DOI:
10.3233/NRE-171471

Document Version
Peer reviewed version

Running head: WHITE MATTER LESIONS

Imaging and neuropsychological correlates of white matter lesions in different subtypes of Mild Cognitive Impairment: A systematic review

Charlene L.M. Lam [1,2], Jenny Yiend [3], Tatia M.C. Lee [1,2,4]

[1] Laboratory of Neuropsychology, The University of Hong Kong, Hong Kong
[2] Institute of Clinical Neuropsychology, The University of Hong Kong, Hong Kong
[3] Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK
[4] The State Key Laboratory of Brain and Cognitive Sciences, The University of Hong Kong, Hong Kong

Correspondence:

Tatia M.C. Lee, Ph.D.
Rm 656, Department of Psychology
The Jockey Club Tower
The University of Hong Kong
Pokfulam Road, Hong Kong.
Tel: 852-3917 8394
E-mail: tmclee@hku.hk

Abstract

BACKGROUND: White matter lesions (WML) are prevalent in older adults. The association between WML and cognition in different subtypes of Mild Cognitive Impairment (MCI) is inconsistent in the literature. OBJECTVES: We aim to provide a systematic review on the impact of WML in different subtypes of MCI, and discuss the recent findings on white matter plasticity. METHODS: We reviewed peer-reviewed articles from January 2011 to August 2016 and identified 12 studies investigating the association between WML and subtypes of MCI with both neuroimaging and cognitive measures. RESULTS: Our review shows that 1) WM abnormality was identified between different subtypes of MCI and healthy controls on diffusion imaging; 2) neither visual ratings of WML nor its volumetry differentiate different subtypes of MCI or its prognosis to dementia; and 3) cognitive correlates of WML were evident in the Amnestic-type MCI in the domains of memory, language, psychomotor speed, attention and executive functions. CONCLUSION: Cognitive reserve and the plasticity of white matter may modulate the impact of WML on the manifestation of the neurodegenerative disease. Further research is needed to study the plasticity of white matter in the MCI population to evaluate its potential clinical application.

Keywords: White Matter, Mild Cognitive Impairment, Cognitive Reserve, Neuroplasticity, Cognition

Introduction

White matter is made up of axons, different types of glial cells, and blood vessels. The destruction of white matter integrity will lead to a less efficient and effective electrical impulse conduction along the white fiber tracts, and hence, interfere with the normal functioning of the brain. White matter lesions (WML), also known as white matter hyperintensities or leukoaraiosis (*Leuko,* meaning white, and *araiosis* meaning rarefaction, in Greek), represent one of the extreme forms of white matter injury and are prevalent in the aging brain. It was estimated that only 5% -13% of brains of older adults are free from WML (de Leeuw et al., 2001). Moreover, WMH severity can account up to 15% of the variance in general cognitive functioning in the healthy elderly population (Brickman et al., 2011). Hence, the impact of WML should not be neglected or underestimated.

WML are also common in individuals with mild cognitive impairment (MCI). MCI describes a transitional stage between normal ageing and dementia. Research on MCI has received much attention in the past decade as researchers and clinicians have pushed for early identification and treatment of dementia. Current research suggests that older adults with MCI are more likely to progress to dementia than their counterparts without MCI (Albert, Blacker, Moss, Tanzi, & McArdle, 2007; Busse, Hensel, Gühne, Angermeyer, & Riedel-Heller, 2006; Landau et al., 2010; Petersen et al., 2001). Petersen and colleagues (2001) reported that most MCI subjects with memory impairment progressed to Alzheimer's disease at a rate of 10% to 15% per annum, in comparison to those healthy controls whose progressed a rate was 1% to 2 %. It was estimated that the prevalence of WML in MCI ranges from 70% to 100 % and the distribution of lesions was more extensive than that in the healthy aging population (Son et al., 2012; Targosz-Gajniak, Siuda, Ochudło, & Opala, 2009; Wallin et al., 2016).

Recently the International Association of Gerontology and Geriatrics Congress issued a guideline for early diagnosis of cognitive impairment (Morley et al., 2015), suggesting that an inclusion of WML investigation as part of the screening for early diagnosis of cognitive impairment. However, reviews focusing on WML in subtypes of MCI are scarce. The findings in the clinical significance of WML in Mild Cognitive Impairment is inconsistent in the literature, with some studies reporting an associated cognitive decline and dementia (B.T. et al., 2012; Bolandzadeh, Davis, Tam, Handy, & Liu-Ambrose, 2012; Coutu, Goldblatt, Rosas, & Salat, 2015), while others fail to demonstrate such association (Mortamais et al., 2013).

The objectives of the present review are two-folded. First, we aimed to extend the previous reviews by considering the impact of WML in the subtypes of MCI, namely 1) the Amnestic-type mild cognitive impairment single domain (aMCI- single domain), 2) Amnestic-type mild cognitive impairment-multiple domains (aMCI- multiple domains); 3) Non-amnesic mild cognitive impairment-single non-memory domain (non-aMCI- single domain), and 4) Non-amnesic mild cognitive impairment (Petersen, 2004). Subtyping MCI in the study of WML has a few advantages. It allows us to compare the findings across studies using a more homogenous group of population. It can also allow us to explore whether there is a differential impact of WML on the pathology of different subtypes of MCI. Second, given that the integrity of white matter is crucial for intact cognitive functioning and healthy aging, we also aimed to review the evidence on white matter plasticity and its potential application in intervening or delaying the progress of WML in MCI.

Methods

The literature search consisted of two parts. First, we conducted a literature search in PubMed from 2011 to Sept 2016. Terms for searching included Mild Cognitive Impairment AND white matter lesion*, Mild cognitive impairment AND white matter hyperintensit*, Mild cognitive impairment AND leukoaraiosis. Only studies between years 2011 and 2016 were included in this review as the neuroimaging technology, especially in diffusion imaging, in recent 5 years has become stable and matured. Studies were included if 1) they were published as a peer-reviewed journal article, 2) in English, 3) conducted in humans, 4) they investigated WML in any subtypes of MCI, and 5) the articles included both neuroimaging data and neuropsychological test results. Neuropsychological assessment was required in the same study as we aimed to determine the clinical significance of neuroimaging findings through correlations with neuropsychological evaluation. Studies were excluded if 1) there is only one MCI group, 2) studies with a focus on other areas such as Depression, Parkinson's disease, Alzheimer's disease; 3) they were single case studies. Figure 1 describes the procedure in identification and selection of studies. We identified a total of 12 articles for our review in this paper.

[Insert Figure 1 here]

Results

Study characteristics

Table 1 shows the characteristics of studies included in this review. Eight of them included participants with amnestic MCI. The other four included compared MCI who progressed to dementia with those who did not. Of the eight studies that investigate aMCI, only three studies further characterized them into single-domain aMCI and multiple-domain aMCI.

