors (false negative).

The biological alterations occurring at sites with increased cortical or subcortical thickness are primarily on a theoretical level. Some suggest a greater arborization per neuron, increased glial volume, or increased regional vasculature (Lazar et al. 2005). Some speculate that neurogenesis could be involved, but there is little evidence to substantiate this claim in response to training; the validated claims for active neurogenesis in all ages come from post-mortem findings in stroke victims (Minger et al. 2007). Selective pruning of synapses, dendrites, or even axons is considered one of the mechanisms occurring during cortical thinning after training (Kanai and Rees 2011; Zatorre et al. 2012). Most CWMT studies acquired images immediately after training cessation (Ghio et al. 2018; Hervais-Adelman et al. 2017; Metzler-Baddeley et al. 2016b; Takeuchi et al. 2011), while our study acquired images at 4 and 16 weeks after training cessation, this could mean that for obtaining images with the most significant cortical change, the closer to training cessation would be optimum. In our study, another scan during training could have provided more information on the dynamic process; we can speculate that there would be an initial increase when sprouting, followed by a decrease/normalization as selective pruning occurs.

Another cause for our study reporting no difference between the adaptive or non-adaptive groups could be related to image resolution and image intensity levels, an explanation could be the magnetic field being limited to 1.5T. Most of the studies that reported significant findings were 3T. In addition, due to our small-medium statistical power, the MCI population's secondary recruitment could be so distributed that the changes are below the method's ability to detect.

White matter *alterations*

Previous studies on the working memory training effect measured by DTI have reported increased FA after computer-based cognitive training (Engvig et al. 2012; Lövdén et al. 2010; Takeuchi et al. 2010), surprisingly both Engvik et al. and Takeuchi et al. (2015) reported regions with increased MD after training, only Lovden reported decreased MD. The primary analysis was performed with both FA and MD; however, secondary analysis, investigating correlations between genetic influence on microstructural integrity trajectory after working memory training, was limited to only

MD as a diffusion parameter. FA is reportedly less sensitive than MD to synaptogenesis, and MD requires fewer patients to detect changes (Luque Laguna et al. 2020). The 124 separate regions for both MD and FA necessitated compensating for multiple comparisons. Using FDR correction reduced the number of significant findings from six to one.

Regions associated with white matter changes after CWMT are limited, perhaps due to the limited number of publications (Dziemian et al. 2021a; Engvig et al. 2012; Lovden et al. 2010; Metzler-Baddeley et al. 2016b; Na et al. 2018; Nichols et al. 2021; Salminen et al. 2016; Takeuchi et al. 2015; Takeuchi et al. 2010). Takeuchi et al. reported in 2010 a generalized increase in the FA value of the brain, but surprisingly also an increased MD in the body of the corpus callosum. Others report more localized changes in FA or MD; some of the causes for this change could be the development of newer computational methods for estimating tensors and the statistical models behind the analysis. The newer reports have used FSL's TBSS, SPM or ACQ, and such studies report a select number of regions with significant changes after CWMT since the method is limited to the tracts specified in TBSS in effort to preserve senstivity. Furthermore, a complicating factor of neoangiogenesis has been reported, supposedly a factor that can increase the MD; without negatively affecting performance, or indeed when positive changes occur to the performance.

In our study, the left sagittal stratum showed decreased MD, which is associated with increased axonal density, high myelination, or WM maturation and can be interpreted as an effect of adaptive cognitive training. However, our study did not find a similar effect in the non-adaptive group; it showed increasing MD, indicating decreased axonal density or neurodegeneration. White matter plasticity could be interpreted as load-dependent. These findings indicate similar microstructural changes as reported by others in response to training (Dziemian et al. 2021a; Metzler-Baddeley et al. 2017; Na et al. 2018; Nichols et al. 2021).

The results put together indicated that the longitudinal effect of our training is primarily measurable in the white matter microstructure even in an MCI population.

9.2.2 Gene effects on trainability

LMX1A

One of the novel findings from our study is the correlation of the influence of APOE4 and *LMX1A* gene effects on brain morphometric measures. The naMCI patients had greater training gain than the aMCI group, especially in those with LMX1A-AA genotype and among APOE-+4-carriers. naMCI with LMX1a-AA maintained gains in verbal learning short delay after 16 weeks, while the APOE-E4 group-maintained gains in Executive function (Hernes et al. 2021). Chang et al. found beneficial properties associated with being an *LMX1A-AA* carrier in a population of HC and HIV subjects. They decreased their FMRI Bold activation, and AA carriers seemed to benefit more from the training (Chang et al. 2017). Bellander et al. reported similar findings that the AA carrier group had more significant benefits from training than the others in the verbal learning domain; however, this was also a small study(n=55) with limited power (Bellander et al. 2011). However, a later study from the same group didn't find any correlation that LMX1a received any benefits of WMT compared to the GG/GA group (Bellander et al. 2015).

In our cortical thickness paper, we found that The *LMX1A-AA* group maintained or had increased cortical thickness compared to GG/GA group at 16 weeks post-training. Nevertheless, the AA group presented with a significantly increased MD in both posterior thalamic radiations longitudinally, which were maintained from baseline to the 16 weeks post-training. There was no significant effect on the ROI associated with working memory training. Mayo et al. found that compared to healthy older adults, individuals with AD had lower FA and higher MD in the hippocampal cingulum and posterior thalamic radiation (Mayo et al. 2017).

Schulz et al. described that the polymorphisms of LMX1A code for a factor involved in the production, differentiation, and preservation of neurons in the midbrain that produce the neurotransmitter dopamine, particularly during embryogenesis(Schultz

2007). The preservation might be linked to LMX1a's mitochondrial regulating function in the adult midbrain dopaminergic neurons (Doucet-Beaupré et al. 2016). Due to these factors, LMX1a has been described as the dopamine pathway gene. Dopamine is an essential neurotransmitter in working memory and essential to the mesocortical and nigrostriatal systems. These systems are involved in working memory and reportedly respond to CWMT (Takeuchi et al. 2015). Studies on Dopamine's involvement in working memory have revealed its importance in working memory function, and polymorphisms play an essential part in the magnitude of gains from working memory training (Bäckman and Nyberg 2013; Braun et al. 2021; Fairfield et al. 2022) and that either LMX1a's effect during embryogenesis on the dopamine receptor distribution or LMX1a's mitochondrial regulating function in the adult midbrain dopaminergic neurons can explain the mechanism by which LMX1a exert an effect on working memory trainability.

The neuropsychological performance was discussed in detail in a different Ph.D. thesis of the MemoryAid project. However, is tempting to draw preliminary conclusions since all the papers point out that AA-carriers, benefits more significantly from the training. However, a cautionary note must be made due to the small sample sizes, and we did not find any changes in the white matter microstructure to support or disprove this claim. Due to our small sample size, this research only provides possible avenues for further studies on a larger scale, not definitive answers.

APOE4

The APOE-E4 carriers did not show any increased response to training compared to the Non-E4 group, neither in Cortical thickness trajectory change nor in white matter microstructural trajectory changes. However, the E4 carriers had significantly lower MD values in two regions at baseline, left and right posterior thalamic radiations and the difference did not significantly change during the follow-up examinations. The result that the E4 did not respond differently to the training compared to the non-E4 is contrary to the results from the neurocognitive part of the study(Hernes et al. 2021), where the E4 carriers had a better response to the training, and had significant gains in the executive function domain. However, the consistently lower MD in several tracts

can perhaps be explained by the pleiotropy hypothesis (Tuminello and Han 2011). Young E4 carriers outperform non-carriers on cognitive performance, and they may recruit additional regions or have higher information flow between regions to achieve this advantage, thus increasing axonal diameters. As Alzheimer's disease starts decades before the cognitive symptoms, this advantage might decrease with age, and consequently, non-significant neurocognitive differences between E4-carriers and non-E4-carriers exist in midlife. However, in later life stages, E4 carriers may begin to recruit right-sided frontal brain regions to maintain cognitive performance comparable to non-carriers, explaining why E4 carriers have lower MD than non-E4 carriers in our study. No other study has performed a similar genetic modulation on training effect correlated to white matter integrity in MCI. However, López-Higes et al. found an that only Non-APOE-E4 carriers had a training effect in a study with cognitively intact older adults (López-Higes et al. 2017). The population in López-Higes's study was older, with an average age 71 years, and the study population was small (25 in each groups); in addition, the MMSE scores were borderline towards cognitive impairment, being 27.2 in the APOE4 carrier group (López-Higes et al. 2017). The difference in the result could be that the APO-E4 carriers were further towards dementia and with less cognitive reserve, unable to have a positive effect from the training. Age, subject selection, and the selection of ROIs could explain some of the differences between our findings and previous research on APO-E4 carriage and microstructural changes compared to a non-E4 carriage in a non-training setting (Adluru et al. 2014; Slattery et al. 2017; Williams et al. 2019). Only Slattery reported increased MD in the posterior thalamic radiation, while the two other studies found either decreased FA or increased MD limited to Cingulum, Hippocampus, or frontal projections.

Due to our small study population, our aMCI findings need validation in a more extensive study.

9.2.3 Amnestic or non-amnestic, whom to train?

The difference in the MCI populations at baseline with increased hippocampal atrophy in the amnestic group was also visible in the white matter microstructure, consistent

with previous research. Gozdas et al. found higher MD in the aMCI group than in HC (Gozdas et al. 2020). Gyebnár et al. reported that their aMCI subjects had higher MD compared to controls or naMCI in several grey and white matter regions (Gyebnár et al. 2018). Our study found a significant difference between the two groups in six of the 24 regions investigated in the secondary DTI analysis, with naMCI consistently having lower MD, indicating a larger axonal diameter or higher glial volume.

Gozdas et al. also reported that focal changes in white matter tract properties along the cingulum tract predicted memory and cognitive functioning in aMCI(Gozdas et al. 2020). In our study, there was a significantly different trajectory in the cingulum for the two groups, with the naMCI decreasing their MD after training and aMCI increasing MD after training; the difference was significant at four weeks but became non-significant at four months.

The lack of a passive control group prevents us from investigating if the training prevented further increase of MD in the amnestic-MCI group during the observational period or if the naMCI group would have maintained its current microstructural level in the cingulum-hippocampal region without the training. Neurocognitive performance was improved in the naMCI while only maintained in the aMCI group (Hernes et al. 2021), though without a correlation analysis, the conclusion is only speculative.

When considering the naMCI group had lower MTA and GCA-F scores than HC and aMCI, it is convenient to speculate that the atrophy of these regions in the amnestic group is also linked to decreased axonal pathways, either due to selective pruning or as part of a neurodegenerative process. The naMCI population might be expected to improve their MD after CWMT since their injury is not affecting the memory domains to the same degree as the aMCI population, while the aMCI population is directly training an impaired function with less room for the primary center and tract improvement, but more secondary recruitment.

So perhaps the expectations for these two MCI entities should be different with maintaining current function as a goal in aMCI while expecting improvement in the naMCI group. However, further studies are needed, with a more extensive study

population to improve the power for improved analysis and a setup with three study groups, active CWMT, active control, and a passive control group.

9.2.4 Is our MCI population representative of the global MCI population?

Our cross-sectional study results are similar to individual visual rating studies, but few have evaluated MCI subclassifications (Duara et al. 2013; Ferreira, Cavallin, Granberg, Lindberg, Aguilar, Mecocci, Vellas, Tsolaki, Kloszewska, et al. 2016; Rhodius-Meester et al. 2017). Most studies only include MCI subjects with predominantly memory problems, and ours is one of the few that also separated into the MCI subtypes. Structural studies found that the hippocampus, amygdala, and the frontal pole were significantly affected in the aMCI, but not in the naMCI (Csukly et al. 2016; Guan et al. 2017), which is similar to our findings.

Neurocognitively the subjects have been through a thorough testing process before inclusion, with receiving an MCI diagnosis at a Memory clinic and being subjected to further testing at baseline per the MCI criteria(Petersen et al. 2014b; Winblad, Palmer, Kivipelto, Jelic, Fratiglioni, Wahlund, Nordberg, Bäckman, et al. 2004) and an additional scoring of the cognitive domains for MCI subclassifications.

We conclude that our MCI population is radiological and neuropsychological representable compared to other reported clinical studies from the EU or North America.

9.2.5 Does MRI have a place in validating effect after computer-based working memory training?

Validating findings on MRI is difficult; few studies have correlated their findings with a post-mortem histopathological examination of thickness and microstructural integrity or density. One study investigated the correlation between the DTI parameters MD and

FA concerning BRAK NFT staging (Kantarci et al. 2017). However, it does not validate that the findings are accurate,

The ground truth in MRI imaging is that the machine's calibration gives size-accurate images. There are many areas of introducing bias in an imaging study; the anatomical atlases that the images are registered onto, the registration method, the bias correction of the images, software technique for analyses, smoothing degree of the data, statistical model, and correction for multiple comparisons. Since so many factors are involved, neuroscientists and imagining specialists investigate the reliability with test-retest studies; several such studies are published often with the introduction of a new method, such as scanner sequences, software algorithms, or bias intensity algorithms. (Buimer et al. 2020; Huang et al. 2016; Nerland et al. 2021). Our study did a test-retest on a phantom before study initiation and validated at the Structural MRI competency center at NTNU/St. Olav. We also scanned both Ph.D. candidates for a longitudinal test-retest and intersite evaluation once a year.

No imaging setup will ever be 100% reliable with many complex factors. Nevertheless, using the gold standard for the setup included in the study is essential to get optimal and reliable results.

We used Freesurfers tested software pipeline and examined the cortical thickness parameter. It was validated as the most reliable morphometric parameter (Winkler et al. 2018). Even though our study was the largest adaptive-CWMT study in MCI patients, we cannot conclude from our results since our power is smaller than intended, and we are categorized as small-to-medium powered, like most treatment validation studies (chapter 4.10). However, the number of MRI studies using different MRI techniques to correlate with neurocognitive findings and elucidate the mechanism behind changes occurring in the brain is growing exponentially, with many positive results(Chapman et al. 2015; Dziemian et al. 2021b; Emch et al. 2019; Gyebnár et al. 2018; Na et al. 2018; Nichols et al. 2021; Tang et al. 2012; Yetkin et al. 2006). We found lasting changes in the left sagittal stratum that demonstrate a possible load-

dependent change and validate the claim of detecting microstructural changes believed to be a sign of synaptic plasticity even in mixed heterogenous MCI patients.

9.3 Strengths and limitations:

The study has several strengths; first, the same neuropsychologist did all the examinations. Standardized internationally recognized methods were used for neuropsychological evaluation and cognitive performance scoring. Secondly, in the baseline article, the radiologists were experienced and blinded to group adherence. Internationally recognized radiological scoring systems are now recommended in everyday clinical use for patients undergoing neurocognitive evaluation in a memory clinic. These MRI measures evaluated both neurodegenerative and vascular factors.

In the second article, Freesurfer's longitudinal framework reduced the bias when comparing image data from different timepoints toward each other. The spatiotemporal LME model for the statistical analysis is a robust way of handling dropouts/missing data. The FDR correction used the modified.

Lastly, the longitudinal setup of the study to validate that the effect is genuinely neuroplastic with a significant lasting change is a benefit compared to most DTI studies which acquire images shortly after training and which might measure a mixed effect from both training and effort related changes.

Study sample

The study sample consisted of patients diagnosed in hospital-based memory clinics by experienced multidisciplinary teams using a standardized national assessment method. Furthermore, the healthy control group for article 1 was matched on SES, age, and sex and recruited in the same region as the patients, with the same cultural background and general diet. Power calculations estimated 82 participants for a god to medium-powered study. Slow recruitment due to competing studies led to an extended recruitment period and the inclusion of an additional recruitment center (Diakonhjemmet hospital). However, there was a distinct difference in the study

populations from Diakonhjemmet hospital compared to the rest of the memory clinics; none of the participants from Diakonhjemmet managed to complete the training.

