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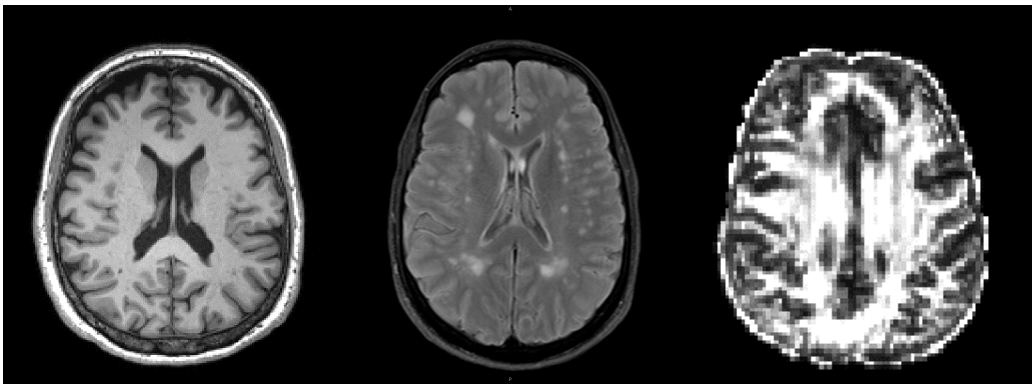
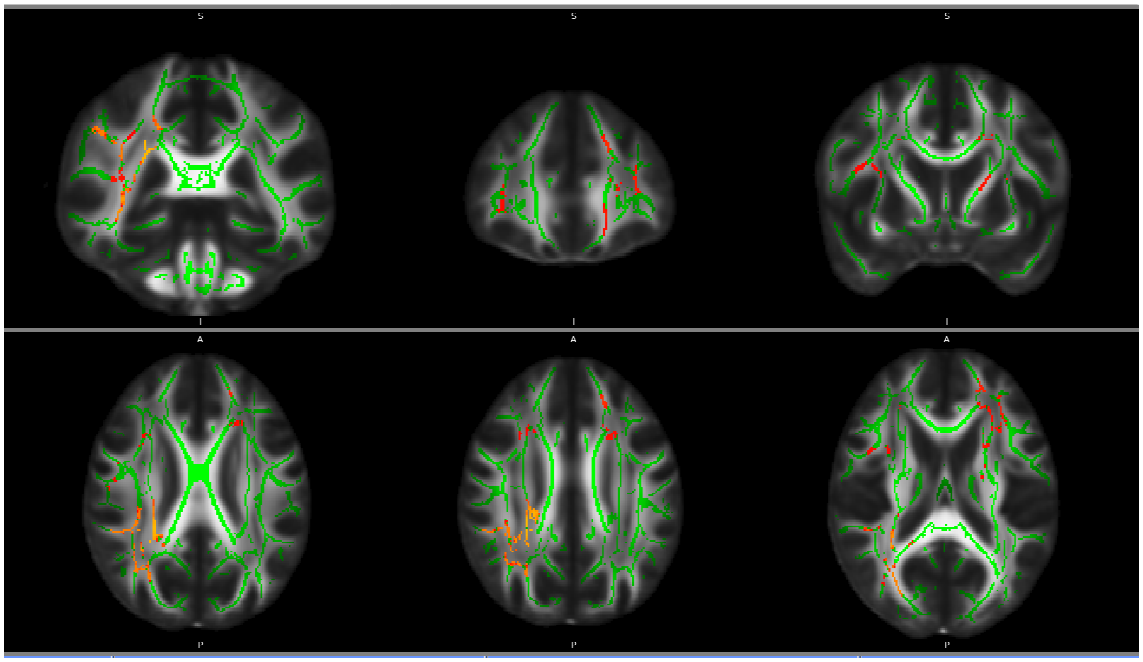
MRI and neuropsychological correlates of white matter hyperintensities in asymptomatic subjects aged 50 to 65 years

Juan José Soriano Raya





MRI and neuropsychological correlates of white matter hyperintensities in asymptomatic subjects aged 50 to 65 years

PhD Thesis **Juan José Soriano Raya**

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UNIVERSITAT DE BARCELONA

Department of Psychiatry and Clinical Psychobiology

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This thesis is presented by

Juan José Soriano Raya

To obtain the degree of Doctor (PhD) from the University of Barcelona

Supervised by

Dr. Maria Mataró Serrat. University of Barcelona, Spain

Doctoral Programme in Biomedicine

Dr. Maria Mataró Serrat, PhD, from the University of Barcelona,

CERTIFIES that she has supervised and guided the PhD thesis entitled “MRI and neuropsychological correlates of white matter hyperintensities in asymptomatic subjects aged 50 to 65 years” presented by Juan José Soriano Raya. She hereby asserts that this thesis fulfils the requirements to be defended to obtain the Degree of Doctor of Psychology.

Signature,

Dr. Maria Mataró Serrat

University of Barcelona

Signature,

Juan José Soriano Raya Barcelona, November 2015

The work presented in this thesis was carried out in the Neuropsychology Group from the Department of Psychiatry and Clinical Psychobiology at the University of Barcelona.

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A mis padres

Y a todas las personas que también han creído en mí

ACKNOWLEDGEMENTS

Todo gran viaje empieza con un pequeño paso. Y después del primero, vienen todos los demás, habría que añadir. Después de muchos pequeños pasos, llego al fin a la meta. Es difícil recoger en estas pocas líneas todos los agradecimientos que pasan por mi mente en estos momentos. Y, con toda seguridad, no estarán todos los que son, aunque sí son todos los que están. Procuraré ser lo menos injusto posible.

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En fin, muchas gracias a todos.

CONTENTS

FOREWORD

This thesis, presented to obtain the degree of Doctor from the University of Barcelona, is the result of three studies carried out at the Department of Psychiatry and Clinical Psychobiology at the University of Barcelona, the Hospital Universitari Clínic in Barcelona, and the Hospital Universitari Germans Trias i Pujol in Badalona, Barcelona.

Studies included in this thesis are presented as articles. Studies I and III have been published in international scientific journals within the first tertile in the categories "Neurosciences", "Clinical Neurology", and "Psychology", with a global impact factor of 8.37 (ISI Web of Knowledge, Journal Citation Reports inferred from 2014). Study II is a working paper.

Study I

Soriano-Raya, J.J.; Miralbell, J.; López-Cancio, E.; Bargalló N; Arenillas, J.F.; Barrios, M.; Cáceres, C.; Toran, P.; Alzamora, M.; Davalos, A.; Mataró, M. (2012). **Deep *versus* Periventricular White Matter Lesions and Cognitive Function in a Community Sample of Middle-Aged Participants.** *Journal of the International Neuropsychological Society, 18*, 874-885. doi: 10.1017/S1355617712000677. Impact Factor: 2.96.

Study II

Soriano-Raya JJ, Miralbell J, López-Cancio E, Bargalló N, Arenillas JF, Barrios M, Cáceres C, Toran P, Alzamora M, Dávalos A, Mataró M (2015). **Regional cortical atrophy in lingual gyrus predicts visuospatial skills in a community sample of participants with white matter lesions.** Working paper.

Study III

Soriano-Raya JJ, Miralbell J, López-Cancio E, Bargalló N, Arenillas JF, Barrios M, Cáceres C, Toran P, Alzamora M, Dávalos A, Mataró M. **Tract-specific fractional anisotropy predicts cognitive outcome in a community sample of middle-aged participants with white matter lesions.** *J Cereb Blood Flow Metab* 2014;34(5):861-9. doi: 10.1038/jcbfm.2014.26. Impact Factor: 5.41.

GLOSSARY OF ABBREVIATIONS

AD: Alzheimer's Disease

ADC: Apparent Diffusion Coefficient

ApoE: Apolipoprotein E

ARWMC: Age-Related White Matter Changes

AsIA: Asymptomatic Intracranial Atherosclerosis

ATR: Anterior Thalamic Radiation

BBB: Blood-Brain Barrier

CAA: Cerebral Amyloid Angiopathy

CADASIL: Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leucoencephalopathy

CMB: Cerebral MicroBleeds

CMI: Cortical MicroInfarcts

CSF: CerebroSpinal Fluid

CT: Computed Tomography

CVD: CerebroVascular Disease

DA: Axial Diffusivity

DTI: Diffusion Tensor Imaging

DWMHs: Deep White Matter Hyperintensities

FA: Fractional Anisotropy

FLAIR: FLuid-Attenuated Inversion Recovery

FSL: FMRIB Software Library

GDS-15: Geriatric Depression Scale 15-item version

GM: Grey Matter

GRE: GRadient Echo

IFOF: Inferior Fronto-Occipital Fasciculus

LI: Lacunar Infarcts

MCI: Mild Cognitive Impairment

MD: Mean Diffusivity

MMSE: Mini-Mental State Examination

MPRAGE: Magnetization-Prepared RApid Gradient Echo)

MRI: Magnetic Resonance Imaging

MTA: Medial Temporal Atrophy

MTR: Magnetization Transfer Ratio

PVHs: PeriVentricular Hyperintensities

PVS: PeriVascular Spaces

RD: Radial Diffusivity

ROI: Region Of Interest

SLF: Superior Longitudinal Fasciculus

SVD: Small Vessel Disease

TBSS: Tract-Based Spatial Statistics

VBM: Voxel-Based Morphometry

VCI: Vascular Cognitive Impairment

VRF: Vascular Risk Factors

WAIS-III: Wechsler Adult Intelligence Scale (3rd edition)

WM: White Matter

WMHs: White Matter Hyperintensities

WMS-III: Wechsler Memory Scale (3rd edition)

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INTRODUCTION

More than a century ago, clinical and pathological studies from Otto Binswanger and Alois Alzheimer were the first to suggest that white matter (WM) atrophy caused by "vascular insufficiency" could result in dementia (Libon et al., 2004). In 1894, Binswanger described patients who experienced a slow progression of dementia in combination with focal neurological signs such as hemianopsia and hemiparesis, enlarged ventricles, and substantial loss of WM with a general sparing of the cortex. A few years later, Alzheimer basically substantiated his colleague's observations providing pathological observations about the disease, that he renamed Binswanger's disease (Román, 1999). Soon after, Emil Kraepelin collected these findings in his textbook of Psychiatry and separated arteriosclerotic dementia associated with extensive WM atrophy from dementia involving cortical atrophy and senile plaques (Román, 2002).

Many years lapsed until the emergence of novel diagnostic techniques highlighted the seminal work from Binswanger and Alzheimer. Meanwhile, all cortical and subcortical dementias were labelled as "senile dementias" despite all previous research and efforts to distinguish them from each other (Libon et al., 2004). However, this changed dramatically in the 1970s with the discovery of computed tomography (CT) and the advent in the 1980s of magnetic resonance imaging (MRI). The increased availability of both techniques in clinical practice revealed incidental findings of WM radiological abnormalities, regarded as small complete infarctions and diffuse rarefaction, that were found not only in cognitively impaired patients but also in individuals without overt cognitive dysfunction. The observed findings were often considered to be an expression of WM damage associated with Binswanger's disease (Hachinski et al., 1987).

In 1987, Hachinski, Potter and Merskey introduced the term "leukoaraiosis" (from the Greek "leuko" = "white", and "araiosis" = "rarefaction") to designate these bilateral and symmetrical areas in WM of the periventricular region and centrum semiovale that appeared hypodense on CT (Hachinski et al., 1987). This radiological term was used to describe a neuroimaging abnormality irrespective of its cause (Scheltens et al., 1998). It was also deemed suitable to define and describe WM damage, and would also function as a trigger for further research aimed at identifying its clinical and imaging correlates (Prins and Scheltens, 2015).

Over the past three decades, the amount of data on the clinical and pathological correlates of these incidental WM findings has vastly increased. They are currently thought to be a consequence of cerebral small-vessel disease (SVD). Previous research has applied different terms, such as white matter changes, white matter lesions, or white matter hyperintensities (WMHs) to label these abnormalities. Following a recent consensus statement (Wardlaw et al., 2013a), the term WMH will be used throughout this thesis.

Definition and classification of white matter hyperintensities

Cerebral WMHs are seen on MRI as more or less confluent areas that are bilaterally and symmetrically sited in the hemispheric WM. These morphological changes do not correspond to specific vascular territories but rather involve the periventricular WM and the centrum semiovale or subcortical WM (Pantoni et al., 2002). They are identified as diffuse areas of hypodensity on CT, and high signal intensities on T2-weighted, proton density and fluid-attenuated inversion recovery (FLAIR) images. On T1-weighted images, they can appear as isointense or hypointense, depending of the severity of the underlying pathological change (Seiler et al., 2012).

WMHs are usually divided into two groups depending on their anatomical position: those immediately adjacent to the ventricles (periventricular hyperintensities or PVHs) and those located in the subcortical white matter (deep white matter hyperintensities or DWMHs) (Fazekas et al., 2002). PVHs typically include caps around the frontal and occipital horns of the lateral ventricles. Periventricular caps extending along the body of the lateral ventricles are called ‘‘lining’’ or when broader ‘‘smooth halo’’. DWMHs can occur as punctate changes or beginning confluent or confluent abnormalities (Schmidt et al., 2011a). **(Figure 1)**

Varying terminology and definitions for PVHs and DWMHs make it sometimes difficult to compare lesion findings across studies, and the dichotomization itself is still controversial (de Carli et al., 2005; Sachdev and Wen, 2005; Schmidt et al., 2011a). Complementary rules have been proposed (Kim et al., 2008), because the most severe PVHs tend to coalesce with DWMHs in advanced stages (Duering et al., 2013). Nevertheless, there are no widely accepted rules for defining PVHs other than the continuity rule.

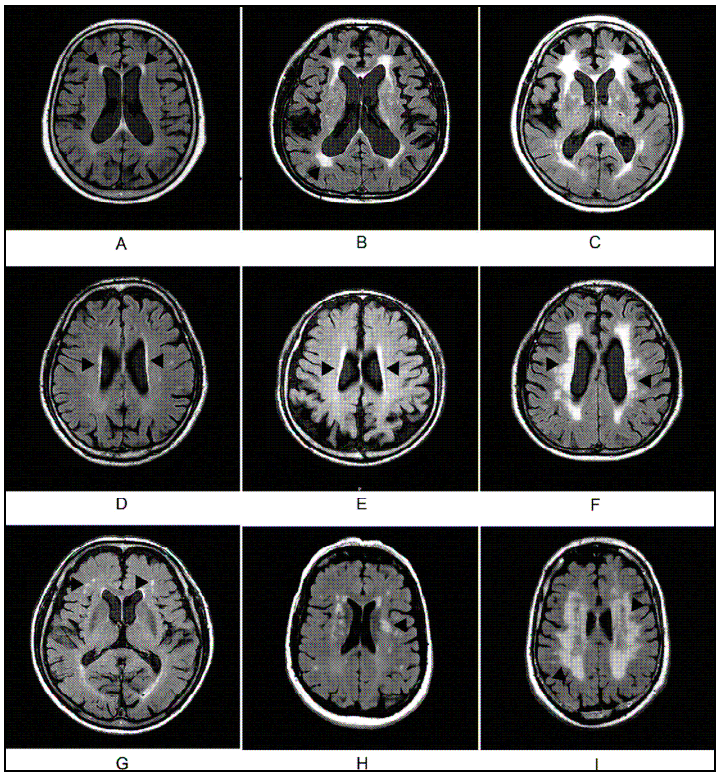

Figure 1. Forms of White Matter Hiperintensities: small caps **(A)**, large caps **(B)**, extending caps **(C)**, thin lining **(D)**, smooth halo **(E)**, irregular PVHs extending to deep WM **(F)**, punctuate DWMHs **(G)**, DWMHs beginning confluence **(H)**, and confluent DWMHs **(I)** (Kim et al., 2008).

Epidemiology of white matter hyperintensities

Cerebral WMHs are common MRI findings in normal aging, stroke patients, as well as in other neurological and psychiatric disorders (Kim et al., 2008). The reported prevalence presents a high variability among studies as a result of differences in imaging techniques, rating methods, and populations that were studied (Pantoni et al., 2007; Prins and Scheltens, 2015).

The prevalence of WMHs ranges from 50% to 98% in normal aging, from 67% to 98% in stroke patients, and from 29% to 100% in Alzheimer's disease (AD) (Xiong and Mok, 2011). Lower prevalence may be explained by low-field-strength MRI (Ylikoski et al., 1995), the exclusion of people with neurological or psychiatric disorders (Schmidt et al., 1997), or the inclusion of young participants (Hopkins et al., 2006). WMHs are now reported in individuals aged 30 or 40 years-old (Sachdev et al., 2008) and prevalence increases gradually with aging (Longstreth et al., 1996).

In community-dwelling elderly samples, more than half of individuals present WMHs on MRI (de Leeuw et al., 2001; Enzinger et al., 2007; Longstreth et al., 1996). For instance, in the population-based Rotterdam Scan Study (de Leeuw et al., 2001), which included participants older than 60 years, the prevalence of WMHs was up to 95%, and the Cardiovascular Health Study (Longstreth et al., 1996) reported a prevalence of 96% of individuals over 65 years with WMHs. Small caps, thin-lining and punctate DWMHs are the most common signal changes identified on MRI in elderly individuals. All other WM abnormalities are considerably less frequent, but up to one third of participants may have severe abnormalities depending on the composition of the sample (van Dijk et al., 2002). In patients with overt cerebrovascular disease (CVD), the frequency of severe WMHs is usually higher (Schmidt et al., 2011a).

Risk factors associated with white matter hyperintensities

According to epidemiological studies, the main risk factors for the development of WMHs are increasing age, vascular risk factors (VRF), symptomatic CVD and cardiovascular disease (Prins and Scheltens, 2015). Among them, the most common risk factors for WMHs are aging (Basile et al., 2006; Breteler et al., 1994a; de Leeuw et al., 2001; Launer, 2004; Liao et al., 1996; Longstreth et al. 1996) and arterial hypertension (Basile et al., 2006; de Leeuw et al., 2002; Dufoil et al., 2001; Kuller et al., 2010; Liao et al., 1996; Longstreth et al. 1996; van Dijk et al., 2004a), which are usually labelled as the main predictors of these abnormalities (Khan et al., 2007; Xiong and Mok, 2011). Diabetes mellitus (van Harten et al., 2007; Verdelho et al., 2007), hypercholesterolemia (Crisby et al., 2010; Vuorinen et al., 2011), obesity (Jagust et al., 2005), smoking (Longstreth et al., 1996) and elevated levels of homocysteine (Kloppenborg et al., 2011; Sachdev et al., 2008) are additional VRF associated with WMHs, although these associations are less prominent (Kim et al., 2008; Xiong and Mok, 2011).

WMHs are also strongly associated with symptomatic CVD (i.e., ischemic or hemorrhagic stroke) (Schmahmann et al., 2008; Wen and Sachdev, 2004). Individuals with WMHs are at increased risk to develop stroke (Debette et al., 2010; Poels et al., 2012a; Weinstein et al., 2013) and suffer vascular death (Debette et al., 2010; Kuller et al., 2007). Likewise, subclinical coronary artery atherosclerosis has been related to WMHs burden in healthy relatives of individuals with early-onset coronary artery disease (Kral et al., 2013) and cardiovascular disease biomarkers are predictive of WMHs in the population-based ARIC Study (Dadu et al., 2013). The strong epidemiological association that exists between WMHs and symptomatic CVD supports that ischemia may be a contributing factor in the emergence of these radiological abnormalities.

Progression of white matter hyperintensities

WMHs tend to progress over time (Schmidt et al., forthcoming). Longitudinal studies have shown considerable progression of WMHs burden within a period of few years in normal aging (Debette et al., 2011; Longstreth et al., 2005; Sachdev et al., 2007; Schmidt et al., 2005; Silbert et al., 2008; van Dijk et al., 2008). There is also mounting evidence that WMHs do not progress randomly. For instance, one recent study found that up to 80% of incident WMHs occurring within 4 years represented extensions of pre-existing lesions (Maillard et al., 2013). Likewise, it is suggested that WMHs usually expands from the periventricular zone preferentially toward the subcortical WM, along the trajectories of small perforating arteries (Duering et al., 2013).

Several studies have reported that WMHs burden at baseline is, apart from age, the strongest predictor of future progression of these abnormalities (Patel and Markus, 2011; Schmidt et al., forthcoming). Mild forms of WMHs usually have minimal progression, whereas early confluent and confluent WMHs progress rapidly (Sachdev et al., 2007; Schmidt et al., 2007). Other commonly reported risk factors for WMHs progression are arterial hypertension (Debette et al., 2011; van Dijk et al., 2008), diabetes mellitus (Gouw et al., 2008a), and elevated levels of homocysteine (Kloppenborg et al., 2014a).

Etiopathogenesis of white matter hyperintensities

The etiology of WMHs is not completely understood. This is probably because the pathophysiological mechanisms and the histological correlates of WMHs are not specific. The radiological features seen on neuroimaging basically reflect an increase of brain water content that can be accounted for several reasons (Pantoni, 2002). Nevertheless, the most commonly accepted hypothesis supports that WMHs are essentially related to chronic ischemic injury due to SVD. Thus, WMHs are considered an expression of cerebral SVD.

Small vessel disease

The term SVD describes a range of pathological, neuroimaging, and clinical features related to the small vessels of the brain (Pantoni, 2010). From a pathological point of view, SVD encompasses all the processes that affect the small vessels, including small arteries, arterioles, venules, and capillaries (Pantoni, 2010; Rincon and Wright, 2014; Wardlaw et al., 2013b).

There are different types of cerebral SVD. The most prevalent forms are arteriolosclerosis and cerebral amyloid angiopathy (CAA) (Pantoni, 2010; Rincon and Wright, 2014). Arteriolosclerosis is also called age-related, VRF-related or hypertensive SVD, since it is strongly related to age, diabetes mellitus, and particularly arterial hypertension (Gouw et al., 2011; Pantoni, 2010; Rincon and Wright, 2014). It is pathologically characterized by loss of smooth muscle cells from the tunica media, deposits of fibro-hyaline material, narrowing of the lumen, and thickening of the vessel wall (Pantoni, 2010). CAA is characterized by the progressive accumulation of beta-amyloid protein in the walls of small-to-medium sized arteries and arterioles, and, to a lesser extent, also in the capillaries and veins (Pantoni, 2010). CAA is also a pathological hallmark of AD, since almost all brains of AD patients present CAA (Jellinger, 2002). Other forms of cerebral SVD include inherited or genetic SVD (Tikka et al., 2014), inflammatory or immunologically mediated SVD (Sarbu et al., 2015), or venous collagenosis (Brown et al., 2002).

The pathological mechanisms linking SVD with brain damage are not completely known. Pathological changes in the small vessels can lead to both ischemic and hemorrhagic lesions (Greenberg et al., 2009; Pantoni, 2010). The main mechanism underlying SVD-related brain injury is usually assumed to be ischemia (Wardlaw et al, 2013b). The vessel lumen restriction is thought to lead to a chronic state of hypoperfusion of the WM, resulting in diffuse rarefaction of the WM and, consequently, the emergence of WMHs. Alternatively, acute occlusion of a small vessel may occur, leading to focal areas of complete tissue necrosis or lacunar infarcts (LI). Cerebral microbleeds (CMB) are the consequence when the vessel wall damage reaches a point of rupture.

Pathophysiological mechanisms of white matter hyperintensities

The cerebral hemispheric WM receives most of its blood supply through long penetrating arteries originating from the pial network located on the surface of the brain. These penetrating arteries arise at right angles from the subarachnoid vessels, run through the cortical layers perpendicular to the brain surface, and enter the WM along the course of myelinated fibers (de Reuck, 1971). Alternatively, long perforating arteries stem directly from the large vessels at the basal brain (van den Bergh, 1969). These two systems converge towards each other and tend to merge in the deepest subcortical WM (Pantoni, 2010).

Each of the distributing vessels from a single artery provides the blood supply to a cylindrically shaped metabolic unit. The scarcity or absence of anastomoses that interconnect

branches of the carrying vessels suggests that WM might be considered a “border zone” or area prone to become seriously ischemic under conditions of moderate blood flow deficit caused by thickening of the wall and narrowing of the vascular lumen (i.e., arteriolosclerosis) (Pantoni and Garcia, 1997; Pantoni, 2002). The combination of arteriolosclerosis of the long penetrating and perforating arterioles on the one hand, and hypoperfusion and impaired autoregulation of cerebral blood flow on the other could result in hypoxia and ischemia of the WM (Prins and Scheltens, 2015).

Alternative mechanisms have been proposed and they can be considered complementary to the ischemic one. Amyloid deposition in small arteries and arterioles may also lead to narrowing and obstruction of the vascular lumen and to the loss of vascular smooth muscle cells, resulting in impaired cerebral blood flow autoregulation (van Dijk et al., 2004b). Small vessel alterations could lead to damage of the blood-brain barrier and chronic leakage of fluid and macromolecules in the WM (Wardlaw et al., 2003). The disruption of the BBB could also trigger a local subclinical inflammatory response (Rosenberg, 2009). The presence of matrix metalloproteinases, gliosis, and activated macrophages in WMHs would confirm this hypothesis (Gouw et al., 2011; Simpson et al., 2007). In neurodegenerative diseases, WMHs have been attributed to Wallerian degeneration (Englund, 1998). Another factor that may be implicated in the formation of WMHs is apoptosis related to aging (Brown et al., 2002).

Finally, it is to note that genetic factors may play a role in the development of WMHs (Choi, 2015). This is supported by evidence from family and twin studies (Prins and Scheltens, 2015). Previous epidemiologic studies have reported positive associations between the presence of the apolipoprotein E (ApoE) e4 allele, and the extent and progression of WMHs (Godin et al., 2009a; van Dijk et al., 2004b). Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) is the most common heritable cause of WMHs (Schmidt et al., 2011a). Clinical and neuroimaging features of CADASIL resemble those of sporadic WMHs. This genetic disease is caused by pathogenetic mutations that alter the number of cysteine residues in the extracellular domain of NOTCH3 (Chabriat et al., 2009). Other genetic factors might also contribute to the development of WMHs (Fornage et al., 2011; López et al., 2015).

Histopathological correlates of white matter hyperintensities

The most consistent histological correlates of WMHs are partial loss of myelin, axons and oligodendroglial cells, astrogliosis, dilatation of perivascular spaces, and activated macrophages

in the vicinity of small vessels (Gouw et al., 2011; Schmidt et al., 2011a). Tissue changes are thought to reflect incomplete infarction, although small complete deep WM infarcts have also been described (Schmidt et., 2011a). Post-mortem histopathological and MRI studies have reported a heterogeneous plethora of alterations in WMHs that ranges from slight disentanglement of the axonal matrix to varying degrees of myelin and axonal loss (Gouw et al., 2011).

Etiopathogenesis of periventricular and deep white matter hyperintensities

According to histopathological studies, ischemic and non-ischemic changes account separately for the formation of PVHs and DWMHs. Most of PVHs are thought to be non-ischemic changes (Schmidt et al., 2011a). PVHs caps and "lining" reflect predominantly a specific anatomic situation, characterized by loosely arranged fine-fiber tracts with low myelin and high extracellular fluid content, whereas band-like lesions and "smooth halos" have been linked to disruption of the ependymal lining with subependymal gliosis and concomitant loss of myelin. Since these changes do not have an ischemic nature, vessel wall changes in the arterioles are not common in these lesions (Fazekas et al., 1993; Scheltens et al., 1995). In contrast, the most severe form of PVHs or "irregular" PVHs extending to deep WM is indeed associated with microcystic infarcts and patchy rarefaction of myelin, which are ischemic in nature (Fazekas et al., 1998).