Other studies included both single domain and multiple domains in defining their group of aMCI. Only two studies included participants with non-amnesic MCI. All of them adopted the Petersen's criteria or modified Petersen's criteria in classifying MCI and its subtypes, which corresponds to 1) memory complaint preferably corroborated by an informant, 2) objective memory impairment which is inconsistent with age and education 3) relatively normal general cognitive functioning, 4) relatively normal activities of daily living and 5) not diagnosed with dementia according to the definition of DSM-IV or ICD-10 (Petersen, 2004; Petersen et al., 2001).

[Insert Table 1 here]

The microstructure of WML in subtypes of MCI

Table 2 summarizes the findings in neuroimaging data of the reviewed studies. All three studies using diffusion imaging indicate microscopic abnormalities of white matter integrity in patients with MCI in comparison to healthy controls. For instance, the non-amnesic attention/executive MCI group had a higher radial diffusivity values in rostral middle frontal, medial orbitofrontal, caudal anterior cingulate, and entorhinal regions than those of the healthy controls (Grambaite et al., 2011). Similarly, Bosch and colleagues (2012) reported a significant increase in radial diffusivity in inferior longitudinal, the occipitofrontal fasciculus, and the posterior cingulum, right longitudinal superior and uncinate fasciculus comparing between a group of aMCI patients and a group of healthy controls. Uncinate fasciculus, which connects anterior temporal lobe to lateral orbitofrontal cortex, and the cingulate bundles are white matter

tracts that have been shown to be involved in memory encoding and retrieval (Wendelken et al., 2015).

Relative to aMCI single domains, individuals suffering from aMCI-multiple domain showed a more extensive white matter abnormality. Li and colleagues (2013) reported a reduction in fractional anisotropy in distributed brain regions including the body of corpus callosum, fornix, bilateral anterior internal capsule, posterior internal capsule, and tapetum.

[Insert Table 2 here]

The macrostructure of WML in subtypes of MCI

Nine studies examined the macrostructure of WML in subtypes of MCI using T2 or FLAIR images. Seven studies of them used visual rating scales of WML and only two computed the volumetric measure in quantifying WML. The findings regarding the macrostructure of WML were less consistent that those from the DTI studies. There were conflicting results regarding the volumetric load or visual ratings of WML in various subtypes of MCI.

Comparing to healthy controls, only one study reviewed here reported a significant increase in WML in aMCI (Naranjoa et al., 2015). The rest of the studies did not find a significant difference in volumetric load or visual ratings of WML between aMCI and healthy controls. Of the three studies which compare MCI who progressed to dementia and those who did not, only one study reported a higher periventricular WML in MCI who progressed to dementia (Defrancesco et al., 2013). However, other research groups failed to replicate these findings(e.g. Eckerström et al., 2015; Nolze-Charron, Mouiha, Duchesne, & Bocti, 2015). In sum,

studies measuring the macrostructure of WML suggest that WML is a weak radiological marker in differentiating MCI from healthy controls and AD, or other subtypes of MCI.

Cognitive correlates of neuroimaging of WML

Table 3 descirbes the cognitive assessment tools that were employed by the studies. Of those who identified a significant association between WML and aMCI diagnosis, it was consistently reported that periventricular WML was associated with poor performance on cognitive measures such as memory, language, psychomotor speed, and attention/executive functions (Defrancesco et al., 2013; Makino et al., 2014; Naranjoa et al., 2015). Total WML burden significantly predicted general cognitive status measured by the Mini-Mental State Examination after controlling for age, education, and gender of the amnesic MCI participants (Kim et al., 2015)

In diffusion imaging studies, the association between imaging indices and cognitive measures were reported in all three studies. For instance, mean diffusivity value of the corpus callosum was associated with MMSE and tasks on processing speed in a group of aMCI and with response/switching task in a group of a/e MCI (Grambaite et al., 2011). The FA index was significantly associated with the memory performance in aMCI and AD patients (Bosch et al., 2012).

[Insert Table 3 here]

Discussion

In this review, we identified 12 recent articles to explore the neuroimaging and neuropsycholgoical correlates of white matter lesions in different subtypes of MCI. Our findings show that 1) WM abnormality was identified between different subtypes of MCI and healthy controls on diffusion imaging; 2) visual ratings of WML or its volumetry did not reliably differentiate different subtypes of MCI or its prognosis to dementia; and 3) WML is associated with a general reduction in cognitive functioning in MCI, and cognitive correlates of WMH was evident in the domains of memory, language, psychomotor speed, attention and executive functions in aMCI.

The findings of the studies reviewed in this article concur with the consensus in the literature on MCI, in which the microstructural change in the white matter of MCI are extensive and affects various brain regions (Radanovic et al., 2013; Sexton et al., 2016). For instance, significant changes in the white matter microstructure were reported in the corpus callosum, fornix, cingulum, parahippocampal region, and longitudinal and uncinate fasciculus in both AD and MCI individuals (Clerx, Visser, Verhey, & Aalten, 2012).

Previous studies using diffusion imaging to investigate the manifestation of WML in different subtypes of MCI suggests that aMCI and non-amnesic MCI follows a different pattern of WM abnormality. For instance, Zhuang and colleagues (2012) reported that WM abnormality was relatively spared in the temporal region of non-amnesic MCI and their WML was anatomically widespread than aMCI (Zhuang et al., 2012). Findings of Li (2013)'s study gave support to their observation, suggesting that the pathology in amnesic MCI is different from that of non-amnesic MCI and they may possibly follow a different clinical progression.

The discrepancy in the findings between the microstructure and macrostructure of WML in subtypes of MCI calls for further clarification in research. The positive findings in the diffusion imaging studies may suggest that diffusion tensor imaging can detect subtle changes in the white matter before they can be seen on T2 or FLAIR images. The inconsistent findings in the macrostructure of WML in MCI may also stem from the different methodologies in collecting data and different experimental design in the studies. For instance, some studies recruited participants from university memory clinics but some recruited the participants from the community. The age range for specifying MCI varies across studies. For instance, Eckerstrom (2015) studied participants of ages between 41and 78 while Nolze-Charron (2015) studied participants of ages between 69 and 85. It was also difficult to make direct comparison across the studies because of the different inclusion and exclusion criteria. For example, Markino and colleagues (2014) excluded aMCI participants with Fazekas rating greater than two while other studies include all MCI participants in their analysis regardless of their ratings on the Fazekas scale. Hence, the findings may not be generalized to other MCI populations.