Bias:

In the baseline article, the neuropsychologist was not blinded toward the group allocation when doing the neuropsychological evaluation. This may lead to a group bias in the evaluation.

The neuropsychological tests' low specificity and high sensitivity may also have impacted the lack of correlation between the GCA-F and the executive function domain tests.

The high education level in Norway may skew the results compared to countries with less general education.

9.4 Conclusion

The MCI group had a higher level of atrophy than the cognitive normal at the baseline imaging. In particular, the aMCI subtype had the most significant degree of atrophy and cognitive decline. Scholten's MTA score was significantly higher in the aMCI group than in the naMCI and healthy control groups. A structure-function relationship between the individual’s cognitive domain function and the level of localized atrophy was identified. These results support the well-established fact that MCI is a heterogeneous condition with various underlying pathologies. For our cohort, age-related cut-offs recently suggested for clinical use were also suitable for our MCI group.

Secondly, we did not find any significant longitudinal differences in cortical thickness response between the adaptive and non-adaptive training groups or the whole MCI group. However, carriers of LMX1a-AA had significantly increased cortical thickness trajectories compared to LMX1a-GG/GA group. The results from our WM training in a heterogeneous population of MCI participants identified the need for further

research. We found no genotypic modulating training effect on the cortical thickness from APOE. No significant difference occurred in the cortical thickness trajectories during the observational period (unpublished results) between the aMCI and naMCI groups, indicating that the naMCI's ability to provide a synaptic response to training is greater than in the aMCI group.

In white matter, only the adaptive training group significantly decreased MD compared to the active control group after training. This seems to be a workload-dependent effect in the left sagittal stratum and indicates increased synaptic density or glial volume. In addition, white matter changes favoring the naMCI group were detected in the left posterior thalamic radiation and left hippocampal cingulum as compared to the aMCI group that was sustained for four months after training.

The post-training effects observed in cortical thickness and white matter gives a radiological correlate to other reports of increase cognitive function. These findings support the theory of maintained neuroplasticity in MCI. Subgroups of MCI and some genotypes might be more available for CWMT effects.

9.5 Future considerations

The heterogeneous pathology in individuals with MCI affects the interpretation of scientific results in this patient group. Within the total MCI population, various dementias and other neurocognitive disorders follow individual trajectories. Affected cognitive domains and radiological findings can aid the clinician in the diagnostic process. Age-adjusted cut-off improves the use of visual scoring systems in everyday clinical settings. Future studies need to describe the MCI sub-populations within each study to ensure the transferability of the results.

The second key message is that the brains of individuals with MCI are trainable and display changes in white matter microstructure after adaptive working memory training. This is a possible angle for new treatment. However, future studies with larger power needs to examine the correlation between structural and neurocognitive findings. Additionally, utilizing three training arms, such as adaptive training, active control, and passive control, might give additional scientific information about the level of plasticity and rate of atrophy within the MCI population.

Future studies should examine the duration of the training period and whether a prolonged training regime improves the microstructural benefits. Another possibility is to examine if several training periods have an additive effect on end results. Furthermore, the observation time after training is in current studies short. Long-term observations are important to evaluate the effect outside the immediate training period.

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11.Paper 1-3 and supplemental material

Paper I

frontiers in Aging Neuroscience

ORIGINAL RESEARCH
published: 21 November 2018
doi: 10.3389/fnagi.2018.00384

Cognitive Profiles and Atrophy Ratings on MRI in Senior Patients With Mild Cognitive Impairment

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In this cross-sectional study, we sought to describe cognitive and neuroimaging profiles of Memory clinic patients with Mild Cognitive Impairment (MCI). 51 MCI patients and 51 controls, matched on age, sex, and socio-economic status (SES), were assessed with an extensive neuropsychological test battery that included a measure of intelligence (General Ability Index, "GAI," from WAIS-IV), and structural magnetic resonance imaging (MRI). MCI subtypes were determined after inclusion, and *z*-scores normalized to our control group were generated for each cognitive domain in each MCI participant. MR-images were scored by visual rating scales. MCI patients performed significantly worse than controls on 23 of 31 cognitive measures (Bonferroni corrected $p = 0.001$), and on 8 of 31 measures after covarying for intelligence (GAI). Compared to nonamnestic MCI patients, amnestic MCI patients had lower test results in 13 of 31 measures, and 5 of 31 measures after co-varying for GAI. Compared to controls, the MCI patients had greater atrophy on Schelten's Medial temporal lobe atrophy score (MTA), especially in those with amnestic MCI. The only structure-function correlation that remained significant after correction for multiple comparisons was the MTA—long delay recall domain. Intelligence operationalized as GAI appears to be an important moderator of the neuropsychological outcomes. Atrophy of the medial temporal lobe, based on MTA scores, may be a sensitive biomarker for the functional episodic memory deficits associated with MCI.

Keywords: MCI, intelligence, memory clinic patients, cognitive dysfunction, brain pathology, structural magnetic resonance imaging, neuropsychological functioning, neuropsychological tests

OPEN ACCESS

Edited by:
Nicola K. Ferdinand, Saarland University, Germany

Reviewed by:
Patrick Darius Gajewski, Leibniz-Institut für Arbeitsforschung an der TU Dortmund (IfADo), Germany
Katharina Schnitzspahn, Université de Genève, Switzerland

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Received: *24 June 2018*
Accepted: *01 November 2018*
Published: *21 November 2018*

Citation:
Flak MM, Hol HR, Hernes SS, Chang L, Ernst T, Engvig A, Bjuland KJ, Madsen B-O, Lindland EMS, Knapskog A-B, Ulstein ID, Lona TEE, Skranes J and Løhaugen GCC (2018) Cognitive Profiles and Atrophy Ratings on MRI in Senior Patients With Mild Cognitive Impairment. Front. Aging Neurosci. 10:384. doi: 10.3389/fnagi.2018.00384

INTRODUCTION

The term "Mild Cognitive Impairment" (MCI) is currently understood as a clinical condition characterized by reduction in memory and/or other cognitive processes not severe enough to meet the criteria for dementia, but more pronounced than the cognitive decline associated with normal aging (Reisberg and Ferris, 1982; Petersen et al., 1997, 1999; Reisberg et al., 2008; Geda and Nedelska, 2012). According to the Petersen criteria, MCI is operationalized as objective impairment on neuropsychological tests, in combination with intact general cognitive functioning and activities of daily living (Petersen et al., 1999). Initially, MCI was constructed as a transition stage between nonimpaired cognitive aging and Alzheimer's disease. Since then the initial focus on memory impairment in the MCI criteria has expanded. The 2004 revised criteria further classified MCI into "amnestic" and "nonamnestic" subtypes (Petersen, 2004; Winblad et al., 2004). When a diagnosis of MCI is established, its subtype is defined by the results of the individuals neuropsychological profile. In amnestic MCI, the profiles indicates deficit within the memory domain. Conversely, nonamnestic MCI indicates intact memory, but impaired function in other domains for instance working memory or executive function (Petersen et al., 1997, 1999; Collie and Maruff, 2002; Collie et al., 2002; Boeve et al., 2003; Lopez et al., 2003, 2006; Winblad et al., 2004; Petersen and Knopman, 2006; Petersen and Negash, 2008). There is a lack of studies that describe cognitive profiles of amnestic and nonamnestic MCI patients diagnosed in a memory clinic by national guidelines. Knowledge about the individuals neuropsychological profiles has clinical and prognostic value, since patients with amnestic MCI, especially with multi-domain cognitive deficits, are more likely to progress more rapidly to dementia (Arnáiz et al., 2001; Bozoki et al., 2001; Tuokko et al., 2003; Luis et al., 2004). In addition to prognosis, knowledge of functional strengths and weaknesses are important for potential treatment, interventions and guidance for caregivers (Ten Kate et al., 2017). New clinical criteria for the diagnosis of Alzheimer's disease recommend the use of biomarkers (e.g., structural brain imaging, and cerebrospinal fluid analyses) also in patients with MCI (Dubois et al., 2007; Albert et al., 2011; Jack et al., 2011; McKhann et al., 2011). Clinical markers of MCI include cognitive function assessed by neuropsychological tests as described above, and signs of structural brain pathology on magnetic resonance imaging (MRI) (Petersen and Negash, 2008; Jak et al., 2009).

Rog and Fink (2013) recommended that cognitive assessment in MCI should include all major neuropsychological domains (i.e., attention, working memory, visual and verbal learning and memory, processing speed, and executive function) and ideally also an estimate of general cognitive ability. The aging brains' ability to tolerate structural damage relates to the resilience, or "reserve," of the brain (Stern, 2013). General cognitive ability is an estimate of an individual's ability prior to the onset of a pathological process, a premorbid function. The notion of "cognitive reserve" as a mediator of structure-function relationship between brain and cognition in aging is well-established (Katzman et al., 1988; Stern, 2002; Robertson, 2013). Intelligence can be considered a proxy for cognitive reserve (Richards and Deary, 2005; Osone et al., 2015). Intelligence is usually assessed with structured psychometric tests. One of the most widely used test batteries worldwide is the Wechsler Adult Intelligence scale—fourth edition (WAIS-IV). WAIS-IV produces a composite score that represents general intellectual ability: The Full Scale Intelligence Quotient (IQ), which includes the following indexes: Verbal comprehension, Perceptual reasoning, Working Memory, and Processing speed. However, a problem of using Full Scale IQ as a measure of cognitive reserve in MCI patients is that this composite score also includes the domains of Working Memory and Processing speed that are vulnerable to aging in general (Schaie, 1994), and MCI in particular (Salthouse and Meinz, 1995). This may result in lower scores on Full Scale IQ in patients with MCI than nonimpaired individuals, without the intellectual ability *per se* being reduced. WAIS-IV also include a composite IQ score that consist only of the Verbal comprehension subtests and Perceptual reasoning subtests: General Ability Index (GAI), resulting in a measure of general ability that is not sensitive to the influence of the working memory- and processing speed abilities (Tulsky et al., 2001). Hence, the GAI is a measure of IQ not including subtests of cognitive proficiency, and may therefore be a better measure of intellectual ability or cognitive reserve than Full scale IQ in a clinical group of patients with MCI.

Most research in this field has been performed with functional MRI, since fMRI incorporates both structural localization and to some degree a measure of function in one examination. However, the most readily available methods in clinical use for evaluating brain structure-function relationships are neuropsychological tests and semi-quantitative scoring systems based on visual reading of MRI. Several radiological scoring systems for clinically evaluating brain pathology markers related to dementia exist (Ferreira et al., 2015, 2016; Rhodius-Meester et al., 2017). Temporal lobe atrophy is mainly evaluated by the medial temporal lobe atrophy score (MTA) (Scheltens et al., 1995). The amnestic MCI subtype, often regarded as prodromal to Alzheimer's disease (AD), is typically associated with hippocampal atrophy assessable by the MTA score, and memory impairment (Petersen and Morris, 2005). Other evaluation tools like the Posterior Atrophy (PA) score (Koedam et al., 2011) and the Global Cortical Atrophy Frontal (GCA-F) sub score (Pasquier et al., 1996; Ferreira et al., 2016) are potential biomarkers for early onset AD, atypical AD, and nonAD dementia (Ferreira et al., 2017). White matter hyperintensities (WMH), depending on lesion frequency and location, were also associated with cognitive decline (Overdorp et al., 2014; Prins and Scheltens, 2015). A clinical scoring system for how extensive the WHI are is the Fazekas score. This WMH scoring system is recommended for cognitive impairment research by the Imaging Cognitive Impairment Network group, together with the radiological atrophy scores (Wahlund et al., 2017). Broad spectra of individual anatomical differences, cognitive reserve, and varieties in brain structural changes exist due to normal aging compared to that of neurodegenerative diseases. Therefore, separating patients with MCI from cognitively nonimpaired individuals based exclusively on structural MRI is difficult (Gómez-Sancho et al., 2018). More research in this field have been recommend by the

Geneva Task Force for the Roadmap of Alzheimer's Biomarkers (Ten Kate et al., 2017).

In the present cross-sectional descriptive study, we aimed to investigate and describe the differences between patients with MCI to nonimpaired individuals on a comprehensive neuropsychological test battery that included an estimate of cognitive reserve (GAI) and visual radiological scoring systems. Further, we aimed to investigate if the degree of brain pathology identified by the clinical visual scoring systems on MRI is correlated with the scores on neuropsychological domains of attention, working memory, visual and verbal episodic learning and memory, processing speed, and executive function in patients with MCI (Rog and Fink, 2013). We hypothesized that the MCI patients would have inferior scores on several cognitive domains, but that GAI would moderate group differences. We also hypothesized that greater degree of brain pathology would be found in those with lower scores on the cognitive domains.

MATERIALS AND METHODS

Participants

The study was approved by the Norwegian Regional Committee for medical and health research ethics, South-Eastern Health region (no: 2013/410) and by the Department of Research at each collaborating hospital. Fifty one patients diagnosed with MCI were recruited from Memory clinics at four hospitals in the South-Eastern Health Region in Norway (Sørlandet Hospital Arendal, Telemark Hospital, Oslo University Hospital, and Diakonhjemmet Hospital). Eligible patients with MCI were invited to participate between August 2013 and December 2016. The study participants were assessed with neuropsychological tests, questionnaires for risk factors ascertainment and MRI of the brain as specified by the Norwegian national guidelines (NorCog) and the diagnoses of MCI were made in accordance with the Petersen/Winblad criteria of MCI (Petersen, 2004; Winblad et al., 2004). Classification of MCI subtypes is not done routinely in the Memory clinics. Therefore, this classification was performed after inclusion, according to the patients cognitive profiles (cut-off at one neuropsychological test impaired per domain, >1.5 SD below age- and gender-appropriate norms). The study neuropsychologist categorized the MCI participants into amnestic and nonamnestic MCI based on their scores on the neuropsychological tests in the baseline assessment. Scores more than −1.5 SD from mean compared to norms on the tasks within the verbal and/or visual episodic memory domain were classified as amnestic MCI. Normal scores in memory domains combined with scores more than −1.5 standard deviation from the mean in one or more of the other domains assessed, resulted in categorization as nonamnestic MCI (Petersen et al., 1999, 2001; Winblad et al., 2004).

A control group of 51 volunteers was recruited through Sørlandet hospital's website, local newspapers, and radio. They were matched to the MCI group by sex, age, and socioeconomic status (SES). SES was calculated using Hollingshead's index of education and occupational position, scaled from 1 (low) to 5 (high) (Hollingshead and Redlich, 1958). The participants underwent neuropsychological assessment and brain MRI. Exclusion criteria included head trauma with post-traumatic loss of consciousness during the lifespan, photosensitive epilepsy, or person unsuitable for MRI because of inserted metal or severe claustrophobia.

See **Tables 1**, **2** for clinical characteristics of the groups.

Neuropsychological Assessment

A neuropsychological test battery assessed the following cognitive domains: intelligence, attention, working memory, processing speed, visual episodic learning/short delay recall, visual episodic memory/long delay recall, verbal episodic learning/short delay recall, verbal episodic memory/long delay recall and executive functions. Standardized, internationally renowned neuropsychological tests were applied. All tests were administered in a fixed order by the same clinical neuropsychologist (MMF) to all study participants. The WAIS-IV is considered a valid and reliable battery for intelligence testing in an adult population. It generates two general measures of cognitive function Full scale IQ and GAI (Strauss et al., 2006; Wechsler, 2008; Sattler and Ryan, 2009; Lezak, 2013). The GAI was chosen as a measure of intelligence in our study. The neuropsychological tests are listed in **Table 3**.

CEREBRAL MRI

Data Acquisition

Images were acquired from three different 1.5 Tesla Siemens Aera MR Systems. Study participants were scanned with a standardized protocol containing volumetric T1-weighted

TABLE 1 | Clinical characteristics and cognitive scores in patients with MCI ($n = 51$) and controls ($n = 51$).