The histopathological correlates of DWMHs are heterogenous (Schmidt et al., 2011a). It is necessary to separate the punctate or mild form of DWMHs from the more extensive early confluent and confluent DWMHs. Punctate hyperintensities are usually non-ischemic, since their most common correlate is widening of perivascular spaces (PVS) accompanied by reduced myelination with atrophy of the neuropil around fibrohyalinotic arteries (Fazekas et al., 1991; Fazekas et al., 1993). On the other hand, early confluent and confluent DWMHs are clearly ischemic changes representing a continuum of increasing tissue damage. They are mostly related to widespread rarefaction of myelin, mild to moderate axonal loss, and varying extents of gliosis (Fazekas et al., 1998; Gouw et al., 2011).

Studies of molecular pathology also support a preferential hypoxic etiology for DWMHs, whereas PVHs are consistently related to non-ischemic changes (Schmidt et al., 2011a). The severity of PVHs has been associated with loss of ventricular ependyma, whereas factors induced by hypoxia are upregulated in DWMHs (Fernando et al., 2006). Likewise, PVHs are reported to contain higher lever of ramified activated microglia, which may result from BBB disruption (Simpson et al., 2007).

Neuroimaging techniques and features in small vessel disease

MRI is a commonly available and useful neuroimaging tool that enables neuroscience researchers to observe and measure the effects of brain aging (Lockhart and de Carli, 2014). SVD is characterized by a series of abnormalities visible on neuroimaging, such as WMHs, LI or CMB. Brain imaging is hence crucial as a diagnosis tool for SVD since these imaging features are commonly silent (Román and Pascual, 2012). If no contraindications are known, MRI, rather than CT, is preferred for routine clinical use because it has higher sensitivity and specificity for detecting most manifestations of SVD (Wardlaw et al., 2013a). It is also a basic choice for follow-up assessments and research due to high image resolution and timely acquisition whilst having no side effects (Gorelick et al., 2011; Hachinski et al., 2006).

Magnetic resonance imaging protocol in small vessel disease

The basic protocol in the neuroimaging work-up of SVD should include T1-weighted, T2-weighted, and FLAIR sequences **(Figure 2)**. The most useful and informative structural MRI methods include those used to acquire high-resolution structural anatomical images of the brain, which are usually T1-weighted sequences. These T1-weighted sequences generate images that typically maximize the contrast difference between grey matter (GM), WM, and cerebrospinal fluid (CSF). On these images, CSF is hypointense (dark), and GM has less intensity (appears darker) than WM. They are generally used to elucidate the size of GM and WM volumes, various cortical and subcortical structures, and the expansion of CSF spaces.

Other important structural MRI sequences are T2-weighted and FLAIR images. On T2-weighted images, CSF is hyperintense (bright) and GM looks brighter than WM. Lesions also appear hyperintense, so it might be difficult to distinguish a lesion from CSF, especially for smaller lesions. FLAIR images are T2-weighted images in which the CSF signal is almost entirely suppressed, whereas lesions still appear hyperintense, which allows the optimal visualization and contrast of WM abnormalities (i.e., WMHs) (Fazekas et al., 2002). Other T2-weighted images are T2*-weighted gradient echo (GRE) or susceptibility-weighted images. These sequences are fairly sensitive to mineral content in the brain, which makes them suitable to identify CMB (van der Flier and Cordonnier, 2012).

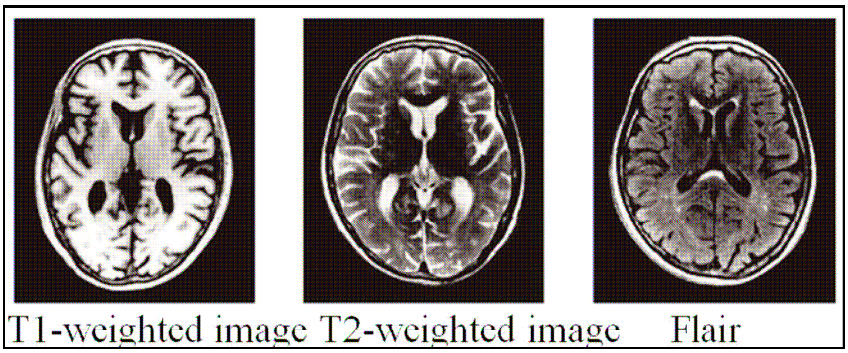

Figure 2. Basic Magnetic Resonance Imaging sequences. Images are taken from one of our participants.

For a comprehensive research MRI protocol for SVD, it would be desirable the use of high-resolution 3.0 T MRI in all the previous sequences, and the use of volume acquisitions with near-isotropic resolution. For quantitative volumetric assessments of GM atrophy, a high-resolution T1-weighted sequence (1,0 mm to 1,5 mm isotropic voxels) with good contrast between GM and WM is highly recommended (Wardlaw et al., 2013a). Further, there is SVD-related damage that can be only detectable on novel and advanced MRI techniques, such as diffusion tensor imaging (DTI) and magnetisation transfer ratio (MTR) images (Prins and Scheltens, 2015; Schmidt et al., forthcoming; Wardlaw et al., 2013b).

Imaging features of small vessel disease

Small vessels can not be properly visualised in vivo. Therefore, imaging features are assumed to be caused by SVD and have been adopted as a putative marker of the disease. The term SVD is often equated with these brain abnormalities (Pantoni, 2010; Rincon and Wright, 2014). Apart from WMHs, the main imaging features of SVD visible on conventional MRI are acute or chronic LI (Vermeer et al., 2007), CMB (Yates et al., 2014), PVS (Potter et al., 2015a), and brain atrophy (Arvanitakis et al., forthcoming). Cerebral microinfarcts (CMI) are a recent addition to the spectrum of SVD which is only detectable at high-field MRI strengths (Smith et al., 2012).

LI are round or ovoid, subcortical, fluid-filled cavities, with similar MRI signal as CSF, which are typically seen in locations such as basal ganglia, internal capsule, thalamus, corona radiata, and pons (Norrving, 2008; Pantoni, 2010). On FLAIR images, LI usually have a central CSF-like hypointensity with a surrounding rim of hyperintensity (Wardlaw et al., 2013a). LI can also be distinguished from WMHs because of decreased signal intensity on T1-weighted MRI (Vermeer et al., 2007). There is no full consensus on the size of LI. A lower limit of 3 mm and an upper limit of 15 mm are usually considered (Fazekas et al., 2002). When neuroimaging reflects a

recent small subcortical infarct occurring in the previous few weeks, the central cavity fluid is not suppressed on FLAIR, and the lesion can appear entirely hyperintense, despite MRI having a clear CSF-like intensity on other sequences such as T1-weighted and T2-weighted images (Moreau et al., 2012).

CMB are visualised as small dot-like lesions on paramagnetic-sensitive MRI such as T2*-weighted GRE or susceptibility-weighted images, since these microbleeds are quite specific for small collections of blood-breakdown products (in particular, haemosiderin contained within perivascular macrophages) (Charidimou and Werring, 2012). When imaged with T2*-weighted GRE sequences, CMB are well-defined round or oval areas with homogeneous low signal. They are not generally seen on T1-weighted, T2-weighted and FLAIR sequences (Wardlaw et al., 2013a). CMB are generally from 2 to 5 mm in diameter, but can be up to 10 mm.

In SVD, brain atrophy is defined as a lower brain volume that is not related to a specific macroscopic focal injury, such as trauma or large-vessel infarction (Wardlaw et al., 2013a). Loss of brain volume is characterized on MRI by widening of the sulci and narrowing of the gyri, as well as enlargement of the ventricles (Appelman et al., 2009). Tissue loss due to SVD is probably secondary to a diffuse process and should not be confused with discrete focal lesions, such as large cortical infarcts.

PVS are fluid-filled spaces around the small vessels of the brain that follow their trajectories as they course from the brain surface into and through the brain parenchyma (Wardlaw et al., 2013b). They are also called Virchow-Robin spaces (Groeschel et al., 2006; Kwee and Kwee, 2007). PVS have similar signal intensity to that of CSF on all sequences, so they must be differentiated from LI. The diameter of PVS is not usually more than 3 mm (Bokura et al., 1998) and spaces are not seen with a hyperintense rim around the fluid-filled space on T2-weighted or FLAIR sequences, unless they traverse an area of WMHs (Wardlaw et al., 2013a).

Recent brain autopsy studies have revealed the presence of very small ischemic lesions (< 1 mm), mostly cortical, in individuals without macroscopic vascular pathology (Brundel et al., 2012). These CMI had been undetected on neuroimaging until the introduction of ultra-high field 7.0 T MRI scanners (Smith et al., 2012, van Veluw et al., 2013), although recent studies suggest that the study of CMI in larger clinical studies is possible using 3.0 T MRI (van Dalen et al., 2015; van Veluw et al., forthcoming).

Assessment and quantification of white matter hyperintensities

Various methods are available nowadays to quantify the presence and severity of WMHs on CT and MRI, ranging from visual rating scales to semi-automated or fully automated volumetric techniques. Although the latter has often been used as a gold standard for reliability and validity of visual scales (Gouw et al., 2008b; Kapeller et al., 2003), it is not clear if volumetric measurements should be consistently regarded as the best choice (Prins and Scheltens, 2015).

Some of the semi-quantitative visual rating scales only provide a global assessment into normal, moderate, and severe WMHs (van Swieten et al., 1991), whereas others are more detailed and divide WMHs into periventricular and subcortical grades, as well as into different anatomical regions (Fazekas et al., 1987; Scheltens et al., 1993; Wahlund et al., 2001).

The Fazekas scale provides two different scores rated on a 0-to-3 point scale of increasing severity (Fazekas et al., 1987). PVHs are graded as 0 = absence, 1 = “caps” or pencil-thin “lining”, 2 = “smooth halo”, and 3 = “irregular” PVHs extending into the deep WM. DWMHs are rated as 0 = absence, 1 = punctate foci, 2 = beginning confluence of foci, and 3 = large confluent areas. The sum of the PVHs and the DWMHs scores provides a total score. The Fazekas scale provides a good but global assessment of WMHs. It is easy to apply in most cases, even on poor-quality MRI scans. For MRI, it may be one of the best choices because of its simplicity and good reliability (Scheltens et al., 1998).

The scale of Scheltens accounts for the size and number of WMHs in different anatomic regions on a 0-to-6 point scale of increasing severity (Scheltens et al., 1993). It provides a single PVHs score and four DWMHs scores separated into frontal, temporal, parietal, and occipital scoring, with a maximum of 24 points. Basal ganglia are divided into caudate nucleus, putamen, globus pallidus, thalamus, and internal capsule, scoring a maximum of 30 points. Infratentorial WMHs are rated in the cerebellum, mesencephalon, pons, and medulla, scoring a maximum of 24 points. The Scheltens scale has a good interobserver and intraobserver reliability for assessment of WMHs (Scheltens et al., 1998).

The Age-Related White Matter Changes (ARWMC) scale was developed to provide a combined CT-MRI tool for the assessment of WMHs (Wahlund et al., 2001). In the ARWMC

scale, five different areas are rated separately in the right and left hemispheres: the frontal area, the parieto-occipital area, the temporal area, the infratentorial area, and the basal ganglia. Each area is rated separately on a 0-to-3 point scale, providing a total maximum score of 30 points.

Visual rating is fast and can be applied to images of different quality obtained on different scanners. In clinical practice and studies involving large amount of participants, it may be preferable to use visual rating scales instead of more time-consuming quantitative measurements to assess WMHs (Schmidt et al., forthcoming). Nevertheless, visual rating scales inevitably have some limitations, including non-linearity of data, lack of sensitivity to small changes, and susceptibility to ceiling effects (Kim et al., 2008). In addition, existing scales are heterogeneous, which may contribute to the inconsistent results in previous research on WMHs (Kloppenborg et al., 2014b).

Although visual rating scales have also been developed for assessing WMHs progression (Prins et al., 2004a; Schmidt et al., 1999), semi-automated or fully automated volumetric methods may be more suitable for joint quantification of WMHs burden and progression (Anbeek et al., 2004; Maillard et al., 2008; van den Heuvel et al., 2006).

Volumetric analysis of WMHs is usually performed on computer screen using scans from an appropriate MRI sequence, such as axial FLAIR or T2-weighted images. In semi-automated methods, hyperintensities are marked and borders are set on each slice using local thresholding, usually by means of home-developed software. Areas of hyperintensities on T2-weighted images around infarctions and lacunes are disregarded. Fully automated methods are based on probabilistic techniques, such as the K-nearest neighbor classification algorithm. This technique generates images representing the probability per voxel of being part of a WMHs. By application of thresholds on these probability maps, binary segmentations can be obtained (Anbeek et al., 2004).

Semi-automated and automated methods have the advantage of providing exact WMHs volumes, which are desirable when research looks for subtle associations (Prins and Scheltens, 2015). However, semi-automated methods are labour intensive, time-consuming, and require well-trained analysts. Fully automated quantification methods of WMHs are not optimal either, because manual correction is usually needed to improve accuracy. Quantification of WMHs does not only require sophisticated tools for image analysis, but it also demands MRI examinations

performed with appropriate and homogenous protocols at high-quality level. Finally, no distinction is usually made between DWMHs and PVHs.

Small vessel disease in vascular cognitive impairment

The term vascular cognitive impairment (VCI) has been proposed to account for the contribution of CVD on cognitive dysfunction, ranging from mild deficits to overt dementia (Bowler and Hachinski, 1995). VCI incorporates the complex interactions between vascular etiologies (VRF and CVD), changes within the brain, and cognitive function (O'Brien et al., 2003). It recognizes that overt dementia represents only a fraction of the total cognitive morbidity, and emphasizes the complexity of the mechanisms and overlap between cerebrovascular and neurodegenerative pathologies in the elderly (Gorelick et al., 2011; Iadecola, 2010).

Nowadays, cerebral SVD is thought to be among the main causes of VCI (Pantoni, 2010). It is probably the second most endemic pathology of the aging brain following AD (Schmidt et al., forthcoming). Over the past 15 years, SVD has been recognised as a serious problem (Wardlaw et al., 2013a), although the focus in cognitive impairment and dementia has been largely set on the amyloid hypothesis, and the influence of SVD, including WMHs, has been sometimes neglected (Prins and Scheltens, 2015).

Gorelick et al. (2011) have recently provided a practical approach to the diagnosis and classification of all forms of VCI. This consensus statement has recommended that diagnostic criteria for VCI should be based on two main factors:

1) Presence of cognitive impairment based on extensive neuropsychological assessment.
2) Evidence of CVD based on neuroimaging.

An often neglected executive dysfunction with slowed information processing, only mild memory impairment, and behavioural symptoms is the cardinal clinical manifestation in SVD (Erkinjuntti, 2007). Because of the slow progressive course of these clinical correlates, symptoms may remain unnoticed in clinical evaluations (Schmidt et al., forthcoming).

White matter hyperintensities and cognitive function

With the advent of neuroimaging as a tool for clinical practice, the high prevalence of age-related WMHs raised questions about their potential impact on cognitive functioning. Some early studies reported that WMHs were associated with cognitive impairment (Junqué et al., 1990; Steingart et al., 1987), whereas other investigations did not (Hunt et al., 1989). Given the high prevalence of WMHs on neuroimaging, even in normal elderly population without cognitive impairment, some researchers reasoned that WMHs were unlikely to be associated with cognitive performance and decline (Fazekas et al., 2009).

Nonetheless, the association of WMHs with cognitive function has been reported in most studies (Frisoni et al., 2007; Kloppenborg et al., 2014b; Pantoni et al., 2007; Schmidt et al 2011b). Cognitive consequences of WMHs have been attributed mostly to fronto-subcortical circuit disruption (Linortner et al., 2012; Schmidt et al., 2006) as well as to cortical association and projection fibers involvement (Nordahl et al., 2006). Damage to neurotransmitter systems, in particular the cholinergic system, could also account for the cognitive consequences of WMHs (Román and Kalaria, 2006).

Cross-sectional studies

WMHs have consistently been associated with cognitive function in most cross-sectional research (Kloppenborg et al., 2014b; Schmidt et al., 2011b). Associations between WMHs and cognitive performance have been reported in community-dwelling healthy participants (Hedden et al., 2012; Mosley et al., 2005; Vernooij et al., 2009), high risk populations (i.e., mild cognitive impairment (MCI)) (Bombois et al., 2007; Debette et al., 2007; Delano-Wood et al., 2008), and individuals with dementia (Bracco et al., 2005; Burns et al., 2005; Shim et al., 2011).

The cognitive domains that are more consistently related to WMHs in community-dwelling healthy participants are executive function and processing speed (de Carli et al., 1995; Pantoni et al., 2007; Rabbitt et al., 2007; Schmidt et al., 2011b; Soderlund et al., 2006; Vannorsdall et al., 2009). Executive dysfunction often affects abstract reasoning, planning, organization, or set-shifting, leading eventually to functional disability (Inzitari et al., 2009). WMHs can also be associated in normal aging with other cognitive functions, such as global cognitive function, attention, memory, motor function, or visuospatial skills (Au et al., 2006; de Carli et al., 1995; de Groot et al., 2000; Leaper et al., 2001; Mosley et al., 2005; O'Brien et al., 2002; Sachdev et al., 2005; Schmidt et al., 1993; Ylikoski et al., 1993).

Longitudinal studies

Several longitudinal studies have reported that WMHs are related not only to cognitive function but also to cognitive decline and incident dementia, with individuals with moderate and severe WMHs declining the most (Longstreth et al., 2005; Prins et al., 2004b).

Previous studies have reported an association between baseline WMHs burden and cognitive decline in global cognition, executive function and processing speed in community samples (de Groot et al., 2002; Godin et al., 2010; Longstreth et al., 2005; Prins et al., 2005; Wakefield et al., 2010). Mild effects have also been found in memory (Godin et al., 2010), visuospatial skills (Schmidt et al., 2005), and motor function (Silbert et al., 2008).

Baseline WMHs burden is also related to an increased risk of incident dementia in community samples (Debette et al., 2010; Prins et al., 2004b), whereas studies in high risk populations (i.e., MCI) have reported conflicting results (Bombois et al., 2008; Smith et al., 2008). Bombois et al. (2008) included 170 consecutive MCI patients during a median follow-up of almost 4 years. Although WMHs were not associated with an increased risk of dementia as a whole, the risk to develop vascular or mixed dementia increased significantly with increasing amounts of WMHs at baseline. On the other hand, Smith et al. (2008) recruited 67 cognitively normal participants and 156 MCI patients. After an annual follow-up of 3 years, high-grade WMHs (above one standard deviation from the study population mean) was an independent predictor of conversion from normal cognition to MCI, but not predicted conversion from MCI to dementia.

As previously noted, WMHs are not static MRI findings (Xiong and Mok, 2011). Reports on the cognitive consequences of WMHs progression have mostly demonstrated an association with global and specific domain cognitive decline (Debette and Markus, 2010; Schmidt et al., forthcoming). Cognitive performances in executive function (Debette et al., 2011; Jokinen et al., 2011; Vannorsdall et al., 2009), processing speed (Longstreth et al., 2005; van Dijk et al., 2008), memory (Debette et al., 2011), and visuospatial skills domains (Schmidt et al., 2005) are usually related to WMHs change over time.

Clinical relevance of the association

When summarizing the findings of previous investigations, WMHs seem to have subtle but noticeable cognitive consequences (Schmidt et al., 2011b). However, the clinical relevance of

this association remains controversial (Andersson, 2010; Wallin and Fladby, 2010). This is probably due to the high prevalence of WMHs in elderly populations and the large inter-individual variability of the clinical presentation in individuals with such abnormalities (Schmidt et al., 2011b). Clinical presentation on the individual level is most likely influenced by severity and regional distribution of WMHs (Desmond, 2002; Pantoni et al., 2007). However, it is still unclear if there is a threshold of WMHs volume which consistently leads to substantial cognitive dysfunction and which anatomical locations are crucial.

Previous studies suggest that the association of WMHs with cognitive function is probably mediated by severity of WM damage. This association is strengthened in those individuals with more severe WMHs, whereas mild degrees are unlikely to be related to worse cognitive performance (de Groot et al., 2000; Pantoni et al., 2007; Prins et al., 2005; Schmidt et al., 2005; Schmidt et al., 2011b; van der Flier et al., 2005). It is likely that a threshold exists in WMHs load (Boone et al., 1992; de Carli et al., 1995; van der Flier et al., 2005), beyond which cognitive function is affected. A recent meta-analysis failed to find support for this threshold, although the authors assume that the distinction in high and low WMHs they used was based on different cut-off points due to the heterogeneity of methods to quantify WMHs (Kloppenborg et al., 2014b).

Similarly, the specific contribution of PVHs and DWMHs to cognitive function is currently undetermined, since not many studies have addressed this issue (Schmidt et al., 2011b). Several years ago, Bowler and Hachinski (2003) argued that both types of WMHs should be analysed separately, given that PVHs and DWMHs may differ in their pathogenesis and clinical significance. Though some investigations have not found cognitive differences between PVHs and DMWHs (Burns et al., 2005; Shenkin et al., 2005), an increasing amount of evidence supports that anatomical location may have a specific role on cognitive functioning (Bolandzadeh et al., 2012; Kloppenborg et al., 2014b).

Previous research has yielded contradictory findings regarding the differential impact of PVHs versus DWMHs. In community-dwelling individuals (de Groot et al., 2000), MCI (Debette et al., 2007) and patients with dementia (Bracco et al., 2005), a predominant role of PVHs has been reported, whereas other studies have found a stronger association with DWMHs in the same population settings (community-dwelling: Sachdev et al., 2005; MCI: Delano-Wood et al., 2008; dementia: Sachdev et al., 2004). De Groot et al. (2000) were the first team to specifically analyse the independent cognitive association of PVHs versus DWMHs in a large sample of normal

elderly participants. They found a predominant role for PVHs related to global dysfunction, verbal memory, and psychomotor slowness. On the other hand, Sachdev et al. (2005) reported a stronger association between DWMHs and motor dysfunction and slowed information processing speed in a young elderly community sample.

Further, both visual rating and volumetric studies have also reported conflicting results. In a sample including dementia-free and early-stage AD participants, Burns et al. (2005) reported a specific association of PVHs scores with associate memory and psychomotor speed in non-demented participants, whereas Baune et al. (2009) also found a specific association of DWMHs scores with verbal memory and psychomotor speed in normal aging individuals. PVHs volume was related to working memory, processing speed, verbal fluency, and verbal and visual memory in a community sample of healthy adults. DWMHs volume was only related to working memory and verbal fluency (Vannorsdall et al. 2009). On the other hand, Silbert et al. (2008) showed that only DWMHs volume was associated with cognitive decline in a sample of cognitively normal individuals during a mean follow-up of 9 years.

Other anatomical locations different from PVHs and DWMHs have been investigated regarding their relationship with cognitive function. Such regions include frontal, parietal, temporal, occipital, cerebellar, or basal ganglia WMHs. However, no common pattern has been identified due to the scarce evidence and the heterogeneity of regions among studies (Bolandzadeh et al., 2012).

Despite all this evidence, caution is mandatory, since WMHs are not the only change in the brain responsible for cognitive dysfunction in the elderly (Frisoni et al., 2007; Pantoni et al., 2007). First, WMHs are only a part of the spectrum of SVD (Pantoni, 2010; Patel and Markus, 2011; Rincon and Wright, 2014). Therefore, their effect should be considered together with that of other SVD-related markers, such as LI or CMB. Second, the cognitive status of elderly participants is not only associated with SVD-related pathology, but also with degenerative changes that often coexist (Prins and Scheltens, 2015). Some of the most intriguing research in recent years suggests a pathological overlap between vascular processes and AD pathology (Costanza et al., 2012; Iadecola, 2010).

Other markers of small vessel disease and cognitive function

Lacunar infarcts or lacunes

LI are mostly consistent with a previous recent or chronic small subcortical infarct. The word "recent" is preferred instead of acute because it includes the first few weeks of the lesion, and not the hyperacute stage only. The term "lacune" is also preferred when including a possible hemorrhagic etiology (Wardlaw et al 2013a). On histological examination, LI or lacunes are found to correspond to irregular cavitations with scattered fat laden macrophages, which can be accompanied by surrounding reactive gliosis and myelin and axonal loss (Gouw et al., 2011).

The first indices supporting the deleterious effect of lacunes on cognition were reported in the Nun Study (Snowdon et al., 1997). In community samples, the presence and number of silent LI have been associated with worse performance in global cognition and executive function (Patel and Markus, 2011). LI in the thalamus have been associated with executive, processing speed and motor function (Benisty et al., 2009), whereas LI in other locations have been related to psychomotor slowness (Vermeer et al., 2003) or memory dysfunction. Silent LI at baseline are also associated with the onset of MCI (Debette et al., 2010; López et al., 2003) and incident dementia (Debette et al., 2010; Vermeer et al., 2003). The incidence of new lacunes has been related with cognitive decline in executive function and psychomotor speed (Jokinen et al., 2011).

LI are frequently associated with WMHs. Some authors find it more appropriate to classify patients with LI as having SVD only when LI are multiple or associated with moderate-to-severe WMHs (Pantoni et al., 2009). The combination of WMHs and multiple lacunes has been associated with a worse performance in global and domain-specific cognitive function, cognitive decline and an increased risk to develop dementia (Aggarwal et al., 2010; Koga et al., 2009).

Cerebral microbleeds

CMB are usually regarded as microscopic bleedings (Gouw et al., 2011). Available data suggest that two main mechanisms can lead to CMB: those seen in deep and infratentorial sites (such as basal ganglia, thalamus, brainstem, and cerebellum) are presumed to result from hypertensive SVD, whereas lobar CMB are thought to be related to CAA (van der Flier and Cordonnier, 2012).

Emerging data shows an existing association between CMB and cognitive dysfunction. In community samples, cross-sectional studies have reported impairment in global cognition, executive function, attention, processing speed, and motor function (Lei et al., 2013; Yates et al.,

2014). It is thought that CMB specifically located in the frontal or temporal region or the basal ganglia are responsible for cognitive impairment (Poels et al., 2012b; van Norden et al., 2011), although some studies do not report associations according to location of CMB, which impedes a systematic comparison (Yates et al., 2014). There are few longitudinal studies addressing the prognostic value of CMB. Lobar microbleeds have been associated with decline in executive function of older adults (Meier et al., 2014). Presence of multiple CMB eventually predicts the development of dementia in the general population, but not in patients with MCI (van der Flier and Cordonnier, 2012).

Perivascular spaces and cortical microinfarcts

Enlargement of PVS is associated with other features of SVD, such as WMH and LI (Doubal et al., 2010; Potter et al., 2015b; Zhu et al., 2010). The association of PVS with cognitive function remains controversial since the scarcity of available data in community samples has provided conflicting results (MacIullich et al., 2004; Yao et al., 2015). It has been suggested that CMI could be the most common type of SVD in the brain, being up to 15 times more frequent than LI (Norrving, 2015). Nonetheless, their role in cognitive function is currently under study.

Brain atrophy, white matter hyperintensities and cognitive function

Brain atrophy in normal aging

A large amount of evidence confirms that whole and regional brain volumes decline with advancing age (Lockhart and de Carli, 2014). Indeed, brain atrophy occurs during the normal aging process, although the extent and course of atrophy is characterized by a higher variability among individuals (Scahill et al., 2003).