Apart from the difference in experimental designs, the null findings in different MCI subgroups may also reflect the heterogeneous pathologies of WML even within the same subtype of MCI. There is still much debate about the pathophysiology of WML and several mechanisms have been proposed, including ischemia, blood- brain barrier alternations, apoptosis, chronic edema, genetic factors or a combination of the above (Pantoni, 2002). One theory proposed that WML occurs as a result of Wallerian degeneration, in which loss of axons runs parallel to the gray matter pathology and begins from the hippocampus and entorhinal region to the temporal and parietal association cortex (Sexton, Kalu, Filippini, Mackay, & Ebmeier, 2011). Conversely, another theory follows the retrogenesis model and proposes that white matter change is

independent of the gray matter pathology. The white matter will follow the reverse order of myelinogenesis, in which white matter will degenerate first in the late-myelinating WM tracts, such as the inferior and super longitudinal fasciculus and the uncinate fasciculus (Meier et al., 2012). In short, our current results suggest that WML detected in T2 or FLARE images of MCI cannot differentiate different subtypes of MCI and is yet to be a reliable prognostic marker in determining the risk of dementia. The various mechanisms and theories suggest a high heterogeneity in the pathology of WML and its manifestation in MCI is complex.

Our review on the cognitive correlates of WML supports the two prevalent notions in the existing literature. First, WML is associated with reduced cognitive functioning in MCI. It is widely accepted that a severe grade of WML has a detrimental impact on cognitive functioning including executive function, attention, processing speed, and global cognition (Jokinen, Lipsanen, & Schmidt, 2012; Meier et al., 2012; Pantoni, Poggesi, & Inzitari, 2007; Prins & Scheltens, 2015; Xiong & Mok, 2011). Second, the location or the spatial distribution of the WML has a differential impact on cognitive functioning. Specifically, periventricular WML, not subcortical WML, has a negative impact on cognitive functions in the MCI population. One speculation is that the periventricular region houses numerous long associating fibers that connect the cortex to various subcortical nuclei and other distant brain regions. Hence damage in the periventricular WML results in impairment in executive functions and processing speed (Bolandzadeh et al., 2012).

WML and White matter plasticity

Despite the gradual deterioration of white matter integrity with age, a growing number of studies have shown the white matter plasticity in the aging brain. Research in the past decade has

identified some factors that modulate the decline and enhance its integrity in healthy older adults, including physical exercise (Fleischman et al., 2015; Gow et al., 2012; Sen et al., 2012), cognitive activities (Wirth, Haase, Villeneuve, Vogel, & Jagust, 2014), and complex leisure activities (Saczynski et al., 2008). In one study, older adults who participated in a life-long high volume and high-intensity exercise training showed a significant 83% reduction in deep white matter lesions and a 44% reduction in total white matter hyperintensities volume relative to their sedentary counterparts. Moreover, this group of physically fit older adults also showed a more preserved front-to-back white matter network that is important for visuospatial function, motor control and coordination (Tsang et al., 2013).

In addition, experience-induced white matter plasticity was also evident in healthy older adults. Lovden and colleagues (2012) found a decrease in the mean diffusivity signals in older participants who were trained to play a spatial navigation video game while walking on a treadmill over a period of 4 months (52 sessions and 50 mins/session). Loveden and colleagues (2010) demonstrated an experience-dependent plasticity of white matter integrity by training older adults on working memory, episodic memory and perceptual speed tasks for half a year. These older adults showed a decrease in RD especially from the anterior part of the corpus callosum. In a randomized control study, Engvig and colleagues (2012) showed that an 8-week of intensive memory training can increase the FA signal in the anterior regions of the brains of the older participants as well as an enhanced performance on the verbal memory tasks. A more recent study on a one-week 3-session of visual perceptual training can induce white matter change beneath the visual cortex (Yotsumoto et al., 2014). These findings suggest an intact ability of the white matter plasticity in the aging brains.

Despite the promising evidence of white matter plasticity, there is currently no effective pharmacological or behavioral intervention for curing white matter lesions or delaying its progress. However, emerging evidence has shown that the brain is capable of regenerating white matter connectivity after a traumatic loss of white matter. For instance, adult rodents with parts of their corpus callosum surgically removed showed a remarkable recovery after 28 days and restored most of its functional connectivity measured by the resting state fMRI connectivity (Zhou et al., 2014).

To date, only a few studies have investigated the plasticity of white matter in older adults with MCI, and inconsistent findings were found. For instance, Podewils et al. (2006) found no association between physical activity and the progression of white matter lesions in MCI. Doi and colleagues (2015) demonstrated that physical exercise was a neuroprotective factor that protects against brain atrophy in a group of older adults with MCI independent of their level of white matter lesions. More research effort is called to investigate the potential plasticity of white matter in older adults with MCI, given the benefits of it may potentially increase the cognitive reserve and lessen the impact of the pathology of the neuro-degenerative disease.

To our best knowledge, there are two on-going rigorous studies that investigate the plasticity of white matter in older adults with MCI. In Flak's study (Flak, Hernes, Skranes, & Løhaugen, 2014), the authors employ a randomized control study design to investigate whether a 5-week 45 minutes of computerized working memory training will relate to changes in their white matter of the brain in patients with MCI. In another study, Cyarto and colleagues (2012) evaluate whether 24 months of moderate, 150 minutes/week home-based physical exercise could delay the progression of white matter changes in older adults with MCI. These two pre-registered studies will offer some insights into the white matter plasticity in older adults with MCI.

Directions for future research

Through reviewing recent evidence of WML in different subtypes of MCI, our review suggests that the clinical significance of WML in subtypes of MCI remains incompletely defined. There is a dearth of research studying the plasticity of white matter in the MCI population and there was insufficient evidence to support the prognostic role of WML as a radiological marker for dementia. However, our review supports that the distribution and the load of WMH are associated with cognitive functioning in MCI.

More research is needed to differentiate the impact of WML on different subtypes of MCI, especially the non-amnesic subtype of MCI. Moreover, there is no gold standard in quantifying WML in the literature. The different quantifying strategy in different studies may give rise to the inconsistent findings and make comparison among studies difficult. The Fazekas Scale (Fazekas et al., 1987), the Sacheltens scale (Scheltens et al., 1993), and the Age-related White matter Change Scale (ARWMC; Wahlund et al., 2001) are commonly used semi-quantitative visual rating scale used to identify hyperintense on MRI images. A previous study compared the three visual rating scales on quantifying WML in AD and MCI patients. Their results suggested that all three rating scales have good face validity and correlate well with the WMH volumetry, but the more complex rating scales correlate better with cognitive measures (Gao et al., 2011). However, one caveat of using visual rating scale is that these scales may subject to a ceiling effect and lead to underestimation of the severity of WML. Hence, quantitative volumetry of WML has an advantage over the conventional visual rating methods, and future studies are encouraged to consider both volumetry and visual rating when quantifying WML.