	MCI $n = 51$	Controls $n = 51$	
	Mean (SD or range)	**Mean (SD or range)**	**Exact *p*-value**
Age at assessment, years	66 (51–80)	66 (53–81)	0.849
Males/females	35/16	35/16	
Education, years	13 (8–20)	14 (10–19)	0.198
Socioeconomic status	3.4 (1.1)	3.7 (1.0)	0.339
Full Scale Intelligence Quotient WAIS-IV	96 (15)	110 (12)	<0.0001
General Ability Index (WAIS-IV)	100 (16)	114 (13)	<0.0001
Verbal comprehension Index (WAIS-IV)	100 (14)	110 (12)	<0.0001
Perceptual organization Index (WAIS-IV)	101 (17)	113 (13)	<0.0001
Working memory Index (WAIS-IV)	92 (13)	106 (17)	<0.0001
Processing speed Index (WAIS-IV)	94 (14)	104 (18)	<0.0001

Mann-Whitney U-tests for nonparametric variables. The significance level is 0.05.
MCI, Mild Cognitive Impairment; SD, Standard Deviation; WAIS-IV, Wechsler Adult Intelligence Scale, 4th edition

TABLE 2 | Clinical characteristics and cognitive scores in patients with amnestic ($n = 35$) and nonamnestic ($n = 16$) MCI.

	aMCI $n = 35$	naMCI $n = 16$	
	Mean (sd or range)	**Mean (sd or range)**	**Exact *p*-value**
Age at assessment, years	66 (53–80)	65 (51–80)	0.707
Males/females	24/11	11/5	
Education, years	13 (8–20)	15 (12–18)	0.026
Socioeconomic status	3.2 (1.2)	3.9 (1.0)	0.030
Full IQ WAIS-IV	91 (13)	107 (10)	<0.0001
General ability Index (WAIS-IV)	95 (15)	112 (12)	<0.0001
Verbal comprehension Index (WAIS-IV)	95 (12)	111 (12)	<0.0001
Perceptual organization Index (WAIS-IV)	97 (17)	110 (13)	0.010
Working memory Index (WAIS-IV)	87 (11)	102 (11)	<0.0001
Processing speed Index (WAIS-IV)	90 (14)	102 (11)	<0.008

Mann-Whitney U-tests for nonparametric variables. The significance level is 0.05. Abbreviations: MCI, Mild Cognitive Impairment; SD, Standard Deviation; WAIS-IV, Wechsler Adult Intelligence Scale, 4th edition.

TABLE 3 | Assessed cognitive domains and neuropsychological tests.

Cognitive domains	Tests
Intelligence (IQ)	WAIS-IV (General Ability Index/GAI)
Attention domain	WAIS-IV Digit Span forward, WMS-III Spatial Span forward, CVLT-II Trial 1, CVLT-II Trial B
Working memory domain	WMS-IV Digit Span backward, WMS-III Spatial Span backward, WMS-III Letter-Number Sequencing
Processing speed domain	WAIS-IV Coding, WAIS-IV Symbol search, D-KEFS Color Word Interference Test 1 color naming, D-KEFS Color Word Interference Test 2 Word reading
Visual episodic learning/short delay recall domain	RCFT Immediate recall, WMS-III Faces I
Visual episodic memory/long delay recall domain	RCFT Delayed Recall, WMS-III Faces II Delayed recall
Verbal episodic learning/short delay recall	WMS-III Logical Memory I, CVLT-II Total learning, CVLT-II Short Delay Free Recall
Verbal episodic memory/ long delay recall	Logical memory II Delayed recall, CVLT-II Long delay free recall, CVLT Total hits
Executive functions	RCFT, D-KEFS Color Word Interference Test 3 Inhibition, D-KEFS Color Word Interference test 4 Inhibit/Switching, D-KEFS Verbal Fluency Test Letter fluency, D-KEFS Verbal Fluency Test Category fluency, D-KEFS Verbal Fluency Test Category switching

WAIS-IV, Wechsler Adult Intelligence Scale 4.ed, WMS-III, Wechsler Memory Scale 3.ed, D-KEFS, Delis-Kaplan Executive Function System, RCFT, Reys Complex Figure Test, CVLT-II, California Verbal Learning Test 2.ed.

magnetization-prepared rapid gradient echo (MP-RAGE) and fluid attenuation inversion recovery (FLAIR) sequences. Following a pilot scan, two three-dimensional (3D) MP-RAGE scans (sagittal, echo time 3.47 ms, repetition time 2,400 ms, TI 1,000 ms, flip angle 8 degrees, 1.2 mm resolution covering the whole brain) and a 3D-T2 weighted fluid attenuated inversion recovery (FLAIR) image (sagittal, echo time 335 ms, repetition time 5,000 ms, TI 1,800 ms, turbo factor 242, 1.2 mm resolution covering the whole brain) were performed. Total scan time was 30 min.

Scoring Systems and Data Analysis

Visual radiological scoring systems were used to assess brain pathology in the MCI patients and controls. These scales included Scheltens Medial temporal lobe atrophy (MTA) score, the Fazekas's scale for WMH, Global cortical atrophy—frontal (GCA-f) sub score and PA score (**Table 4**).

We evaluated the MTA, PA, and GCA-F scores on the T1w images, and the Fazeka's score on the FLAIR images. For the visual rating, two experienced radiologists viewed the images independently at separate locations. Both radiologists were blinded toward group allocation. Reference images for all scores were provided for both radiologists as suggested by Harper et al. (2015). A consensus rating was held if a disagreement existed. For all scores except the Fazekas and PA scores, both brain hemispheres were scored and a mean score was calculated (Schoonenboom et al., 2008; Ferreira et al., 2016). A mean score was calculated based on both brain hemispheres for the MTA and GCA-F (Schoonenboom et al., 2008; Ferreira et al., 2016). The MTA score cut-offs were set at $\geq$1.0 for persons under 65, at $\geq$1.5 for persons between 66 and 74 years of age, and at $\geq$2 for those $\geq$ 75 years (Ferreira et al., 2017; Rhodius-Meester et al., 2017). The MTA score ranges from 0 to 4 (from 0 = no atrophy to 4 = most severe atrophy), which describes the relative size of the hippocampus at a fixed position on T1 images. GCA-F utilized a cutoff at $\geq$1.5 for all ages (Rhodius-Meester et al., 2017). The GCA-F describes the atrophy severity of the frontal lobe, and scores range from 0 to 3 (0 = no atrophy, 1 = mild atrophy, 2 = moderate atrophy, 3 = severe atrophy). The PA scoring system (PA) also ranges from 0 to 3 (0 = no atrophy, 1 = mild, 2 = moderate, 3 = severe atrophy) and was used with the original age cutoff for PA $\geq$2 (Koedam et al., 2011). Fazekas scores categorize the nonspecific white matter hyperintensity load. The scores range from 1 to 3 (from absent to higher white matter lesion load depending on the location of the hyperintensities, see footnote in **Table 7**); a score >1 was considered pathological for all age groups (Fazekas et al., 1987) For all radiological scoring systems, scores above the set cut-off values were considered pathological.

Statistical Analysis

Statistical analyses were performed using IBM SPSS statistics, version 23.0. The Mann-Whitney *U*-tests for nonparametric variables were used to explore group differences in demographic variables (see **Tables 1**, **2**). Multivariate analyses of variance within the General linear model, was used for between-group analyses (MCI patients and controls). Covarying for sex, age, SES,

TABLE 4 | Radiological scoring systems, range, region and age cut off.

Radiological scoring system	Anatomical region/structure	Range	Pathological age cut off
MTA	Medial temporal lobes/hippocampus	0–4	1.0 ≤ 64 years 1.5 ≥ 65–74 years ≥ 2 >75 y.
PA	Parietal lobes	0–3	≥2 for all ages.
GCA-F	Frontal lobes	0–3	≥1.5 for all ages.
FAZEKAS	White matter	0–3	1 for all groups.

MTA, Scheltens Medial temporal lobe atrophy score, PA, Koedam's posterior atrophy score. GCA-F, Passchier's Global cortical atrophy score—frontal subscore. Fazekas, Fazekas white matter hyperintensity (WHI) score.

and years of education in the statistical model did not change the significance levels or frequency. The only covariate in the mixed model was the GAI.

In order to compare cognitive performance across groups and for the different domains, a z-score was calculated for each domain in each participant, based on the difference from the median score of the neuropsychological test scores in the control group divided by the standard deviation of the control group ($z = \frac{x - median_{controls}}{sd}$) (Yonelinas et al., 2002). An alpha level <0.001 was considered statistically significant after Bonferroni-adjustment for multiple comparisons of the 31 neuropsychological outcomes. In order to reduce the number of variables in the structure-function correlation analyses, the neuropsychological z-scores were clustered into cognitive domains (Rog and Fink, 2013). Each neuropsychological domain score was correlated with each radiological score in linear regression analysis. The linear regression analysis was performed for each radiological score separately as a part of a hierarchic regression analyses. Age and sex were added as covariates.

The z-score domains were analyzed with and without GAI as a covariate in the model. For the MTA, PA, GCA-F, and Fazekas scores, two-tailed independent sample *T*-tests were applied to investigate possible differences in radiological scores between the MCI and the control group, and between the amnestic and nonamnestic MCI groups. For prevalence calculations, the radiological scores were dichotomized, according to their age cut-off. A Chi Square test was applied to investigate associations between groups and the dichotomized scores. We used linear regressions to model the relationship between the cognitive domains and the radiological scores. Statistical significance for these analyses was set to a $p < 0.05$.

RESULTS

Table 1 displays clinical characteristics of the study participants. Age, gender distribution, education, and SES showed no significant group differences. Conversely, there were significant group differences for the results on the WAIS-IV including the intelligence indices Full Scale IQ and GAI.

MCI Subtypes

In the MCI group, 35 participants were classified into the amnestic subtype, while 16 participants were classified into the nonamnestic subtype. **Table 2** describes the characteristics of the two MCI subtypes. Statistically significant differences between the groups were found on all test variables with lowest scores in the amnestic subtype group.

Neuropsychological Test Results

Compared to the controls, the MCI group showed lower performance on 23 out of 31 of the cognitive outcomes (Bonferroni adjusted $p < 0.001$). However, fewer results, 8 out of 31 outcomes, remained significantly different between the two groups when the GAI was included as a covariate to adjust for premorbid cognitive functioning. Specifically, tasks assessing the verbal episodic learning domain and verbal episodic memory domain (California Verbal Learning Test-II, and Logical memory I and II) remained significantly different between the groups. Furthermore, significant group differences remained on a test of executive function (Verbal Fluency Test Category Fluency) (**Table 5**).

Analyses of group differences between the amnestic and nonamnestic MCI subtypes revealed significantly inferior scores in the amnestic group on 13 out of 31 cognitive outcomes. In the multivariate model, with GAI as covariate, only eight measures remained significantly different between groups (**Table 6**). See **Figure 1** for visual display of data.

Z-score Comparison

Figures 2, **3** show the z-scores of the MCI patients on all the neuropsychological measures with controls as reference, on a scale that ranges from + 0.4 standard deviations (z-score = 0.4) to – 2.0 standard deviations (z-score = −2) from the mean, in addition to the domain scores. **Figures 2**, **3** shows the results of the amnestic and nonamnestic MCI subtype, respectively. The amnestic MCI subtype results displayed reduced scores (below zero) as compared to the control group on every neuropsychological measure and for all cognitive domains, and several measures were 2 standard deviations below the mean of the control group. For the nonamnestic MCI subtype, some of the results were on the positive side of zero ranging from +0.4 to −0.9 standard deviations from the mean of the controls. Only the domains scores were used in the structure-function analyses.

The amnestic MCI subtype results displayed reduced scores (below zero) as compared to the control group on every neuropsychological measure and for all cognitive domains, and several measures were two standard deviations below the mean of the control group (**Figure 2**). For the nonamnestic MCI subtype, some of the results were on the positive side of zero ranging

TABLE 5 | Neuropsychological test results in patients with MCI ($n = 51$) compared to matched controls ($n = 51$).

Cognitive domain	Subtask	MCI ($n = 51$)	Controls ($n = 51$)	*p*-value unadjusted	*p*-value adjusted*
Attention	WAIS-IV Digit Span forward (items correct)	8.0 (1.7)	9.4 (2.4)	0.003	0.250
	WAIS-IV Digit Span forward, longest number of digits	5.4 (1.0)	6.3 (1.3)	**<0.0001**	0.101
	WMS-III Spatial Span forward (items correct)	6.4 (2.0)	7.3 (1.9)	0.025	0.624
	WMS-III Spatial Span forward, longest number of items	4.6 (1.2)	5.2 (1.0)	0.005	0.203
	CVLT-II Trial 1 (number of correct words)	4.0 (1.6)	5.8 (1.5)	**<0.0001**	**<0.0001**
	CVLT-II Trial B interference (number of correct words)	3.7 (1.6)	5.4 (2.1)	**<0.0001**	**0.001**
Working memory	WAIS-IV Digit Span backward (items correct)	6.7 (2.0)	8.0 (2.6)	0.011	0.645
	WAIS-IV Digit Span backwards, longest number of digits	3.8 (1.0)	4.5 (1.4)	0.013	0.510
	WMS-III Spatial Span backward (items correct)	5.8 (2.0)	7.6 (1.4)	**<0.0001**	0.002
	WMS-III Spatial Span backward, longest number of items	4.3 (1.0)	5.2 (0.8)	**<0.0001**	0.004
	WMS-III Letter-Number Sequencing (correct items)	7.4 (2.6)	10.1 (2.6)	**<0.0001**	0.008
Processing speed	WAIS-IV Coding (WAIS-IV) (number of items)	43.0 (14.4)	55.0 (13.4)	**<0.0001**	0.038
	WAIS-IV Symbol search (WAIS-IV) number of items	22.0 (7.5)	27.4 (8,0)	0.002	0.190
	D-KEFS Color Word Interference Test 1 color naming (seconds to complete)	40.0 (14.5)	31.6 (6.1)	**0.001**	0.051
	D-KEFS Color Word Interference Test 2 word reading (seconds to complete)	30.4 (15.1)	22.6 (4.2)	**0.001**	0.094
Visual episodic learning/ short delay recall	Rey Complex Figure Test Immediate recall (items remembered)	13.0 (8.0)	19.0 (6.0)	**<0.0001**	0.011
	WMS-III Faces I (items correct)	34.2 (4.7)	36.4 (4.1)	0.035	0.088
Visual episodic memory, long delay recall	Rey Complex Figure Test Delayed Recall (items correct)	12.0 (8.0)	18.5 (5.1)	**<0.0001**	0.002
	WMS-III Faces II Delayed recall (items correct)	32.3 (4.6)	36.2 (5.7)	**<0.0001**	0.006
Verbal episodic learning/ short delay recall	WMS-III Logical Memory I(number of items)	27.9 (12.4)	40.5 (8.4)	**<0.0001**	**<0.0001**
	CVLT-II Total learning (number of correct words)	33.5 (11.0)	47.8 (10.6)	**<0.0001**	**<0.0001**
	CVLT-II Short Delay Free Recall (number of word)	5.5 (4.0)	10.2 (3.2)	**<0.0001**	**<0.0001**
Verbal episodic memory, long delay recall	Logical memory II Delayed recall (number of items)	13.2 (9.4)	25.3 (6.2)	**<0.0001**	**<0.0001**
	CVLT-II Long delay free recall (number of words remembered)	5.2 (4.5)	10.0 (3.5)	**<0.0001**	**<0.0001**
	CVLT Total hits (words recognized)	12.7 (4.7)	15.1 (1.4)	**0.001**	0.053
Executive functions	Rey Complex figure Copy trial (number of items)	31.0 (6.0)	34.5 (2.0)	**<0.0001**	0.090
	D-KEFS Color Word Interference Test 3 Inhibition (seconds to complete)	86.0 (35.6)	60.9 (15.0)	**<0.0001**	0.019
	D-KEFS Color Word Interference test 4 Inhibit/Switching (seconds to complete)	101.0 (38.5)	70.1 (18.0)	**<0.0001**	0.002
	D-KEFS Verbal Fluency Test Letter fluency (number of words)	41.0 (17.7)	45.8 (11.8)	0.087	0.967
	D-KEFS Verbal Fluency Test Category fluency (number of words)	34.6 (11.5)	46.9 (11.1)	**<0.0001**	**<0.0001**
	D-KEFS Verbal Fluency Test Category switching (number correct)	11.2 (3.7)	14.0 (3.5)	**0.001**	0.038

*Mann Whitney U-test for nonparametric variables. *General linear model, multivariate, with General Ability Index as covariate. Bonferroni correction for multiple comparisons: significant p-values ($p < 0.001$) in bold.*

MCI, Mild Cognitive Impairment, CVLT-II, California Verbal Learning Test 2rd edition, WAIS-IV, Wechsler Adult Intelligence Scale 4th edition, WMS-III, Wechsler Memory Scale 3rd edition, D-KEFS, Delis Kaplan Executive Function System.

from +0.4 to −0.9 standard deviations from the mean of the controls (**Figure 3**).