Measures of GM and WM volumes during lifespan show different patterns reflecting differential vulnerability (Raz et al., 2005). There is a normal age-related reduction of GM volume, which is thought to represent cortical neuronal degeneration and loss of synaptic connectivity (Lockhart and de Carli, 2014). Overall, GM volume begins to decline steadily in young adulthood and continues linearly until late life, although it usually accelerates over 60 years of age (Fotenos et al., 2005; Ge et al., 2002; Giorgio et al., 2010). Relatively fewer studies have explored age-related changes in WM volume (Lockhart and de Carli, 2014). Reports suggest that WM tend to increase until the fifth decade of life before decreasing with an accelerated quadratic trend (Fotenos et al., 2005).

While almost all research shows reduction of brain volumes in association with advancing age, there are substantial regional differences, resembling an anterior-to-posterior gradient. Brain volumes decrease particularly in frontal lobes, with smaller differences for the temporal lobes, and relative sparing of the parietal and occipital lobes (Jerningan et al., 2001; Pfefferbaum et al., 2013; Raz et al., 2005).

Brain atrophy and white matter hyperintensities in normal aging and small vessel disease

Many studies have reported that the presence and severity of SVD is related to brain atrophy, including global atrophy, corpus callosum atrophy, central atrophy (e.g., increased ventricular size and atrophy of the basal ganglia), mesencephalic atrophy, and hippocampal atrophy (Appelman et al., 2009; Aribisala et al., 2013). Therefore, measures of brain atrophy are regarded to be important in studies assessing SVD burden in the brain (Wardlaw et al 2013a).

Previous research has also shown a significant association between WMHs and whole brain atrophy (brain parenchyma, including GM and WM tissues) in normal aging and SVD (Ikram et al., 2008; Jokinen et al., 2012; Schmidt et al., 2005). In the population-based Rotterdam Scan Study, Ikram et al. (2008) found that people with a higher load of WMHs had smaller brain volumes. In a longitudinal study, Schmidt et al. (2005) reported that progression of WMHs volume at 3-year and 6-year follow-up was also associated with brain parenchyma loss in a community sample. In the LADIS Study, a large longitudinal multi-center research investigating the role of WMHs in transition to disability, WMHs volume has been associated with global atrophy assessed with a visual rating scale (Jokinen et al., 2012).

However, prior work has yielded conflicting results when taking into account only whole brain specific tissues (Godin et al., 2009b; Ikram et al., 2008; Wang et al., 2014, Wen et al., 2006). Ikram et al. (2008) reported that higher WMHs volume was associated with reduced WM volume, whereas WMHs volume was not significantly related with GM volume. This pattern was reversed in the population-based study from Wen et al. (2006), where WMHs volume was related to GM volume, but not to WM volume. On the other hand, Godin et al. (2009b) found that WMHs volume was associated with reduced GM volume and increased CSF volume, after controlling for age, sex, education, arterial hypertension and ApoE genotype, in a population-based sample of 1792 elderly individuals. Recent work has reported that WMHs load, assessed using both a visual rating scale and a volumetric approach, is significantly associated with lower GM volume and

higher ventricular volume, which may be considered a surrogate marker of WM volume, in a community sample (Wang et al., 2014).

An alternative approach to volumetric studies is voxel-based morphometry (VBM) (Ashburner and Friston, 2000; Good et al., 2001), which enables whole brain analysis of brain morphology and allows the detection of regional areas of brain atrophy without a prior delimitation of a region-of-interest (ROI). Previous studies on a voxel-by-voxel basis in normal aging and SVD have shown a regional pattern of reduced GM volume in participants with WMHs compared to healthy controls (Quinque et al., 2012; Rossi et al., 2006). Individuals with early cerebral microangiopathy (ARWMC score > 2) presented reduced GM volume in bilateral frontal regions compared to controls (Quinque et al., 2012). Rossi et al. (2006) assessed the correspondence between WMHs location and regional GM volume in individuals without cognitive impairment. Participants with predominant frontal WMHs showed bilateral frontal atrophy (medial, superior, and inferior gyrus) compared with a group of controls without WMHs, whereas participants with mainly parieto-occipital WMHs presented a more diffuse pattern of reduced GM volume, involving frontal areas but also the right insular region and the left fusiform gyrus.

Likewise, regression studies have consistently reported a significant negative association between WMHs burden and GM volume in several areas (Crane et al., 2015; Raji et al., 2012; Wen et al., 2006). In the large community-dwelling Path Through Life Study (Wen et al., 2006), VBM analysis showed that whole brain WMHs volume was significantly associated with reduced GM volume in nearly every lobe. This association was more prominent between the WMHs volume and the GM volume within the same lobe. In the Cardiovascular Health Study, Raji et al. (2012) found that higher WMHs scores were associated with lower GM volumes throughout the brain, most prominently in frontal areas but also in the temporal lobe, the parahippocampal gyrus, and the inferior parietal cortex. Recently, Crane et al. (2015) have reported a significant negative association between WMHs volume and GM volume in the lingual gyrus and the hippocampus in elderly non-demented adults with mild to severe WMHs.

Brain atrophy and cognitive function in normal aging and small vessel disease

Studies of brain structural measures and their relation to concurrent or future cognitive performance have become an important part of developing the ability to understand and predict cognitive decline (Lockhart and de Carli, 2014). For example, participants with larger baseline

whole brain volumes and smaller baseline WMHs volumes have shown a better cognitive performance in executive function, semantic, and episodic memory (Carmichael et al., 2012).

In normal aging and SVD, different measures of brain atrophy have been related to cognitive dysfunction and cognitive decline. Smaller GM and WM volumes have been associated with cognitive function in community-dwelling samples (Arvanitakis et al., forthcoming; Smith et al., 2015). Global, cortical and subcortical atrophy assessed with a visual rating scale have predicted a lower global and domain-specific cognitive function in non-disabled participants with mild to severe WMHs (Jokinen et al., 2012). Progression of whole brain volume has predicted cognitive decline in the general population (Schmidt et al., 2005). Cognitive decline and the risk of severe cognitive deterioration were significantly increased in participants with smaller hippocampus volume in a large population-based study (Godin et al., 2010).

The concurrence of WMHs and brain atrophy may have some impact on cognitive outcome. Although there is scarce evidence in normal aging and SVD, brain atrophy is thought to amplify the effects of WMHs on cognition. In a work from van der Flier et al. (2005), the presence of either severe WMHs or severe medial temporal atrophy (MTA) was associated with a modest but non-significant increase in frequency of mild cognitive deficits (Mini-Mental State Examination (MMSE) score < 26 points) in 581 non-disabled participants from the LADIS Study. However, the combination of severe MTA and severe WMHs was positively related to a four-fold increased risk of mild cognitive deficits. In a recent longitudinal study, also from the LADIS Study, baseline WMHs and brain atrophy measures independently predicted cognitive decline. Moreover, significant interactions were found between baseline WMHs, LI and brain atrophy measures in the rate of cognitive decline after a 3-year follow-up (Jokinen et al., 2012).

Brain atrophy is also thought to mediate the effects of WMHs on cognition. In the population-based Austrian Stroke Prevention Study, progression of WMHs volume and loss of whole brain volume were separately associated with declining performance in executive function (i.e., conceptualisation), attention, memory, processing speed, and visuospatial skills. However, when both changes in WMHs volume and whole brain volume were included in regression analyses, the associations between WMHs progression and cognitive decline were no longer significant, whereas brain volume loss was the strongest predictor for future cognitive function (Schmidt et al., 2005). On the other hand, Arvanitakis et al. (forthcoming) have tested recently the independent associations of WMHs and GM volume with cognition in community-dwelling

individuals without dementia or MCI. They reported that only the relation of WMHs to cognitive function remains significant when both MRI measures are simultaneously entered in the analyses, while GM volume is no longer related.

One of the main drawbacks of previous research is that there is a large heterogeneity in the definition of brain atrophy used. Brain atrophy is a term that may include whole brain atrophy (Godin et al., 2010; Jokinen et al., 2012; Schmidt et al., 2005), GM atrophy (Arvanitakis et al., forthcoming; Jokinen et al., 2012; Mosley et al., 2005; Mungas et al., 2001; Smith et al., 2015), WM atrophy (Breteler et al., 1994b; Jokinen et al., 2012; Mosley et al., 2005; Smith et al., 2015), or regional atrophy in predetermined specific regions, mostly the hippocampus (Godin et al., 2010; Hedden et al., forthcoming; Jokinen et al., 2012; Mungas et al., 2001; Raji et al., 2012; van der Flier et al., 2005), but also frontal areas, the basal ganglia or the cerebellum (Hedden et al., forthcoming; Raji et al., 2012; Smith et al., 2015; Tullberg et al., 2004).

While whole brain atrophy has been consistently associated with cognitive function in normal aging and individuals with WMHs (Godin et al., 2010; Jokinen et al., 2012; Schmidt et al., 2005), reports relating GM volume to cognitive function have provided controversial results (Arvanitakis et al., forthcoming; Raji et al., 2012; Smith et al., 2015; Tullberg et al., 2004). In community samples, Arvanitakis et al. (forthcoming) showed that GM volume is related to attention, verbal memory, and psychomotor speed, whereas Smith et al. (2015) reported that WM volume, and not GM volume, is associated with attention and psychomotor speed. Raji et al. (2012) found an association of frontal GM with attention and psychomotor speed in the Cardiovascular Health Study, while Tullberg et al. (2004) reported that frontal GM was only related to verbal memory in elderly individuals.

Novel techniques of neuroimaging: diffusion tensor imaging

The role of WM damage in cognitive dysfunction is not fully determined, partly because previous research has found that correlations between WMHs and cognitive function are modest (Frisoni et al., 2007; Schmidt et al., 2011b). This limited association may be a reflection of both the pathological heterogeneity of WMHs and the lack of pathological specificity of conventional MRI (Gouw et al., 2011; Schmidt et al., 2011a). There is also accumulating evidence that there are pathological changes which are 'invisible' to conventional MRI (Smith et al., 2012). It is suggested that WMHs may represent only the extreme end of a diffuse and ongoing process of WM injury

and degeneration (Maillard et al., 2014; Prins and Scheltens, 2015). The evidence of a penumbra surrounding lesions supports the notion that WMHs may fail to capture the full extent and degree of WM damage (Maillard et al., 2013).

Novel imaging techniques that allow a more direct assessment of the composition and organization of WM are promising tools to explain cognitive dysfunction related to WMHs beyond what can be expected from conventional MRI (Seiler et al., 2012). These novel techniques also have the potential to provide additional information about the underlying pathophysiology and consequences of cerebral damage in WMHs (Patel and Markus, 2011).

Description of diffusion tensor imaging

DTI enables the measurement of diffusion of water molecules within the brain (Le Bihan et al., 2001). In regions with limited constraints imposed by physical boundaries, such as CSF in the ventricles, water movement is random and uniform in every direction and is therefore called isotropic. In contrast to CSF, the motion of water molecules in the WM is restricted by the parallel-oriented fibers and water diffusion is therefore highly anisotropic (Chanraud et al., 2010). Such anisotropy reflects, to some extent, the underlying fiber structure. Pathological processes that modify or disrupt WM microstructure can result in altered diffusion measurements, which can be measured in vivo with DTI.

The diffusion tensor refers to a 3 x 3 matrix which provides for each voxel a three-dimensional representation of the directionality and magnitude of water diffusion (Wozniak and Lim, 2006). This diffusion tensor is constructed from measurements of water diffusion in at least six different non-collinear directions to calculate three major eigenvectors, e_1, e_2, and e_3, in order from largest to smallest magnitude. The magnitude of each eigenvector is the corresponding eigenvalue, which is the water diffusion coefficient along each eigenvector direction (Neil, 2008). Graphically, these three eigenvectors and eigenvalues describe an ellipsoid representing the directionality and magnitude of water diffusion within each voxel **(Figure 3)**.

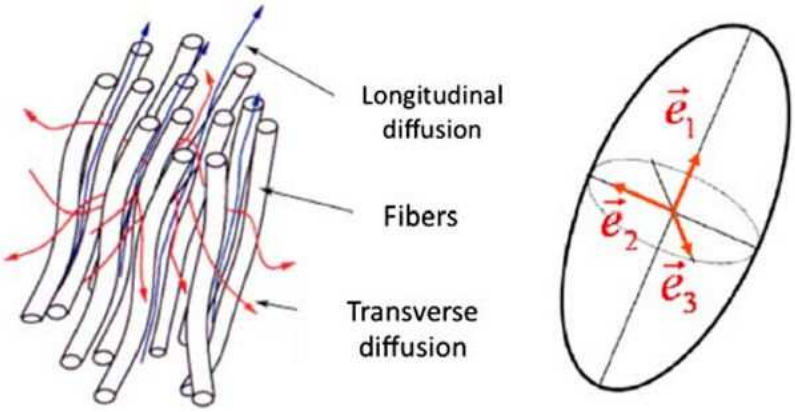

Figure 3. Model of diffusion of water molecules and its representation by a tensor

Left: Diffusion in anisotropic tissue. Water molecules (movement represented in the *blue* and *red* arrows) preferentially diffuse parallel to fibers. *Right*: Representation of diffusion tensor. Ellipsoid with principal axis e_1 reflecting the preferential orientation of diffusion (longitudinal or axial diffusivity, DA); e_2 and e_3 are the short axes of the ellipsoid and their mean equals transverse or radial diffusivity (RD) (Chanraud et al., 2010).

Parameters in diffusion tensor imaging

The eigenvalue average or "trace" reflects the magnitude of diffusion, referred to as mean diffusivity (MD) or apparent diffusion coefficient (ADC). The extent to which one eigenvalue, λ1, dominates the other two, λ2 and λ3, determines the degree of anisotropy, that is, the degree of orientational preference within a voxel, typically measured as fractional anisotropy (FA). The largest eigenvalue (λ1) is the axial or longitudinal diffusivity (DA), whereas radial or transverse diffusivity (RD) is defined by the average of the eigenvalues (λ2, λ3) perpendicular to the primary axis (Chanraud et al., 2010).

FA and MD are the most commonly reported DTI measures (Madden et al., 2009). FA values ranges between 0 and 1 according to the characteristics of the tissue microstructure. For example, FA of the ventricular system is near 0, whereas FA of the corpus callosum, where tracts are arranged in a regular and parallel fashion, can approach 0.8 to 0.9. Lower than expected FA (and the typically associated higher MD) in a region of fully packed WM suggest that WM microstructure is compromised (Chanraud et al., 2010). Nonetheless, it should be kept in mind that MD varies with time after injury. MD values reach a minimum at two to four days after injury and then gradually return to normal over a time period of approximately one week. After that, MD values are higher than normal in the area of injury and remain so (Neil, 2008).

DA and RD are important as additional sources of information across DTI data, but interpreting the underlying substrate is limited without determining the orientation of the principal

eigenvector (Madden et al., 2009). Data from animal models show that primary injury to myelin is associated with an increase in RD, presumably because there are fewer myelin membranes to hinder water displacements in this direction. Conversely, primary injury to axons, such as Wallerian degeneration, is associated with a decrease in DA, presumably because of disruption of the fiber tracts along which water molecules can diffuse (Neil, 2008).

Analysis of diffusion tensor imaging data

There are several methods for DTI analysis, including ROI analysis, voxel-wise analysis, histograms, and quantitative fiber tracking and tractography.

ROI analysis is suitable when a study focuses in a particular brain region. Regions are manually selected by an operator, in order to subsequently carry out statistics on the relevant parameters calculated within the same anatomical region across different subjects. Automated segmentation routines are sometimes employed, but manual correction is usually required. Placement of a ROI in a reliable and accurate manner, however, can be challenging (Madden et al., 2009). ROI analysis is highly operator-dependent and time-consuming, although it can allow relevant correlation analyses with cognitive measures and provide convergent validity to whole brain analysis (Chanraud et al., 2010).

In voxel-wise analysis, each subject's diffusion images are registered into standard space, and then voxel-wise statistics are carried out to detect regional differences between groups or identify areas related to a variable of interest (i.e., cognitive measure). Although the observer-independent VBM-style analysis of DTI circumvents the problems of ROI analyses, it has also limitations because of imperfect image registration and random selection of smoothing factors (Smith et al., 2006).

Histogram analysis provides an assessment of the frequency distribution of selected DTI measures across a range of voxels. The frequency distribution can be derived from any selected set of voxels (i.e., a ROI), but histogram analysis has most often been applied to whole brain data (Madden et al., 2009). Several features (the most common being peak height, peak location and mean parameter value) can be extracted from the histogram. Changes in the mean parameter value are assumed to reflect compromised WM microstructure. Histograms minimize any observer-dependent bias but a major issue with the use of histograms is the segmentation process (Bozzali and Cherubini, 2007).

Quantitative fiber tracking and tractography are conceptually similar to ROI analysis, but in this case, fiber tracts are the ROIs that are automatically (probabilistic tractography) or manually (deterministic tractography) defined by tractography algorithms. The degree to which the main diffusion orientation within a voxel is similar to its neighbours, that is, show intervoxel coherence, serves the conceptual basis for quantitative fiber tracking and tractography. Analogous to following the linear trajectory of the longitudinal axis of bricks in a path, intervoxel coherence requires that neighbouring eigenvectors do not vary by more than a set criterion and that intravoxel FA reaches a minimum value (Chanraud et al., 2010).

Diffusion tensor imaging in normal aging and cognitive function

Age-related alteration of diffusion metrics is well documented. Across studies, the predominant findings are decreased FA and increased MD, suggesting that normal aging is associated with degradation in the composition and organization of WM microstructure (Bennett and Madden, 2014). This evidence is further supported by longitudinal data (Barrick et al., 2010; Teipel et al. 2010). Age-related differences are also found to be more prominent for RD than DA, since RD is consistently higher for older adults relative to younger adults, whereas increases and decreases in DA have been reported (Bennett et al., 2010; Zhang et al., 2010). Therefore, it is suggested that the effects of aging on DTI data may be likely driven by changes in underlying myelin.

During the process of normal aging, individuals exhibit age-related cognitive decline, although there is a high variability regarding functional loss (Salthouse, 2012). On the one hand, cognitive abilities relying on past knowledge and expertise exhibit little or no decline until very late in life. On the other hand, there is a nearly linear decline from early adulthood on abilities relying on processing or perceptual speed, usually involving manipulations or transformations of abstract or familiar material (Salthouse, 2010). The constellation of frontally-mediated functions, including working memory, problem-solving, attention and other executive functions, seem particularly vulnerable to aging (Cummings, 1993; Salthouse, 2010).

Findings from DTI research on cognitive aging support a strong and positive association between diffusion data and cognitive performance (Bennett and Madden, 2014; Chanraud et al., 2010). That is, normal aging is related to altered DTI measures (e.g., lower FA or higher MD), and these altered diffusion metrics are related to a worse cognitive function. Reported data suggest a stronger relation between diffusion metrics and cognition for executive function and processing speed than for memory (Borguesani et al., 2013; Vernooij et al., 2009; Ystad et al., 2011). There

is also a minimal regional specificity of the relation, with the exception that the association between DTI data and cognitive function has shown larger effect sizes in frontal areas (Madden et al., 2012). Likewise, age-related decline in diffusion metrics appears to correlate differentially with processing speed and executive function (located in anterior regions) and memory (located in posterior regions) (Kennedy and Raz, 2009).

Taken together, these findings support the notion that normal aging is related to cortical disconnection, which contributes to cognitive decline in healthy older adults.

White matter hyperintensities, diffusion tensor imaging and cognitive function

The relative contribution of microstructural versus macrostructural variability in WM integrity to cognitive performance is currently under study. DTI studies typically use image thresholding techniques on conventional MRI to separate normal-appearing tissue (that is, apparently undamaged WM) from macroscopic lesions (i.e., WMHs), and data analyses with cognitive function are usually limited to one tissue class or the other. However, it is known that the distinction between normal-appearing tissue with altered diffusion metrics and a frank lesion is not entirely clear-cut (Bennett and Madden, 2014).

It is thought that WMHs seen on conventional MRI and altered DTI measures in normal-appearing tissue, such as lower FA or increased MD, may represent two related processes affecting the WM that are commonly seen in aging (Maillard et al., 2013; Vernooij et al., 2008; Zhuang et al., 2010). It is therefore important to investigate the relation between diffusion measures and WMHs. Previous studies have consistently reported that MD and FA are more affected in WMHs than in normal-appearing WM (Bastin et al., 2009; Lee et al., 2009; Muñoz-Maniega et al., 2015; O'Sullivan et al., 2004a, 2004b; Vernooij et al., 2009). Further, there are several studies reporting a significant association between WMHs volume and DTI measures in the normal-appearing WM (Gunning-Dixon et al., 2009; Meier et al., 2012; O'Sullivan et al., 2001a; Schmidt et al., 2010; Shenkin et al., 2005; Sun et al., 2014; Taylor et al., 2007). Overall, these findings indicate that age-related SVD is a diffuse process affecting the entire brain and that WMHs are probably only the tip of the iceberg.

Most prior studies have been performed using a ROI approach or segmentation methods to calculate DTI measures within specific brain tissues. However, diffusion measures can also be investigated on a voxel-by-voxel basis for a more precise location of areas of abnormal diffusion

related to WMHs. This approach has been mostly used to characterize individuals with overt cognitive impairment (Agosta et al., 2011; Borroni et al., 2007; Bosch et al., 2012; Rose et al., 2006; Zhang et al., 2007, 2009; Zhuang et al., 2010). Nevertheless, there is scarce evidence of the relation between WMHs and FA on a voxel-by-voxel basis in normal aging. Only two studies have reported a widespread pattern of reduced FA in the WM of participants with WMHs compared with healthy controls (Quinque et al., 2012; Sun et al., 2014) whereas another study has found an association of WMHs volume and decreased FA in extensive areas of WM (Leritz et al., 2014). Quinque et al. (2012) compared DTI measures between individuals with early cerebral microangiopathy (ARWMC score > 2) and healthy controls, reporting a pattern of lower FA throughout the whole WM skeleton. Despite its significance, the effect size of lower FA was small. Sun et al. (2014) showed reduced FA bilaterally in several WM regions, including the inferior fronto-occipital fasciculus (IFOF), the uncinate fasciculus, the anterior thalamic radiation (ATR), the cortico-spinal tract, the superior longitudinal fasciculus (SLF), and the cingulum bundle, in participants with mild WMHs compared with participants without WMH. Leritz et al. (2014) found that total WMHs volume was related to lower FA in widespread brain regions in individuals recruited from two separate community-dwelling studies.

Previous research has related diffusion metrics to cognitive function in community-dwelling samples (Charlton et al., 2010; Hedden et al., forthcoming; Shenkin et al., 2005; Vernooij et al., 2009) and participants with WMHs (Della Nave et al., 2007; Gons et al., 2012; Jokinen et al., 2013; O'Sullivan et al., 2001a; O'Sullivan et al., 2004a; Quinque et al., 2012; Schmidt et al., 2010; van Norden et al., 2012a, 2012b, 2012c). Specifically, FA has been associated with cognitive abilities such as executive function (Hedden et al., forthcoming; Quinque et al., 2012; van Norden et al., 2012b), processing speed (Gons et al., 2012; Vernooij et al., 2009), verbal fluency (Shenkin et al., 2005), memory (Hedden et al., forthcoming; van Norden et al., 2012a), or motor function (Della Nave et al., 2007; Hedden et al., forthcoming; Vernooij et al., 2009).

AIMS

Most research about WMHs has involved participants who are older than 65 years. However, these radiological abnormalities are also seen commonly in middle-aged individuals in their 50s and early 60s, especially those with risk factors for WMHs, such as arterial hypertension and diabetes mellitus (Sachdev et al., 2008; Schmidt et al., 1997). Studies using 3.0 T MRI to examine the presence and severity of SVD-related pathology, such as WMHs, in middle age are lacking. The association of WMHs with cognitive status in this age range is not well determined either. Further, the associations of different types of WMH with structural GM and WM measures on a voxel-by-voxel basis and their relation with cognitive function are not completely understood in community samples younger than 65 years.

The general aim of this thesis was to study the association between WMHs, their related MRI structural correlates, and cognitive function in a community sample of stroke- and dementia-free individuals aged 50 to 65 years old. To that end, participants were recruited from an ongoing population-based study, different MRI techniques were applied, and a comprehensive neuropsychological assessment was implemented, following VCI harmonization standards (Hachinski et al., 2006).

The specific aims of this thesis were:

I. To determine the specific contribution of high grade PVHs and DWMHs to cognitive function (Study I)
II. To examine the presence and severity of SVD-related pathology (Study I)
III. To investigate the separate association of PVHs and DWMHs with GM volume on a voxel-by-voxel basis (Study II)
IV. To assess the predictive value to cognition of reduced GM volume within specific areas separately related to high grade PVHs and DWMHs (Study II)
V. To investigate the separate association of PVHs and DWMHs with FA on a voxel-by-voxel basis (Study III)
VI. To assess the predictive value to cognition of FA within specific WM tracts separately associated with high grade PVHs and DWMHs (Study III)

MATERIALS AND METHODS

This thesis consists of three studies that examine the associations between WMHs, their MRI structural correlates, and cognitive function, using a community or population-based setting. In the three studies, the healthy middle-aged sample was selected from primary healthcare centers following population-based selection criteria. This approach proposes a suitable frame for properly interpreting results to be representative of the reference population.

All studies were approved by the ethics committees of the University of Barcelona and the Hospital Universitari Germans Trias i Pujol. They were conducted in accordance with the ethical standards of the Declaration of Helsinki. Written informed consent was obtained from all participants. The specific methodological characteristics are described in detail in each study. Nonetheless, the common methodology employed throughout the three studies is concisely described below.

Study design and sample selection

The Barcelona-AsIA (Asymptomatic Intracranial Atherosclerosis) Study is an ongoing population-based study that involves 28 primary healthcare centers and a tertiary stroke center. Complete details for the Barcelona-AsIA protocol have been described elsewhere (López-Cancio et al., 2011). In brief, a random sample of participants over 50 years old without previous history of stroke or ischemic heart disease underwent clinical examination, blood analysis, complete extra and transcranial Duplex ultrasound study, and neuropsychological assessment. The Barcelona-AsIA Neuropsychology Study is a related prospective study whose objectives are (1) to investigate the associations between cognition and VRF, asymptomatic cervicocerebral atherosclerosis, and MRI signs of SVD, and (2) to identify clinical and radiological features and biological mechanisms underlying these associations.

For the Barcelona-AsIA Study, the Barcelona-AsIA Neuropsychology Study and, consequently, for this thesis, participants were recruited from the PERART Study, a related ongoing population-based study to determine the prevalence of peripheral arterial disease and to evaluate the predictive value of ankle-arm index in relation to cardiovascular mortality and morbidity (Alzamora et al., 2007). Details of the recruitment process for this thesis are described in Study I. Briefly, a total of 132 participants aged 50 to 65 years were selected to undergo a

comprehensive neuropsychological assessment and brain MRI. Exclusion criteria were: history of stroke or transient ischemic attack, coronary heart disease, neurological disease, or severe psychiatric disorder; a MMSE score < 25 or severe disability; other medical diseases that could affect cognitive assessment and function; contraindications to undergo MRI, and unexpected incidental findings seen on MRI (Vernooij et al., 2007). Consequently, the final sample included 100 participants aged 50 to 65 stratified by sex and educational level.