Effective interventions for WML are lacking. On top of the plasticity of white matter, the potential role of cognitive or brain reserve in mitigating the impact or progress of WML may shed light into the intervention of WML. In the context of normal aging, positive evidence has been established in the association between reserve, WML and cognitive functioning (Brickman et al., 2011). In a large population study of healthy elderly subjects aged 64 to 76 years, education, as a proxy for cognitive reserve, was found to modulate the consequences of WMH on their cognitive performance (Dufouil, Alpérovitch, & Tzourio, 2003). In other words, those with higher cognitive or brain reserves can withstand more severe WML than those with a lower reserve. The empirical evidence for the resilient effect of reserve in the MCI group awaits further substantiation. In a recent study by Serra et al. (2015), the authors showed that cognitive reserve could modulate the impact of the AD pathology in aMCI patients with WML.

After almost three decades of extensive research in the area of WML, the clinical significance of WML has been increasingly recognized. WML is part of the aging process, but the presence of WML should not be taken as merely incidental, especially in the cognitive at-risk population i.e. MCI. More research is needed to clarify the nature of WML in various subtypes of MCI in order to improve the clinical management of WML. Given the evidence of the plasticity in the white matter of aging brain and the potential role of cognitive or brain reserve in modulating the impact of WML, more research effort is called for to harness this remarkable resilience of our brains and protect it from the deleterious impact of WML.

Declaration of interest

There are no conflicts of interest to report.

Figure 1. Flow chart of identification and selection of studies

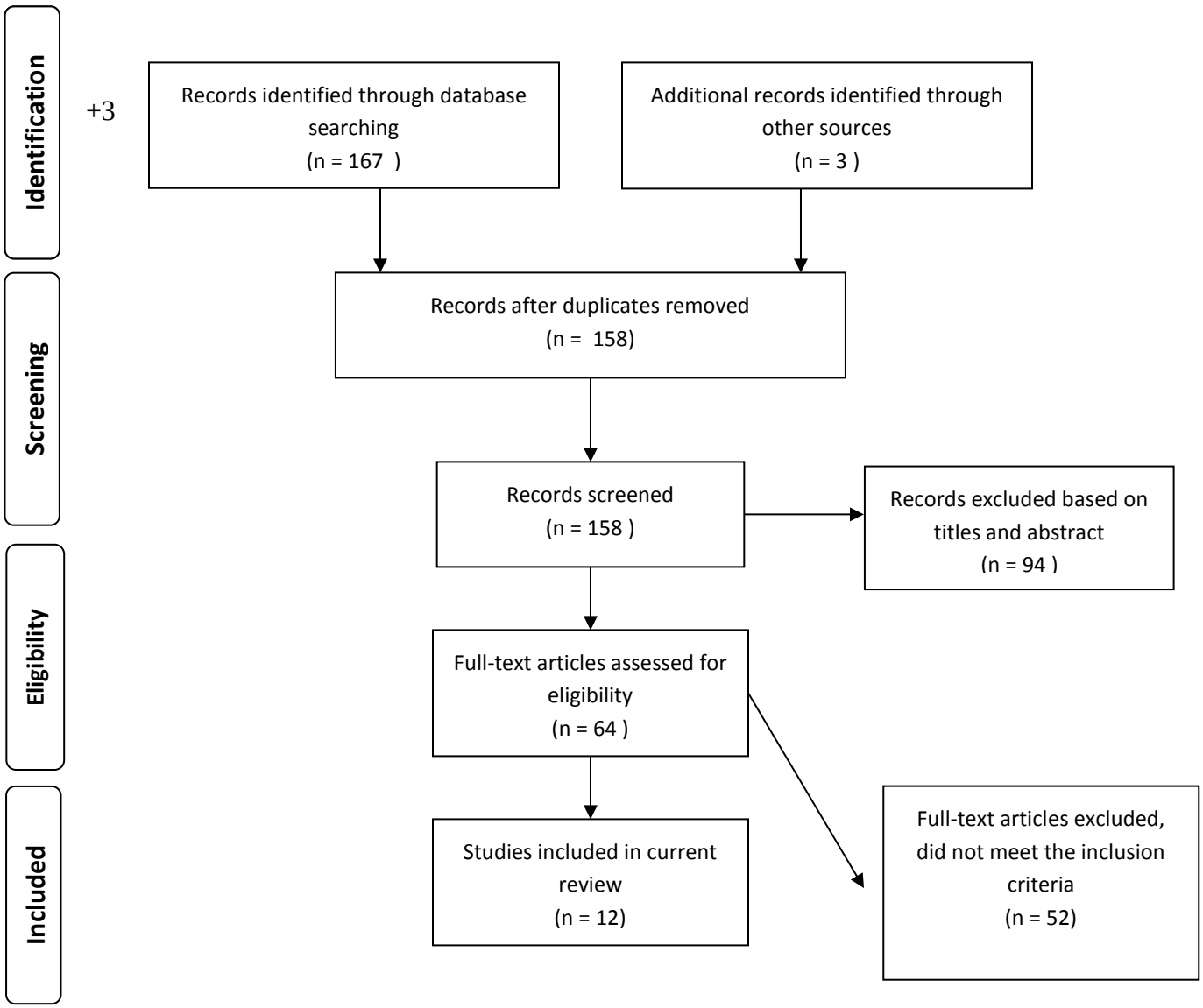

Table 1 Characteristics of studies

	Research design	**Types of MCI**	**N**	**Age**	**MCI classification**	**MRI magnet**

Li et al., 2013	Cross-sectional	aMCI – single domain ;
		aMCI-multiple domain
			aMCI-SD(n=19);
			aMCI-MD(n=21);
			controls (n=37)
				50-85	Petersen's criteria	3T

Grambaite et al., 2014	Cross-sectional	a/eMCI;	a/e MCI (n=23); control (n=23)	53- 72	Petersen's criteria. 1.3 standard deviations below the mean for the normative sample, on at least 2 out of 7 measures of a/e tests	1.5T
Bosch et al., 2012	Cross-sectional	aMCI	aMCI (n=16); AD (n=15); controls (n=15)	67 -82	Modified Petersen's criteria. Using 1.5 SD below the control group mean on episodic memory test	3T
Huey et al., 2013	Longitudinal	aMCI; dMCI; multiple MCI with executive dysfunction; MCI multiple MCI without executive dysfunction	aMCI (98); dMCI (33); MCI-MCDE (103); MCI-MCDN (51); controls (882)	68-89	Petersen's criteria	1.5T
Makino et al., 2014	Cross-sectional	aMCI	aMCI (n=40) (19 single domain, 21 multiple domain) ; AD (n=160)	61-90	Petersen's criteria	1.5T