Neuroimaging Results

Table 7 presents the number of persons with pathological scores on the different MRI scoring systems. Thirty one individuals (61%) in the MCI group and 17 (33%) in the control group had at least one pathological neuroimaging score ($p = 0.010$), and 17 (33%) MCI patients and 7 (14%) controls had pathological results on more than one neuroimaging scale ($p = 0.057$). Hippocampal atrophy, measured by a pathological MTA score, according to the age cut-off, were found in 24 of the participants; 19 (54%) in the amnestic MCI group, two (12, 5%) in the nonamnestic MCI group and three (6%) in the control group. The MTA score differed significantly when comparing the MCI group with controls, when using two tailed independent *t*-test

TABLE 6 | Neuropsychological test results in patients with amnestic MCI (aMCI) ($n = 35$) and nonamnestic MCI (naMCI) ($n = 16$).

Cognitive domain	Subtask	aMCI $n = 35$	naMCI $n = 16$	*p*-value unadjusted	*p*-value Adjusted*
Attention	WAIS-IV Digit Span forward (items correct)	7.5 (1.4)	9.2 (1.7)	**0.001**	0.028
	WAIS-IV Digit Span forward, longest number of digits	5.1 (0.8)	6.2 (0.8)	**<0.0001**	0.012
	WMS-III Spatial Span forward (items correct)	5.9 (1.9)	7.4 (1.8)	0.017	0.330
	WMS-III Spatial Span forward, longest number of items	4.4 (1.1)	5.1 (1.2)	0.054	0.203
	CVLT-II Trial 1 (number of correct words)	3.6 (1.5)	4.8 (1.6)	0.009	0.088
	CVLT-II Trial B interference (number of correct words)	3.4 (1.4)	4.3 (2.1)	0.073	0.375
Working memory	WAIS-IV Digit Span backward (items correct)	6.1 (1.7)	8.0 (1.9)	0.010	0.091
	WAIS-IV Digit Span backwards, longest number of digits	3.5 (0.9)	4.4 (1.0)	0.005	0.115
	WMS-III Spatial Span backward (items correct)	5.3 (1.7)	6.9 (2.0)	**<0.0001**	0.298
	WMS-III Spatial Span backward, longest number of items	4.1 (1.0)	4.9 (1.0)	0.017	0.004
	WMS-III Letter-Number Sequencing (correct items)	6.5 (2.2)	9.5 (2.0)	**<0.0001**	0.028
Processing speed	WAIS-IV Coding (number of items)	38.2 (13.4)	53.2 (11.0)	**<0.0001**	0.083
	WAIS-IV Symbol search (number of items)	21.0 (7.8)	24.5 (6.3)	0.108	0.437
	D-KEFS Color Word Interference Test 1 color naming (seconds to complete)	43.9 (15.5)	31.6 (6.9)	0.002	0.168
	D-KEFS Color Word Interference Test 2 word reading (seconds to complete)	33.5 (17.0)	23.7 (6.1)	0.020	0.505
Visual episodic memory, short delay recall	Rey Complex Figure Test Immediate recall (items remembered)	9.9 (6.8)	19.9 (6.2)	**<0.0001**	**0.001**
	WMS-III Faces I (items correct)	33.4 (4.9)	35.9 (3.7)	0.061	0.239
Visual episodic memory, long delay recall	Rey Complex Figure Test Delayed Recall (items correct)	8.9 (6.4)	19.0 (6.4)	**<0.0001**	**<0.0001**
	WMS-III Faces II Delayed recall (items correct)	31.6 (5.1)	33.9 (2.9)	0.101	0.229
Verbal episodic memory, short delay recall	WMS-III Logical Memory I (number of items)	24.6 (11.9)	35.2 (10.6)	0.005	0.049
	CVLT-II Total learning (number of correct words)	29.2 (9.3)	42.9 (8.7)	**<0.0001**	**0.001**
	CVLT-II Short Delay Free Recall (number of word)	3.8 (3.2)	9.3 (2.5)	**<0.0001**	**<0.0001**
Verbal episodic memory, long delay recall	Logical memory II Delayed recall (number of items)	10.4 (8.2)	19.3 (9.2)	0.003	0.017
	CVLT-II Long delay free recall (number of words remembered)	3.5 (3.7)	8.9 (4.0)	**<0.0001**	**<0.0001**
	CVLT-II Total hits (words recognized)	11.7 (5.3)	14.8 (1.7)	0.016	0.441
Executive functions	Rey Complex figure Copy trial (number of items)	30.3 (6.6)	33.7 (3.1)	**<0.0001**	0.847
	D-KEFS Color Word Interference Test 3 Inhibition (seconds to complete)	97.5 (36.2)	60.6 (16.0)	**0.001**	0.066
	D-KEFS Color Word Interference test 4 Inhibit/Switching (seconds to complete)	112.0 (38.3)	76.1 (25.4)	**<0.0001**	0.079
	D-KEFS Verbal Fluency Test Letter fluency (number of words)	36.6 (14.1)	51.0 (15)	0.004	0.026
	D-KEFS Verbal Fluency Test Category fluency (number of words)	32.0 (10.1)	40.1 (11.1)	0.009	0.066
	D-KEFS Verbal Fluency Test Category switching (number correct)	10.3 (3.7)	13.5 (2.8)	0.002	0.081

*Mann Whitney U-test for nonparametric variables. *General linear model, multivariate, with General Ability. Bonferroni correction for multiple comparisons: significant p-values ($p < 0.001$) in bold.*

MCI, Mild Cognitive Impairment, CVLT-II, California Verbal Learning Test 2rd edition, WAIS-IV, Wechsler Adult Intelligence Scale 4th edition, WMS-III, Wechsler Memory Scale 3rd edition, D-KEFS. Delis Kaplan Executive Function System.

(p <0.0001), and when comparing the amnestic MCI and nonamnestic MCI group ($p = 0.006$). A pathological PA score was found in 23 subjects; nine (26%) in the amnestic group, four (25%) in the nonamnestic group and 10 (20%) in the control group ($p = 0.477$). Similarly, Fazekas score was rated as pathological for 23 subjects, nine (26%) in the amnestic MCI group, four (25%) in the nonamnestic MCI group, and 10 (20%) in the control group ($p = 0.477$). A total of 11 participants had pathological GCA-F scores; seven (20%) in the amnestic subgroup, none in the nonamnestic subgroup and four (7%) in the control group. The mean GCA-F score was not different between MCI patients and controls, but there was a significant mean group difference ($p = 0.002$) between the amnestic and the nonamnestic MCI groups.

Structure—Function Relationships

Table 8 shows the relationships between cognitive domain z-scores and the different MRI scores in the MCI group. The MTA score showed a significant correlation with episodic memory/long delay recall domain score ($R^2 = 0.100$, $p = 0.043$). PA score significantly correlated with working memory domain scores ($R^2 = 0.106$, $p = 0.043$), while GCA-F score significantly correlated with episodic learning/short delay recall domain scores ($R^2 = 0.100$, $p = 0.036$). An increased radiological atrophy score correlated to lower performance score. Fazekas score showed no significant correlation with either of the cognitive domain scores. When looking at structure-function relationships in the control group, no correlations were found between MRI scores and domain scores, except between the GCA score and processing speed ($p = 0.006$). However, only four controls obtained pathological GCA scores.

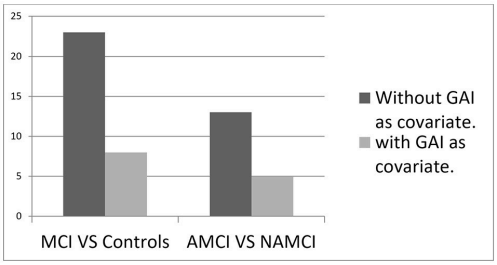

FIGURE 1 | The number of significantly inferior test ($p < 0.001$) in MCI compared to controls or in amnestic MCI (AMCI) compared to nonamnestic MCI (NAMCI).

DISCUSSION

The study presents descriptive cross-sectional data on functional and structural profiles of Memory clinics patients with MCI. As expected, patients diagnosed with MCI had overall lower performance on the neuropsychological tests and higher scores on visually rated MRI pathology scales compared to age, gender and SES-matched controls. Interestingly, after controlling for intelligence assessed by GAI from the test WAIS-IV, fewer of the neuropsychological tests remained abnormal in amnestic and nonamnestic MCI patients. One possible interpretation of this finding is that intelligence is a moderator of neuropsychological performance. Another interpretation is that intelligence is a confounder. One might argue that GAI is not a valid proxy of cognitive reserve in an MCI population, as the results of the tests that are included in the GAI may be reduced due to a disease process. It is one standard deviation (SD) difference between the MCI group and the control group. Nevertheless, the mean of all the individual subtests in the GAI in the MCI group lies within a normal range.

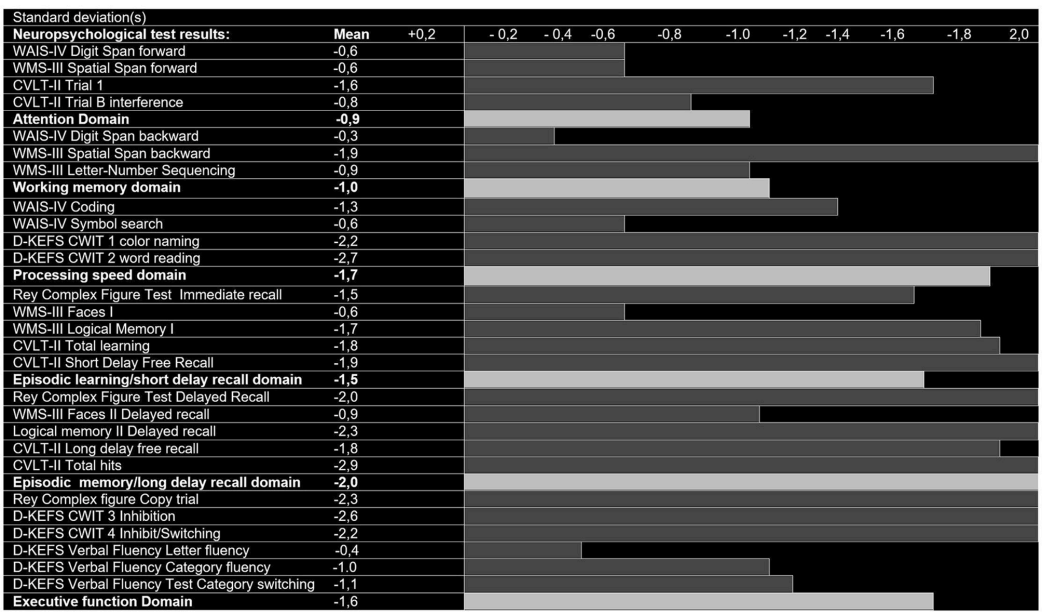

FIGURE 2 | Neuropsychological test results (SD below zero), control group-derived z-scores in patients with amnestic Mild Cognitive Impairment (aMCI, $n = 35$).

Apparently, intelligence operationalized as GAI moderates group differences on the cognitive profiles in patients with MCI compared to controls. GAI also moderates the difference on the profiles between patients with amnestic and nonamnestic MCI. These findings are consistent with the literature that emphasized low test scores do not equal pathology—obtaining multiple low scores may or may not be a sign of a pathological condition. Brooks and Iverson (2010) recommend utilizing knowledge of the frequency of low test scores (base rates) to interpret reduced performance in neuropsychological assessment in general. The base rates of low scores vary in relation to intelligence (Ingraham and Aiken, 1996; Crawford et al., 2007; Brooks and Iverson, 2010; Smith and Bondi, 2013). Without a robust operationalization of, or correction for, general cognitive function, too much emphasis may be placed on low scores for those with low general cognitive function, and similarly, too little on reduced test scores for those with high general cognitive function. Having one or more scores 1,5 SD below the mean is uncommon in cognitively healthy people with superior intelligence, and common in cognitively healthy people with lower intelligence (Brooks et al., 2007). If a clinician applies the same cut-off score for patients with either low or high general cognitive ability, this may lead to an underestimation of the cognitive deficits as "normal" in a high cognitively functioning person, or an overestimation of the cognitive deficits as "not normal" in a low cognitively functioning person. This might apply to commonly used cut-off scores for identifying MCI. One interpretation of our data is that it might be useful to control for intelligence by the use of GAI from WAIS-IV, in the interpretation of test results of patient suspected of having MCI. This might help minimize the risk of false positive diagnosis in individuals with low premorbid general abilities, and false negative diagnosis in individuals with high premorbid general abilities.

We found that individuals with amnestic MCI had significantly overall lower neuropsychological test performance compared to controls, with cognitive profiles that indicate severe functional impairment. They also had lower overall performance compared to the nonamnestic MCI subtype. This is in accordance with the large body of existing research on MCI, viewing amnestic MCI as a more severe pathological condition that diverges from cognitive changes associated with normal aging (Petersen et al., 1997; Petersen and Morris, 2005; Smith and Bondi, 2013).

As hypothesized, we found that the MCI group had higher MTA scores on the visual MRI scales compared to controls, which indicate higher prevalence of brain pathology in this patient group. The MCI group displayed significantly higher MTA scores than the control group. No significant difference was found between the groups when comparing the other visual scores. This is in accordance with Duara et al. (2013) and Rhodius-Meester et al. (2017) who reported MTA as the only scale that differentiated MCI patients from controls. In the present study, MTA scores also differentiated amnestic and nonamnestic MCI patients, but not nonamnestic MCI patients from controls. These results are consistent with findings of larger hippocampal volumes in nonamnestic MCI subtypes compared to amnestic subtypes, as reported by Vos et al. (2013) and van de Pol et al. (2009). However, our findings are contrary to studies reporting greater MTA scores in the nonamnestic MCI subtypes compared to controls (van de Pol et al., 2009; Vos et al., 2013). These different results may partly be explained by a higher average age of the patients with nonamnestic MCI subtypes compared to controls in previous studies. MTA score is considered age sensitive (Rhodius-Meester et al., 2017) and more frequently present in individuals older than 70 years of age (van de Pol et al., 2009).

GCA-F scores indicated greater frontal lobe atrophy in the amnestic MCI subtype compared to the nonamnestic subtype. Whitwell et al. (2008) showed regional frontal atrophy in both the amnestic multiple domain MCI group and the single domain nonamnestic MCI group by using an automated segmentation method. None of our nonamnestic participants had high GCA-F scores. One explanation might be that the atrophy is more localized in these individuals and therefore not severe enough to be identified by the GCA-F scale. Our sample size of nonamnestic patients is small, and the results may diverge in a larger study sample.