Magnetic resonance imaging acquisition protocol

The MRI scanning protocol was performed with a Siemens Magnetom Trio 3.0 T scanner (Siemens Diagnostics Healthcare, Erlangen, Germany) at the Medical Image Core Facility (IDIBAPS, Hospital Clinic, Barcelona, Spain).

The MRI protocol included a set of 3-dimensional magnetization-prepared rapid gradient echo (MPRAGE) T1-weighted images (repetition time: 2300 ms; echo time: 3 ms; flip angle: 15°; field of view: 245 mm; and voxel size: 1x1x1 mm, no gap), and two sets of DTI images acquired along 30 non-collinear directions (TR: 9300 ms; TE: 94 ms; flip angle: 15°; field of view: 240 mm; voxel size: 2x2x2 mm, no gap; and b=1000 s/mm^2) with an additional acquisition for each set without diffusion weighting (b=0 s/mm^2). The two acquisitions of DTI were averaged.

Axial FLAIR images (repetition time: 9040 ms; echo time: 85 ms; inversion time: 2500 ms; and voxel size: 1.1 x 0.9 x 5 mm, gap: 1.5 mm) and axial T2-weighted images (TR: 5520 ms; TE: 92 ms; and voxel size: 0.5 x 0.4 x 5mm, gap: 1.5 mm) were also collected for assessing WMHs and LI.

Rating of white matter hyperintensities and lacunar infarcts

Location and severity of WMHs were estimated on T2 and FLAIR images by a trained and blind neuroradiologist using the Fazekas scale (Fazekas et al., 1987). Participants were classified as having no WMHs, or mild, moderate, or severe WMHs (0, 1, 2, or 3 points, respectively) in each location. LI were defined as lesions with increased signal intensity on T2-weighted images and decreased signal intensity on T1-weighted and FLAIR images with a diameter of 5-15 mm, which were not located in areas with high prevalence of widened PVS (Fazekas et al., 2002).

Neuropsychological assessment

All participants completed an extensive neuropsychological assessment (**Table 1**). Cognitive measures were grouped into 8 cognitive domains which include tests assessing similar cognitive function (Strauss et al., 2006): executive functioning, working memory, attention, verbal fluency, verbal memory, visual memory, visuospatial skills, and psychomotor speed. Neuropsychological assessment also included the MMSE (Folstein et al., 1975) as a global cognitive function test and the Vocabulary subtest from the WAIS-III as a measure of premorbid intelligence. Depressive symptoms were assessed with the Geriatric Depression Scale 15-item version (GDS-15) (Sheikh and Yesavage, 1986).

Table 1. Neuropsychological assessment in the Barcelona-AsIA Neuropsychology Study

Cognitive domain	Neuropsychological tests (measures)
Executive functioning	Wisconsin Card Sorting Test 64-item version (perseverative errors)
	Wisconsin Card Sorting Test 64-item version (non perseverative errors)
	Stroop Test (interference)
Working memory	Digit Span Backwards (WAIS-III)
	Trail Making Test (part B)
Attention	Digit Span Forward (WAIS-III)
	Continuous Performance Test (total errors)
	Symbol Search (WAIS-III)
	Digit Symbol Coding (WAIS-III)
Verbal fluency	Letter fluency (p, m, r letters)
	Semantic fluency (Animals)
Verbal memory	Word List (WMS-III) (total recall)
	Word List (WMS-III) (delayed recall)
Visual memory	Visual Reproduction (WMS-III) (immediate recall)
	Visual Reproduction (WMS-III) (delayed recall)
Visuospatial skills	Visual Discrimination (WAIS-III)
	Visual Reproduction (WMS-III) (copy)
Psychomotor speed	Trail Making Test (part A)
	Grooved Pegboard Test (preferred hand)
	Grooved Pegboard Test (non preferred hand)

Note: WAIS-III = Weschler Adult Intelligence Scale (3rd edition); WMS-III = Weschler Memory Scale (3rd edition).

RESULTS

Study I

Soriano-Raya, J.J.; Miralbell, J.; López-Cancio, E.; Bargalló N; Arenillas, J.F.; Barrios, M.; Cáceres, C.; Toran, P.; Alzamora, M.; Davalos, A.; Mataró, M. (2012). **Deep *versus* Periventricular White Matter Lesions and Cognitive Function in a Community Sample of Middle-Aged Participants.** *Journal of the International Neuropsychological Society, 18*, 874-885. doi: 10.1017/S1355617712000677. Impact Factor: 2.96.

Study II

Soriano-Raya JJ, Miralbell J, López-Cancio E, Bargalló N, Arenillas JF, Barrios M, Cáceres C, Toran P, Alzamora M, Dávalos A, Mataró M (2015). **Regional cortical atrophy in lingual gyrus predicts visuospatial skills in a community sample of participants with white matter lesions.** Working paper.

Study III

Soriano-Raya JJ, Miralbell J, López-Cancio E, Bargalló N, Arenillas JF, Barrios M, Cáceres C, Toran P, Alzamora M, Dávalos A, Mataró M. **Tract-specific fractional anisotropy predicts cognitive outcome in a community sample of middle-aged participants with white matter lesions.** *J Cereb Blood Flow Metab* 2014;34(5):861-9. doi: 10.1038/jcbfm.2014.26. Impact Factor: 5.41.

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Deep *versus* Periventricular White Matter Lesions and Cognitive Function in a Community Sample of Middle-Aged Participants

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Abstract

The association of cerebral white matter lesions (WMLs) with cognitive status is not well understood in middle-aged individuals. Our aim was to determine the specific contribution of periventricular hyperintensities (PVHs) and deep white matter hyperintensities (DWMHs) to cognitive function in a community sample of asymptomatic participants aged 50 to 65 years. One hundred stroke- and dementia-free adults completed a comprehensive neuropsychological battery and brain MRI protocol. Participants were classified according to PVH and DWMH scores (Fazekas scale). We dichotomized our sample into low grade WMLs (participants without or with mild lesions) and high grade WMLs (participants with moderate or severe lesions). Analyses were performed separately in PVH and DWMH groups. High grade DWMHs were associated with significantly lower scores in executive functioning (−0.45 standard deviations [*SD*]), attention (−0.42 *SD*), verbal fluency (−0.68 *SD*), visual memory (−0.52 *SD*), visuospatial skills (−0.79 *SD*), and psychomotor speed (−0.46 *SD*). Further analyses revealed that high grade DWMHs were also associated with a three- to fourfold increased risk of impaired scores (i.e.,<1.5 *SD*) in executive functioning, verbal fluency, visuospatial skills, and psychomotor speed. Our findings suggest that only DWMHs, not PVHs, are related to diminished cognitive function in middle-aged individuals. (*JINS*, 2012, *18*, 874–885)

Keywords: Leukoencephalopathies, MRI, Neuropsychology, Cognition disorders, Executive function, Visuospatial skills

INTRODUCTION

Cerebral white matter lesions (WMLs) comprise diffuse areas of hypodensity on computerized tomography (CT) and high signal intensities on T2, proton density, and FLAIR magnetic resonance image (MRI) sequences. Also known as leukoaraiosis (Hachinski, Potter, & Merskey, 1987), these morphological changes do not correspond to specific vascular territories but rather involve the periventricular white matter and the centrum semiovale or subcortical white matter (Pantoni, 2002). WMLs are common MRI findings in normal aging, stroke patients, as well as in other neurological and psychiatric disorders. More than half of all elderly individuals have WMLs on MRI (De Leeuw et al., 2001; Enzinger, Fazekas, Ropele, & Schmidt, 2007; Longstreth et al., 1996), although prevalence depends on methodological issues, such as study design, reference population and WMLs assessment method (Pantoni, Poggesi, & Inzitari, 2007).

WMLs are considered an expression of cerebrovascular small vessel disease (SVD), since previous studies have

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identified the possible ischemic nature of these brain changes (Pantoni, 2002). Several studies reported an association between cerebrovascular risk factors and WMLs—primarily age, hypertension, and diabetes mellitus (Basile et al., 2006; Van Swieten et al., 1991; Verdelho et al., 2007). Individuals with these brain lesions also have a higher risk of stroke (Debette & Markus, 2010; Kuller et al., 2004; Yamauchi, Fukuda, & Oyanagi, 2002) and vascular death (Debette & Markus, 2010; Inzitari, Cadelo, Marranci, Pracucci, & Pantoni, 1997; Kuller et al., 2007). WMLs are also commonly associated with other signs of SVD, such as lacunar infarcts and microbleeds (Van Dijk, Prins, Vermeer, Koudstaal, & Breteler, 2002; Wardlaw, Lewis, Keir, Dennis, & Shenkin, 2006).

The advent of neuroimaging as a tool for clinical practice and the high prevalence of detected age-related WMLs have raised questions about the potential impact of WMLs on cognitive functioning (Fazekas, Enzinger, Ropele, & Schmidt, 2009). Some early studies (Junqué et al., 1990; Steingart et al., 1987) reported that WMLs were associated with cognitive impairment. Histopathological data suggested that such MRI findings corresponded to myelin reduction (Fazekas et al., 1991). Other investigations (Hunt et al., 1989) did not find this association. Given the high prevalence of these lesions, even in the normal aging population, sceptics reasoned that WMLs were unlikely to be associated with cognitive consequences. Nevertheless, WMLs have consistently been associated with cognitive function in many other recent studies (Frisoni, Galluzzi, Pantoni, & Filippi, 2007; Pantoni et al., 2007; Schmidt et al., 2011). Cognitive consequences have been attributed to frontal-subcortical circuit involvement (Linortner et al., 2010; Schmidt, Enzinger, Ropele, Schmidt, & Fazekas, 2006), and the cognitive domains more related to WMLs are executive functions and processing speed (Cohen et al., 2002; De Groot et al., 2000; DeCarli et al., 1995; O'Brien et al., 2003; Pantoni et al., 2007; Schmidt et al., 1993; Ylikoski et al., 1993). Associations between WMLs and cognitive function have been reported in community-dwelling healthy participants (De Groot et al., 2000), high risk populations [i.e., mild cognitive impairment (MCI)] (Bombois et al., 2007), and individuals with dementia (Graham, Emery, & Hodges, 2004). In community-dwelling healthy participants, WMLs have been related to deficits in processing speed, attention, abstract reasoning, planning, memory, and global mental functioning (DeCarli et al., 1995; Pantoni et al., 2007; Schmidt et al., 2011; Vannorsdall, Waldstein, Kraut, Pearlson, & Schretlen, 2009). Several longitudinal studies have reported that WMLs are related not only to cognitive function but also to cognitive decline and incident dementia, with individuals with moderate and severe lesions declining the most (Longstreth et al., 2005; Prins et al., 2004).

Despite considerable data, caution is mandatory, since WMLs are not the only change in the brain responsible for cognitive disturbances in the elderly (Pantoni et al., 2007). First, WMLs are only a part of the spectrum of SVD. Therefore, their effect should be considered together with that of other SVD-related lesions such as lacunar infarcts. Second, the cognitive status of elderly participants is not only associated with SVD-related pathology, but also with degenerative changes that often coexist.

Although previous research has provided evidence for some impact of WMLs on cognitive function, the clinical relevance of this association remains controversial (Andersson, 2010; Wallin & Fladby, 2010). Clinical presentation on the individual level is most likely influenced by severity and regional distribution of WMLs (Desmond, 2002; Pantoni et al., 2007). The association of WMLs with cognitive function is probably mediated by severity of white matter damage, with mild degrees unlikely to be related to worse cognitive performance (Pantoni et al., 2007; Prins et al., 2005; Schmidt et al., 2005, 2011; van der Flier et al., 2005). It is likely that a threshold exists in WMLs load (Boone et al., 1992; DeCarli et al., 1995; van der Flier et al., 2005), beyond which cognitive function is affected.

Regarding regional distribution, WMLs are usually divided into two groups depending on their anatomical position: those immediately adjacent to the ventricles (periventricular hyperintensities or PVHs) and those located in the subcortical or deep white matter (deep white matter hyperintensities or DWMHs). Both regions can contain not only SVD-related lesions but also non-ischemic changes (Fazekas, Schmidt, & Scheltens, 1998). In the periventricular area, "caps", "lining", "bands", or "halos" reflect non-ischemic changes on MRI. Histopathological correlates include disruption of the ependymal lining, myelin pallor, and some subependymal astrogliosis (Schmidt et al., 2011). In the subcortical or deep white matter, "punctate" DWMHs may also result from non-ischemic etiologies, such as widening of perivascular spaces (Fazekas et al., 1993). Only "irregular" PVHs extending to deep white matter and "early confluent" and "confluent" DWMH are clearly related to SVD. They mostly relate to extensive demyelination and axonal loss (Fazekas et al., 1998).

Bowler and Hachinski (2003) have argued that both types of WMLs should be analyzed separately, given that PVHs and DWMHs may differ in their pathogenesis and clinical significance. While some investigations did not find any differences between the clinical presentation of each lesion type (Burns et al., 2005; Jokinen et al., 2005), an increasing amount of evidence supports a specific role for PVHs *versus* DWMHs on cognitive functioning. The differential impact of PVHs *versus* DWMHs remains unclear, since previous research has yielded contradictory findings. In community-dwelling individuals (De Groot et al., 2000), MCI (Debette et al., 2007) and demented samples (Bracco et al., 2005), a predominant role of PVHs has been reported, while other studies have found a stronger association with DWMHs in the same settings (community-dwelling: Sachdev, Wen, Christensen, & Jorm, 2005; MCI: Delano-Wood et al., 2008; demented: Sachdev et al., 2004). De Groot et al. (2000) were the first team to specifically analyze the independent cognitive association of PVHs *versus* DWMHs in a large sample of elderly participants. They found a predominant role for PVHs related to global dysfunction, verbal memory, and psychomotor slowness. On the other hand, Sachdev et al. (2005)

reported a stronger association between DWMHs with motor abnormality and slowed information processing speed in a young elderly community sample. Both visual rating (PVHs: Bracco et al., 2005; DWMHs: Leaper et al., 2001) and volumetric studies (PVHs: Vannorsdall et al., 2009; DWMHs: Sachdev et al., 2005) also reported conflicting results.

Most research about WMLs has involved participants who are older than 65 years. However, these lesions are also seen commonly in individuals in their 50s and early 60s, especially those with risk factors for SVD, such as hypertension and diabetes (Sachdev et al., 2005; Schmidt et al., 1997). The association of WMLs with cognitive status and the specific influence of regional distribution of WMLs on cognitive functioning are not well understood in middle-aged individuals. Some data suggest that DWMHs are distributed in a more extensive area than PVHs (Inzitari, 2000) and that their histopathological correlates may exert more severe damage to white matter tracts than PVHs (Stenset et al., 2008; Wen, Sachdev, Chen, & Anstey, 2006). Our hypothesis is that high grade DWMHs will be more related to cognitive function than high grade PVHs. In addition, to our knowledge, studies using 3T MRI to examine the presence and severity of SVD-related pathology in middle age are lacking. Thus, we also sought to determine the prevalence and severity of WMLs and lacunar infarcts in a community-dwelling sample aged 50 to 65 years.

METHODS

Study Design and Sample Selection

The Barcelona-AsIA (Asymptomatic Intracranial Atherosclerosis) Study is an ongoing collaborative research project that includes 28 primary healthcare centers and a tertiary stroke center. Complete details for the Barcelona-AsIA protocol have been described elsewhere (López-Cancio et al., 2011). In brief, participants underwent clinical examination, blood analysis, complete extra- and transcranial Duplex ultrasound study, and neuropsychological assessment.

The Barcelona-AsIA Neuropsychology Study is a related prospective cross-sectional study that also includes the University of Barcelona whose objectives are (1) to investigate the associations between cognition and vascular risk factors, asymptomatic extracranial and intracranial atherosclerosis, and asymptomatic cerebrovascular disease, and (2) to identify clinical and radiological features and biological mechanisms underlying these associations.

Participants were recruited from the PERART Study, an ongoing population-based study to determine the prevalence of peripheral arterial disease and to evaluate the predictive value of ankle-arm index in relation to cardiovascular mortality and morbidity (Alzamora et al., 2007). For the present study, we consecutively recruited 132 participants aged 50 to 65 years who gave consent to undergo an extensive neuropsychological assessment and brain MRI. Of the original 132 participants, we excluded individuals with neurological disease or severe psychiatric disorder ($n = 11$); a Mini-Mental State Examination score <25 or severe disability ($n = 3$); other medical diseases that could affect cognitive assessment and function ($n = 4$), such as tumors and blindness; contraindications to undergo MRI ($n = 10$), such as metallic prosthesis and claustrophobia; unexpected brain findings (Vernooij et al., 2007) detected on MRI ($n = 2$), and other causes (i.e., less than 75% of neuropsychological data available) ($n = 2$). Each excluded participant was replaced by a participant with the same sex and educational level. The final sample included 100 participants aged 50 to 65 years stratified by sex and educational level.

This study has been approved by the ethics committees of the University of Barcelona and the Germans Trias i Pujol University Hospital. It was conducted in accordance with the ethical standards of the Declaration of Helsinki. Written informed consent was obtained from all participants.

Evaluation of Vascular Risk Factors and Depressive Symptoms

Diagnosis of a particular vascular risk factor, such as arterial hypertension, diabetes mellitus, dyslipidemia, or current smoking status, was based on clinical history or use of medication for the particular condition at the time of the clinical examination. Depressive symptoms were assessed with the Geriatric Depression Scale 15-item version (GDS-15) (Sheikh & Yesavage, 1986). GDS-15 scores > 5 are indicative of probable depression. Per our exclusion criteria, none of our participants had GDS-15 scores > 5.

Neuropsychological Assessment

All participants completed an extensive neuropsychological battery. Cognitive measures were grouped into eight cognitive domains: executive functioning, working memory, attention, verbal fluency, verbal memory, visual memory, visuospatial skills, and psychomotor speed. Executive functioning (i.e., conceptualization, planning, and inhibition) was assessed with the 64-item computerized version of the Wisconsin Card Sorting Test (WCST-64) (Kongs, Thompson, Iverson, & Heaton, 2000) and the interference score of the Color-Word Stroop Test (Golden, 1978). Working memory was examined with Digit Span Backwards from the Wechsler Adult Intelligence Scale 3rd edition (WAIS-III) (Wechsler, 1997a) and part B of the Trail Making Test (Tombaugh, 2004). Attentional abilities were assessed with a computerized version of the Continuous Performance Test (Conners, 1995) and Digit Span Forward, Symbol Search, and Digit Symbol Coding subtests from the WAIS-III. Verbal fluency was measured with letter fluency (letters P, M and R) (Artiola, Hermosillo, Heaton, & Pardee, 1999) and semantic category fluency (animals) (Strauss, Sherman, & Spreen, 2006) in 60s. Word Lists and Visual Reproduction from the Wechsler Memory Scale 3rd edition (WMS-III) (Wechsler, 1997b) were administrated to measure verbal and visual memory, respectively. Visual Discrimination and the Copy from the Visual Reproduction subtest (WMS-III) were used to evaluate visuospatial skills. Psychomotor speed

Table 1. Distribution of composite Z-scores for cognitive domains and distribution of raw test scores according to severity and regional distribution of WMLs

	Low grade PVHs (without/mild) $n = 80$	High grade PVHs (moderate) $n = 16$	Low grade DWMHs (without/mild) $n = 80$	High grade DWMHs (moderate) $n = 16$
Executive functioning	−0.02 (0.69)	0.18 (0.73)	0.11 (0.84)	−0.38 (0.74)
WCST-64 perseverative errors	14.19 (6.56)	13.44 (4.79)	14.30 (6.46)	12.88 (5.32)
WCST-64 non-perseverative errors	15.95 (8.06)	14.44 (8.07)	14.44 (6.44)	22.00 (11.82)
Stroop Interference	0.78 (6.84)	2.14 (8.49)	−0.08 (6.42)	0.44 (8.09)
Working memory	0.06 (0.85)	−0.10 (0.81)	0.05 (0.63)	−0.19 (0.64)
Digit Span Backwards	4 (3–5)	4 (3.25–5)	4 (3–5)	3 (3–4)
Trail Making Test B	132.62 (61.57)	148.60 (67.05)	130.39 (61.03)	163.08 (65.42)
Attention	0.00 (0.76)	0.01 (0.84)	0.07 (0.76)	−0.36 (0.76)
Digit Span Forward	5 (4–6)	5.5 (4–6)	5 (4–6)	5 (4–6)
CPT total errors	22.48 (15.77)	16.00 (8.42)	21.81 (15.51)	19.31 (12.09)
Symbol Search	19.89 (7.20)	22.31 (9.34)	20.73 (7.58)	18.13 (7.54)
Digit Symbol Coding	40.30 (14.15)	38.00 (12.99)	41.25 (13.69)	33.25 (13.58)
Verbal fluency	0.01 (0.80)	−0.06 (1.00)	0.12 (0.79)	−0.60 (0.81)
Letter (PMR)	11.38 (4.22)	9.94 (4.11)	29.34 (10.63)	24.00 (10.32)
Semantic (Animals)	16.79 (3.67)	16.75 (4.88)	17.38 (3.70)	13.81 (3.37)
Verbal memory	0.00 (0.88)	0.03 (1.02)	0.04 (0.90)	−0.16 (0.89)
Word List (total recall)	26.64 (5.04)	26.25 (5.60)	26.89 (5.17)	25.00 (4.65)
Word List (delayed recall)	5.76 (2.21)	6.06 (2.57)	5.83 (2.27)	5.75 (2.27)
Visual memory	−0.02 (0.91)	0.04 (0.54)	0.07 (0.85)	−0.44 (0.78)
Visual Reproduction (immediate recall)	63.98 (16.98)	67.19 (10.93)	66.25 (16.03)	55.81 (13.98)
Visual Reproduction (delayed recall)	42.79 (19.72)	42.31 (15.97)	44.41 (19.19)	34.19 (16.45)
Visuospatial skills	0.03 (0.77)	−0.12 (0.68)	0.14 (0.62)	−0.67 (1.23)
Visual Discrimination	7 (7–7)	7 (6.25–7)	7 (7–7)	7 (6–7)
Visual Reproduction (copy)	95 (92.25–99)	91 (89–97.50)	95.5 (92–99)	91.5 (87–98.75)
Psychomotor speed	0.02 (0.77)	−0.14 (0.72)	0.08 (0.63)	−0.47 (1.12)
Trail Making Test A	49.36 (19.63)	53.06 (22.77)	48.41 (17.09)	57.81 (23.45)
Grooved Pegboard (preferred hand)	74.09 (12.43)	74.13 (12.53)	72.91 (10.37)	79.88 (18.82)
Grooved Pegboard (non preferred hand)	82 (75–88)	86.5 (74.5–101)	82 (75–89)	85 (80–95.75)

Note. WMLs = white matter lesions; PVHs = periventricular hyperintensities; DWMHs = deep white matter hyperintensities; WCST-64 = Wisconsin Card Sorting Test (64-item computerized version); CPT = Continuous Performance Test. Values are means (standard deviations) in Z-scores for each cognitive domain. Values are means (standard deviations) or medians (interquartile range) for each raw test score. Trail Making Test and Grooved Pegboard results are expressed in seconds.

was assessed with part A of the Trail Making Test and Grooved Pegboard (Ruff & Parker, 1993). Participants' raw scores were normalized to Z-scores using the mean and standard deviation of the sample. Composite Z-scores for each participant in each cognitive domain were calculated by averaging the Z-scores of all tests within that domain (Table 1).

Neuropsychological assessment also included the Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975) as a global cognitive function test and the Vocabulary subtest of the WAIS-III as a measure of premorbid intelligence.

MRI Scanning Protocol and Analysis

The MRI scanning protocol was performed with a Siemens Magnetom Trio 3T scanner (Siemens Diagnostics Healthcare, Erlangen, Germany) at the Image Diagnosis Center (Hospital Clinic, Barcelona, Spain). The MRI protocol included a set of three-dimensional magnetization-prepared rapid gradient echo (MPRAGE) T1-weighted images [repetition time (TR): 2300 ms; echo time (TE): 3 ms; flip angle: 15°; field of view: 245 mm; and voxel size: 1 × 1 × 1 mm, no gap], axial T2-weighted images (TR: 5520 ms; TE: 92 ms; and voxel size: 0.5 × 0.4 × 5 mm, gap: 1.5 mm) and axial fluid attenuated inversion recovery (FLAIR) images [TR: 9040 ms; TE: 85 ms; inversion time (TI): 2500 ms; and voxel size: 1.1 × 0.9 × 5 mm, gap: 1.5 mm].

Location and severity of WMLs were estimated on T2 and FLAIR scans by a trained neuroradiologist (N.B.) using the Fazekas scale (Fazekas, Chawluk, Alavi, Hurtig, & Zimmerman, 1987). On MRI, WMLs appear hyperintense on T2-weighted images. They also remain bright on FLAIR, a T2-weighted sequence that suppresses the signal from fluid-filled spaces. When only T2-weighted images are considered, confusion may occur with lacunes, small infarcts, and perivascular spaces (Fazekas et al., 2002). The Fazekas scale provides two different scores (PVH and DWMH), rated on a 0- to 3-point scale of increasing severity. The sum of the PVH and the DWMH scores provides a total score. Participants were classified as having no lesion, or mild, moderate, or severe lesions (0, 1, 2, or 3 points, respectively) in each

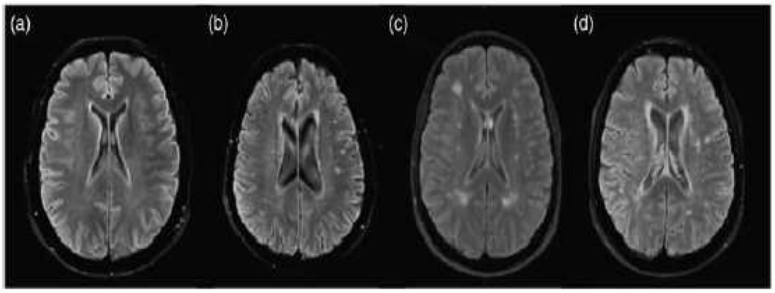

Fig. 1. Fazekas scale ratings. (a) shows a participant with no periventricular hyperintensities (PVHs) or deep white matter hyperintensities (DWMHs). (b) shows a participant with small caps and thin lining (mild) PVHs and punctuate (mild) DWMHs. (c) shows a participant with thin lining (mild) PVHs and early confluent (moderate) DWMHs. (d) shows a participant with smooth halo (moderate) PVHs and early confluent (moderate) DWMHs. There were no participants with severe lesions.

location. Examples of different ratings are shown in Figure 1. The intrarater reliability was determined with 20 randomly selected scans that were scored twice. Reliability was good both for grading PVHs {weighted kappa with quadratic weights = 0.69 [95% confidence interval (CI): 0.41 to 0.99]} and for grading DWMHs [weighted kappa with quadratic weights = 0.7 (95% CI: 0.41 to 0.99)].

Lacunar infarcts were defined as lesions with increased signal intensity on T2-weighted images and decreased signal intensity on T1-weighted and FLAIR images with a diameter of 5–15 mm, which were not located in areas with high prevalence of widened perivascular spaces (Fazekas et al., 2002; Vernooij et al., 2007). Their centers are isointense to cerebrospinal fluid (CSF), and thus they should not be mistaken for WMLs.

Gray matter volume (GM), white matter volume (WM), and total brain volume (TBV) were calculated with SIENAX software (http://www.fmrib.ox.ac.uk/fsl/siena/index.html) on high resolution T1-weighted images (Smith et al., 2002). Brain parenchymal volume (BP = GM + WM) was also calculated to use the ratio BP/TBV as a normalized measure of brain atrophy (Schmidt et al., 2005).