Naranjo et al., 2015	Cross-sectional	aMCI – single domain ;
		aMCI-multiple domain
			aMCI -SD (n=24);
			aMCI -MD (n=81);
			controls (n=76)
				70-82	1.5 SD below the average score of healthy controls subjects on cognitive testing	1.0T

Lamar et al., 2011	Cross-sectional	aMCI	aMCI (n=20);
			controls (n=11);
			subjective cognitive impairment group (n=12)
				52-82	Petersen's criteria	1.5T

Kim et al., 2011	Cross-sectional	aMCI-single domain	AD (n=37); aMCI (n=23); controls (n=22)	59-75	Petersen's' criteria; using 1.28D (10^{th} percentile) cut off.	1.5T
Peters et al., 2014	Longitudinal	sMCI pMCI	sMCI (22); pMCI (n=18);	65-80	Based on who progressed to dementia in a 2-year follow-up	3T

			Controls (n=20)			
Nolze-Charron et al., 2015	Longitudinal	sMCI pMCI	sMCI (n=124); pMCI (n=186)	69-85	Based on who progressed to dementia in a 3-year follow up	1.5T
Eckerstrom et al., 2015	Longitudinal	sMCI pMCI	sMCI (n=39); pMCI (n=34)	41-78	Based on who progressed to dementia in a 10-year follow up	0.5T and 1.5T
Defrancesco et al., 2013	Longitudinal	sMCI pMCI	pMCI (n=31); sMCI (n=29)	66-81	Based on who progressed to dementia in a 2-year follow up	1.5T

Note. aMCI = amnesic MCI; dMCI = dysexecutive MCI; aMCI-SD = amnesic MCI – single domain; aMCI-MD= amnesic MCI-multiple-domain; MCI-MCDE = multiple MCI with executive dysfunction; a/eMCI = attention/executive MCI; sMCI =MCI patients who remained cognitively stable in follow-up; pMCI = MCI patients who progressed to dementia at follow-up.

Table 2. Findings on neuroimaging data in the studies

	White matter	Imaging Sequence	Quantification	Main findings on WML
Diffusion imaging				
Li et al., 2013	Microstructure	DTI –TBSS	--	• aMCI-MD showed reduced FA, increased AD, radial diffusivity, and mean diffusivity in multiple white matter tracts, including corpus callosum, fornix, bilateral anterior internal capsule, left posterior internal capsule and tapetum.
Grambaite et al., 2014	Microstructure	DTI	--	• DR was significantly higher in a/e MCI than controls, with significant changes in the temporal and frontal lobes and less prominent changes in the parietal and occipital lobes. • Comparing to controls, a/e MCI group has a higher DR/MD in rostral middle frontal, medial orbitofrontal, caudal anterior cingulate, posterior cingulate, retrosplenial and entorhinal
Bosch et al., 2014	Microstructure	DTI-TBSS	--	• Progressive decrease of mean FA from HC to aMCI to AD. • Significant DR increase in posterior associative pathways among aMCI cases, including bilateral inferior longitudinal, the occipitofrontal fasciculi, posterior cingulum, right longitudinal superior and uncinate fasciculus. • DTI metric changes are largely secondary to gray matter atrophy. • Higher FA, lower MD, DR, and DA values were related to better performance in memory tests.
Structural imaging				
Huey et al., 2013	Macrostructure	FLAIR	Volumetric	• Mean amount of WML volume did not vary significantly by diagnostic groups. • dMCI are less likely to progress to dementia than aMCI.
Makino et al., 2014	Macrostructure	FLAIR	The Fazekas Scale	• 22.5% of aMCI (n=9) did not show periventricular WML vs 27.5% of AD (n =44) did not show periventricular WML • 30% of aMCI (n=12) did not show subcortical WML vs 31.8% of AD (n=51) did not show subcortical WML • Periventricular WML had a significant influence on performance on category fluency and letter fluency test. • Individuals without periventricular WML had higher scores on the category fluency test. • Subcortical WML did not affect the performance of neuropsychological tests.
Naranjo et al., 2015	Macrostructure	FLAIR	Age-related White Matter Changes scale (ARWMC)	• Severe periventricular WML in aMCI vs. Control = 8.6% vs 1.5% • Severe subcortical WML in aMCI vs Control = 1.9% vs 1.5% • A significant association between aMCI and WML load (regardless of its location). • No significant difference between WML load between aMCI single domain and aMCI-multiple domain • WML in the periventricular regions, but not in the subcortical regions, was associated with poorer results on tests that assess memory, attention/executive function, language, and visuospatial ability.
Lamar et al., 2011	Macrostructure	T2-weighted	Leukoaraiosis Scale	• No significant difference between Junque total score between controls and aMCI

			of Junque	• WMH did not contribute to the memory profile of the aMCI group.
Kim et al., 2011	Macrostructure	T2 weighted and FLAIR	Volumetric	• Higher load of WML in AD than MCI, and that in HC. • Greater severity of WML in the frontal regions and parietal-occipital regions, than in the temporal regions (for all three groups) • No significant difference between sd-aMCI group and control group in WML • Total and regional volumes of WML correlated with performance on the MMSE, attention, memory, and language tasks. • Only periventricular WML volume, not subcortical WML volume significantly correlated with cognitive measures
Peters et al., 2014	Macrostructure	FLAIR & T2	ARWMC	• No significant difference between groups on baseline WML measured by ARWMC.
Nolze-Charron et al., 2015	Macrostructure	T2-weighted & PD sequence	ARWMC for overall WML; CHIPS for measuring cholinergic tract WML	• No association between WMH at baseline and conversion from MCI to AD for global WMH burden or WMH within the cholinergic pathways. • Almost half (47.8%) of all MCI subjects had few or no WMH.
Eckerström et al., 2015	Macrostructure	T2 2D TSE	Fazekas scale	• WML was not significant between pMCI and sMCI
Defrancesco et al., 2013	Macrostructure	Diffusion-weighted images and FLAIR	Modified Fazekas rating scale and the Scheltens scale	• Higher scores in periventricular WML in pMCI than sMCI at both baseline and follow-up • No difference in WML of subcortical regions between groups. • Periventricular WML was negatively associated with psychomotor speed, and subcortical WML were negatively correlated with visual memory at baseline. • Increase of WML severity was associated with MMSE and naming