The PA rating showed similar mean group scores between the amnestic MCI and nonamnestic MCI subtype groups. This finding is consistent with previous volumetric studies that found no difference in parietal lobe volumes between subtypes of MCI patients (Whitwell et al., 2008; van de Pol et al., 2009). Similarly, the Fazekas scale ratings did not differentiate the subtype groups in the present study. Previous studies of MCI patients have found a stronger association to age than MCI subtypes using the Fazekas scale (Bombois et al., 2007; Rhodius-Meester et al., 2017). Hence, the lack of group differences in pathological Fazekas score between MCI patients and controls in the present study is in agreement with previous population studies (Schmidt et al., 2011; Prins and Scheltens, 2015; Claus et al., 2016). The MCI-patients with higher MTA scores had the greatest reduction in performance on tests related to episodic memory. This finding is in line with the large body of prior studies demonstrating that the hippocampus is one of the neural substrates for episodic memory formation (Ranganath et al., 2005; Nichols et al., 2006; Lewis-Peacock and Postle, 2008).

In contrast, the frontal lobe score GCA-F correlated with performance on the episodic learning. This is in accordance with studies reporting that episodic learning (encoding) is mediated by brain structures involving the prefrontal cortex in addition to hippocampus (Nee and Jonides, 2011; Harding et al., 2015). Although the frontal lobes is known to be involved in executive function, the frontal lobe score GCA-F did not correlate with performance on the executive functioning domain scores in the MCI patients in our study. The problems with operationalizing executive functions has been addressed previously in a meta-analysis by Alvarez and Emory (2006), were they examine the validity of the executive function-construct as measured by cognitive tests in relation to frontal lobe damage. They concluded with "inconsistent support for the historical association between executive functions and the frontal lobes" (Alvarez and Emory, 2006, p. 33). Recent studies has focused on executive functions in relation to neural networks, rather than a regional anatomical/structural frame of reference (Weiler et al.,

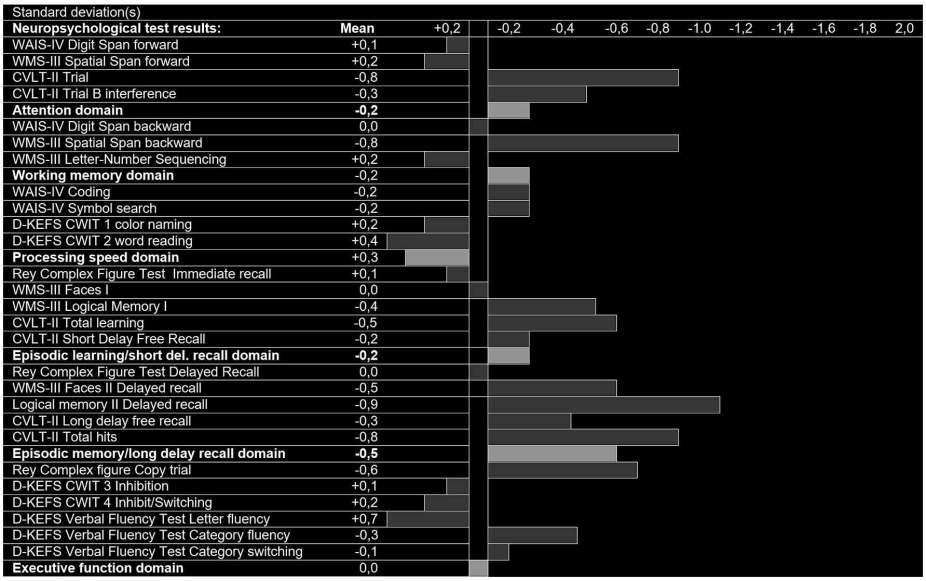

FIGURE 3 | Neuropsychological test results (SD below zero), control group-derived z-scores in patients with nonamnestic Mild Cognitive Impairment (naMCI, $n = 16$).

TABLE 7 | Prevalence of pathological MRI scores and their statistical characteristics according to diagnosis.

MRI scoring systems/prevalence:	Controls $n = 51$	MCI $n = 51$	*p*-value	aMCI $n = 35$	naMCI $n = 16$	*p* -value
MTA (%)	3(6%)	21(41%)	***0.000***	19(54%)	2 (12,5%)	***0.006***
PA (%)	10(20%)	13(25%)	*0.477*	9(26%)	4(25%)	*0.957*
GCA-F (%)	4(7%)	7(14%)	*0.338*	7(20%)	0(0%)	*0.054*
Fazekas Dicom (SD) (%)	10(20%)	13(25%)	0.477	9(26%)	4(25%)	0.957
# N with pathological score (%)	17(33%)	31(61%)	***0.010***	25(71%)	6(37.5%)	*0.031*
# N with ≥ 2 pathological scores (%)	7(13%)	16(31%)	*0.057*	13(37%)	3(18%)	*0.329*
MRI SCORING SYSTEMS/CHAR:						
MTA combined mean (SD)	0.314(0.469)	0.902(0.860)	***0.000***	1.04(0.915)	0.594(0.66)	*0.054*
PA mean(SD)	0.94(0.732)	1.04(0.732)	*0.776*	0.97(0.568)	0.69(0.704)	*0.776*
GCA-F mean (SD)	0.71(610)	0.75(0.688)	*0.761*	0.91(0.702)	0.38(0.500)	***0.002***
Fazekas (SD)	1.14(0.722)	1.23(0.690)	*0.398*	0.94(0.772)	1.02(0.678)	*0.184*

Prevalence group difference significance by Chi Square, Mean difference by two tailed independent sample T-test.
MCI, Mild cognitive impairment, aMCI, amnestic MCI, naMCI, nonamnestic MCI, MTA, Medial temporal lobe atrophy score; GCA-F, Global cortical atrophy score—Frontal subscore; PA, Koedam score for parietal atrophy. Significant p-values ($p < 0.05$) in bold.

2014; Beaty et al., 2015; Crittenden et al., 2015; Brown et al., 2017; Filippi et al., 2017). The lack of correlation between the GCA-F scores and the executive function domain may also be due to the fact that some executive function tests have high sensitivity for assessing brain injury, but may have low specificity. Damage to a wide variety of brain regions may affect executive function test performance while isolated frontal damage may not always result in deficits in executive function that can be detected by tests (Mesulam, 1998; Strauss et al., 2006; Hestad and Egeland, 2010; Lezak, 2013). Furthermore, in our MCI patients, the scores on the working memory domain correlated inversely with the parietal lobe atrophy score. This finding is similar to a previous study that found decreased connectivity between the prefrontal cortex and posterior parietal regions in early onset AD (Filippi et al., 2017). Atrophy of parietal regions is also correlated with reduced working memory function in functional MRI (fMRI) studies of healthy controls (Honey et al., 2002). PA score on structural MRI may be a useful indicator

TABLE 8 | Correlations between MRI scores and cognitive domains Z-scores in MCI patients.

Domain name/ radiological score		MTA	PA	Fazekas	GCA-F
Attention domain	*p(CI95)*	*0.565*(−0.319–0.176)	*0.231*(−0.455–0.087)	*0.377*(−0.477–0.172)	*0.159*(−0.553–0.093)
	R^2	0.019	0.042	0.029	0.053
Processing speed domain	*p(CI95)*	*0.157*(−0.757– 0.126)	*0.778*(−0.450–0.597)	*0.573*(−0.725–0.406)	*0.094*(−0.088–1.076)
	R^2	0.088	0.050	0.012	0.104
Working memory domain	*p(CI95)*	*0.139*(−0.521–0.075)	***0.043*(–0.690– – 0.011)**	0.759(−0.443–0.325)	*0.093*(−0.729–0.059)
	R^2	0.069	**0.106**	0.026	0.081
Episodic learning/short delay recall domain	*p(CI95)*	*0.105*(−0.623–0.061)	*0.247*(−0.637–0.168)	*0.832*(−0.489–0.395)	***0.036*(–0.924– – 0.031)**
	R^2	0.065	0.039	0.005	**0.100**
Episodic memory/long delay recall domain	*p(CI95)*	***0.043*(–0.706–−0.011)**	*0.355(−0.612–0.224)*	*0.659*(−0.556–0.335)	*0.072*(−0.896–0.040)
	R^2	0.**100**	0.035	0.022	0.084
Executive function domain	*p(CI95)*	*0.876*(−0.113–0.132)	*0.224*(−0.226–0.054)	*0.787*(−0.175–0.133)	0.*662*(−0.127–0.199)
	R^2	0.006	0.036	0.007	0.009

MTA, Scheltens Middle temporal lobe atrophy score, Fazekas White matter hyperintensity score. (Fazekas score). Average Frontal subscore of Global Cortical Atrophy score (GCA-F). Posterior atrophy score (PA). CI(95%) for Beta. Domain Z scores are composed from a mean score from the respective domain scores. Linear regression analyses were performed with age and sex as covariates. Significant p-values ($p < 0.05$) in bold.

of reduced working memory function in MCI patients. Since the PA score may be more readily used in clinical settings than fMRI and semi-automated morphometric analyses, it may be a convenient tool for clinicians as an objective biomarker to corroborate with neuropsychological assessment of the patients' working memory function. The lack of correlation between the Fazekas score and any neuropsychological domain scores in our MCI patients may be a result of the minimal regional information included in the Fazekas rating scale. The literature regarding WMH and their relationship to neuropsychological domains remains somewhat controversial. Some studies have reported that a greater white matter hyperintensity frequency is associated with poorer executive function and/or slower processing speed (Tullberg et al., 2004; Prins and Scheltens, 2015). Other studies have reported a lack of domain-specific relationship, but found an impact on global cognition (Overdorp et al., 2014).

STRENGTHS AND LIMITATIONS

A strength of this study is that the study sample is well-defined, consisting of patients diagnosed in hospital-based Memory clinics by experienced multidisciplinary teams using national assessment guidelines. Furthermore, we matched the groups on SES in addition to age and sex. We used three scales for the brain MRI measures that took in to consideration both neurodegenerative and vascular factors. We included comprehensive neuropsychological assessment in order to cover all major neuropsychological domains, administrated by the same experienced neuropsychologist. The MRI scoring was performed by two experienced radiologists blinded to the group adherence and viewing the images independently and had consensus ratings when discrepancies occurred. A limitation is that the study population is small; therefore the results should be interpreted with caution. As such, nonsignificant group differences may be due to insufficient power from the relatively small sample size. Low specificity and high sensitivity of the neuropsychological tests may have impacted the lack of correlation between the GCA-F and the executive function domain tests.

CONCLUSION AND CLINICAL APPLICATIONS

Intelligence emerges as a strong covariate in the analyses of group differences in the cognitive profiles. Based on our data, we consider GAI useful as an operationalization of the general cognitive function criteria of MCI. Further, applying the GAI in general clinical assessments of MCI patients may be helpful in the diagnostic process to reduce the risk of false positive or false negative diagnosis by relating the neuropsychological test results to each individual's GAI-result before confirming the diagnosis of MCI.

The tests less influenced by GAI in our study were the tasks within the verbal episodic learning and memory domain, and a verbal fluency (categorizing) task within the executive function domain. Patients with the amnestic MCI subtype was expected to have poorer cognitive outcomes. In this material their neuropsychological profiles emerged as significantly impaired in multiple cognitive domains compared to the nonamnestic MCI patients.

Our findings may suggest that neuropsychological tests and the MRI rating scores measure different aspects of the MCI condition. Also, patients with MCI is a heterogeneous group that have a variety of reasons for their cognitive impairment, and the impairment do not necessarily have a structural brain correlate. However, the usefulness of the MRI rating scores, except for the MTA scores, appears to be low in identifying an MCI condition. In older adults with MCI, a pathological MTA score suggests that the patient should be further assessed for MCI. However, a MTA score within the normal range does not exclude MCI.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the Norwegian Regional Committee

for medical and health research ethics, South-Eastern Health region (no: 2013/410) and by the Department of Research at each collaborating hospital with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Norwegian Regional Committee for medical and health research ethics, South-Eastern Health region (no: 2013/410).

AUTHOR CONTRIBUTIONS

MF conception and design of the study's neuropsychological part, data collection, data analysis and interpretation, drafting the article, critical revision of the article and final approval of the version to be published. HH conception and design of the study's radiological part, data collection, data analysis and interpretation, drafting the article, critical revision of the article and final approval of the version to be published. SH and JS conception and design of the study, data collection, data analysis and interpretation, drafting the article, critical revision of the article and final approval of the version to be published. LC conception and design of the study, data interpretation, critical revision of the article and final approval of the version to be published. TE conception and design of the study's radiological part and final approval of the version to be published. AE, B-OM, A-BK, and TL data collection and critical revision of the article and final approval of the version to be published. KB data analysis, critical revision of the article and final approval of the version to be published. EL data analysis and interpretation of the study's radiological part, critical revision of the article and final approval of the version to be published. IU input on the study design, data collection and critical revision of the article and final approval of the version to be published. GL P.I of the study, conception and design of the study, data collection, data analysis and interpretation, drafting the article, critical revision of the article and final approval of the version to be published.

FUNDING

This work was funded by the South-Eastern Norway Regional Health Authority (MF, Grant No. 2013059 and HH, Grant No. 2015046) and Sørlandet Hospital HF.

ACKNOWLEDGMENTS

We thank senior researcher PhD Vanessa Douet-Vannucci, ON(e)Life, R&D Department, Marseille, and statistician Are Pripp, Oslo Centre of Biostatistics and Epidemiology Research Support Services, Oslo University Hospital, Professor Yonas E. Geda, Department of Psychiatry & Psychology and Department of Neurology, Mayo Clinic, Scottsdale for valuable input on the manuscript. We thank the study participants for their interest and cooperation in the project, and acknowledge the Norwegian Registry for persons being evaluated for cognitive symptoms in specialized care (NorCog) for patient data. We also thank Sørlandet Hospital, Norway.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Paper II

frontiers | Frontiers in Aging Neuroscience

ORIGINAL RESEARCH
published: 04 April 2022
doi: 10.3389/fnagi.2022.796110

Cortical Thickness Changes After Computerized Working Memory Training in Patients With Mild Cognitive Impairment

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Edited by:
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Specialty section:
This article was submitted to Neurocognitive Aging and Behavior, a section of the journal Frontiers in Aging Neuroscience

Received: *15 October 2021*
Accepted: *21 February 2022*
Published: *04 April 2022*

Citation:
Hol HR, Flak MM, Chang L, Løhaugen GCC, Bjuland KJ, Rimol LM, Engvig A, Skranes J, Ernst T, Madsen B-O and Hernes SS (2022) Cortical Thickness Changes After Computerized Working Memory Training in Patients With Mild Cognitive Impairment. Front. Aging Neurosci. 14:796110. doi: 10.3389/fnagi.2022.796110

Background: Adaptive computerized working memory (WM) training has shown favorable effects on cerebral cortical thickness as compared to non-adaptive training in healthy individuals. However, knowledge of WM training-related morphological changes in mild cognitive impairment (MCI) is limited.

Objective: The primary objective of this double-blind randomized study was to investigate differences in longitudinal cortical thickness trajectories after adaptive and non-adaptive WM training in patients with MCI. We also investigated the genotype effects on cortical thickness trajectories after WM training combining these two training groups using longitudinal structural magnetic resonance imaging (MRI) analysis in Freesurfer.

Method: Magnetic resonance imaging acquisition at 1.5 T were performed at baseline, and after four- and 16-weeks post training. A total of 81 individuals with MCI accepted invitations to undergo 25 training sessions over 5 weeks. Longitudinal Linear Mixed effect models investigated the effect of adaptive vs. non-adaptive WM training. The LME model was fitted for each location (vertex). On all statistical analyzes, a threshold was applied to yield an expected false discovery rate (FDR) of 5%. A secondary LME model investigated the effects of *LMX*1A and *APOE*-ε4 on cortical thickness trajectories after WM training.