Statistical Analysis

Data analyses were carried out using statistical package SPSS 17.0 for Windows (SPSS Inc., Chicago, IL). Descriptive statistics were calculated for demographic, clinical, neuropsychological, and MRI data. Outlier analyses were conducted for all continuous variables. There were no outliers. The assumption of normal distribution for continuous variables was tested by Kolmogorov-Smirnov test. The mean and standard deviation, or the median and the interquartile range, were used to describe participants' characteristics for continuous variables (Table 2).

The distribution of the WMH scores was positively skewed as expected, with most participants having no lesions or mild lesions. Since mild lesions represent minimal cerebral abnormalities and pathological correlations indicate that they are of mixed origin, but moderate and severe lesions are usually ischemic and related to cognitive function, we dichotomized our sample into low grade WMLs (participants with no lesions or mild lesions) and high grade WMLs (participants with moderate or severe lesions). High grade PVHs were thus defined as PVH > 1 and high grade DWMHs as DWMH > 1.

To identify associations of demographic and clinical variables with WMH burden, continuous variables were evaluated with the Student's *t* test for independent samples or the Mann-Whitney test as appropriate. Categorical variables were evaluated with Pearson's χ^2 test or the Fisher's exact test as appropriate. Associations of demographic and clinical variables with cognitive function were also tested with Pearson or Spearman rank correlation coefficients to identify other potential confounding and mediating variables that might influence the association of WMLs with cognitive function (Table 3).

Two types of analyses evaluated the specific contribution of PVHs and DWMHs to cognitive function. In the first set of analyses, cognitive test scores were analyzed as continuous variables. Differences in cognitive performance (Z-scores) were calculated between participants with high and low grade WMLs using multivariate linear regression, with separate analyses for PVHs and DWMHs. Linear regression models were first adjusted (Model 1) for age, sex, years of education, and treatable cardiovascular risk factors associated with WMH burden or cognitive function ($p \leq .1$). Models were also adjusted (Model 2) for other brain changes usually related to cognitive disturbances (brain atrophy and lacunar infarcts).

In the second set of analyses, cognitive test scores and composite Z-scores were dichotomized into normal *versus* impaired. Individual Z-scores < -1.5 on a cognitive test were considered to be impaired (Lezak, Howieson, & Loring, 2004). A cognitive domain was considered impaired if at least one of the tests within it was impaired. Multivariate logistic regression was used to determine the odds ratios for impaired cognitive performance associated with high grade WMLs, with separate analyses for PVHs and DWMHs. Logistic regression models were adjusted for potential confounders as described above.

RESULTS

Due to technical difficulties on MRI acquisition, four participants were excluded from the sample. There were no differences in demographic and clinical variables between the

Table 2. Demographic, clinical, and MRI data

	Low grade PVHs (without or mild) ($n = 80$)	High grade PVHs (moderate) ($n = 16$)	p	Low grade DWMHs (without or mild) ($n = 80$)	High grade DWMHs (moderate) ($n = 16$)	p
Age (years)[1]	59.48 (3.48)	61.00 (2.48)	.10	59.48 (3.35)	61.00 (3.25)	.10
Sex (n (%) female)[2]	48 (60.0)	9 (56.3)	.78	48 (60.0)	9 (56.3)	.78
Education (years)[3]	8 (6–9)	8 (6.25–10)	.71	8 (6–10)	8 (6.25–8.75)	.98
MMSE[3]	29 (28–30)	30 (28.25–30)	.20	29 (28–30)	30 (28–30)	.71
Vocabulary (WAIS-III)[1]	38.91 (8.76)	37.56 (10.56)	.59	39.36 (8.85)	37.50 (9.47)	.50
GDS-15[3]	2 (1–3)	1 (0–2)	.08	2 (0–3)	1 (1–2.75)	.89
Vascular risk factors (n (%))						
Hypertension[2]	38 (47.5)	7 (43.8)	.78	34 (42.5)	11 (68.8)	.04*
Dyslipidemia[2]	48 (60.0)	9 (56.3)	.78	47 (58.8)	10 (62.5)	.78
DM[4]	15 (18.8)	2 (12.5)	.73	15 (18.8)	2 (12.5)	.73
Current smoker[4]	12 (15.0)	3 (18.8)	.71	13 (16.3)	2 (12.5)	1.00
MRI measures[1]						
GM (cm^3)	590.82 (35.38)	580.80 (45.11)	.41	586.12 (36.22)	581.74 (45.14)	.72
WM (cm^3)	564.90 (60.69)	542.24 (63.28)	.19	543.56 (55.53)	546.50 (64.83)	.87
BP (cm^3)	1155.72 (93.52)	1123.04 (104.70)	.25	1129.68 (88.42)	1128.24 (106.39)	.96
TBV (cm^3)	1450.51 (118.78)	1420.00 (128.76)	.38	1424.18 (109.25)	1425.27 (130.96)	.98
Ratio BP/TBV (%)	79.71 (2.03)	79.08 (1.44)	.25	79.33 (1.80)	79.16 (1.52)	.67
LI present (n (%))[4]	4 (5.1)	3 (18.8)	.09	6 (7.5)	1 (6.3)	1.00

Note. PVHs = periventricular hyperintensities; DWMHs = deep white matter hyperintensities; MMSE = Mini-Mental State Examination; GDS-15 = Geriatric Depression Scale, 15-item version; DM = diabetes mellitus; GM = gray matter volume; WM = white matter volume; BP = brain parenchymal volume = GM + WM; TBV = total brain volume; LI = lacunar infarcts. Values are means (standard deviations) in Student's t-test or medians (interquartile range) in Mann-Whitney test for continuous variables. Values are n (%) for categorical variables in chi-square test and Fisher's exact test. p shows statistical comparison between participants with high grade and low grade white matter lesions.

[1]Student's t-test.

[2]Chi-square test.

[3]Mann-Whitney test.

[4]Fisher's exact test.

*$p < .05$.

remaining 96 participants and those recruited from the PERART Study but excluded from the analyses. Demographic, clinical, and MRI characteristics of the remaining 96 participants (mean age = 59.7 years; 59% women; median education = 8 years) are summarized in Table 2. As expected, their intelligence, general cognitive function, and depressive symptoms were within the normal range.

Association of Demographic and Clinical Variables With WMH Burden

Arterial hypertension was the only clinical variable associated with WMH burden (Table 2). Arterial hypertension was more frequent in participants with high grade DWMHs (68.8%) *versus* low grade DWMHs (42.5%). There was no association between arterial hypertension and PVH burden. There were no associations between demographic variables and WMH burden, either PVH or DWMH. Age showed only a statistical trend for high grade PVHs and high grade DWMHs ($p = .1$).

Association of Demographic and Clinical Variables With Cognitive Function

To identify other potential confounders in the association between WMLs and cognitive function, association of demographic and clinical variables with cognitive domains was tested (Table 3). In summary, age was inversely related to psychomotor speed. Men had higher scores than women on attention, verbal fluency, and visual memory. Years of education was positively related to working memory, attention, verbal fluency, visual memory, and visuospatial skills. Participants with arterial hypertension had lower scores for verbal fluency, and participants with diabetes mellitus and current smokers had lower scores for psychomotor speed.

Prevalence and Severity of WMLs and Lacunar Infarcts

PVH ratings revealed 51 participants (53.1%) with no PVHs, 29 participants (30.2%) with mild PVHs (caps and pencil-thin lining), and 16 participants (16.7%) with moderate PVHs (smooth halo). DWMH ratings identified 19 participants (19.8%) without DWMHs, 61 participants (63.5%) with mild DWMHs (punctuate), and 16 participants (16.7%) with moderate DWMHs (early confluent). Seven participants (7.3%) had both moderate PVHs and moderate DWMHs. None of the participants had severe PVHs (irregular) or severe DWMHs (confluent). PVH scores were correlated with DWMH scores ($r_s = 0.46$; $p < .001$) and total Fazekas score ($r_s = 0.88$; $p < .001$). DWMH scores were also correlated with total Fazekas score ($r_s = 0.81$; $p < .001$).

Table 3. Association of demographic and clinical variables with cognitive domains

	EF	WM	Attention	VF	Verbal M	Visual M	VS	PS
Age	0.01 (0.91)	−0.15 (0.18)	0.05 (0.65)	0.03 (0.76)	−0.15 (0.14)	−0.02 (0.83)	−0.06 (0.58)	−0.25 (0.02)§
Sex	0.00 (1.00)	1.20 (0.23)	2.33 (0.02)§	2.07 (0.04)§	−1.65 (0.10)§	2.39 (0.02)§	0.06 (0.95)	−0.56 (0.58)
Education	0.01 (0.96)	0.44 (<0.001)§	0.54 (<0.001)§	0.31 (<0.01)§	0.15 (0.16)	0.29 (<0.01)§	0.34 (<0.01)§	0.17 (0.10)§
GDS-15	0.12 (0.26)	0.05 (0.65)	0.02 (0.83)	0.01 (0.93)	0.17 (0.10)§	−0.06 (0.59)	−0.10 (0.32)	−0.02 (0.85)
HTA	0.65 (0.52)	1.12 (0.27)	1.36 (0.18)	2.53 (0.01)§	−0.15 (0.88)	0.33 (0.74)	1.79 (0.08)§	1.99 (0.05)§
DL	−0.59 (0.56)	1.91 (0.06)§	0.80 (0.43)	0.19 (0.85)	−0.53 (0.60)	0.79 (0.43)	0.65 (0.52)	1.55 (0.12)
DM	1.98 (0.05)§	1.37 (0.17)	1.31 (0.19)	0.39 (0.70)	−0.64 (0.52)	0.40 (0.69)	1.19 (0.24)	2.10 (0.04)§
Smoker	−0.12 (0.90)	1.07 (0.29)	−0.29 (0.77)	−0.01 (0.99)	1.95 (0.05)§	0.41 (0.69)	1.86 (0.07)§	2.12 (0.04)§

Note. EF = Executive Functioning; WM = Working Memory; VF = Verbal Fluency; Verbal M = Verbal Memory; Visual M = Visual Memory; VS = Visuospatial Skills; PS = Psychomotor Speed; Education = years of education; GDS-15 = Geriatric Depression Scale, 15-item version; HTA = arterial hypertension; DL = Dyslipidemia; DM = Diabetes Mellitus. Values are Pearson correlation coefficients (p value) in age. Values are Spearman rank correlation coefficients (p value) in years of education and GDS-15. Values are Student's t (p value) in sex and in the treatable cardiovascular risk factors.
§Confounding factor ($p \leq .1$).

Thirteen lacunar brain infarcts were present across 7 participants (7.3%). Four of them had one lacunar infarct, two had two infarcts, and one person had three infarcts. Eight of the lacunar infarcts were located in the basal ganglia, and there was one lacunar infarct each in the pons, intern capsule, and corona radiata. The presence of lacunar infarcts was not associated with WMH burden, although the presence of high grade PVHs showed a statistical trend with the presence of lacunar infarcts ($p = .09$).

Cognitive Function Associated With High Grade PVHs and DWMHs

Table 4 shows Z-score differences in cognitive performance between participants with high *versus* low grade WMLs using linear regression models. Participants with high grade DWMHs had significantly lower scores in executive functioning [−0.50 standard deviations (*SD*)], attention (−0.43 *SD*), verbal fluency (−0.71 *SD*), visual memory (−0.51 *SD*), visuospatial skills (−0.82 *SD*), and psychomotor speed (−0.56 *SD*). Adjustments for age, sex, years of education, and cardiovascular risk factors related to cognitive performance (Model 1) generally reduced these associations, but they were still significant in each cognitive domain. These associations were essentially unaltered by additional adjustment for brain atrophy ratio and lacunar infarcts (Model 2). High grade PVHs were not related to lower scores in any cognitive domain.

Table 5 shows odds ratios (OR) and 95% confidence intervals (CI) for risk of cognitive impairment associated with high *versus* low grade WMLs using logistic regression models. High grade DWMHs were associated with a three- to fourfold increased risk of cognitive impairment in executive functioning (OR = 4.41; 95% CI: 1.38–14.10), verbal fluency (OR = 4.20; 95% CI: 1.25–14.08), visuospatial skills (OR = 3.65; 95% CI: 1.19–11.15), and psychomotor speed (OR = 3.56; 95% CI: 1.13–11.17). The association with impairment in verbal fluency was not significant after adjusting for age, sex, years of education, and diagnosis of arterial hypertension (Model 1). All associations remained significant when subsequently adjusted for other brain changes (Model 2). High grade PVHs were not related to an increased risk of cognitive impairment.

DISCUSSION

This study investigated the independent contributions of PVHs and DWMHs to cognitive function, as well as the prevalence and severity of WMLs and lacunar infarcts using a 3T MRI scanner, in a community-dwelling sample of middle-aged individuals. The principle finding was that high grade DWMHs were associated with lower scores in executive functioning, attention, verbal fluency, visual memory, visuospatial skills, and psychomotor speed. On the other hand, high grade PVHs were not associated with lower scores in any cognitive domain.

In an effort to increase the clinical relevance of our study, we also evaluated the independent association of PVHs and DWMHs with the risk of cognitive impairment (i.e., <−1.5 *SD*).

Table 4. Differences in cognitive performance (Z-scores) between participants with high grade WMLs versus participants with low grade WMLs using multivariate linear regression models

	Unadjusted model		Model 1		Model 2	
	Z-score (*SE*)	*p* value	Z-score (*SE*)	*p* value	Z-score (*SE*)	*p* value
High *vs.* low PVHs						
EF	0.20 (0.19)	.30	0.17 (0.19)	.37	0.17 (0.20)	.40
Working memory	−0.17 (0.24)	.49	−0.12 (0.23)	.59	−0.18 (0.24)	.47
Attention	0.01 (0.21)	.97	0.03 (0.19)	.89	−0.05 (0.20)	.81
Verbal fluency	−0.07 (0.23)	.77	−0.11 (0.22)	.62	−0.20 (0.23)	.39
Verbal memory	0.03 (0.25)	.91	0.11 (0.25)	.67	0.21 (0.26)	.43
Visual memory	0.06 (0.24)	.79	0.08 (0.24)	.73	0.06 (0.25)	.80
VS	−0.15 (0.21)	.46	−0.14 (0.21)	.50	−0.14 (0.22)	.53
PS	−0.16 (0.21)	.45	−0.07 (0.20)	.72	−0.06 (0.22)	.80
High *vs.* low DWMHs						
EF	−0.50 (0.25)	.03*	−0.46 (0.24)	.04*	−0.45 (0.25)	.04*
Working memory	−0.24 (0.19)	.21	−0.29 (0.20)	.15	−0.31 (0.20)	.13
Attention	−0.43 (0.21)	.04*	−0.40 (0.19)	.04*	−0.42 (0.19)	.03*
Verbal fluency	−0.71 (0.22)	.001**	−0.67 (0.21)	.002**	−0.68 (0.21)	.002**
Verbal memory	−0.20 (0.25)	.42	−0.19 (0.25)	.47	−0.19 (0.26)	.45
Visual memory	−0.51 (0.23)	.03*	−0.52 (0.24)	.03*	−0.52 (0.24)	.03*
VS	−0.82 (0.19)	<.001***	−0.80 (0.19)	<.001***	−0.79 (0.20)	<.001***
PS	−0.56 (0.20)	.007**	−0.46 (0.20)	.03*	−0.46 (0.21)	.03*

Note. WMLs = white matter lesions; SE = standard error; PVHs = periventricular hyperintensities; DWMHs = deep white matter hyperintensities; high grade = moderate lesions; low grade = without or mild lesions; EF = Executive Functioning; VS = Visuospatial Skills; PS = Psychomotor Speed. Model 1 = adjusted for age, sex, years of education, and treatable cardiovascular risk factors related to cognitive performance ($p \leq .1$); Model 2 = Model 1 plus adjustment for brain atrophy ratio (%) and presence of lacunar infarcts.
*$p < .05$.
**$p < .01$.
***$p < .001$.

Despite the relatively young age of the sample and the mild severity of the WMLs observed, high grade DWMHs were associated with a three- to fourfold increased risk of impaired performance in executive functioning, verbal fluency, visuospatial skills, and psychomotor speed. High grade PVHs were not associated with impaired cognitive performance in any cognitive domain either.

Disturbances in executive function and processing speed were related to WMLs as expected (De Groot et al., 2000; DeCarli et al., 1995; Pantoni et al., 2007; Schmidt et al., 2011; Vannorsdall et al., 2009). We also found a dysfunction in verbal fluency, which is a frontally-mediated function that can provide information relevant to executive control and processing speed (Hachinski et al., 2006; Strauss et al., 2006). In contrast with previous research (Stenset et al., 2008; Vannorsdall et al., 2009), high grade DWMHs were not associated with working memory dysfunction. This discrepancy may be explained by the high rate of missing data (almost 20%) for part B of the Trail Making Test, given the low educational level of the sample (median = 8 years). High grade DWMHs were also related to worse visual memory and visuospatial skills, which is consistent with previous investigations (Leaper et al., 2001; Schmidt et al., 2005; Stenset et al., 2008). Most of the associations between high grade DWMHs and poorer cognitive function in our sample were clinically relevant. This remarkable finding was present in the associations with executive functioning, visuospatial skills, and psychomotor speed.

Based on etiology and histopathological evidence, Kim, MacFall, and Payne (2008) have suggested that WMLs should be divided into ischemic and non-ischemic. The new classification would include PVHs and DWMHs as well. Ischemic PVHs would be defined as being from 3 to 13 mm from the ventricles, affecting long associating tracts. PVHs within 3 mm of the ventricles are non-ischemic and their functional effect on cognition is unlikely (Pantoni, 2002). Ischemic DWMHs would be defined as 13 mm or further from the ventricles (i.e., centrum semiovale), also affecting long associating tracts. Likewise, DWMHs within 4 mm from cortical GM would also be considered ischemic, causing disruption of short cortico-cortical connections consisting of arcuate U-fibers and affecting the integrity of frontal-subcortical circuits, probably leading to executive deficits (Fazekas et al., 1998; Inzitari, 2000).

In our sample, high grade DWMHs consisted of "early confluent" (moderate) DWMHs, which would be considered ischemic WMLs, whereas high grade PVHs consisted of "smooth halos" (moderate), which reflect primarily non-ischemic changes. We did not find severe PVHs, which are related to ischemic damage in long associating tracts. This fact may explain the lack of association between PVHs and cognition in our study and the incongruent results within the literature. The moderate correlation between PVH and DWMH scores described here ($r_s = 0.46$; $p < .001$) suggests that each type of WMLs may have dissimilar pathogenic

Table 5. Odds ratio (OR) and 95% confidence interval (CI) for risk of cognitive impairment in participants with high grade versus participants with low grade WMLs using logistic regression models

	Unadjusted model		Model 1		Model 2	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value
High *vs.* low PVHs						
EF	1.44 (0.41–5.11)	.57	1.25 (0.35–4.52)	.74	1.21 (0.31–4.73)	.79
Working memory	0.72 (0.14–3.61)	.69	0.72 (0.13–3.95)	.71	0.61 (0.09–3.96)	.61
Attention	0.38 (0.05–3.13)	.37	0.32 (0.04–2.72)	.30	0.27 (0.03–2.69)	.27
Verbal fluency	1.19 (0.30–4.77)	.81	1.36 (0.30–6.22)	.70	1.82 (0.35–9.57)	.48
Verbal memory	2.08 (0.49–8.88)	.32	1.94 (0.37–10.28)	.44	1.36 (0.23–7.97)	.74
Visual memory	0.00 (0.00–0.00)	1.00	0.00 (0.00–0.00)	1.00	0.00 (0.00–0.00)	1.00
VS	0.92 (0.27–3.17)	.90	0.92 (0.36–3.32)	.90	0.87 (0.22–3.37)	.84
PS	2.52 (0.79–8.02)	.12	2.32 (0.70–7.68)	.17	2.70 (0.74–9.84)	.13
High *vs.* low DWMHs						
EF	4.41 (1.38–14.10)	.01*	4.27 (1.23–14.87)	.02*	4.77 (1.33–17.11)	.02*
Working memory	0.88 (0.17–4.48)	.88	0.86 (0.15–4.82)	.86	0.70 (0.12–4.09)	.69
Attention	0.90 (0.18–4.49)	.89	0.52 (0.09–2.92)	.46	0.59 (0.10–3.34)	.55
Verbal fluency	4.20 (1.25–14.08)	.02*	3.59 (0.88–14.62)	.07	4.43 (1.02–19.23)	.04*
Verbal memory	1.13 (0.22–5.79)	.89	0.87 (0.12–6.27)	.89	1.05 (0.14–7.90)	.96
Visual memory	1.89 (0.52–6.84)	.33	1.58 (0.41–6.07)	.51	1.44 (0.36–5.70)	.60
VS	3.65 (1.19–11.15)	.02*	3.61 (1.10–11.90)	.04*	3.46 (1.04–11.50)	.04*
PS	3.56 (1.13–11.17)	.03*	3.52 (1.04–11.85)	.04*	3.59 (1.04–12.33)	.04*

Note. WMLs = white matter lesions; PVHs = periventricular hyperintensities; DWMHs = deep white matter hyperintensities; high grade = moderate lesions; low grade = without or mild lesions; EF = Executive Functioning; VS = Visuospatial Skills; PS = Psychomotor Speed. Model 1 = adjusted for age, sex, years of education and treatable cardiovascular risk factors related to cognitive performance ($p \leq .1$); Model 2 = Model 1 plus adjustment for brain atrophy ratio (%) and presence of lacunar infarcts.
*$p < .05$.

mechanisms in our sample. In contrast to the observed PVHs (caps, thin lining, bands, or halos), which appear to be more strongly related to age (Fernando et al., 2004), the observed DWMHs suggest an underlying vascular risk (Fazekas et al., 1998; Fernando et al., 2006). Specifically, arterial hypertension was related to DWMH burden in our sample. On the other hand, age and the presence of lacunar infarcts only showed statistical trends with PVH and DWMH burden. The narrow and young age range and the mild severity of WMLs (especially PVHs) in our sample may account for this finding.

In this study, brain MRI was performed with a 3T scanner instead of 1.5T scanners used so far. Since higher magnetic fields can provide improved sensitivity and diagnostic capacity (Kim et al., 2008; Scarabino et al., 2003), SVD-related pathology should be more easily detected. Nevertheless, the prevalence of participants with WMLs in our sample was lower than compared with other studies with participants of similar age (Wen & Sachdev, 2004). The prevalence of moderate lesions was similar to previous reports (Mosley et al., 2005; Schmidt et al., 1997) but none of our participants showed severe lesions. The prevalence of lacunar infarcts in our sample was slightly lower than seen elsewhere (Chen, Wen, Anstey, & Sachdev, 2009). Overall, these figures may be suggestive of a minor prevalence of SVD-related pathology in our sample. Lifestyle (i.e., dietary patterns) or genetic factors may be the basis of this lower prevalence (Alzamora et al., 2008; Tunstall-Pedoe et al., 1999).

One potential weakness of the present study is the use of a visual rating scale (Fazekas et al., 1987) to assess prevalence and severity of WMLs. Visual rating scales have some limitations, such as non-linearity of data, lack of sensitivity to small changes, and susceptibility to ceiling effects (Kim et al., 2008). Quantitative methods (i.e., volumetric analyses) have been regarded as more reliable and robust (Mosley et al., 2005). However, there is conflicting evidence regarding the idea that volumetric approaches for assessing WMLs may be more sensitive to clinical features than visual scores (Gouw et al., 2006). In most community-dwelling studies, WMLs are measured using visual rating scales, which are widely used in clinical practice (De Groot et al., 2000; Longstreth et al., 1996; Pantoni et al., 2005). Visual scales usually offer separate assessment of PVHs and DWMHs, which semi- and fully-automated quantitative methods often overlook.

Other possible limitations need to be considered. Cross-sectional studies with small size samples may report conflicting results regarding the association of WMLs with cognition, which is probably attributable to the low statistical power of samples (Desmond, 2002). Our sample size does not allow us to study the association of cognitive function with lobar locations of PVHs and DWMHs (frontal, parietal, temporal, or occipital), which may have some importance (Debette et al., 2007). The cross-sectional design also precludes us from making causal inferences regarding these associations.

Overall, our results corroborate the hypothesis that PVHs and DWMHs differentially impact cognitive function in middle-aged individuals and support the ongoing distinction between both types of WMLs. High grade (moderate) DWMHs were related to extensive cognitive dysfunction in

several domains whereas high grade (moderate) PVHs were not. Remarkably, most of these disturbances were clinically relevant in that they conferred a substantial increase in risk of cognitive impairment, making individuals with high grade DWMHs three to four times as likely to present with neuropsychological impairments. These results suggest that neuroradiologists should characterize separately PVHs and DWMHs in their reports, which should be available for neuropsychologists. The predominant role of DWMHs may be attributed to underlying ischemic processes, since only ischemic WMLs seem to exert histopathological changes that are located in white matter areas with potential functional relevance. This highlights the importance of primary prevention and treatment of modifiable risk factors, especially arterial hypertension, in middle-aged individuals. Further research is needed to more clearly elucidate whether WMLs types arise from dissociable forms of pathogenesis in middle-aged individuals.

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Regional cortical atrophy in lingual gyrus predicts visuospatial skills in a community sample of participants with white matter lesions

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Abstract

Cerebral white matter lesions (WMLs) and brain atrophy are concurrent findings in normal aging with potential impact on cognitive functioning. We investigated the separate association of high grade periventricular hyperintensities (PVHs) and deep white matter hyperintensities (DWMHs) with grey matter (GM) volume in community-dwelling middle-aged individuals. We also assessed the predictive value to cognition of GM atrophy within specific cortical areas related to high grade WMLs. One hundred participants from the Barcelona-AsIA Neuropsychology Study were divided into groups based on low and high grade WMLs. Voxel-by-voxel GM was compared between groups, with separate analyses for high grade PVHs and DWMHs. GM volume within areas showing differences between groups was extracted for linear regression analyses. Participants with high grade DWMHs showed reduced GM volume in different areas, whereas participants with high grade PVHs did not. GM atrophy in the lingual gyrus predicted cognitive outcome in visuospatial skills. Our data support the notion that PVHs and DWMHs are differentially associated with regional GM volume and cognitive function in middle-aged individuals.

Keywords: Neuroimaging, Cerebrovascular disease, White matter lesions, Brain atrophy, Cognition, Vascular cognitive impairment

1. Introduction

Structural changes such as cerebral white matter lesions (WMLs) and brain atrophy are common findings in normal aging (De Leeuw et al., 2001; Ikram et al., 2008). WMLs comprise diffuse areas of hypodensity on computerized tomography (CT) and high signal intensities on T2 and FLAIR magnetic resonance image (MRI) sequences. They have been consistently related to cognitive dysfunction and decline (Schmidt et al., 2011). Cognitive consequences have been attributed to frontal-subcortical circuit involvement (Linortner et al., 2012), with executive function and processing speed impairing the most. WMLs are usually divided into two groups: those immediately adjacent to the ventricles (periventricular hyperintensities or PVHs) and those located in the deep white matter (deep white matter hyperintensities or DWMHs) (Fazekas et al., 2002). Brain atrophy is characterized on MRI by widening of the sulci and narrowing of the gyri, as well as enlargement of the ventricles. Brain atrophy has been also related to cognitive dysfunction (Arvanitakis et al., forthcoming; Smith et al., 2015) and cognitive decline (Godin et al., 2010; Jokinen et al., 2012; Schmidt et al., 2005).