Note. ARWMC = Age-Related White Matter Change rating scale; CHIPs =The Cholinergic Pathways Hyper Intensities Scale ; DTI –TBSS = Diffusion Tensor Imaging – Tract-based Spatial Statistics; FLAIR = Fluid Attenuation Inversion Recovery; aMCI = amnesic MCI; dMCI = dysexecutive MCI; aMCI-SD = amnesic MCI – single domain; aMCI-MD= amnesic MCI-multiple-domain; MCI-MCDE = multiple MCI with executive dysfunction; a/eMCI = attention/executive MCI; sMCI =MCI patients who remained cognitively stable in follow-up; pMCI = MCI patients who progressed to dementia at follow-up; AD = Alzhimer's disease; HC= healthy controls

Table 3.Outcome measures: Cognitive tests used in the studies

	General cognitive status	General cognitive ability	Processing speed	Attention	Memory	Working memory	Executive function	Visual spatial	Language
Li et al, 2013	MMSE		Processing speed index of WAIS-RC		AVLT Rey-O complex figure test	Digit span of WAIS-RC	Trial making; Similarities subtest (verbal reasoning)	Copy of Rey-Osterrieth complex figure test	Boston naming test
Huey et al., 2013					Benton visual retention test Selective reminding Test		Letter fluency; category fluency; similarities of WAIS-R	Rosen Drawing; Benton Visual Retention test matching	Boston naming test Boston Diagnostic Aphasia Evaluation repetition and comprehension tests
Grambaite et al., 2014	MMSE	Vocabulary of WASI; Matrix of WAIS-III		TMT-A Digit Symbol coding of WAISIII	WMS-R, RAVLT; Rey Complex figure test (RCFT)	Letter-number sequence subtest, verbal fluency of COWAT-FAS)	TMT-B; Response inhibition (Color-word interference from Delis-Kaplan Executive Function System) CWIT-condition 3. Response inhibition switching: CWIT-condition4.	RCFT copy	Boston naming test
Makino et al., 2014	MMSE		Digit Symbol subtest of WAIS-R		Logical memory I and II WMS-R	Digit Span Forward and Backward subtest of WAIS-R; Category fluency; Letter fluency test	Controlled inhibition: Stroop colored word test		
Bosch et al., 2012	MMSE				Composite memory score from Consortium to Establish a Registry for Alzheimer's Disease		Composite frontal score: Digit span of WAIS-III; symbol search of WAIS III Similarities of WAIS –III, COWAT	Composite visuospatialscore: Incomplete letters, number location of VOSP ; Ideomotor praxis,	Boston Naming Test Boston Diagnostic Aphasia Battery comprehension

			(CERAD); Free and cued selective reminding test		constructional praxis of CERAD	
Naranjo et al., 2015	MMSE	Symbol digit modalities test	Free and cued selective reminding test ;		Rey-Osterrieth complex figure copy and recall	Letter fluency, animal fluency
Lamar et al., 2011	CAMCOG	TMT-A	WMS-III	Mental flexibility : TMT-B ; Verbal fluency FAS ; category fluency		Verbal fluency FAS ; category fluency
Kim et al., 2011		SNSB (Forward and backward digit span, letter cancellation test)	Seoul Verbal memory test; RCFT for visual memory	Motor impersistence, contrasting program, go-no-go, fist-edge-palm, alternating hand movement, alternating square and triangle, Luria, COWAT, Korean version of Stroop Color and Word test	SNSB (ideomotor, buccofacial praxis test) RCFT- copy	Reading, writing, comprehension, repetition, Korean version of Boston Naming test, finger naming, right-left orientation, body part identification, calculation,
Eckerstrom et al., 2015	MMSE		RAVLT	TMT-B		BNT
Nolze-Charron et al., 2015				TMT-B		
Defrancesco et al., 2013	MMSE	TMT-A	CERAD verbal and figural memory	TMT-B Planning (CLOX Test)	Copy geometrical shapes, CERAD	BNT-short version Category verbal fluency

Note. MMSE = Mini-mental State Examination; WAIS = Wechsler Abbreviated Scale of Intelligence ; RAVLT = Rey Auditory Verbal Learning test ; COWAT= Controlled Oral Word Association Test ; VOSP = Visuo-Object and Space Perception Battery ; CAMCOG = Cambridge Cognitive Examination ; RCFT = Rey Complex Figure Test ; SNSB = Seoul Neuropsychological Screening Battery; TMT = Trail Making Test ; CERAD

Reference

Albert, M., Blacker, D., Moss, M. B., Tanzi, R., & McArdle, J. J. (2007). Longitudinal change in cognitive performance among individuals with mild cognitive impairment. *Neuropsychology*, *21*(2), 158–169. http://doi.org/10.1037/0894-4105.21.2.158

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

Bolandzadeh, N., Davis, J. C., Tam, R., Handy, T. C., & Liu-Ambrose, T. (2012). The association between cognitive function and white matter lesion location in older adults: a systematic review. *BMC Neurology*, *12*(1), 126. http://doi.org/10.1186/1471-2377-12-126

Bosch, B., Arenaza-Urquijo, E. M., Rami, L., Sala-Llonch, R., Junqué, C., Solé-Padullés, C., … Bartrés-Faz, D. (2012). Multiple DTI index analysis in normal aging, amnestic MCI and AD. Relationship with neuropsychological performance. *Neurobiology of Aging*, *33*(1), 61–74. http://doi.org/10.1016/j.neurobiolaging.2010.02.004

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

Busse, A., Hensel, A., Gühne, U., Angermeyer, M. C., & Riedel-Heller, S. G. (2006). Mild cognitive impairment: Long-term course of four clinical subtypes. *Neurology*, *67*(12), 2176–2185. http://doi.org/10.1212/01.wnl.0000249117.23318.e1

Cyarto, E. V, Lautenschlager, N. T., Desmond, P. M., Ames, D., Szoeke, C., Salvado, O., … Cox, K. L. (2012). Protocol for a randomized controlled trial evaluating the effect of physical activity on delaying the progression of white matter changes on MRI in older adults with memory complaints and mild cognitive impairment: the AIBL Active trial. BMC Psychiatry, 12(1), 167. http://doi.org/10.1186/1471-244X-12-167

Clerx, L., Visser, P. J., Verhey, F., & Aalten, P. (2012). New MRI markers for alzheimer's disease: A meta-analysis of diffusion tensor imaging and a comparison with medial temporal lobe measurements. *Journal of Alzheimer's Disease*, *29*(2), 405–429. http://doi.org/10.3233/JAD-2011-110797

Coutu, J.-P., Goldblatt, A., Rosas, H. D., & Salat, D. H. (2015). White Matter Changes are Associated with Ventricular Expansion in Aging, Mild Cognitive Impairment, and Alzheimer's Disease. *Journal of Alzheimer's Disease : JAD*, *49*, 1–52. http://doi.org/10.3233/JAD-150306

de Leeuw, F. E., de Groot, J. C., Achten, E., Oudkerk, M., Ramos, L. M., Heijboer, R., … Breteler, M. M. (2001). Prevalence of cerebral white matter lesions in elderly people: a population based magnetic resonance imaging study. The Rotterdam Scan Study. *J Neurol Neurosurg Psychiatry*, *70*(1), 9–14. http://doi.org/10.1136/jnnp.70.1.9

Defrancesco, M., Marksteiner, J., Deisenhammer, E., Kemmler, G., Djurdjevic, T., & Schocke, M. (2013). Impact of white matter lesions and cognitive deficits on conversion from mild cognitive impairment to alzheimer's disease. *Journal of Alzheimer's Disease*, *34*(3), 665–672. http://doi.org/10.3233/JAD-122095

Doi, T., Makizako, H., Shimada, H., Tsutsumimoto, K., Hotta, R., Nakakubo, S., … Suzuki, T.