Results: A total of 62 participants/patients completed the 25 training sessions. Structural MRI showed no group difference between the two training regimes in our MCI patients, contrary to previous reports in cognitively healthy adults. No significant structural cortical changes were found after training, regardless of training type, across all participants. However, *LMX*1A-AA carriers displayed increased cortical thickness trajectories or lack of decrease in two regions post-training compared to those with

*LMX*1A-GG/GA. No training or training type effects were found in relation to the *APOE*-ε4 gene variants.

Conclusion: The MCI patients in our study, did not have improved cortical thickness after WM training with either adaptive or non-adaptive training. These results were derived from a heterogeneous population of MCI participants. The lack of changes in the cortical thickness trajectory after WM training may also suggest the lack of atrophy during this follow-up period. Our promising results of increased cortical thickness trajectory, suggesting greater neuroplasticity, in those with *LMX*1A-AA genotype need to be validated in future trials.

Keywords: cortical thickness, MCI, *APOE* genotype, *LMX*1A, working memory training

INTRODUCTION

Mild Cognitive Impairment (MCI) describes individuals with reduced cognitive function with age not severe enough to meet the criteria of dementia, but more pronounced than the normal age-related cognitive decline reported in healthy controls (Petersen et al., 1997; Langa and Levine, 2014). Individuals with MCI have a 10-fold higher risk of developing dementia compared to healthy adults at the same age (Petersen et al., 1999; Petersen, 2009). Worldwide, the cost of dementia was estimated to be more than 1 trillion USD in 2020 (Prince et al., 2015). Any treatment that can prevent or delay the conversion from MCI to dementia would thus impact the global economy significantly.

Currently, there is no treatment available for MCI, but studies suggest that cognitive training based on the principles of neuroplasticity may aid in delaying the decline in cognitively unimpaired older adults (Smith et al., 2009; Zelinski et al., 2011; Butler et al., 2018). Repeated cognitive stimulation is thought to improve myelination and increase synaptic density in the brain, thereby improving function (Maas and Angulo, 2021). Adaptive computerized cognitive training, with dynamically increased workloads, was found to be effective in improving untrained cognitive functions utilizing the same neural connections as trained tasks (Klingberg et al., 2002). Effects of training may persist for up to 10 years post intervention (Rebok et al., 2014). Studies focusing on the effect of cognitive training in MCI patients have demonstrated improvement of cognitive functions and transfer effects to non-trained domains (Belleville et al., 2006; Talassi et al., 2007; Flak et al., 2019). However, these few studies showed mixed results, possibly due to the heterogeneous phenotypes within the MCI population with various underlying brain pathologies or co-morbid conditions. In addition, the lack of standardized training methods and outcome measures in the field of cognitive training further complicates comparison across studies.

A pair of recent meta-analytic reviews of efficacy of cognitive intervention in individuals with MCI indicates significant overall effects for intervention content, with memory focused interventions appearing to be more effective than multidomain approaches (Sherman et al., 2017; Zhang et al., 2019a). Since reduced working memory (WM) is prevalent in MCI patients and occurs both in the amnestic (memory impaired) and non-amnestic (memory intact) MCI subtypes (Salthouse and Meinz, 1995), focused WM training may be particularly effective. WM is considered to be a core cognitive function and refers to the temporary maintenance of information that is no longer present in the environment for use in ongoing cognition (Nee and D'Esposito, 2018). WM capacity is dependent on a widespread brain network that includes, but not limited to, the supramarginal gyrus, the dorsolateral prefrontal cortex, and medial prefrontal and lateral parietal cortex and the insular bilaterally (Tomasi et al., 2005, 2007; Rottschy et al., 2012), as shown on functional magnetic resonance imaging (MRI) studies.

Furthermore, structural MRI provides a non-invasive *in vivo* approach to visualize the brain changes associated with neuroplasticity beyond theories and models. In healthy middle aged and older adults, Engvig et al. (2010) found increased insular thickness after cognitive training. In addition, increased thickness in the right caudal middle frontal cortex and increased volume of the right pallidum were found in healthy adults only after adaptive computerized WM training, but not after non-adaptive training (Metzler-Baddeley et al., 2016). In contrast, Takeuchi et al. (2011) found decreased thickness both in the frontoparietal region and left temporal superior gyrus after an adaptive multiplication task in a group of students, while Lawlor-Savage et al. (2019) reported no quantitative change after a WM task (N-back) training. Only a few morphometry studies of cognitive training were performed in patients with brain pathologies; no changes after training were found in stroke patients (Nyberg et al., 2018), and a meta review from 2018 found small but supporting evidence of structural neuro plasticity in brain-injured patients after training (Caeyenberghs et al., 2018).

Genetic factors may also impact the effect of cognitive training. Specifically, since dopaminergic function plays an important role in WM and other executive functions (Goldman-Rakic, 1996; Salami et al., 2019), polymorphism of the Lim homeobox transcription factor-alpha (*LMX*1A) gene, which is involved in the maintenance of dopaminergic neurons, was evaluated in relation to WM training (Bellander et al., 2011). Dopaminergic synapses are critical in plasticity (Soderqvist et al., 2012), and reduction in dopaminergic transporters or receptors were related to the effects of aging and cognitive deficits (Chang et al., 2008; Li et al., 2010). Chang et al. (2017)

found that functional gain after WM training was greater in patients with HIV-associated neurocognitive disorders who had the *LMX*1A-AA genotype compared to those with the *LMX*1A-GG/GA genotypes. Further, Hernes et al. (2021) found that patients with non-amnestic MCI had greater training gains than a group with amnestic MCI, especially in those with the *LMX*1A-AA genotype.

Another gene that may impact the effects of cognitive training is apolipoprotein epsilon 4 (*APOE*ε4) since having this allele is a potent risk factor for late onset Alzheimer's disease (Huang and Mucke, 2012). Reduced synaptic plasticity in older adults with *APOE*ε4 carriers (Belleville et al., 2011) may theoretically be related to reduced effect of cognitive training. However, Hernes et al. (2021) found improved WM training gains in MCI patients with the *APOE*ε4 allele, since this allele may demonstrate an antagonistic pleiotropy effect benefiting younger and middle age individuals (Tuminello and Han, 2011; Chang et al., 2016). Similarly, compared to individuals without the *APOE*ε4 allele, the ε4 carriers showed greater compensation, both in magnitude and extent in neuronal activation in the inferior frontal gyrus in the prefrontal cortex during a WM task (Scheller et al., 2017). Nevertheless, *APOE*ε4-carriers with the amnestic type of MCI may not benefit from this allele; in the study by Hernes et al. (2021) amongst the *APOE*ε4-carriers, the amnestic MCI patients showed significant decline in executive function at 16 weeks after the WM training while the non-amnestic MCI patients showed significant improvements. How the *APOE*ε4 allele might impact brain morphometry after WM training is unknown and was explored in the current study.

In this prospective randomized controlled multicenter trial, we investigated the effects of adaptive and non-adaptive WM training on gray matter morphology in individuals with MCI. Based on prior reports, we hypothesized that cortical thickness would increase in regions associated with WM, in particular the prefrontal cortices and the precuneus, after WM training. Furthermore, we explored possible training effects in cortical thickness associated with allelic variations in *APOE*ε4 and *LMX*1A genotypes through secondary analyzes.

MATERIALS AND METHODS

Ethics

The Norwegian Regional Committee for medical and health research ethics, South-Eastern Health region (no: 2013/410) and the Department of Research at each collaborating hospital approved the study registered in ClinicalTrials.gov (NCT01991405).

Study Design

This is a multicenter randomized controlled double-blind trial (Flak et al., 2014). Individuals with MCI were recruited from the memory clinics at four hospitals in the South-Eastern Health Region of Norway (Sørlandet Hospital Arendal, Telemark Hospital, Oslo University Hospital, and Diakonhjemmet Hospital). The study period was from August 2013 to December 2016.

Participants/Sample

A total of 461 individuals were diagnosed at the four centers during the study period; 85 of these individuals consented to participate in the current study. The participants were assessed with neuropsychological tests, questionnaires regarding their risk factors, and MRI of the brain as specified by the Norwegian national guidelines established by the Norwegian register of persons assessed for cognitive symptoms (NorCog). Diagnosis of MCI was made in accordance with the Petersen/Winblad criteria for MCI (Petersen, 2004; Winblad et al., 2004). The Socioeconomic status (SES) was assessed with Hollingshead's index of education and occupational position, scaled from 1 (low) to 5 (high) (Hollingshead and Redlich, 2007).

The participants underwent neuropsychological assessment and brain MRI as previously described (Flak et al., 2014, 2019). Exclusion criteria included head trauma with a history of post-traumatic brain injury with loss of consciousness, photosensitive epilepsy or any contraindication for MRI (e.g., ferromagnetic metallic implants or severe claustrophobia), use of acetylcholinesterase inhibitors or other antidementia drugs. From the 85 participants enrolled initially, one declined due to MRI contraindications, and two were not willing to travel for the MRI examinations. Eighty-two participants were then randomized for the study; from these participants, 64 completed the training, and 62 had MRI scans from at least two timepoints and were included in the current analysis. Fifty-eight of the 62 participants consented to donate saliva for genetic analysis, but 4 of these participants dropped out of the study and four samples yielded inconclusive results, see **Figure 1**.

Cognitive Training

The participants were randomized to either adaptive or non-adaptive cognitive training in accordance with the framework proposed by Simon et al. (2016). The cognitive training was performed at home on the participant's own computer using the Cogmed WM training program (Klingberg et al., 2005; Klingberg, 2010; Flak et al., 2019). The Cogmed training program consists of several "games" challenging various types of WM. The adaptive training version increases the difficult as the user becomes more skilled, whereas the non-adaptive remains fixed at a low level. The trainers were Cogmed certified, followed the recommended coaching procedures, and monitored the individual participant's progress continuously *via* reports from the Cogmed software. During training, all participants received phone calls, at least once a week, to follow up on their progress and to motivate them; the calls were made by one of the researchers who followed the participants' training through an online secured site. Both intervention groups followed the standard protocol (30–40 min of training per day, 5 days per week for 5 weeks). We considered the training completed if the participants finished 20 or more of 25 training sessions (Flak et al., 2019). The different tasks in the program are described in detail in the **Supplementary Material**.

Imaging

Magnetic resonance imaging's were obtained before the initiation of training at baseline (timepoint 1 = tp1), time from cessation

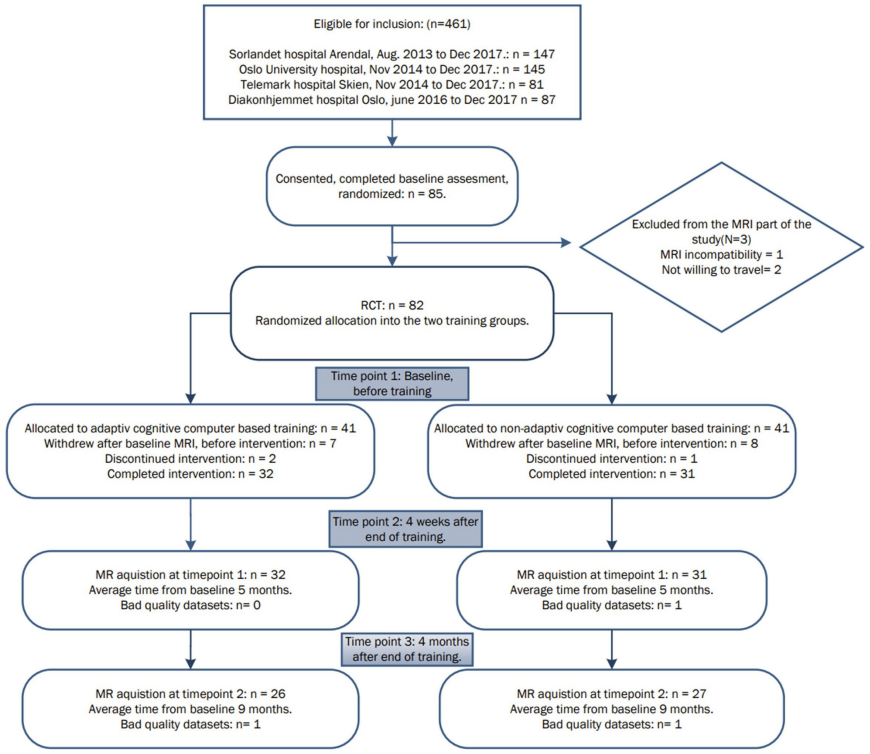

FIGURE 1 | Overview of the patient inclusion process and visits during the study.

of training to second and third image acquisition were kept at similar time intervals; four ± 0.19 weeks after training (timepoint 2 = tp2), and 16 ± 0.72 weeks after training cessation (timepoint 3 = tp3). The total period of follow-up from baseline were 22 ± 1.24 weeks across all participants. Images were acquired on two Siemens 1.5 T Aera scanners (one located in Sorlandet Hospital, Arendal and one at Oslo University Hospital – Rikshospitalet). The MRI setup was identical at both scanners, with the same versions of 20 channel head and neck coils and software (VE11). The MRI sequences included two three-dimensional magnetization-prepared rapid gradient-echo (3D MP-RAGE) scans (sagittal, echo time 3.47 ms, repetition time 2,400 ms, TI 1,000 ms, flip angle 8 degrees, 1.2 mm resolution covering the whole brain). Two test persons were scanned on both machines to assess systematic errors on brain volumes. The participants were scanned on the same scanner at baseline and at each follow-up timepoint. All images were inspected at the MRI console for motion artifacts or other artifacts before the patients were discharged from the MRI facility. Scans with visible motion artifacts were repeated within the same MRI session (Reuter et al., 2015). However, one scan at timepoint 2 and 2 scans at timepoint 3 were discarded due to excessive head motion.

Postprocessing

Images were converted from DCM image format to Nifti format by the DCM2NIX software.[1] The FreeSurfer V.6.0[2] longitudinal processing pathway was used on a small HT condor[3] computer cluster consisting of three AMD Ryzen© 1800x/1700x CPU equipped workstations, and one AMD Threadripper© 1950x CPU equipped workstation all with ECC memory correction. Cortical reconstruction and segmentation were conducted within the FreeSurfer software suite as described in previous publications (Segonne et al., 2004; Reuter et al., 2010; Reuter and Fischl, 2011).

The longitudinal pathway utilized all the available images for each patient. Twelve participants only had baseline images (tp1) and images 4 weeks after cessation of training (tp2), and 51 participants had MRI images from all three timepoints.

[1]https://github.com/rordenlab/dcm2niix
[2]https://surfer.nmr.mgh.harvard.edu/
[3]https://research.cs.wisc.edu/htcondor

We inspected each scan for skull stripping failure as well as other known errors. The resulting longitudinal cortical thickness parameter was chosen, as it was considered the most reliable for being a surrogate biomarker (Winkler et al., 2018) for a potential WM training effect. Surface maps were resampled to the fsaverage sample provided with Freesurfer, and smoothed with the standard 2D Gaussian smoothing kernel at a value of 30 mm (fwhm) supplied with Freesurfer, as part of the postprocessing procedure, before statistical analysis. Furthermore, the rationale behind the smoothing was to minimize false-positive while still retaining maximum statistical power and counteract some of the anatomical differences between the subjects that the registration process didn't adapt perfectly and decrease inter-subject variability (Lerch and Evans, 2005; Stelzer et al., 2014; Zeighami and Evans, 2021).