WMLs and brain atrophy are both considered expressions of cerebral small vessel disease (SVD), which is probably one of the most prevalent brain conditions described (Wardlaw et al., 2013). For this reason, both SVD signs are frequently concomitant on neuroimaging. Different studies have reported a significant association between WMLs and whole brain atrophy (brain parenchyma, including grey matter (GM) and white matter (WM) tissues) (Ikram et al., 2008; Jokinen et al., 2012; Schmidt et al., 2005), but previous research has yielded mixed results when taking into account only whole brain GM volume (Godin et al., 2009; Ikram et al., 2008; Wang et al., 2014).

An alternative approach to whole brain volumetric studies is voxel-based morphometry (VBM) (Ashburner and Friston, 2000), which enables whole brain analysis of brain morphology and allows the detection of regional areas of brain atrophy without delimitation a priori of a region-

of-interest (ROI). Previous studies on a voxel-by-voxel basis in normal aging have consistently shown a regional pattern of reduced GM volume in participants with WMLs compared to healthy controls (Quinque et al., 2012; Rossi et al., 2006) or a significant negative association between WMLs burden and GM volume in several areas (Crane et al., 2015; Raji et al., 2012; Wen et al., 2006). Most previous studies, however, have focused on a single measure of WMLs and only one study distinguished between PVHs and DWMHs (Wen et al., 2006).

The concurrence of WMLs and brain atrophy may have some impact on cognitive outcome. Brain atrophy is thought to amplify or mediate the effects of WMLs on cognition (Jokinen et al., 2012; Schmidt et al., 2005). However, reports relating GM atrophy to cognitive function in normal aging and participants with WMLs have yielded controversial results (Arvanitakis et al., forthcoming; Raji et al., 2012; Smith et al., 2015; Tullberg et al., 2004). Further, most research relating GM atrophy to cognitive function has either employed a prior delimitation of region-of-interest (ROI) approach to calculate regional GM (i.e., frontal GM or hippocampus) or has applied segmentation methods to calculate a single whole brain GM volume. These approaches may overlook that regional GM atrophy related to WMLs can develop in distinct areas and the specific contribution of each area of reduced GM volume to cognitive function.

In this study, our objective is twofold. First, we aim to investigate the separate association of high grade PVHs and DWMHs with GM volume on a voxel-by-voxel basis in a community-dwelling sample of middle-aged participants. Following previous VBM research (Crane et al., 2015; Quinque et al., 2012; Raji et al., 2012; Rossi et al., 2006), we expect that participants with high grade WMLs will show a regional pattern of reduced GM volume compared with participants with low grade WMLs. Previous VBM data also suggest that DWMHs are more related to regional GM atrophy than PVHs (Wen et al., 2006). Accordingly, we hypothesize that the spatial pattern of GM volume reduction will be found in a greater extent in participants with high grade DWMHs. Second, we aim to assess the predictive value to cognition of reduced GM volume within specific

cortical areas related to high grade WMLs. In a previous study, we found a predominant role of high grade DWMHs in cognitive dysfunction of middle-aged individuals (Soriano-Raya et al., 2012). Consequently, we hypothesize that areas of reduced GM volume related to high grade DWMHs will be more associated with cognitive function than areas of reduced GM volume related to high grade PVHs.

2. Materials and methods

2.1 Study design and sample selection

The Barcelona-AsIA (Asymptomatic Intracranial Atherosclerosis) Study is an ongoing population-based study that involves 28 primary healthcare centers and a tertiary stroke center. Complete details for the Barcelona-AsIA protocol have been described elsewhere (López-Cancio et al., 2011). In brief, a random sample of participants over 50 years old without previous history of stroke or ischemic heart disease underwent clinical examination, blood analysis, complete extra and transcranial Duplex ultrasound study, and neuropsychological assessment. The Barcelona-AsIA Neuropsychology Study is a related prospective study whose objectives are (1) to investigate the associations between cognition and vascular risk factors, asymptomatic cervicocerebral atherosclerosis, and MRI signs of SVD, and (2) to identify clinical and radiological features and biological mechanisms underlying these associations.

For this study, 132 participants aged 50 to 65 years were selected to undergo a comprehensive neuropsychological assessment and brain MRI. Details of the recruitment process have been previously described (Soriano-Raya et al., 2012). Exclusion criteria were: history of stroke or transient ischemic attack (TIA), coronary heart disease, neurological disease, or severe psychiatric disorder (n = 11); a MMSE score < 25 or severe disability (n = 3); other medical diseases that could affect cognitive assessment and function (n = 4); contraindications to undergo MRI (n = 10), unexpected findings seen on brain MRI (n = 2) or other causes (i.e., less

than 75% of neuropsychological assessment available) (n = 2). Consequently, the final sample included 100 participants aged 50 to 65 years stratified by sex and educational level.

This study has been approved by the ethics committees of the University of Barcelona and the Hospital Germans Trias i Pujol University Hospital. It was conducted in accordance with the ethical standards of the Declaration of Helsinki. Written informed consent was obtained from all participants.

2.2 Evaluation of vascular risk factors

Diagnosis of a particular vascular risk factor, such as arterial hypertension, diabetes mellitus, dyslipidemia, or current smoking status, was based on clinical history or use of medication for the particular condition at the time of the clinical examination. Ten-year cardiovascular risk was calculated following the REGICOR function, which is a validated calibration of the Framingham function for Spanish population (Marrugat et al., 2007). The REGICOR function includes non-modifiable, such as age and sex, and modifiable vascular risk factors, such as arterial hypertension, diabetes mellitus, dyslipidemia and smoking status.

2.3 Neuropsychological assessment

All participants completed an extensive neuropsychological battery. Cognitive measures were grouped into 8 cognitive domains, which include tests assessing similar cognitive function (Lezak et al., 2004): executive functioning, working memory, attention, verbal fluency, verbal memory, visual memory, visuospatial skills, and psychomotor speed. Executive functioning (i.e., conceptualization, planning, and inhibition) was assessed with the 64-item computerized version of the Wisconsin Card Sorting Test (WCST-64) (Kongs et al., 2000) and the interference score of the Color-Word Stroop Test (Strauss et al., 2006). Working memory was examined with Digit Span Backwards from the Wechsler Adult Intelligence Scale 3rd edition (WAIS-III) (Strauss et al.,

2006) and part B of the Trail Making Test (Strauss et al., 2006). Attentional abilities were assessed with the Continuous Performance Test (Strauss et al., 2006) and Digit Span Forward, Symbol Search, and Digit Symbol Coding subtests from the WAIS-III. Verbal fluency was measured with letter fluency (letters P, M and R) and semantic category fluency (animals) in 60 seconds each (Strauss et al., 2006). Word List and Visual Reproduction from the Wechsler Memory Scale 3rd edition (WMS-III) (Strauss et al., 2006) were administrated to measure verbal and visual memory, respectively. Visual Discrimination and the Copy from the Visual Reproduction subtest (WMS-III) were used to evaluate visuospatial skills. Psychomotor speed was assessed with part A of the Trail Making Test and Grooved Pegboard (Strauss et al., 2006). Participants' raw scores were normalized to z scores using the mean and standard deviation (SD) of the sample. Composite z scores for each participant in each cognitive domain were calculated by averaging the z scores of all tests within that domain.

Neuropsychological assessment also included the Mini-Mental State Examination (Strauss et al., 2006) as a global cognitive function test and the Vocabulary subtest from the WAIS-III as a measure of premorbid intelligence. Depressive symptoms were assessed with the Geriatric Depression Scale 15-item version (GDS-15) (Sheikh and Yesavage, 1986).

2.4 Magnetic Resonance Imaging acquisition protocol

The MRI scanning protocol was performed with a Siemens Magnetom Trio 3T scanner (Siemens Diagnostics Healthcare, Erlangen, Germany) at the Medical Image Core Facility (IDIBAPS, Hospital Clinic, Barcelona, Spain).

The MRI protocol included a set of 3-dimensional magnetization-prepared rapid gradient echo (MPRAGE) T1-weighted images [repetition time (TR): 2300 ms; echo time (TE): 3 ms; flip angle: 15°; field of view (FOV): 245 mm; and voxel size: 1x1x1 mm, no gap]. Axial fluid attenuated inversion recovery (FLAIR) images [TR: 9040 ms; TE: 85 ms; inversion time (TI): 2500

ms; and voxel size: 1.1x0.9x5 mm, gap: 1.5mm] and axial T2-weighted images (TR: 5520 ms; TE: 92 ms; and voxel size: 0.5x0.4x5mm, gap: 1.5mm) were also collected for rating WMLs and lacunar infarcts (see below).

2.5 Magnetic Resonance Imaging data processing

High resolution T1-weighted images were analyzed with FSL-VBM (Douaud et al., 2007) version 1.1, an optimised VBM-style analysis implemented in FSL (Smith et al., 2004) version 5.0.1. First, structural images were brain-extracted using the Brain Extraction Tool (BET) (Smith et al., 2002). Next, tissue-type segmentation was carried out and the resulting GM partial volume images were then aligned to MNI152 standard space using the affine registration tool FLIRT followed by a nonlinear registration using FNIRT, which uses a b-spline representation of the registration warp field. The resulting images were averaged and flipped along the x-axis to create a left-right symmetric, study-specific GM template, to which the native GM images were then non-linearly re-registered. The registered GM partial volume images were then modulated (to correct for local expansion or contraction) by dividing by the Jacobian of the warp field. The modulated GM images were finally smoothed with an isotropic Gaussian kernel with a sigma of 3 mm, and the resulting data were fed into voxel-wise statistics.

Individual brain tissue volumes (GM, WM, CSF) were calculated with SIENAX software (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/SIENA) on high resolution T1-weighted images (Smith et al., 2002) and further summed into total brain volume (TBV), which is a potential confounder in VBM studies. The ratio between brain parenchyma volume (BP=GM+WM) and total brain volume (TBV) was computed to obtain a normalized measure of global brain atrophy (Schmidt et al., 2005) for regression analyses purposes.

2.6 Rating of white matter lesions and lacunar infarcts

Location and severity of WMLs were estimated on T2 and FLAIR images by a trained and blind neuroradiologist (N.B.) using the Fazekas scale (Fazekas et al., 1987). On MRI, WMLs appear hyperintense on T2-weighted images. They also remain bright on FLAIR, a T2-weighted sequence that suppresses the signal from fluid filled spaces. The Fazekas scale provides two different scores (PVHs and DWMHs), rated on a 0- to 3-point scale of increasing severity within the whole brain. The sum of the PVHs and the DWMHs scores provides a total score. Participants were classified as having no lesions, or mild, moderate, or severe lesions (0, 1, 2, or 3 points, respectively) in each location. The intrarater reliability was determined on 20 randomly selected scans scored twice. Reliability was good for grading both PVHs (weighted kappa=0.66, 95% CI: 0.33-0.96), and DWMHs (weighted kappa=0.7, 95% CI: 0.41-0.99).

Lacunar infarcts were defined as lesions with increased signal intensity on T2-weighted images and decreased signal intensity on T1-weighted and FLAIR images with a diameter of 5-15 mm, which were not located in areas with high prevalence of widened perivascular spaces (Fazekas et al., 2002).

2.7 Statistical analyses

The distribution of the WMLs scores was positively skewed as expected, with most participants having no lesions or mild lesions. We dichotomized our sample into low grade WMLs (participants with no lesions or mild lesions) and high grade WMLs (participants with moderate or severe lesions). High grade PVHs were thus defined as PVH > 1 and high grade DWMHs as DWMH > 1. We compared voxel-by-voxel GM volume between high grade and low grade WMLs, with separate analyses for PVHs and DWMHs groups, regressing out age, sex, vascular risk factors (REGICOR function), TBV, and the other Fazekas score (PVHs score in the comparison between DWMHs groups, DWMHs score in the comparison between PVHs groups).

For the voxel-wise analysis of group differences, a permutation-based program (randomise) with standard general linear model (GLM) implemented in FSL was performed with 5000 random permutations. A developed algorithm, known as Threshold-Free Cluster Enhancement (TFCE) (Smith and Nichols, 2009) was used to obtain the GM voxels significantly different between groups at significance level of $p<0.05$, after accounting for multiple comparisons by controlling for Family-Wise Error (FWE) rates. Significant clusters were also required to have an extent of at least 50 voxels.

From the results of voxel-wise group comparisons, areas showing significant GM volume reduction were located and labelled anatomically by mapping the FWE-corrected statistical map of $p<0.05$ to the Harvard-Oxford Cortical Structural Atlas (Desikan et al., 2006). A binarized mask of significant results was made and superimposed onto probabilistic masks of labelled cortical areas showing volume reduction for each group comparison. The GM volume within areas showing significant differences of GM volume between groups was then extracted in each labelled cortical area for linear regression analyses.

Linear regression analyses were carried out using the Statistical Package for Social Sciences (SPSS for Windows, version 20.0, SPSS Inc., Chicago, Illinois, USA). A standardized z-score of the extracted GM volume for each cortical area was calculated and entered into a series of linear regression analyses to assess its specific contribution to cognitive function, with separate analyses for cortical areas showing differences in PVHs and DWMHs groups. The z-scores for all cortical areas were first entered as predictive variables with cognitive domains as the dependent variables. Linear regression models were first adjusted (Model 1) for age, sex, years of education, and treatable vascular risk factors associated with cognitive function ($p \leq 0.1$) that we have reported previously (Soriano-Raya et al., 2012). Briefly, hypertensive participants had lower scores on verbal fluency, visuospatial skills and psychomotor speed. Participants with dislipydemia had lower scores on working memory. Participants with diabetes mellitus had lower

scores on executive functioning and psychomotor speed. Higher scores on verbal memory and visuospatial skills were observed in current non-smoker participants. Models were also adjusted (Model 2) for other brain changes usually related to cognitive disturbances (ratio of global brain atrophy and lacunar infarcts).

3. Results

3.1 Sample characteristics

Due to technical difficulties on MRI acquisition, four participants were excluded from the sample. There were no differences in demographic and clinical variables between the remaining 96 participants and those recruited from the PERART Study but excluded from the analyses. Demographic, clinical, and MRI characteristics of the remaining 96 participants (mean age = 59.7 years, 59% women, median education = 8 years) are summarized in Table 1. Their estimated premorbid intelligence, general cognitive function and depressive symptoms were within the normal range. A significantly higher proportion of participants with high grade DWMHs (68.8%) had arterial hypertension compared to participants with low grade DWMHs (42.5%).

According to the PVHs score, there were 80 participants (83.3%) with low grade PVHs and 16 participants (16.7 %) with high grade PVHs. According to the DWMHs score, 80 participants (83.3%) were classified as low grade DWMHs and 16 participants (16.7%) were classified as high grade DWMHs. Seven participants (7.3%) had both high grade DWMHs and high grade PVHs (moderate lesions). None of the participants had severe (irregular) PVHs or severe (confluent) DWMHs. Eleven lacunar brain infarcts were present across 7 participants (7.3%). Eight of the lacunar infarcts were located in the basal ganglia, and there was one lacunar infarct each in the pons, intern capsule, and corona radiata.

3.2 Areas of reduced GM volume in participants with high grade WMLs

Participants with high grade DWMHs showed a pattern of reduced GM volume in several areas compared to participants with low grade DWMHs, after regressing out age, sex, vascular risk factors, TBV and the PVHs score (Table 2 and Figure 1). Specifically, peak-value voxels of GM reduction were located in frontal (superior and middle frontal gyrus), temporal (inferior temporal gyrus), parietal (angular gyrus) and occipital (lingual gyrus) areas, and the insula lobe. No significant results were found for the reverse contrast.

Participants with high grade PVHs did not show areas of reduced GM volume compared to participants with low grade PVHs after regressing out age, sex, vascular risk factors, TBV and the DWMHs score. Crude analyses without adjustments did not yield areas of reduced GM volume either. Likewise, no significant results were found for the reverse contrast.

3.3 Predictive value to cognitive outcome of areas of reduced GM volume (Table 3)

Areas of reduced GM volume in the lingual gyrus were related to lower scores in visuospatial skills ($R^2 = 0.10$; $\beta = 0.31$). Adjustments for age, sex, years of education, and vascular risk factors (Model 1) and additional adjustment for ratio of global brain atrophy and lacunar infarcts (Model 2) left the association essentially unaltered ($R^2 = 0.13$; $\beta = 0.33$, and $R^2 = 0.15$; $\beta = 0.33$, respectively). There was no association between the rest of cortical areas with GM volume reduction in participants with high grade DWMHs and cognitive function.

4. Discussion

This study first investigated the different pattern of association of high grade PVHs and DWMHs with reduction of GM volume on a voxel-by-voxel basis in a middle-aged community-dwelling sample. We found that participants with high grade DWMHs showed reduced GM volume in different areas, whereas participants with high grade PVHs did not. Our second aim was to assess the predictive value to cognitive function of those areas with GM volume reduction. The

main finding was that one area showing reduced GM volume in participants with high grade DWMHs was related to cognition. Specifically, reduction of GM volume in the lingual gyrus predicted cognitive outcome in visuospatial skills. This is the first study showing a specific association of high grade DWMHs, reduced GM volume in specific cortical areas and cognitive function.

Only participants with high grade DWMHs showed a regional pattern of reduced GM volume in several areas, including the superior and middle frontal gyrus, the inferior temporal gyrus, the angular gyrus, the lingual gyrus, and the insula lobe. Our results are in line with previous VBM research regarding the association between WMLs burden and regional GM atrophy, which reports the greatest volume loss in the frontal lobe (Quinque et al., 2012; Raji et al., 2012; Rossi et al., 2006; Wen et al., 2006). The temporal cortex (Raji et al., 2012; Wen et al., 2006), the inferior parietal lobe (Raji et al., 2012), and the lingual gyrus (Crane et al., 2015; Raji et al., 2012; Wen et al., 2006) are also common findings in the literature.

Likewise, the singular association of high grade DWMHs with regional areas of GM atrophy supports previous research set in a large community sample suggesting that DWMHs have a more significant relationship with regional structural changes than PVHs (Wen et al., 2006). One of the underlying factors of the association between WMLs and brain atrophy is the variable degree of tissue destruction under WMLs (Jouvent et al., 2010). Ischemic-related changes are usually associated with high grade DWMHs whereas non-ischemic age-related changes are usually related to PVHs (Schmidt et al., 2011). The severity of tissue damage is therefore more extensive in DWMHs. Only severe PVHs extending to deep WM are clearly vascular-related changes, but no one of our participants with high grade PVHs were rated with severe lesions.

Several mechanisms may underlie the association between WMLs and regional GM atrophy. WMLs and brain atrophy are considered expressions of SVD, so that they share

common risk factors such as aging and vascular risk factors (Appelman et al., 2009; Wardlaw et al., 2013). Interestingly, our findings remained after adjustment for age and vascular risk factors, suggesting the independence of the association from these shared factors in our sample. The microvasculature damage of SVD can lead to an impairment of cerebral blood flow and chronic cerebral hypoperfusion that may induce ischemia and infarction in the WM and the GM through a series of pathological mechanisms, such as inflammation and edema, gliosis, dehydration, demyelination, and axonal loss (Nitkunan et al., 2011). WMLs can also disrupt anatomic pathways through demyelination and axonal loss, leading to functional and structural alterations of the cortex (i.e., neuronal loss) (Schmidt et al., 2005; Wen et al., 2006). A complementary explanation is that ischemia and infarction in the GM, resulting in neuronal loss and GM atrophy, can lead to WMLs through Wallerian degeneration (Godin et al., 2009; Wen et al., 2006). One interesting question is the temporal relation between WMLs and GM atrophy. Several lines of evidence suggest that it is more likely that WMLs precede the emergence of GM atrophy (Schmidt et al., 2005; Sun et al., 2014; Zhuang et al., 2012). This notwithstanding, the cross-sectional design of our study precludes us to determine direction of causality in our sample.

We found that the reduction of GM volume in the lingual gyrus in participants with high grade DWMHs was related to cognitive performance. This singular association supports the predominant role for these lesions in cognitive function. In a recent study, the cortical thickness of extensive fronto-temporal regions negatively associated with WMLs burden was related to several cognitive domains, such as executive function, attention, verbal fluency or psychomotor speed (Tuladhar et al., 2015). One possible explanation for differences with our results may be that VBM and cortical thickness are different approaches to investigate GM atrophy. Cortical thickness is only based on the measurement of the one-dimensional thickness of the cortex. In VBM, the quantity of tissue within a voxel is dependent on the local cortical surface area and cortical folding, as well as the local cortical thickness (Hutton et al., 2009). Other methodological

issues such as sample selection and size, specific location of WMLs, correction for multiple comparisons in neuroimaging analyses or covariates introduced in voxel-wise and linear regression analyses may also account for the different findings.

Reduced GM volume in the lingual gyrus was positively related to visuospatial skills. A decrease of 1 SD in GM volume was related to a 0.31 SD decrease in visuospatial skills. The lingual gyrus is a crucial structure in visual processing (Kravitz et al., 2011). Visuospatial skills refers to the ability to resemble the elements of a model object in the correct spatial relation, including visuospatial abilities to process and understand the spatial relations between different components of the object, executive abilities involved in planning drawing, and attention to the overall extent and local aspects of the object (Trojano et al., 2009). A higher activation in the left lingual gyrus has been previously reported in copying concrete objects (Ferber et al., 2007). Furthermore, errors of spatial position has been associated with lesions within the lingual gyrus (Chechlacz et al., 2014). It is also thought that the lingual gyrus plays a role in cross modal attention and spatial working memory (Macaluso et al., 2000; Russell et al., 2010).

The application of a VBM approach in this study enables the whole brain regional analysis of GM volume. It overcomes the potential limitations of ROI methodology, which is a subjective and time-consuming procedure, with limited reliability and reproducibility (Ashburner 2009). Likewise, segmentation of brain tissues to obtain a global volumetric measure (i.e., total GM volume) may be relatively insensitive to identify focal cortical GM atrophy, whereas VBM appears to be as sensitive as segmentation methods to detect global GM atrophy (Voormolen et al., 2010). Nevertheless, like all imaging methods, VBM has inherent limitations. Its main drawback is that inter-subject registration errors can alter the accuracy of analysis. The FSL-VBM procedure that we applied follows the optimised VBM protocol (Good et al., 2001) to address potential registration problems.

One of the strengths of this study is the selection of a community-dwelling sample, clinically well-characterized without overt cerebrovascular disease and cognitive impairment. Other strengths of this study are our extensive neuropsychological assessment and the use of high-resolution 3T MRI to detect WMLs with an increased sensitivity and obtain high-quality T1-weighted images. VBM analyses were conducted with extensive adjustment for confounders, as previously suggested (Appelman et al., 2009). The analyses of the predictive value of GM volume to cognitive function were also carried out thoroughly bearing in mind possible confounders. One potential weakness of the present study is the use of a visual rating scale (Fazekas et al., 1987) to rate location and severity of WMLs. Volumetric quantification of WMLs has been regarded as more reliable and robust. However, visual scales usually offer separate assessment of PVHs and DWMHs, which semi- and fully-automated quantitative methods often overlook. Other possible limitations need to be considered. The most severe grades of WMLs are under-represented in our community-dwelling sample. The small sample size of participants with high grade DWMHs (n=16) may preclude the generalization of the results. Also, the cross-sectional design also prevent us from making causal inferences regarding high grade DWMHs, areas of GM atrophy and cognitive function. Finally, we can not rule out that other unknown factors may be playing a role in our results.

In conclusion, our main finding is that one area of reduced GM volume in the lingual gyrus, associated to high grade DWMHs, is related to lower cognitive performance in a community-dwelling sample of middle-aged participants. The use of VBM allows to identify regional areas of GM atrophy in individuals with high grade DWMHs. Our data support the notion that PVHs and DWMHs are differentially associated with regional GM volume. These novel results also support the hypothesis that PVHs and DWMHs are differentially related to cognitive function and suggest that the ongoing distinction between both types of WMLs is worthy. Further research is needed to more clearly elucidate whether both types arise from dissociable forms of

pathogenesis. Longitudinal data are required to determine the time and course of the association between WMLs and regional GM atrophy, and the diagnostic value of regional GM atrophy associated with high grade DWMHs to assess cognitive dysfunction in community samples.

Disclosure/conflict of interest

The authors declare no conflict of interest.

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Table 1. Demographic, clinical and MRI data

	Low grade PVHs (without or mild) (n = 80)	High grade PVHs (moderate) (n = 16)	p	Low grade DWMHs (without or mild) (n = 80)	High grade DWMHs (moderate) (n=16)	p
Age (years) [1]	59.48 (3.48)	61.00 (2.48)	0.10	59.48 (3.35)	61.00 (3.25)	0.10
Sex (n (%) female) [2]	48 (60.0)	9 (56.3)	0.78	48 (60.0)	9 (56.3)	0.78
Education (years) [3]	8 (6-9)	8 (6.25-10)	0.71	8 (6-10)	8 (6.25-8.75)	0.98
MMSE [3]	29 (28-30)	30 (28.25-30)	0.20	29 (28-30)	30 (28-30)	0.71
Vocabulary (WAIS-III) [1]	38.91 (8.76)	37.56 (10.56)	0.59	39.36 (8.85)	37.50 (9.47)	0.50
GDS-15 [3]	2 (1-3)	1 (0-2)	0.08	2 (0-3)	1 (1-2.75)	0.89
REGICOR [3]	5 (4-7)	6.5 (4.25-8.5)	0.26	5 (4-7)	6.5 (4.25-8)	0.32
Vascular risk factors (n (%))						
Hypertension [2]	38 (47.5)	7 (43.8)	0.78	34 (42.5)	11 (68.8)	0.04*
Dyslipidemia [2]	48 (60.0)	9 (56.3)	0.78	47 (58.8)	10 (62.5)	0.78
DM [4]	15 (18.8)	2 (12.5)	0.73	15 (18.8)	2 (12.5)	0.73
Current smoker [4]	12 (15.0)	3 (18.8)	0.71	13 (16.3)	2 (12.5)	1
MRI measures [1]						
GM (cm^3)	590.82 (35.38)	580.80 (45.11)	0.41	586.12 (36.22)	581.74 (45.14)	0.72

WM (cm^3)	564.90 (60.69)	542.24 (63.28)	0.19	543.56 (55.53)	546.50 (64.83)	0.87
BP (cm^3)	1155.72 (93.52)	1123.04 (104.70)	0.25	1129.68 (88.42)	1128.24 (106.39)	0.96
TBV (cm^3)	1450.51 (118.78)	1420.00 (128.76)	0.38	1424.18 (109.25)	1425.27 (130.96)	0.98
Ratio GM / TBV (%)	40.97 (1.73)	40.83 (1.35)	0.73	41.22 (1.51)	40.89 (1.39)	0.38
Ratio WM / TBV (%)	38.74 (1.55)	38.25 (1.50)	0.27	38.11 (1.51)	38.27 (1.54)	0.71
Ratio BP / TBV (%)	79.71 (2.03)	79.08 (1.44)	0.25	79.33 (1.80)	79.16 (1.52)	0.67
LI present (n (%)) [4]	4 (5.1)	3 (18.8)	0.09	6 (7.5)	1 (6.3)	1

Note. PVHs = Periventricular Hyperintensities; DWMHs = Deep White Matter Hyperintensities; MMSE = Mini-Mental State Examination; GDS-15 = Geriatric Depression Scale, 15-item version; REGICOR = Registre Gironí del Cor; DM = Diabetes Mellitus; GM = Gray Matter volume; WM = White Matter volume; BP = Brain Parenchyma volume = GM + WM; TBV = Total Brain Volume; LI = Lacunar Infarcts. Values are means (standard deviations) in Student's t-test or medians (interquartile range) in Mann-Whitney test for continuous variables. Values are n (%) for categorical variables in chi-square test and Fisher's exact test. p shows statistical comparison between participants with high grade and low grade white matter lesions.