(2015). Objectively measured physical activity, brain atrophy, and white matter lesions in older adults with mild cognitive impairment. Experimental Gerontology, 62, 1–6. http://doi.org/10.1016/j.exger.2014.12.011

Eckerström, C., Olsson, E., Klasson, N., Berge, J., Nordlund, A., Bjerke, M., & Wallin, A. (2015). Multimodal prediction of dementia with up to 10 years follow up: The Gothenburg MCI study. *Journal of Alzheimer's Disease*, *44*(1), 205–214. http://doi.org/10.3233/JAD-141053

Engvig, A., Fjell, A. M., Westlye, L. T., Moberget, T., Sundseth, Ø., Larsen, V. A., & Walhovd, K. B. (2012). Memory training impacts short-term changes in aging white matter: A Longitudinal Diffusion Tensor Imaging Study. Human Brain Mapping, 33(10), 2390–2406. http://doi.org/10.1002/hbm.21370

Fazekas, F., Chawluk, J. B., Alavi, A., Hurtig, H. I., & Zimmerman, R. A. (1987). MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. American Journal of Neuroradiology, 8(3), 421-426.

Flak, M. M., Hernes, S. S., Skranes, J., & Løhaugen, G. C. (2014). The Memory Aid study: protocol for a randomized controlled clinical trial evaluating the effect of computer-based working memory training in elderly patients with mild cognitive impairment (MCI). *Trials*, *15*, 156. http://doi.org/10.1186/1745-6215-15-156

Fleischman, D. A., Yang, J., Arfanakis, K., Arvanitakis, Z., Leurgans, S. E., Turner, A. D., … Buchman, A. S. (2015). Physical activity, motor function, and white matter hyperintensity burden in healthy older adults. *Neurology*, *84*(13), 1294–1300. http://doi.org/10.1212/WNL.0000000000001417

Gao, F. Q., Swartz, R. H., Scheltens, P., Leibovitch, F. S., Kiss, A., Honjo, K., & Black, S. E.

(2011). Complexity of MRI white matter hyperintensity assessments in relation to cognition in aging and dementia from the sunnybrook dementia study. *Advances in Alzheimer's Disease, 2*, 679–688. http://doi.org/10.3233/978-1-60750-793-2-679

Gow, A. J., Bastin, M. E., Muñoz Maniega, S., Valdés Hernández, M. C., Morris, Z., Murray, C., … Wardlaw, J. M. (2012). Neuroprotective lifestyles and the aging brain. *Neurology*, *79*(17), 1802–1808. http://doi.org/10.1212/WNL.0b013e3182703fd2

Grambaite, R., Selnes, P., Reinvang, I., Aarsland, D., Hessen, E., Gjerstad, L., & Fladby, T. (2011). Executive dysfunction in mild cognitive impairment is associated with changes in frontal and cingulate white matter tracts. *Journal of Alzheimer's Disease*, *27*(2), 453–462. http://doi.org/10.3233/JAD-2011-110290

Jokinen, H., Lipsanen, J., & Schmidt, R. (2012). Brain atrophy accelerates cognitive decline in cerebral small vessel disease : The LADIS study Brain atrophy accelerates cognitive decline in cerebral small vessel disease The LADIS study, 1785–1792. http://doi.org/10.1212/WNL.0b013e3182583070

Kim, S., Choi, S. H., Lee, Y. M., Kim, M. J., Kim, Y. D., Kim, J. Y., … Kim, D. K. (2015). Periventricular white matter hyperintensities and the risk of dementia: a CREDOS study. *International Psychogeriatrics / IPA*, *27*(12), 2069–77. http://doi.org/10.1017/S1041610215001076

Landau, S. M., Harvey, D., Madison, C. M., Reiman, E. M., Foster, N. L., Aisen, P. S., … Jagust, W. J. (2010). Comparing predictors of conversion and decline in mild cognitive impairment. *Neurology*, *75*(3), 230–238. http://doi.org/10.1212/WNL.0b013e3181e8e8b8

Makino, T., Umegaki, H., Suzuki, Y., Yanagawa, M., Nonogaki, Z., Nakashima, H., & Kuzuya, M. (2014). Relationship between small cerebral white matter lesions and cognitive function

in patients with Alzheimer's disease and amnestic mild cognitive impairment. *Geriatrics & Gerontology International*, *14*(4), 819–826. http://doi.org/10.1111/ggi.12176

Meier, I. B., Manly, J. J., Provenzano, F. A., Louie, K. S., Wasserman, B. T., Griffith, E. Y., … Brickman, A. M. (2012). White Matter Predictors of Cognitive Functioning in Older Adults. *Journal of the International Neuropsychological Society*, *18*(3), 414–427. http://doi.org/10.1017/S1355617712000227

Morley, J. E., Morris, J. C., Berg-Weger, M., Borson, S., Carpenter, B. D., del Campo, N., … Vellas, B. (2015). Brain Health: The Importance of Recognizing Cognitive Impairment: An IAGG Consensus Conference. *Journal of the American Medical Directors Association*, *16*(9), 731–739. http://doi.org/10.1016/j.jamda.2015.06.017

Mortamais, M., Reynes, C., Brickman, A. M., Provenzano, F. A., Muraskin, J., Portet, F., … Artero, S. (2013). Spatial Distribution of Cerebral White Matter Lesions Predicts Progression to Mild Cognitive Impairment and Dementia. *PLoS ONE*, *8*(2), 1–9. http://doi.org/10.1371/journal.pone.0056972

Naranjoa, I. C., Cuenca, J. C. P., Juan De, B. D. S., García, A. F., Sevilla, R. R., Cabrer, A. S., … Moreno, J. M. R. (2015). Association of vascular factors and amnestic mild cognitive impairment: A comprehensive approach. *Handbook of Depression in Alzheimer's Disease*, (October), 237–246. http://doi.org/10.3233/978-1-61499-542-5-237