Genotyping/DNA Collection

Saliva for genotyping was harvested in Oragene Self collection Kit (DAN Genoteck, Inc., Ottawa, ON, Canada) from the participants at study enrolment. Genomic DNA was analyzed with Restriction Fragment Length Polymorphism (RFLP-PCR) for genotype analyzes of *APOE*ε (rs429358 and rs7412) and *LMX*1A (rs4657412), as reported previously (Hernes et al., 2021).

Statistics

The sample size was calculated on the primary outcome: any group difference in the cortical thickness trajectories. Cohen's effect size was used to calculate the number of patients for inclusion. To obtain a strong medium effect with Cohen's effect size of 0.6, approximately 45 patients in either group were needed.

Longitudinal cortical data were analyzed in MATLAB (Mathworks, version 2016a) using a spatiotemporal linear mixed effects model (LME) module supplied with the Freesurfer software. The LME model was fitted for each location (vertex) of the cortical surface (Bernal-Rusiel et al., 2013). To adjust for multiple comparisons, the two p-maps from left and right hemispheres were combined to give equal threshold for both hemispheres. On all statistical analyzes, a threshold was applied to yield an expected false discovery rate (FDR) of 5% (Benjamini et al., 2006) across both hemispheres, to correct for multiple comparisons and prevent false positive results.

First, in order to investigate whether the two groups had similar brain morphometry trajectories over time, a LME model was fitted with cortical thickness as the dependent variable and time (months since first scan), sex, training type (adaptive or non-adaptive), age (at baseline), scanner site (1 at Arendal and 2 at Oslo), and interaction (time × training type) as independent variables. We also used intecept as random factor in all our LME models (**Supplementary Table 1**).

Cohen's D for effect size maps were created using a GLM model fitted for each location (vertex), creating maps of the training types' effect size in a MATLAB model for each timepoint, with the same variables as with the LME model without interaction and random factor.

Secondary analyzes of genotype effects on cortical thickness were conducted on the 50 participants with valid genotype data. Since the two training types showed no group differences on cortical thickness trajectories, the analysis was performed by combining both training types into one group, as we had done in previous analyzes (Hernes et al., 2021). To investigate a possible influence of the *LMX*1A genotype, an LME model was fitted with cortical thickness as dependent variable and time, gender, training type, age, study site, *LMX*1A (AA vs. GG/GA variant), and interaction (time × *LMX*1A genotype) as independent variables, and intercept as random factor. Since only two participants had the GG alleles in the *LMX*1A group, they were combined with the AG alleles group.

To investigate a possible influence of the *APOE*ε gene variants on cortical thickness trajectories, a LME model was fitted with cortical thickness as a dependent variable and time, sex, training type, age, scanner site, presence of *APOE*ε4 allele (ε2/ε2, ε2/ε3, or ε3/ε3 versus ε2/ε4, ε3/ε4 or ε4/ε4), and interaction (time × *APOE*ε gene variants) as independent variables (Chang et al., 2017; Hernes et al., 2021).

Results

No significant baseline group differences between the two training groups were found for age, sex, socioeconomic status, years of education and full-scale IQ (**Table 1**). By chance, more of the participants with the *LMX1*A-AA genotype were enrolled in the adaptive training group than the non-adaptive training group.

TABLE 1 | Clinical characteristics for the adaptive and non-adaptive training groups including genome.

	Adaptive training (*n* = 32)	Non-adaptive training (*n* = 30)	*p*-value	Total (*n* = 62)
	Mean (SD)	Mean (SD)		Mean (SD)
Age (years)†	66 (9)	68 (9)	0.326	67 (9)
Sex$^{\chi 2}$	24 Men/8 Women	17 Men/13 Women	0.127	41 Men/21 Women
Socioeconomic status $^{\chi 2}$	3.4 (1.19)	3.38 (1.18)	0.934	3.39 (1.18)
Years of education†	14 (3)	13 (3)	0.701	14 (3)
Baseline FSIQ†	97 (13)	98 (14)	0.772	97 (13)
Valid gene results:	30	24		54
LMX1A genotype (AA or GA/GG) $^{\chi 2}$	14 AA (46.7%)/16 GA/GG	5 AA (20.8%)/19 GA/GG	0.014	33 AA (61%)/21 GA/GG
APOE ε (ε4 or non-ε4) $^{\chi 2}$	13 ε4 (43,3%)/17 ε3/ε2	11 ε4 (45,8%)/13 ε3/ε2	0.858	23 ε4 (43%)/31 ε3/ε2

FSIQ, Full Scale Intelligence Quotient; APOE, ε Apolipoprotein e; LMX1A, Lim homeobox transcription factor-alpha; χ^2, Chi Square. †Independent T-test.

Adaptive vs. Non-adaptive Training Effects on Cortical Thickness

On a linear mixed effects model (**Supplementary Table 1**), no significant differences were found between the adaptive and non-adaptive training groups in the longitudinal cortical thickness trajectories below the established threshold for FDR correction of 0.000084. The averaged cortical thickness maps for each training group, together with mean cortical thickness difference maps are shown in **Figure 2**.

Furthermore, no significant group differences were found when assessing the main effect of time without the interaction term when using a groupwise comparison. Finally, no significant cortical thickness change was found over time when combining the two training type groups. Uncorrected effect sizes expressing longitudinal thickness change between different timepoints in both groups separately are visualized in together with uncorrected cortical trajectory maps in **Figure 3**.

LMX1A Genotype Effect on Cortical Thickness After Cognitive Training (Across All Subjects)

In the LME model with the Time**LMX*1A interaction, significant differences between the AA and GG/GA carriers were found after FDR correction (corrected threshold 0.00043), which are visualized in **Figure 4**. Significant clusters of increased cortical thickness trajectory were found in the right superior frontal gyrus, in the AA carriers compared to the GG/GA carriers. In the left hemisphere, the AA carriers showed no different trajectories compared to GG/GA carriers. The mean cortical thickness at each timepoints, and the *p*-values for the interaction effects for the significant clusters per region, and the size of the significant clusters in each region are included in **Table 2**. No other brain regions showed significant interaction effects, see **Figure 4**.

*APOE*ε4 Genotype Effect on Cortical Thickness After Cognitive Training (Across All Subjects)

The LME with Time**APOE*ε4 interaction did not show significant differences in cortical thickness trajectories between the *APOE*ε4 carriers and non-carriers after FDR correction (corrected threshold 0.000126).

DISCUSSION

This study has the following major findings. Contrary to our hypothesis, cortical thickness did not show significant increase 6 months after WM training in our MCI participants. In addition, the cortical thickness changes were not different between the adaptive and non-adaptive computerized WM training groups. However, a subgroup of MCI participants, those with the *LMX*1A-AA genotype, showed significant increase or lack of decrease of cortical thickness in the right frontal superior region and right paracentral region across WM training groups compared to the GG group. No significant difference in the cortical thickness trajectories after WM training was found between carriers of *APOE*ε4 and non-carriers.

Few studies of patients with MCI investigated quantitative changes in brain morphology after cognitive training (Belleville and Bherer, 2012). A recent study by Zhang et al. (2019b) reported a significant correlation between gray matter volume trajectory of the right angular gyrus and the immediate recall component of Hopkins Verbal Learning Test-Revised (HVLT-R) after a multidomain training program in individuals with amnestic MCI. The study is limited by a small sample ($n = 12$) and a non-RCT design. Two studies that evaluated cognitively healthy adults also reported improved cortical thickness after adaptive WM training, but not in those that had non-adaptive training (Metzler-Baddeley et al., 2016; Wu et al., 2021). In contrast, the present study of participants with MCI did not find significant differences in cortical thickness changes between these two types of training. This lack of training type difference on the cortical thickness might have resulted from similar low difficulty levels between the adaptive and non-adaptive training in these MCI patients, that both groups reached a ceiling with regard to the training effect. Currently optimal training time for MCI patients is unknown. Edmonds et al. (2020) reported a 0.05 mm annual atrophy rate in the temporal lobes in individuals with MCI. In our study, no change in the cortical thickness trajectories were observed, which might suggest a lack of decline in cortical thickness after working memory training (WMT). This needs to be explored in further studies.

The lack of group difference on cortical thickness after the two training types may also be due to the study participants' older age and the heterogeneous etiologies for their MCI (Flak et al., 2019). Therefore, they had limited compensatory processes caused by underlying brain pathologies that might have diminished the training effects on cortical thickness. We speculate that the accumulated degenerative processes in the brains of older MCI individuals might have induced different and less optimal neuroplasticity mechanisms than those present in younger "healthier brains," leading to the lack of cortical thickness changes after WM training. Some support for this explanation is found in previous reports on task-activated fMRI with greater activity in compensatory brain regions in older adults (Belleville and Bherer, 2012), suggesting a redistribution of the training effects to more widespread brain regions as compared to a more localized effect in younger individuals (Hampstead et al., 2012; Simon et al., 2020).

We further explored the possible genotypic contributions on cortical trajectory changes after WM training since two genotype variants were shown to influence the WM training effects on cognitive outcomes (Hernes et al., 2021). The *LMX*1A gene is involved in the maintenance of dopaminergic neurons, and dopamine is essential for WM function (Puig et al., 2014). Regardless of the WM training type, MCI participants with the *LMX*1A-AA genotype showed significantly increased cortical thickness trajectories after WM training in brain regions associated with WM function. Only one previous longitudinal study has evaluated the effects of WM training on the brain in individuals with the *LMX*1A-AA genotype; Chang et al. (2017) reported decreased BOLD activation on a 2-back fMRI

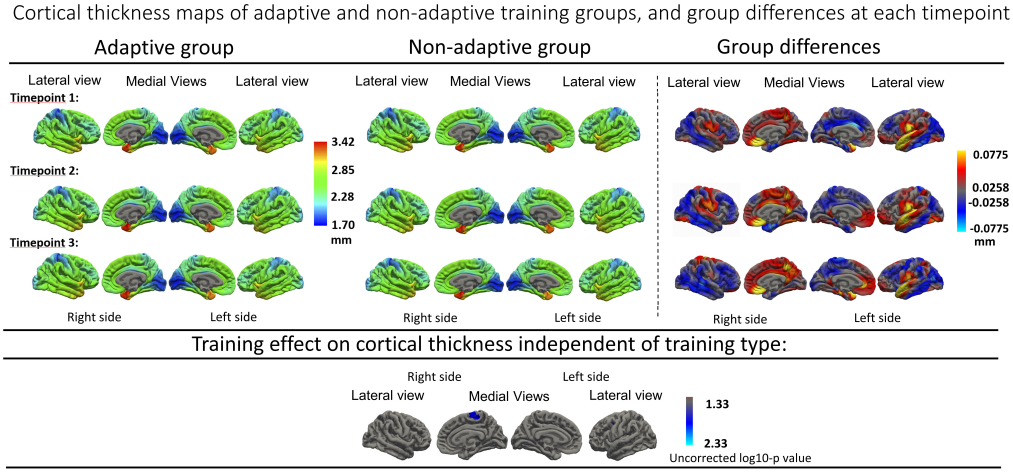

FIGURE 2 | Top panels: Average cortical thickness maps of adaptive and non-adaptive training group, with mean differences from all three timepoints. Timepoint 1: Baseline, timepoint 2: 4 weeks after training cessation. Timepoint 3: 16 weeks after training cessation. Bottom panel: Cortical thickness analysis of training effect independent of training type (time, uncorrected), show no significant region after FDR correction (significance threshold of log10-p: 2.76 = 0.0017). Resampled surface maps, were smoothed with kernel factor of 30 mm (fwhm).

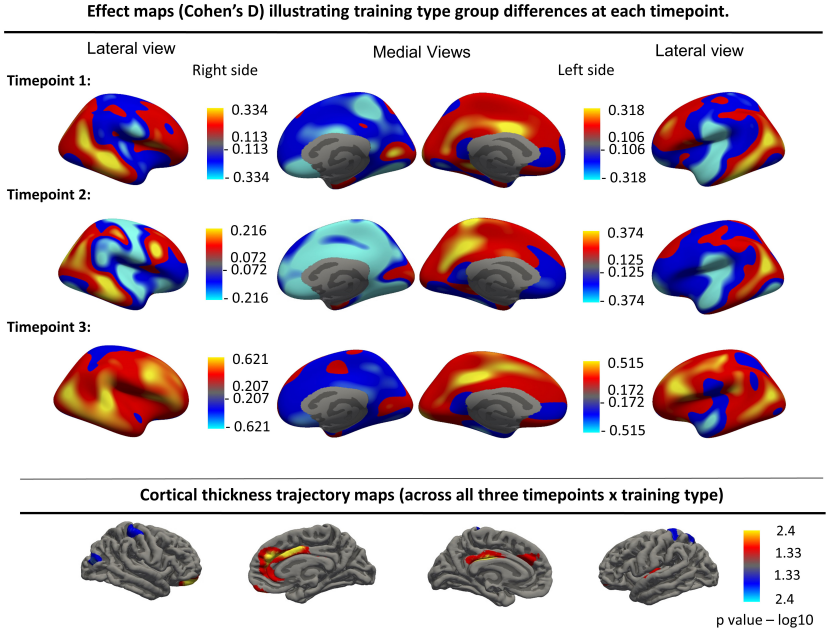

FIGURE 3 | Top panels: Effect maps (Cohen's D) illustrating training type group differences at each timepoint for the left and right hemispheres. Bottom row: Cortical thickness trajectory maps showing the interaction effect (Time × Training type, uncorrected). These interaction effects were no longer significant after FDR correction. Resampled surface maps, were smoothed with kernel factor of 30 mm (fwhm).

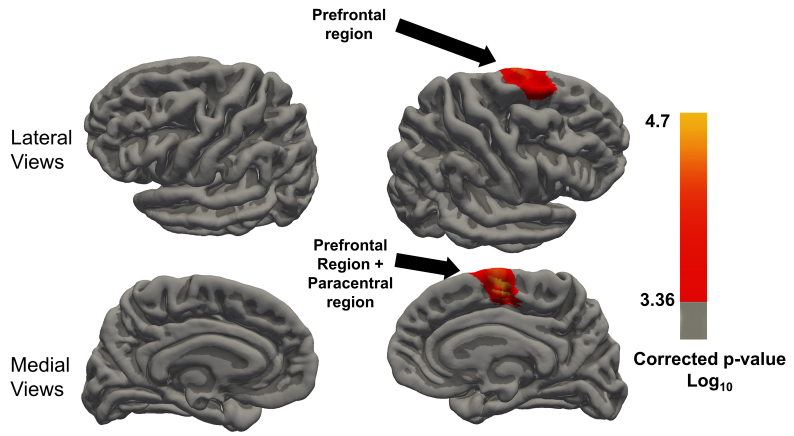

FIGURE 4 | Regions with significant Time x LMX1A (AA vs. GA and GG) interaction on cortical thickness after FDR correction of the *P*-value, minimal significant FDR corrected P threshold is $10^{(-2.58)}$ = 0.00043. Resampled surface maps, were smoothed with kernel factor of 30 mm (fwhm). Brain regions showing significant group differences (after FDR correction) in the right hemisphere include the superior frontal region, and paracentral region. In the left hemisphere, there was no significant group difference in any region.

TABLE 2 | Cortical thickness (Mean(±SE)) of regions of interest that show training LMX1A effects, with cluster size of significant vertices.