[1]Student's t-test; [2]chi-square test; [3]Mann-Whitney test; [4]Fisher's exact test. *p<0.05.

Table 2. MNI coordinates of clusters showing significant reduction of grey matter volume in subjects with high grade (moderate) DWMHs

Location	MNI coordinates			t	p	Vox
	x	y	z			
Right Superior Frontal Gyrus	14	4	60	4.51	0.013	602
Right Insula	30	26	12	4.09	0.030	75
Left Angular Gyrus	-48	-56	22	3.46	0.020	395
Left Lingual Gyrus	-8	-72	0	3.80	0.031	264
Left Inferior Temporal Gyrus	-64	-38	-26	3.11	0.023	97
Left Middle Frontal Gyrus	-42	48	-8	3.47	0.030	72

Note. MNI = Montreal Neurological Institute; DWMHs = Deep White Matter Hyperintensities; Vox = Cluster size in number of voxels. MNI coordinates (mm) represent peak-value voxel location.

Table 3. Predictive value of areas showing GM volume reduction in participants with high grade DWMHs versus participants with low grade DWMHs using multivariate linear regression models

	Unadjusted model		Model 1		Model 2	
	Beta	p value	Beta	p value	Beta	p value
EF						
r SFG	0.03	0.79	0.03	0.79	0.04	0.73
r Insula	0.16	0.13	0.17	0.12	0.20	0.07
l AngG	0.08	0.46	0.08	0.48	0.06	0.60
l ITG	-0.09	0.40	-0.09	0.42	-0.06	0.55
l MiFG	-0.10	0.32	-0.13	0.27	-0.13	0.28
l LingG	0.07	0.54	0.08	0.48	0.06	0.60
W Memory						
r SFG	-0.06	0.62	-0.12	0.29	-0.09	0.41
r Insula	0.11	0.30	0.11	0.30	0.10	0.35
l AngG	-0.06	0.64	-0.08	0.48	-0.07	0.54
l ITG	0.02	0.87	0.00	0.99	-0.01	0.91
l MiFG	-0.15	0.18	-0.19	0.12	-0.19	0.14
l LingG	0.07	0.52	0.12	0.25	0.13	0.25
Attention						
r SFG	-0.01	0.89	-0.08	0.41	-0.06	0.52
r Insula	0.13	0.21	0.06	0.60	0.07	0.54
l AngG	-0.06	0.54	-0.04	0.69	-0.05	0.63
l ITG	-0.04	0.72	-0.07	0.48	-0.06	0.56
l MiFG	-0.07	0.53	-0.02	0.88	-0.01	0.91
l LingG	0.07	0.48	0.03	0.72	0.01	0.89
Verbal fluency						
r SFG	-0.05	0.62	-0.10	0.35	-0.08	0.46
r Insula	0.19	0.07	0.15	0.16	0.15	0.16
l AngG	0.01	0.93	0.05	0.61	0.05	0.62

l ITG	0.08	0.44	0.06	0.58	0.06	0.53
l MiFG	-0.16	0.12	-0.12	0.29	-0.11	0.31
l LingG	-0.01	0.95	-0.03	0.80	-0.04	0.69
Verbal memory						
r SFG	0.02	0.87	0.03	0.76	0.02	0.83
r Insula	-0.10	0.35	-0.12	0.27	-0.11	0.30
l AngG	0.03	0.79	-0.03	0.80	-0.02	0.87
l ITG	-0.09	0.39	-0.07	0.49	-0.09	0.41
l MiFG	0.19	0.07	0.14	0.23	0.14	0.24
l LingG	0.01	0.93	0.02	0.85	0.03	0.80
Visual memory						
r SFG	0.16	0.12	0.11	0.30	0.10	0.36
r Insula	0.08	0.48	0.05	0.62	0.05	0.60
l AngG	-0.15	0.15	-0.13	0.21	-0.13	0.23
l ITG	-0.09	0.37	-0.11	0.29	-0.12	0.26
l MiFG	-0.06	0.55	0.02	0.85	0.02	0.84
l LingG	0.07	0.49	0.06	0.55	0.07	0.51
VS						
r SFG	0.19	0.07	0.19	0.08	0.17	0.12
r Insula	-0.06	0.56	-0.08	0.47	-0.06	0.59
l AngG	-0.08	0.47	-0.08	0.45	-0.08	0.48
l ITG	-0.05	0.61	-0.06	0.58	-0.09	0.42
l MiFG	0.04	0.73	0.05	0.67	0.05	0.66
l LingG	0.31	0.002**	0.33	0.002**	0.33	0.002**
PS						
r SFG	0.12	0.26	0.10	0.36	0.11	0.30
r Insula	0.04	0.72	0.07	0.50	0.07	0.52
l AngG	-0.06	0.60	-0.10	0.35	-0.09	0.40
l ITG	-0.04	0.72	-0.03	0.79	-0.04	0.72
l MiFG	-0.01	0.91	-0.01	0.90	-0.01	0.90

l LingG	-0.06	0.54	-0.09	0.36	-0.09	0.42

Note: GM = grey matter; DWMHs = Deep White Matter Hyperintensities; high grade = moderate lesions; low grade = without or mild lesions; EF = Executive Functioning; W Memory = Working Memory; VS = Visuospatial Skills; PS = Psychomotor Speed; r = right; l = left; SFG = Superior Frontal Gyrus; AngG = Angular Gyrus; ITF = Inferior Temporal Gyrus; MiFG = Middle Frontal Gyrus; LingG = Lingual Gyrus. Beta values from linear regression models relating areas of reduced grey matter volume in each labelled cortical area (participants with high grade vs. low grade DWMHs) to cognitive function. Model 1 = adjusted for age, sex, years of education and cardiovascular risk factors; Model 2 = Model 1 plus adjustment for brain parenchyma ratio (%) and presence of lacunar infarcts.

*p<0.05; **p<0.01.

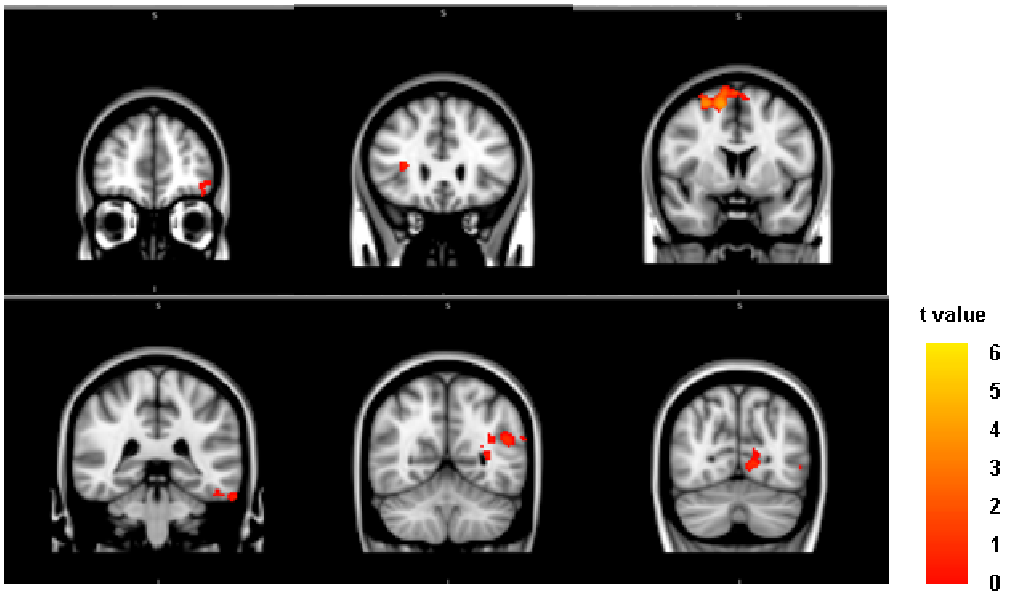

Figure 1. Regional areas of reduction of grey matter volume

Clusters showing significant reduction of grey matter volume in subjects with high grade deep white matter lesions are displayed on coronal sections of a T1-weighted brain image. The first row shows grey matter reduction in left middle frontal gyrus (y=48), right insula (y=26) and right superior frontal gyrus (y=4), respectively. The second row shows grey matter reduction in left inferior temporal gyrus (y=-38), angular gyrus (y=-56) and lingual gyrus (y=-72), respectively. The color scale indicates the magnitude of t values with lowest appearing in dark red and the highest in bright yellow. Images are displayed in radiological convention (right side represents left side and left side represents right side of the brain).

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ORIGINAL ARTICLE

Tract-specific fractional anisotropy predicts cognitive outcome in a community sample of middle-aged participants with white matter lesions

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Cerebral white matter lesions (WMLs) have been consistently related to cognitive dysfunction but the role of white matter (WM) damage in cognitive impairment is not fully determined. Diffusion tensor imaging is a promising tool to explain impaired cognition related to WMLs. We investigated the separate association of high-grade periventricular hyperintensities (PVHs) and deep white matter hyperintensities (DWMHs) with fractional anisotropy (FA) in middle-aged individuals. We also assessed the predictive value to cognition of FA within specific WM tracts associated with high-grade WMLs. One hundred participants from the Barcelona-AsIA Neuropsychology Study were divided into groups based on low- and high-grade WMLs. Voxel-by-voxel FA were compared between groups, with separate analyses for high-grade PVHs and DWMHs. The mean FA within areas showing differences between groups was extracted in each tract for linear regression analyses. Participants with high-grade PVHs and participants with high-grade DWMHs showed lower FA in different areas of specific tracts. Areas showing decreased FA in high-grade DWMHs predicted lower cognition, whereas areas with decreased FA in high-grade PVHs did not. The predictive value to cognition of specific WM tracts supports the involvement of cortico-subcortical circuits in cognitive deficits only in DWMHs.

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INTRODUCTION

Cerebral white matter lesions (WMLs) comprise diffuse areas of hypodensity on computerized tomography and high signal intensities on T2, proton density, and fluid-attenuated inversion recovery (FLAIR) magnetic resonance image (MRI) sequences. White matter lesions are commonly found in normal aging.[1] They are considered an expression of cerebrovascular small vessel disease (SVD), so that WMLs are commonly associated with other signs of SVD, such as lacunar infarcts and microbleeds.[2]

White matter lesions have been consistently related to cognitive dysfunction and decline.[3] Cognitive consequences have been attributed to frontal-subcortical circuit involvement,[4] with executive function and processing speed impairing the most. The association of WMLs with cognitive function is probably mediated by severity of white matter (WM) damage, with mild lesions unlikely to be related to cognitive dysfunction.[3] White matter lesions are usually divided into two groups: those immediately adjacent to the ventricles (periventricular hyperintensities (PVHs)) and those located in the deep white matter (deep white matter hyperintensities (DWMHs)).[5] The relative contribution of PVHs or DWMHs to cognitive function is still controversial.[3]

Despite the abundant evidence for the association between WMLs and cognition, the role of WM damage in cognitive impairment is not fully determined. Previous research has found that correlations between WMLs and cognitive function are modest.[3,6] The evidence of a penumbra of subtle WM injury surrounding lesions supports the notion that WMLs may fail to capture the full extent and degree of WM damage.[7] Novel imaging techniques that allow a more direct assessment of the composition and organization of WM are promising tools to explain impaired cognition related to WMLs beyond what can be expected from conventional MRI.[8] Diffusion tensor imaging (DTI) enables the measurement of diffusion of water molecules within the brain. In regions with few or no constraints imposed by physical boundaries, such as cerebrospinal fluid in the ventricles, water movement is random and uniform in every direction and is therefore isotropic. In contrast to cerebrospinal fluid, the motion of water molecules in the WM is restricted by the parallel-oriented

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fibers and diffusion is therefore highly anisotropic.[9] Degradation of the WM microstructure organization is accompanied by changes in measurable DTI parameters, such as a decrease in fractional anisotropy (FA).[10] Prior studies have related diffusion metrics to cognitive function in community-dwelling samples[11] and patients with ischemic leukoaraiosis.[12,13] Fractional anisotropy has been associated with cognitive abilities such as executive function,[13] processing speed,[11] verbal fluency,[12] or motor function.[11]

White matter lesions detected by conventional MRI and lower FA values measured by DTI may represent two processes affecting the WM that are commonly seen in aging.[9] There is scarce evidence of the relation between WMLs and FA on a voxel-by-voxel basis in normal aging. Only one study has reported a widespread pattern of reduced FA in the WM of participants with WMLs compared with healthy controls,[13] whereas another study has found an association of WMLs volume and decreased FA in extensive areas of WM.[14] Further, most research relating FA to cognitive function in participants with WMLs has employed a region of interest approach[12] or has applied segmentation methods to calculate mean FA and other histogram metrics within specific brain tissues (i.e., gray matter, WM, WMLs).[11] These approaches may overlook the relative contributions of major WM tracts to cognitive function, which may have some importance given the complex functional anatomy of cognitive processes.[15]

In this study, our objective is twofold. First, we aim to investigate the separate association of high-grade PVHs and DWMHs with FA on a voxel-by-voxel basis in a community-dwelling sample of middle-aged participants. After previous research,[13,14] we expect that participants with high-grade WMLs will show a spatial pattern of lower FA throughout the whole WM compared with participants with low-grade WMLs. Some data suggest that DWMHs are distributed in a more extensive area than PVHs and that their histopathological correlates may exert more severe damage to WM tracts than PVHs.[16] Accordingly, we also expect that this spatial pattern of lower FA will be found in a greater extent in participants with high-grade DWMHs. Second, we aim to assess the predictive value to cognition of lower FA within specific WM tracts related to high-grade PVHs and DWMHs. Cognitive consequences may rely on severity and location of WMLs.[3,17] In a previous study, we found a predominant role of high-grade DWMHs in cognitive dysfunction of middle-aged individuals.[18] Consequently, we hypothesize that lower FA in tracts related to high-grade DWMHs will be more associated with cognitive function than lower FA in tracts related to high-grade PVHs.

MATERIALS AND METHODS

Study Design and Sample Selection

The Barcelona-AsIA (Asymptomatic Intracranial Atherosclerosis) Study is an ongoing population-based study that involves 28 primary healthcare centers and a tertiary stroke center. Complete details for the Barcelona-AsIA protocol have been described elsewhere.[19] In brief, a random sample of participants over 50 years old without previous history of stroke or ischemic heart disease underwent clinical examination, blood analysis, complete extra and transcranial Duplex ultrasound study, and neuropsychological assessment. The Barcelona-AsIA Neuropsychology Study is a related prospective study whose objectives are (1) to investigate the associations between cognition and vascular risk factors, asymptomatic cervicocerebral atherosclerosis, and MRI signs of SVD, and (2) to identify clinical and radiologic features and biologic mechanisms underlying these associations.

Our participants were recruited from the PERART Study, a related ongoing population-based study to determine the prevalence of peripheral arterial disease and to evaluate the predictive value of ankle–arm index in relation to cardiovascular mortality and morbidity.[20] Details of the recruitment process have been previously described.[18] Briefly, a total of 132 participants aged 50 to 65 years were selected to undergo a comprehensive neuropsychological assessment and brain MRI. Exclusion criteria were as follows: history of stroke or transient ischemic attack, coronary heart disease, neurologic disease, or severe psychiatric disorder ($n=11$); a mini-mental examination score $\leqslant 25$ or severe disability ($n=3$); other medical diseases that could affect cognitive assessment and function ($n=4$); contraindications to undergo MRI ($n=10$), unexpected findings seen on brain MRI ($n=2$) or other causes (i.e., less than 75% of neuropsychological assessment available) ($n=2$). Consequently, the final sample included 100 participants aged 50 to 65 stratified by sex and educational level.

This study has been approved by the ethics committees of the University of Barcelona and the Germans Trias i Pujol University Hospital. It was conducted in accordance with the ethical standards of the Declaration of Helsinki. Written informed consent was obtained from all participants.

Evaluation of Vascular Risk Factors

Diagnosis of a particular vascular risk factor, such as arterial hypertension, diabetes mellitus, dyslipidemia, or current smoking status, was based on clinical history or use of medication for the particular condition at the time of the clinical examination. Ten-year cardiovascular risk was calculated after the REGICOR function, which is a validated calibration of the Framingham function for Spanish population.[19] The REGICOR function includes non-modifiable, such as age and sex, and modifiable vascular risk factors, such as arterial hypertension, diabetes mellitus, dyslipidemia, and smoking status.

Neuropsychological Assessment

All participants completed an extensive neuropsychological battery. Cognitive measures were grouped into eight cognitive domains, which include tests assessing similar cognitive functions:[21] executive functioning, working memory, attention, verbal fluency, verbal memory, visual memory, visuospatial skills, and psychomotor speed. Executive functioning (i.e., conceptualization, planning, and inhibition) was assessed with the 64-item computerized version of the Wisconsin Card Sorting Test[22] and the interference score of the Color-Word Stroop Test.[21] Working memory was examined with Digit Span Backwards from the Wechsler Adult Intelligence Scale 3rd edition (WAIS-III)[21] and part B of the Trail Making Test.[21] Attentional abilities were assessed with the Continuous Performance Test[21] and Digit Span Forward, Symbol Search, and Digit Symbol Coding subtests from the WAIS-III. Verbal fluency was measured with letter fluency (letters P, M, and R) and semantic category fluency (animals) in 60 seconds each.[21] Word List and Visual Reproduction from the Wechsler Memory Scale 3rd edition (WMS-III)[21] were administrated to measure verbal and visual memory, respectively. Visual Discrimination and the Copy from the Visual Reproduction subtest (WMS-III) were used to evaluate visuospatial skills. Psychomotor speed was assessed with part A of the Trail Making Test and Grooved Pegboard.[21] Participants' raw scores were normalized to *z*-scores using the mean and standard deviation (s.d.) of the sample. Composite *z*-scores for each participant in each cognitive domain were calculated by averaging the *z*-scores of all tests within that domain.

Neuropsychological assessment also included the Mini-Mental State Examination[21] as a global cognitive function test and the Vocabulary subtest from the WAIS-III as a measure of premorbid intelligence. Depressive symptoms were assessed with the Geriatric Depression Scale 15-item version.[23]

Magnetic Resonance Imaging Acquisition Protocol

The MRI scanning protocol was performed with a Siemens Magnetom Trio 3T scanner (Siemens Diagnostics Healthcare, Erlangen, Germany) at the Medical Image Core Facility (IDIBAPS, Hospital Clinic, Barcelona, Spain).

The MRI protocol included a set of three-dimensional magnetization-prepared rapid gradient echo T1-weighted images (repetition time: 2,300 milliseconds; echo time: 3 milliseconds; flip angle: 15°; field of view: 245 mm; and voxel size: $1 \times 1 \times 1$ mm, no gap), and two sets of DTI images acquired along 30 non-collinear directions (repetition time: 9,300 milliseconds; echo time: 94 milliseconds; flip angle: 15°; field of view: 240 mm; voxel size: $2 \times 2 \times 2$ mm, no gap; and $b=1{,}000$ seconds/mm^2) with an additional acquisition for each set without diffusion weighting ($b=0$ second/mm^2). The two acquisitions of DTI were averaged.

Axial FLAIR images (repetition time: 9,040 milliseconds; echo time: 85 milliseconds; inversion time: 2,500 milliseconds; and voxel size: $1.1 \times 0.9 \times 5$ mm, gap: 1.5 mm) and axial T2-weighted images (repetition time:

5,520 milliseconds; echo time: 92 milliseconds; and voxel size: 0.5 × 0.4 × 5 mm, gap: 1.5 mm) were also collected for rating WMLs and lacunar infarcts (see below).

Magnetic Resonance Imaging Data Processing

Individual processing of DTI data was performed using the FMRIB's Diffusion Toolbox, part of the FMRIB Software Library (FSL) version 4.1.6.[24] First, the raw DTI images were visually inspected and corrected for eddy currents and head motion by registering each participant's images to their reference volume ($b = 0$). Brain extraction was performed to remove non-brain structures using the Brain Extraction Tool implemented in FSL. Then, diffusion tensor was reconstructed by fitting a tensor model to each image voxel of the preprocessed DTI data, using the DTIfit program included in FSL.

The resulting FA maps were fed into Tract-Based Spatial Statistics,[25] which is also a part of FSL, to carry out the voxel-wise statistical analysis. The FA maps for all participants were first aligned into the MNI standard space using the higher-resolution FA template by the nonlinear registration method FNIRT, which uses a B-spline representation of the registration warp field. The nonlinearly registered images were further averaged to generate a mean FA image of all participants. Next, the mean FA image was thinned to create a mean FA skeleton, which represents the centers of all common tracts. The mean FA skeleton was further thresholded by a FA value of 0.25 to exclude the skeleton voxels that may contain partial volume (i.e., gray matter) or cross-subject image misalignment. After the thresholding of the mean FA skeleton, each subject's aligned FA map was then projected onto this skeleton and the resulting skeletonized, fully nonlinearly aligned FA data were then used for voxel-wise statistical analysis.

Brain tissue volumes (gray matter, WM, cerebrospinal fluid) were calculated with SIENAX software (http://www.fmrib.ox.ac.uk/fsl/siena/index.html) on high resolution T1-weighted images.[26] The ratio between brain parenchymal volume (BP = GM + WM) and total brain volume was computed to obtain a normalized measure of brain atrophy.[27]

Rating of White Matter Lesions and Lacunar Infarcts

Location and severity of WMLs were estimated on T2 and FLAIR images by a trained and masked neuroradiologist (NB) using the Fazekas scale.[28] On MRI, WMLs appear hyperintense on T2-weighted images. They also remain bright on FLAIR, a T2-weighted sequence that suppresses the signal from fluid-filled spaces. The Fazekas scale provides two different scores (PVHs and DWMHs), rated on a 0- to 3-point scale of increasing severity within the whole brain. The sum of the PVHs and the DWMHs scores provides a total score. Participants were classified as having no lesions or mild, moderate, or severe lesions (0, 1, 2, or 3 points, respectively) in each location. The intra-rater reliability was determined on 20 randomly selected scans scored twice. Reliability was good for grading both PVHs (weighted kappa = 0.66, 95% CI: 0.33–0.96), and DWMHs (weighted kappa = 0.7, 95% CI: 0.41–0.99).

Lacunar infarcts were defined as lesions with increased signal intensity on T2-weighted images and decreased signal intensity on T1-weighted and FLAIR images with a diameter of 5 to 15 mm, which were not located in areas with high prevalence of widened perivascular spaces.[5]

Statistical Analyses

The distribution of the WMLs scores was positively skewed as expected, with most participants having no lesions or mild lesions. We dichotomized our sample into low-grade WMLs (participants with no lesions or mild lesions) and high-grade WMLs (participants with moderate or severe lesions). High-grade PVHs were thus defined as PVH > 1 and high-grade DWMHs as DWMH > 1. We compared voxel-by-voxel skeletonized FA values between high-grade and low-grade WMLs, with separate analyses for PVHs and DWMHs groups, regressing out age, sex, vascular risk factors (REGICOR function) and the other Fazekas score (PVHs score in the comparison between DWMHs groups, DWMHs score in the comparison between PVHs groups).

For the voxel-wise analysis of group differences, a permutation-based program (randomise) with standard general linear model implemented in FSL was performed with 5,000 random permutations. A developed algorithm, known as Threshold-Free Cluster Enhancement[29] was used to

Table 1. Demographic, clinical and MRI data

	Low-grade PVHs (without or mild) (n = 80)	*High-grade PVHs (moderate) (n = 16)*	P	*Low-grade DWMHs (without or mild) (n = 80)*	*High-grade DWMHs (moderate) (n = 16)*	P
Age (years)[a]	59.48 (3.48)	61.00 (2.48)	0.10	59.48 (3.35)	61.00 (3.25)	0.10
Sex (*n* (%) female)[b]	48 (60.0)	9 (56.3)	0.78	48 (60.0)	9 (56.3)	0.78
Education (years)[c]	8 (6–9)	8 (6.25–10)	0.71	8 (6–10)	8 (6.25–8.75)	0.98
MMSE[c]	29 (28–30)	30 (28.25–30)	0.20	29 (28–30)	30 (28–30)	0.71
Vocabulary (WAIS-III)[a]	38.91 (8.76)	37.56 (10.56)	0.59	39.36 (8.85)	37.50 (9.47)	0.50
GDS-15[c]	2 (1–3)	1 (0–2)	0.08	2 (0–3)	1 (1–2.75)	0.89
REGICOR[c]	5 (4–7)	6.5 (4.25–8.5)	0.26	5 (4–7)	6.5 (4.25–8)	0.32
Vascular risk factors (n (%))						
Hypertension[b]	38 (47.5)	7 (43.8)	0.78	34 (42.5)	11 (68.8)	0.04*
Dyslipidemia[b]	48 (60.0)	9 (56.3)	0.78	47 (58.8)	10 (62.5)	0.78
DM[d]	15 (18.8)	2 (12.5)	0.73	15 (18.8)	2 (12.5)	0.73
Current smoker[d]	12 (15.0)	3 (18.8)	0.71	13 (16.3)	2 (12.5)	1
MRI measures[a]						
GM (cm^3)	590.82 (35.38)	580.80 (45.11)	0.41	586.12 (36.22)	581.74 (45.14)	0.72
WM (cm^3)	564.90 (60.69)	542.24 (63.28)	0.19	543.56 (55.53)	546.50 (64.83)	0.87
BP (cm^3)	1,155.72 (93.52)	1,123.04 (104.70)	0.25	1,129.68 (88.42)	1,128.24 (106.39)	0.96
TBV (cm^3)	1,450.51 (118.78)	1,420.00 (128.76)	0.38	1,424.18 (109.25)	1,425.27 (130.96)	0.98
Ratio GM/TBV (%)	40.97 (1.73)	40.83 (1.35)	0.73	41.22 (1.51)	40.89 (1.39)	0.38
Ratio WM/TBV (%)	38.74 (1.55)	38.25 (1.50)	0.27	38.11 (1.51)	38.27 (1.54)	0.71
Ratio BP/TBV (%)	79.71 (2.03)	79.08 (1.44)	0.25	79.33 (1.80)	79.16 (1.52)	0.67
LI present (n (%))[d]	4 (5.1)	3 (18.8)	0.09	6 (7.5)	1 (6.3)	1

BP, brain parenchymal volume = GM + WM; DM, diabetes mellitus; DWMHs, deep white matter hyperintensities; GDS-15, geriatric depression scale, 15-item version; GM, gray matter volume; LI, lacunar infarcts; MMSE, mini-mental state examination; MRI, magnetic resonance imaging; PVHs, periventricular hyperintensities; REGICOR, Registre Gironí del Cor; TBV, total brain volume; WAIS-III, Wechsler Adult Intelligence Scale 3rd edition; WM, white matter volume. Values are means (s.d.) in Student's *t*-test or medians (interquartile range) in Mann–Whitney test for continuous variables. Values are *n* (%) for categorical variables in χ^2 test and Fisher's exact test. *P* shows statistical comparison between participants with high-grade and low-grade white matter lesions. *$P < 0.05$. [a]Student's *t*-test. [b]χ^2 test. [c]Mann–Whitney test. [d]Fisher's exact test.

obtain the skeleton voxels significantly different between groups at significance level of $P<0.05$, after accounting for multiple comparisons by controlling for Family-Wise Error rates. Significant clusters were also required to have an extent of at least 50 voxels.