Nolze-Charron, G., Mouiha, A., Duchesne, S., & Bocti, C. (2015). White Matter Hyperintensities in Mild Cognitive Impairment and Lower Risk of Cognitive Decline. *Journal of Alzheimer's Disease : JAD*, *46*(4), 855–62. http://doi.org/10.3233/JAD-140618

Pantoni, L. (2002). Pathophysiology of age-related cerebral white matter changes. *Cerebrovascular Diseases (Basel, Switzerland)*, *13 Suppl 2*(Suppl. 2), 7–10.

http://doi.org/49143

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

Petersen, R. C. (2004). Mild cognitive impairment as a clinical entity and treatment target. *Archives of Neurology*, *62*(7), 1160–1163; discussion 1167. http://doi.org/10.1001/archneur.62.7.1160

Petersen, R. C., Doody, R., Kurz, a, Mohs, R. C., Morris, J. C., Rabins, P. V, … Winblad, B. (2001). Current concepts in mild cognitive impairment. *Archives of Neurology*, *58*, 1985–1992. http://doi.org/nsa10002 [pii]

Podewils, L. J., Guallar, E., Beauchamp, N., Lyketsos, C. G., Kuller, L. H., & Scheltens, P. (2007). Physical activity and white matter lesion progression: Assessment using MRI. Neurology, 68(15), 1223–1226. http://doi.org/10.1212/01.wnl.0000259063.50219.3e

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

Radanovic, M., Pereira, F. R. S., Stella, F., Aprahamian, I., Ferreira, L. K., Forlenza, O. V., & Busatto, G. F. (2013). White matter abnormalities associated with Alzheimer's disease and mild cognitive impairment: a critical review of MRI studies. *Expert Review of Neurotherapeutics*, *13*(5), 483–93. http://doi.org/10.1586/ern.13.45

Saczynski, J. S., Jonsdottir, M. K., Sigurdsson, S., Eiriksdottir, G., Jonsson, P. V, Garcia, M. E., … Launer, L. J. (2008). White matter lesions and cognitive performance: the role of

cognitively complex leisure activity. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *63*(8), 848–54. http://doi.org/http://dx.doi.org/10.1093/gerona/63.8.848

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

Sen, A., Gider, P., Cavalieri, M., Freudenberger, P., Farzi, A., Schallert, M., … Schmidt, H. (2012). Association of cardiorespiratory fitness and morphological brain changes in the elderly: Results of the Austrian stroke prevention study. *Neurodegenerative Diseases*, *10*(1–4), 135–137. http://doi.org/10.1159/000334760

Sexton, C. E., Betts, J. F., Demnitz, N., Dawes, H., Ebmeier, K. P., & Johansen-Berg, H. (2016). A systematic review of MRI studies examining the relationship between physical fitness and activity and the white matter of the ageing brain. *NeuroImage*, *131*(August 2015), 81–90. http://doi.org/10.1016/j.neuroimage.2015.09.071

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

Son, S. J., Lee, K. S., Na, D. L., Seo, S. W., Kim, C. H., Kim, J. H., … Hong, C. H. (2012). The effect of anemia and white matter hyperintensities (WMH) on cognitive impairment in patients with amnestic mild cognitive impairment (MCI). *Archives of Gerontology and Geriatrics*, *55*(2), 251–256. http://doi.org/10.1016/j.archger.2011.10.015

Targosz-Gajniak, M., Siuda, J., Ochudło, S., & Opala, G. (2009). Cerebral white matter lesions in patients with dementia - from MCI to severe Alzheimer's disease. *Journal of the Neurological Sciences*, *283*(1–2), 79–82. http://doi.org/10.1016/j.jns.2009.02.314

Tsang, R. S. M., Sachdev, P. S., Reppermund, S., Kochan, N. a, Kang, K., Crawford, J., … Brodaty, H. (2013). Sydney Memory and Ageing Study: an epidemiological cohort study of brain ageing and dementia. *International Review of Psychiatry (Abingdon, England)*, *25*(6), 711–25. http://doi.org/10.3109/09540261.2013.860890

Wahlund, L. O., Barkhof, F., Fazekas, F., Bronge, L., Augustin, M., Sjögren, M., … Scheltens, P. (2001). A new rating scale for age-related white matter changes applicable to MRI and CT. *Stroke; a Journal of Cerebral Circulation*, *32*(6), 1318–22. http://doi.org/10.1161/01.STR.32.6.1318

Wallin, A., Nordlund, A., Jonsson, M., Blennow, K., Zetterberg, H., Öhrfelt, A., … Bjerke, M. (2016). Alzheimer's disease - Subcortical vascular disease spectrum in a hospital-based setting: Overview of results from the Gothenburg MCI and dementia studies. *Journal of Cerebral Blood Flow and Metabolism*, *36*(1), 95–113. http://doi.org/10.1038/jcbfm.2015.148

Wendelken, C., Lee, J. K., Pospisil, J., Sastre, M., Ross, J. M., Bunge, S. A., & Ghetti, S. (2015). White matter tracts connected to the medial temporal lobe support the development of mnemonic control. *Cerebral Cortex*, *25*(9), 2574–2583. http://doi.org/10.1093/cercor/bhu059

Wirth, M., Haase, C. M., Villeneuve, S., Vogel, J., & Jagust, W. J. (2014). Neuroprotective pathways: Lifestyle activity, brain pathology, and cognition in cognitively normal older adults. *Neurobiology of Aging*, *35*(8), 1873–1882.

http://doi.org/10.1016/j.neurobiolaging.2014.02.015

Xiong, Y. Y., & Mok, V. (2011). Age-Related White Matter Changes. *Journal of Aging Research*, *2011*, 1–13. http://doi.org/10.4061/2011/617927

Yotsumoto, Y., Chang, L. H., Ni, R., Pierce, R., Andersen, G. J., Watanabe, T., & Sasaki, Y. (2014). White matter in the older brain is more plastic than in the younger brain. *Nat Commun*, *5*, 5504. http://doi.org/10.1038/ncomms6504

Zhou, I. Y., Liang, Y. X., Chan, R. W., Gao, P. P., Cheng, J. S., Hu, Y., … Wu, E. X. (2014). Brain resting-state functional MRI connectivity: Morphological foundation and plasticity. *NeuroImage*, *84*, 1–10. http://doi.org/10.1016/j.neuroimage.2013.08.037

Zhuang, L., Sachdev, P. S., Trollor, J. N., Kochan, N. a., Reppermund, S., Brodaty, H., & Wen, W. (2012). Microstructural white matter changes in cognitively normal individuals at risk of amnestic MCI. *Neurology*, *79*(8), 748–754. http://doi.org/10.1212/WNL.0b013e3182661f4d