	Timepoint 1		Timepoint 2		Timepoint 3				
Region of interest:	***LMX*1A-AA**	***LMX*1A-GA/GG**	***LMX*1A-AA**	***LMX*1A-GA/GG**	***LMX*1A-AA**	***LMX*1A-GA/GG**	**Cluster size of region (%)**	**Cluster size in mm^2**	**Range of corrected *P*-value**
Right superior frontal region	2.523 (0.0280)	2.487 (0.0259)	2.508 (0.0318)	2.459 (0.0284)	2.526 (0.0259)	2.472 (0.0282)	21	1438	0.00043–0.000025
Right paracentral region	2.314 (0.02113)	2.316 (0.02269)	2.317 (0.0265)	2.278 (0.0336)	2.344 (0.257)	2.321 (0.0335)	2	30	0.00043–0.000025

LMX1A, Lim homeobox transcription factor-alpha.

task in those with the AA genotype, suggesting improved neural efficiency, but no change or increased activation in those with GG/GA genotype in the middle frontal gyrus at 1-month after the same WM training. A significant increase in cortical thickness trajectories was observed in the right superior frontal region and continuing over into the paracentral region medially in MCI participants with the *LMX1A*-AA genotype, but not in participants with the GG/GA genotypes. The right superior frontal region is associated with WM functions. Nissim et al. (2016), and a meta review concluded that the superior frontal region was especially sensitive to spatial content (Nee et al., 2012), and right paracentral gyrus was recruited during WM tasks to compensate for having a poor night's sleep by recruiting the necessary resources to complete the task in a recent neural network study (Lauharatanahirun et al., 2020). Suggesting that it can be involved as a secondary center in WM. Our reported selective increase in cortical thickness trajectory after WM training only in those with the *LMX*1A-AA genotype together with previously published results of increased WM function tests after WM training from the Memory Aid study, suggest that carriers of individuals with *LMX*1A-AA in particular might benefit more from WM training (Hernes et al., 2021) than GG/GA carriers. However, future studies that evaluate this genotypic variant on brain morphometry with a larger sample size are needed.

There were no differences in cortical thickness trajectories among our participant with or without the *APOE*-ε4 allele after WM training. In our previous reports from the same population, *APOEε4* carriers improved in some cognitive tests after WM training as compared to non-carriers (Hernes et al., 2021); therefore, we had expected differential trajectories in cortical thickness changes after WM training. Nevertheless, this negative result should be interpreted with caution due to the relatively small sample size, and further studies with larger sample sizes are needed. To our knowledge, this is the first study that has evaluated the impact of genotypes on brain morphometry after WM training.

Strengths and Limitations

This study has several strengths. This is a longitudinal follow-up study in a cohort of participants with MCI, which allowed intra-subject assessment of the possible structural brain changes after WM training. Each participant was scanned on the same MRI machines for the baseline and follow-up scans using

the identical imaging protocol, thereby minimizing possible variabilities from image contrast, signal-to-noise ratio, contrast-to-noise ratio, intensity non-uniformity or geometric distortion (Lee et al., 2019). Despite these strengths, a limitation to this study is the relatively small sample size for the subgroups, both for comparing the morphological changes between the adaptive and non-adaptive training group, and the comparisons between the morphometric trajectories of the participants with different genotypes. Therefore, these findings should be viewed as preliminary. Furthermore, the manual skull removal that was required for some of the MRI scans might have introduced subjectivity in the early steps of the image processing. Lastly, we also did not evaluate a cognitively healthy control group to determine whether the training effects on cortical thickness might be different between participants with MCI and cognitively healthy individuals. Furthermore the study didn't include a passive MCI control group, this is in accordance with the framework proposed by Simons et al. (2016) to ensure high-quality computer-based WM training studies.

CONCLUSION

The current results from WM training in a heterogeneous population of MCI participants identified the need for further research, especially with respect to genotypic variations in brain neuroplasticity. Promising results of greater neuroplasticity in *LMX*1A-AA carriers should be further investigated in future trials since these individuals may benefit the most from WM training.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because the Norwegian Regional Committee for medical and health research ethics limit data sharing, and de-identified data can only be shared after an application process. The study protocol is publicly available. The statistical analysis plan is available upon request by members of the academic community for the next five years. The generated datasets are available by request to the corresponding author, though no imagesets can be shared, the completed freesurfer data can be requested. Requests to access the datasets should be directed to HH, haakon.ramsland.hol@ous-hf.no.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Norwegian Regional Committee for medical and health research ethics, South-Eastern region (2013/410) approved the study (clinicaltrials.gov NCT01991405). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SH, MF, GL, JS, and LC conceptualized and designed the study. MF, GL, AE, B-OM, and HH collected the data. HH, MF, SH, and LC analyzed the data. SH, HH, KB, LR, and LC interpreted the data. HH, SH, KB, AE, LR, and LC drafted the manuscript. All authors have critically revised the article and approved the final version of manuscript to be published.

FUNDING

This study was funded by research grants from the South Eastern Norway Regional Health Authority (Grant Nos: 2015046 and 2013059), and Sørlandet Hospital HF. Chang's effort was supported by the University of Maryland, School of Medicine, and the John A. Burns School of Medicine at the University of Hawai'i at Manoa.

ACKNOWLEDGMENTS

We thank radiographer Marianne Rognli, Sørlandet Sykehus – Arendal, and senior radiographer Anders Tomtestad, Oslo University Hospital – Rikshospitalet, for their help in managing the participants during scans. We thank the study participants for their interest and cooperation in the project, and acknowledge the Norwegian Registry for persons being evaluated for cognitive symptoms in specialized care (NorCog) for patient data. We also thank Sørlandet Hospital, Telemark hospital, University of Maryland, School of Medicine and Oslo University Hospital - Rikshospitalet, Norway for their assistance in this project.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2022.796110/full#supplementary-material

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Supplemental

DEMENS SCORINGSSKJEMA (av MK Beyer/EL/HRH)

Bilder vurdert av	**Haakon**

PASIENT ID		Kjønn	Alder
	F.år	mann	

Undersøkelses dato	Sammenlignes med	Tolknings dato	Tolkning nr

MEDIAL TEMPORAL LOBE ATROPHY (MTA)

Gradering høyre[1]	none	1	2	3	4
	x				
Gradering venstre[1]	none	1	2	3	4
	x				

Fazekas scale[2]	0	1	2	3	
		x			

Global cortical atrophy scale-Frontal	0	1	2	3
GCA scale[3] (0-3) Frontal	x			

Hvis atrofigrad er lik på begge sider settes et kryss for atrofigrad i hver region.
Hvis det er ulik grad på hø og ve side setter man Hø i riktig rute og Ve i riktig rute, som angir atrofigraden eks Hø i grad 0 og Ve i grad 1.

Posterior atrophy scale	0	1	2	3
		x		

0 = no atrophy, 1 = minimal atrophy, 2 = moderate atrophy and 3 = severe atrophy
Hvis atrofigrad er lik på begge sider settes et kryss for atrofigrad i hver region.
Hvis det er ulik grad på hø og ve side setter man Hø i riktig rute og Ve i riktig rute, som angir atrofigraden eks Hø i grad 0 og Ve i grad 1. Hvis man får ulik gradering på ulike orienteringer –velges den høyeste (konf artikkelen)

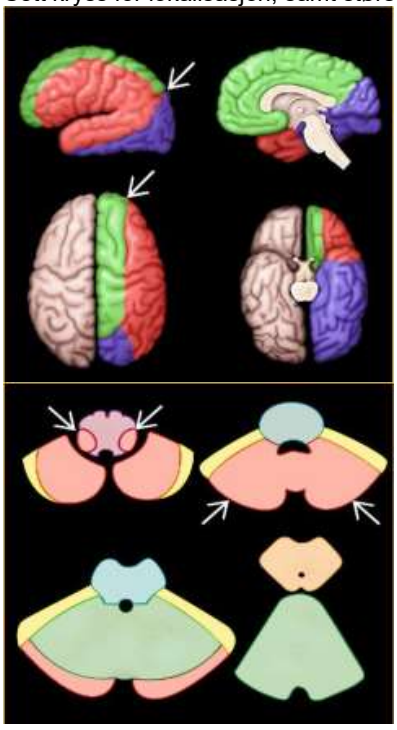
Kommentarer/andre funn:
Koedam: Kun axial snitt gir utslag, ellers 0-

[1]minimal =1, mild=2, moderat =3, alvorlig =4

[2] 0= ingen, 1 =multiple punktformede WMH, 2= begynnende sammenflytende/konfluerende punktformede, grad 3 = konfluerende WMH

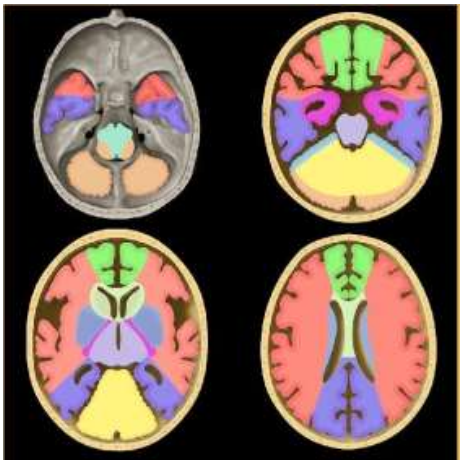
[3] atrophy scale: 0-none, 1-mild (widening of sulci), 2-moderate (substance loss in gyri), 3-severe (sharp gyri/chicken bone)

INFARKTVURDERING, SE NEDENFOR.
Sett kryss for lokalisasjon, samt største målte diameter



MCA =rød
ACA=grønn
PCA= blå

SCA =
grønn
PICA=rød
AICA=gul



Errata

Errata for
Brain plasticity after cognitive intervention in patients with mild cognitive impairment (MCI) evaluated by multimodal MR imaging in a randomized, controlled trial.

Haakon Ramsland Hol

Thesis for the degree philosophiae doctor (PhD)

at the University of Bergen

18.11.2022 Haakon R Hol

(date and sign. of candidate)

18.11.22

(date and sign. of faculty)

Errata

Page, paragraph, line:	Original text	Corrected text	Types of correction
3,4,1-2	bilder	MR undersøkelser	Language correction
3,5,3	Indentifisert	Indentifiserte	Spelling correction
4,3,4	Er har	Rommer	Language correction
12,2,1	TheaMCI	The aMCI	Spelling correction
18,2,5	representable	representative	Language correction
22,2,1	In naMCI, impairments are found in domains	In naMCI, domains	Language correction
32,1,10	While a third organization	Concurrently, a third organization	Language correction
34,3,1-2	Researchers and clinicians interchange the terms Lewy body dementia (LBD) and dementia with Lewy bodies (DLB).	Researchers and clinicians use the terms Lewy body dementia (LBD) and dementia with Lewy bodies (DLB) interchangeably.	Language correction

36,1,4	pharmacological	pharmacologically	Language correction
36,1,8-9	Furthermore, no research shows a favorable long-term effect	Furthermore, there is an absence of research showing a favorable long-term effect	Language correction
46,3,6	that improvement	that the improvement	Language correction
48,2,1		Standardized training effect size	Language correction, and graph not display correctly.
49,1,5-9		N-back training involves the serial presentation of a stimulus with n number of stimuli the participant is subjected to after the initial stimulus. The participant has to decide if the current stimuli match the one displayed n stimuli ago. N determines the cognitive load (Au et al. 2015).	Language correction and missing reference.
51,1,4-5		Dual-N back is an N-back modification with the simultaneous presentation of two independent sequences,	Language correction and missing reference.

		such as one auditory and one visual (Jaeggi et al. 2003).	
53,2, Equation	Ration	Ratio	Spelling error.
54,1,4	Emits	Emit	Language correction
55,1,8-11	Fourier transform is the key to generating an image; it is a mathematical method that, in MRIs are, decomposing the MRI signal into a sum of sine waves consisting of the spatial frequency (Gallagher et al. 2008).	Fourier transform(FT) is the mathematical procedure enabling image generation from a complicated MRI signal. It decomposes the signal and transfers it into K-space(Fourier space), transforming the signal into a sum of sine waves consisting of spatial frequency and amplitude information (Gallagher et al. 2008). The inverse FT is then used to reconstruct the data into an image or volume.	Languange correction
57-58, 3-1,4-1	The initial method was highlighting the problem they experienced nwith age-related hippocampal atrophy.	The initial study highlighted the problem they experienced with age-related hippocampal atrophy; it decreased the sensitivity.	Language correction

64,3,10-11	while complex algorithms are always as good as the algorithm	while complex algorithms are always limited to the parameters of the algorithm, much stricter	Language correction
68,3,15	ICV	Intracranial volume(ICV)	Language correction
69, 3,1	instead of the registration as with VBM	instead of the registration step performed in VBM	Language correction
70,3,11	at a cost	But at a cost,	Language correction
70,3,4	the motion is going in the unhindered direction	, the diffusion is in unrestricted directions	Language correction
71,2,3	Pixel	Voxel	Language correction
71,2,4	the anisotropic transport of water molecules	describe the motion of water molecules within	Language correction
72,2,2	Logical	Procedural	Language correction
74,3, headline	Tensorestimation	Tensor estimation	Language correction
77, 2,1-3	Several statistical	. Using statistical models that can handle dropouts/missing data reduces the significance of	Language correction

	methods for handling dropouts/missing data can be utilized, such as the	this problem. Some examples of such models are the	
86,2,2	In accordance with age	with respect to age	Language correction
86,3,2	initially, one declined due to MRI incompatibility, and two were not willing to travel for the MRI examinations	one declined due to MRI incompatibility, and two were unwilling	Language correction
87,3,1	Population	Cohort	Language correction
93,2,18	XX13	20	Spelling correction
108,3,3	sammenlignet med andre…	which is younger than the average reported in all 24 studies evaluated in a systematic review of technology-based cognitive and rehabilitation interventions in MCI patients (Ge et al. 2018). However, age is included as a covariate in all the statistical models, and our main aim was to compare the adaptive training group with the non-adaptive, where the	Language correction, missing reference.

		average age difference was insignificant. However, for the secondary analysis, it is a point to be considered when comparing with other studies.	
109,2,1	can be discussed. It was	not typical for neuroscientific studies currently due to the increased availability of higher B0 MRI machines. However, it was	Language correction
110,3,4	(ref).	(Haller et al. 2021) (Gregoire et al. 2009).	Missing references.
110,4,6	Modification	Modifications	Language correction
111,2,12	T1-weighted	T1-weighted(T1w)	
111,2,22	limited to the cortical structure analysis	limited to cortical structure analysis	Language correction
113,2,4	(ref)	(Hernes et al. 2021)	Missing reference.
114,3,7	(ref)	(Farras-Permanyer et al. 2015)	Missing reference.
124,4,8	At the time of study initiation, recently suggested age-related cut-	For our cohort, age-related cut-offs recently suggested for	Languange correction

	offs were suitable for our MCI group.	clinical use were also suitable for our MCI group.	
188,3,4	Comment		Editing error
188,2-3,3-9	No differences between aMCI and naMCI were observed at baseline. After 4 weeks the two groups differed significantly in 6 out of 12 brain regions. At 16 weeks after training significant changes were observed favoring the naMCI group as compared to the aMCI group in the left posterior thalamic radiation and left hippocampal cingulum. There was no modulating effect of APOE or LMX1a on white matter after training. There was a significantly higher MD in APOE4 carriers in both posterior thalamic radiations as compared to non carriers. GG/GA carriers had consistently lower MD in the same regions, as compared to AA carriers.	Individuals with aMCI had consistently higher MD in all regions as compared to naMCI. There was no modulating effect of APOE or LMX1a on white matter after training. There was a significantly higher MD in APOE4 carriers in both posterior thalamic radiations as compared to non-carriers. GG/GA carriers had consistently lower MD in the same regions compared to AA carriers (all p <.0000).	Language correction
188,4,1	Conclusion: Adaptive	Conclusion:	Editing error.
190,4,1-8	Bellander2	(Bellander et al. 2015)	Missing ref.
194,1,2	dropped	excluded	Language correction

195,1,1		Added title to Y-axis.	Language correction of figure
200,2,1	Striatum	Stratum	Spelling error
200,2,6-10		Removed yellow color	Editing error.
202, 2,1	Strengths	Strength	Language correction

Graphic design: Communication Division, UiB / Print: Skipnes Kommunikasjon AS

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ISBN: 9788230846650 (print)
9788230850879 (PDF)