From the results of voxel-wise group comparisons, the skeleton areas showing significant lower FA were located and labeled anatomically by mapping the Family-Wise Error-corrected statistical map of $P<0.05$ to the Johns Hopkins University DTI WM atlas.[30] A binarized mask of significant results was made and superimposed onto probabilistic masks of labeled WM tracts showing lower FA for each group comparison. The mean FA value within areas showing significant differences of FA between groups was then extracted in each WM tract for the linear regression analyses.

Linear regression analyses were carried out using the Statistical Package for Social Sciences (SPSS for Windows, version 18.0, SPSS, Chicago, IL, USA). A standardized *z*-score of the extracted mean FA value for each tract was calculated and entered into a series of linear regression analyses to assess its specific contribution to cognitive function, with separate analyses for WM tracts showing differences in PVHs and DWMHs groups. The *z*-scores for all WM tracts were first entered as predictive variables with cognitive domains as the dependent variables. Linear regression models were first adjusted (Model 1) for age, sex, years of education, and treatable vascular risk factors associated with WMLs or cognitive function ($P\leqslant 0.1$) that we have reported previously.[18] Briefly, hypertensive participants had lower scores on verbal fluency, visuospatial skills, and psychomotor speed. Participants with dyslipidemia had lower scores on working memory. Participants with diabetes mellitus had lower scores on executive functioning and psychomotor speed. Higher scores on verbal memory and visuospatial skills were observed in current non-smoker participants. Models were also adjusted (Model 2) for other brain changes usually related to cognitive disturbances (brain atrophy and lacunar infarcts).

Table 2. Areas of lower FA in participants with high-grade DWMHs

		MNI coordinates					
Location	*Lobe*	*x*	*y*	*z*	*t*	P	*Vox*
Right ATR	Sub-lobar	25	−37	26	4.16	0.014	4,868
Right SLF	Frontal	42	6	18	3.18	0.048	459
Right IFOF	Frontal	35	36	−1	3.21	0.048	299
Left IFOF	Frontal	−17	36	30	3.06	0.041	2,502

ATR, anterior thalamic radiation; DWMHs, deep white matter hyperintensities; FA, fractional anisotropy; IFOF, inferior fronto-occipital fasciculus; MNI, Montreal Neurological Institute; SLF, superior longitudinal fasciculus; Vox, cluster size in number of voxels. MNI coordinates (mm) represent peak-value voxel location.

RESULTS

Sample Characteristics

Owing to technical difficulties on MRI acquisition, four participants were excluded from the sample. There were no differences in demographic and clinical variables between the remaining 96 participants and those recruited from the PERART Study but excluded from the analyses. Demographic, clinical, and MRI characteristics of the remaining 96 participants (mean age = 59.7 years, 59% women, median education = 8 years) are summarized in Table 1. Their estimated premorbid intelligence, general cognitive function and depressive symptoms were within the normal range. A significantly higher proportion of participants with high-grade DWMHs (68.8%) had arterial hypertension compared with participants with low-grade DWMHs (42.5%).

According to the PVHs score, there were 80 participants (83.3%) with low-grade PVHs and 16 participants (16.7%) with high-grade PVHs. Among the participants with low-grade PVHs, 51 participants (53.1% from the total sample) were without lesions and the remaining 29 participants (30.2%) showed mild (caps and pencil-thin lining) PVHs. All the 16 participants with high-grade PVHs had moderate (smooth halo) PVHs. According to the DWMHs score, 80 participants (83.3%) were classified as low-grade DWMHs and 16 participants (16.7%) were classified as high-grade DWMHs. Among the participants with low-grade DWMHs, 19 participants (19.8% from the total sample) were without DWMHs and 61 participants (63.5%) had mild (punctuate) DWMHs. All the 16 participants with high-grade DWMHs presented moderate (beginning to confluent) DWMHs. Seven participants (7.3%) had both high-grade DWMHs and high-grade PVHs (moderate lesions). None of the participants had severe (irregular) PVHs or severe (confluent) DWMHs. Eleven lacunar brain infarcts were present across seven participants (7.3%). Eight of the lacunar infarcts were located in the basal ganglia, and there was one lacunar infarct each in the pons, intern capsule, and corona radiata.

Areas of Lower Fractional Anisotropy in Participants with High-Grade White Matter Lesions

Participants with high-grade DWMHs showed a pattern of lower FA in several areas throughout the whole WM skeleton compared with participants with low-grade DWMHs, after regressing out

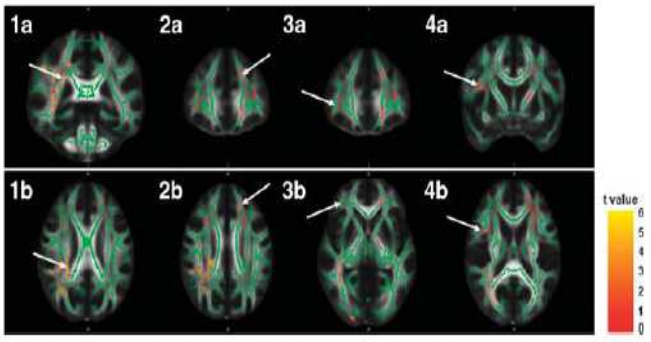

Figure 1. Regional areas of reduction of fractional anisotropy (FA). Clusters showing significant reduction of FA in participants with high-grade deep white matter hyperintensities are displayed on coronal and axial sections of an FA map. The FA skeleton used for statistical analyses is superposed in green. White arrows at images 1a ($y=-37$) and 1b ($z=26$) show peak-value voxel location of reduced FA in the right anterior thalamic radiation. White arrows at images 2a ($y=36$) and 2b ($z=30$) show peak-value voxel of reduced FA in the left inferior fronto-occipital fasciculus (IFOF). White arrows at images 3a ($y=36$) and 3b ($z=-1$) show peak-value voxel of reduced FA in the right IFOF. White arrows at images 4a ($y=6$) and 4b ($z=18$) show peak-value voxel of reduced FA in the right superior longitudinal fasciculus. The color scale indicates the magnitude of *t*-values with lowest appearing in dark red and the highest in bright yellow. Images are displayed in radiologic convention (right side represents left side and left side represents right side of the brain).

age, sex, vascular risk factors and the PVHs score (Table 2 and Figure 1). Specifically, peak-value voxels of decreased FA were located in the right anterior thalamic radiation, the right superior longitudinal fasciculus, and the bilateral inferior fronto-occipital fasciculus (IFOF). No significant results were found for the reverse contrast.

Participants with high-grade PVHs also showed lower FA values in several areas throughout the whole WM skeleton compared with participants with low-grade PVHs, after regressing out age, sex, vascular risk factors, and the DWMHs score (Table 3 and Figure 2). Peak-value voxels of decreased FA were located in the left anterior thalamic radiation, the left superior longitudinal fasciculus and the bilateral IFOF. No significant results were found for the reverse contrast.

Predictive Value to Cognitive Outcome of Areas of Lower Fractional Anisotropy in Specific White Matter Tracts

Table 4 shows the predictive value to cognition of areas showing decreased FA between participants with high-grade DWMHs versus participants with low-grade DWMHs. Areas of lower FA in the left IFOF were related to lower scores in executive functioning ($R^2 = 0.13$; $\beta = 0.48$) and verbal fluency ($R^2 = 0.13$; $\beta = 0.48$). Areas of lower FA in the right anterior thalamic radiation were related to lower scores in attention ($R^2 = 0.10$; $\beta = 0.36$) and visuospatial skills ($R^2 = 0.09$; $\beta = 0.35$). Areas of lower FA in the right IFOF were also related to visuospatial skills ($R^2 = 0.09$; $\beta = 0.35$). Adjustments for age, sex, years of education, and vascular risk factors (Model 1) reduced the associations with executive functioning, attention, and verbal fluency, but they were still significant and increased associations with visuospatial skills. These associations were essentially unaltered by additional adjustment for brain atrophy ratio and lacunar infarcts (Model 2).

Areas showing decreased FA between participants with high-grade PVHs versus participants with low-grade PVHs were not related to lower cognitive scores (data not shown).

Figure 3 shows the significant associations between mean FA values extracted within areas showing significant differences of FA in participants with high-grade DWMHs and cognitive domains.

Table 3. Areas of lower FA in participants with high-grade PVHs

		MNI coordinates					
Location	*Lobe*	*x*	*y*	*z*	*t*	P	*Vox*
Right IFOF	Frontal	33	37	0	4.22	0.042	239
Left ATR	Sub-lobar	−20	11	11	3.46	0.035	3,199
Left IFOF	Occipital	−24	−79	1	2.84	0.048	571
Left SLF	Temporal	−35	−55	28	3.43	0.048	300

ATR, anterior thalamic radiation; FA, fractional anisotropy; PVHs, periventricular hyperintensities; MNI, Montreal Neurological Institute; IFOF, inferior fronto-occipital fasciculus; PVHs, periventricular hyperintensities; SLF, superior longitudinal fasciculus; Vox, cluster size in number of voxels. MNI coordinates (mm) represent peak-value voxel location.

DISCUSSION

Our study first aimed at investigating the different pattern of lower FA in participants with high-grade PVHs and DWMHs compared with participants with low-grade PVHs and DWMHs on a voxel-by-voxel basis in a community-dwelling sample. We found that participants with high-grade PVHs and participants with high-grade DWMHs showed lower FA in different areas of specific WM tracts. Our second aim was to assess the predictive value to cognitive function of those areas with decreased FA within specific tracts. Interestingly, only areas showing decreased FA in participants with high-grade DWMHs were related to cognitive performance, whereas areas with decreased FA in high-grade PVHs were not. Specifically, lower FA areas in high-grade DWMHs predicted cognitive outcome in executive functioning, attention, verbal fluency, and visuospatial skills. This is the first study showing a specific association of high-grade DWMHs, lower FA areas within specific tracts, and cognitive function.

Participants with high-grade WMLs showed a pattern of reduced FA throughout the WM skeleton. This extensive reduction of FA supports the increased sensitivity of DTI to detect WM damage.[8] However, previous research on a voxel-by-voxel basis has reported a more widespread pattern of reduced FA in participants with WMLs than we found.[13,14] Different findings may be due to methodological issues such as sample selection or covariates introduced in the voxel-wise analysis. High-grade DWMHs were associated with areas of decreased FA in the right anterior thalamic radiation, the right superior longitudinal fasciculus and the bilateral frontal IFOF. High-grade PVHs were associated with areas of lower FA in the left anterior thalamic radiation, the left superior longitudinal fasciculus, and the left

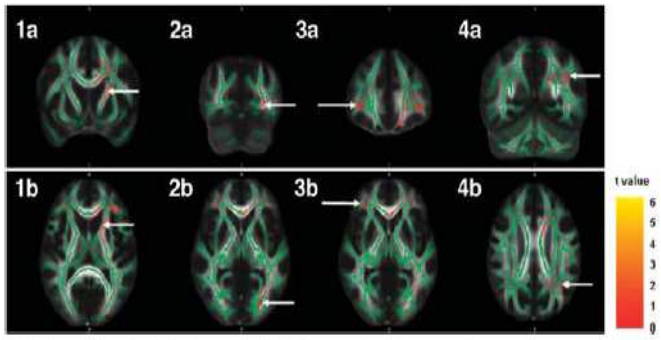

Figure 2. Regional areas of reduction of fractional anisotropy (FA). Clusters showing significant reduction of FA in participants with high-grade periventricular hyperintensities are displayed on coronal and axial sections of an FA map. The FA skeleton used for statistical analyses is superposed in green. White arrows at images 1a ($y = 11$) and 1b ($z = 11$) show peak-value voxel location of reduced FA in the left anterior thalamic radiation. White arrows at images 2a ($y = -79$) and 2b ($z = 1$) show peak-value voxel of reduced FA in the left inferior fronto-occipital fasciculus (IFOF) within the occipital area. Images 3a ($y = 37$) and 3b ($z = 0$) show peak-value voxel of reduced FA in the right IFOF. Images 4a ($y = -55$) and 4b ($z = 28$) show peak-value voxel of reduced FA in the left superior longitudinal fasciculus. The color scale indicates the magnitude of *t*-values with lowest appearing in dark red and the highest in bright yellow. Images are displayed in radiologic convention (right side represents left side and left side represents right side of the brain).

Table 4. Predictive value of areas showing FA differences between participants with high-grade DWMHs versus participants with low-grade DWMHs using multivariate linear regression models

	Unadjusted model		*Model 1*		*Model 2*	
	Beta	*P-value*	*Beta*	*P-value*	*Beta*	*P-value*
EF						
r ATR	0.26	0.22	0.25	0.27	0.26	0.25
r SLF	0.28	0.16	0.27	0.20	0.30	0.16
r IFOF	−0.44	0.09	−0.43	0.11	−0.43	0.11
l IFOF	0.48	0.004**	0.40	0.006**	0.38	0.01*
W Memory						
r ATR	0.06	0.85	0.07	0.82	0.05	0.87
r SLF	−0.01	0.96	0.11	0.69	0.18	0.51
r IFOF	−0.23	0.49	−0.21	0.54	−0.23	0.50
l IFOF	0.17	0.27	0.05	0.77	0.03	0.86
Attention						
r ATR	0.36	0.01*	0.32	0.02*	0.30	0.03*
r SLF	−0.15	0.50	0.04	0.85	0.07	0.75
r IFOF	−0.19	0.51	−0.25	0.36	−0.27	0.32
l IFOF	0.22	0.10	0.08	0.55	0.09	0.49
Verbal fluency						
r ATR	0.21	0.41	0.26	0.31	0.24	0.34
r SLF	−0.32	0.08	−0.32	0.08	−0.29	0.11
r IFOF	−0.07	0.82	−0.13	0.66	−0.16	0.61
l IFOF	0.48	0.001**	0.41	0.005**	0.43	0.004**
Verbal memory						
r ATR	−0.17	0.56	−0.19	0.52	−0.19	0.52
r SLF	0.28	0.28	0.23	0.39	0.21	0.45
r IFOF	−0.13	0.70	−0.06	0.86	−0.05	0.88
l IFOF	0.01	0.98	0.01	0.94	0.03	0.87
Visual memory						
r ATR	0.10	0.72	0.07	0.79	0.06	0.83
r SLF	0.06	0.80	0.09	0.73	0.12	0.65
r IFOF	−0.34	0.29	−0.30	0.36	−0.33	0.32
l IFOF	0.23	0.12	0.20	0.19	0.22	0.16
VS						
r ATR	0.35	0.01*	0.38	0.008**	0.37	0.008**
r SLF	0.18	0.42	0.25	0.28	0.26	0.26
r IFOF	0.36	0.01*	0.38	0.008**	0.36	0.009**
l IFOF	0.00	1.00	−0.05	0.69	−0.04	0.78
PS						
r ATR	0.04	0.87	0.16	0.49	0.16	0.52
r SLF	0.21	0.35	0.24	0.28	0.25	0.28
r IFOF	−0.21	0.47	−0.30	0.30	−0.30	0.29
l IFOF	−0.03	0.82	−0.08	0.53	−0.08	0.58

ATR, anterior thalamic radiation; DWMHs, deep white matter hyperintensities; EF, executive functioning; high-grade, moderate lesions; IFOF, inferior fronto-occipital fasciculus; l, left; low-grade, without or mild lesions; PS, psychomotor speed; r, right; SLF, superior longitudinal fasciculus; VS, visuospatial skills. Beta values from linear regression models relating areas of decreased FA values in each white matter tract (participants with high-grade versus low-grade DWMHs) to cognitive function. Model 1, adjusted for age, sex, years of education, and treatable cardiovascular risk factors related to cognitive performance ($P \leqslant 0.1$); Model 2, Model 1 plus adjustment for gray matter ratio (%) and presence of lacunar infarcts. *$P < 0.05$; **$P < 0.01$.

occipital and right frontal IFOF. These findings confirm our hypothesis that the spatial pattern of lower FA would be found in a greater extent in participants with high-grade DWMHs (~8,000 voxels) than in participants with high-grade PVHs (~4,000 voxels).

It has been proposed that WMLs and reduced FA have similar underlying etiologies. Pathologic correlates common to both processes include vascular-related changes, such as myelin reduction and axonal loss, or non-ischemic age-related changes, such as widening of perivascular spaces and gliosis.[3] Vascular-related changes are usually associated with high-grade DWMHs, whereas non-ischemic age-related changes are usually related to PVHs.[3,16] Specifically, the diagnosis of arterial hypertension was related to high-grade DWMHs in our sample. Only severe PVHs extending to deep WM are clearly vascular-related changes, but none of our participants with high-grade PVHs were rated with severe lesions. Likewise, it has been suggested that reduced FA may precede the development of WMLs seen on conventional MRI. A decreasing FA may indicate an early stage of WM pathology in the microstructural level and WMLs may represent the extreme end of WM damage in the macrostructural level.[7] However, WMLs

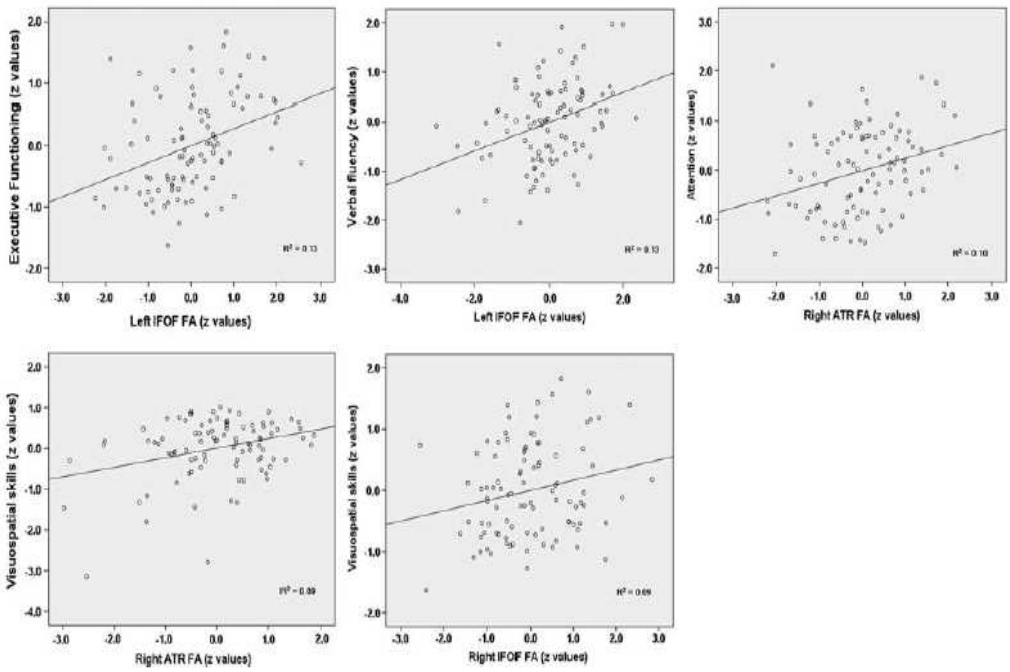

Figure 3. Predictive value to cognitive outcome of areas of lower fractional anisotropy (FA) in specific white matter tracts. The selected scatter plots illustrate positive associations between areas showing decreased FA in participants with high-grade deep white matter hyperintensities and different cognitive domains. The mean FA value within the areas showing significant differences of FA was extracted in each white matter tract, standardized, and entered into a series of linear regression analyses. The *z*-values for all WM tracts were first entered as predictive variables with cognitive domains as the dependent variables. Cognitive domains are also represented by *z*-values. R^2 = effect size in unadjusted linear regression models.

may also influence reduction of FA in normal-appearing WM via processes such as diaschisis or Wallerian degeneration.[14] The exact temporal relation between WMLs and FA changes should be explored further.

We found that only areas showing lower FA within specific WM tracts in participants with high-grade DWMHs were related to cognitive performance. This preeminent association of high-grade DWMHs with areas of decreased FA and cognition reinforces a predominant role for these lesions in cognitive function. Executive functioning, attention, verbal fluency, and visuospatial skills were associated with areas of lower FA in specific tracts. These cognitive domains have been usually related to cortico-subcortical dysfunction and WMLs.[3,17]

Areas of decreased FA in the bilateral frontal inferior fronto-occipital fasciculus were positively related to executive functioning, verbal fluency, and visuospatial skills. A decrease of 1 s.d. in FA was related to a 0.48 s.d. decrease in executive functioning and verbal fluency, and a 0.36 s.d. decrease in visuospatial skills. The IFOF is a long association bundle of fibers, which interconnects the frontal lobe with the posterior part of the parietal and temporal lobe, and with the occipital lobe.[31] It is suggested that this tract may have a role in processing visuospatial information,[32] which is coherent with the association between lower FA and diminished visuospatial skills that we found. Decreased FA in frontal regions of the IFOF has also been associated with diminished executive function, such as a worse task-switching and inhibition performance.[33] Lower FA in left frontal WM regions has also been related to poorer outcome in verbal fluency in participants with WMLs.[13]

Areas of lower FA in the right anterior thalamic radiation were also positively associated with attention and visuospatial skills. A decrease of 1 s.d. in FA was related to a 0.36 s.d. decrease in attention and a 0.35 s.d. decrease in visuospatial skills. The anterior thalamic radiation is a WM projection bundle that connects the anterior and medial dorsal nuclei with the frontal lobe and the anterior cingulate cortex via the anterior limb of the internal capsule.[31] It is a critical component of the cortico-subcortical circuits, thereby serving as an important integrative center for networks underlying the ability to modulate behaviors.[34] Some studies have shown that the anterior thalamic radiation may have a role in attention-related disorders such as spatial neglect[35] or attention deficit hyperactivity disorder.[36] Likewise, a better performance in a visual detection task has been associated with higher FA in the anterior limb of the internal capsule in elderly adults.[37]

Our findings may provide additional support for the notion that cognitive dysfunction related to WMLs could be a disconnection syndrome,[38] as areas of lower FA within specific tracts were related to cognitive performance in our sample. However, the interpretation of reduced FA as a marker of WM damage should be considered with caution. Fractional anisotropy can be related to several tissue characteristics, such as degree of myelination, axon density, axon diameter, or axonal membrane integrity, but it is also quite sensitive to the organization and alignment of fibers within a voxel and partial volume effects.[9,10]

The application of a voxel-based approach in this study circumvents the potential limitations of region of interest methodology for DTI analysis, such as subjective operator-dependent placement, limited reliability and reproducibility, and partial volume effects.[9,39] It also overcomes the lack of information on a regional level of segmentation methods.[11] In particular, the Tract-Based Spatial Statistics procedure that we applied has been developed to retain the strengths of voxel-based analysis while addressing registration and smoothing issues that are potential pitfalls of data preprocessing for such approach.[25] Other main strengths of this study are our extensive neuropsychological

assessment and the use of 3T MRI to detect WMLs. Higher magnetic fields can provide improved sensitivity and diagnostic capacity.[16] Also, the predictive value of FA to cognitive function was investigated with extensive adjustment for possible confounders, such as education, vascular risk factors (including arterial hypertension, diabetes mellitus, dyslipidemia, and current smoking status), brain atrophy, and lacunar infarcts.

One potential weakness of the present study is the use of a visual rating scale[28] to rate location and severity of WMLs. Quantitative methods (i.e., volumetric analyses) have been regarded as more reliable and robust. However, visual scales are considered more appropriate for defining WMLs groups.[40] Visual scales usually offer separate assessment of PVHs and DWMHs, which semi- and fully-automated quantitative methods often overlook. Other possible limitations need to be considered. The most severe grades of WMLs are under-represented in our community-dwelling sample. The cross-sectional design also precludes us from making causal inferences regarding high-grade WMLs, areas of lower FA, and cognitive function.

White matter lesions are considered a radiologic expression of SVD. The term SVD encompasses all the pathologic processes that affect the small vessels of the brain. Biologic aging of the brain is partly attributable to aging of the cerebrovascular circulation and the effects of these changes on the brain.[41] Small vessel disease is thought to be possibly the most frequent cause of vascular cognitive impairment.[2] There is also increasing evidence that cerebrovascular dysfunction has a role in neurodegenerative diseases such as Alzheimer's disease.[42] As well as cognitive disorders, other clinical characteristics of SVD also include slower gait, impaired balance, depressed mood, urinary disturbances, and overall functional disability.[2,3] Neuroimaging has a central role in the definition of SVD. Its neuroimaging correlates (i.e., WMLs) have been the object of abundant research and new MRI techniques such as DTI are expected to contribute in the understanding of the pathophysiology of WMLs and their clinical correlates. In this line, two important findings emerge from our study. First, the identification of areas of decreased FA in specific WM tracts. Second, and most novel, we found that only areas of decreased FA in high-grade DWMHs are related to cognitive function. Taken together, these novel results could contribute to understand the different mechanisms and clinical consequences of DWMHs and PVHs. Our results also suggest that the concomitant use of conventional MRI and novel techniques such as DTI may be useful to predict cognitive function in SVD. Alternative approaches (i.e., fiber tracking or functional connectivity) could provide additional information about composition, organization, and functional status of WM networks.

In conclusion, only areas of lower FA within specific WM tracts, associated to high-grade DWMHs, are related to lower cognitive performance in a middle-aged community-dwelling sample. The combination of DTI and voxel-based analysis allows to allocate patterns of reduced FA to WM tracts in participants with high-grade WMLs. Diffusion tensor imaging could therefore serve as a additional tool to conventional MRI to investigate extension of WM damage. The predictive value to cognition of specific WM tracts supports the involvement of cortico-subcortical circuits in cognitive deficits associated with WMLs. Our data also corroborates the hypothesis that PVHs and DWMHs are differentially associated with cognitive function and suggests that the ongoing distinction between both types of WMLs is worthy. Further research is needed to more clearly elucidate whether both types arise from dissociable forms of pathogenesis, as the lack of radiologic–pathologic association studies is a key limitation to our understanding of the neuroimaging findings. The advantages of multimodal imaging should be used to advance understanding of pathophysiology. Further research is also needed to determine if lower FA areas associated with DWMHs might have diagnostic value to assess cognitive dysfunction in community and clinical samples.

DISCLOSURE/CONFLICT OF INTEREST

The authors declare no conflict of interest.

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SUMMARY OF RESULTS AND DISCUSSION

This thesis comprises three studies addressing the association between WMHs, MRI structural correlates, and cognitive function in a community-dwelling sample of stroke- and dementia-free middle aged individuals. Results from these studies contribute to determine the cognitive profile related to WMHs in this group of age, and provide additional evidence regarding the specific associations of PVHs and DWMHs with GM and DTI measures, and their predictive value to cognitive performance. The first study was focused on the separate role of each type of WMHs to cognitive function. In the second and third studies, a voxel-based approach was used to locate respectively specific areas of reduced GM volume and WM tracts with lower FA that were associated with PVHs and DWMHs. Further, the relation of such areas or tracts with cognition was analysed.

Although some investigators were sceptical about their potential role, most previous research has consistently reported a relation of WMHs with cognitive function (Frisoni et al., 2007; Kloppenborg et al., 2014b; Pantoni et al., 2007; Schmidt et al 2011b). However, this association has not been regularly investigated in healthy middle-aged individuals, even though WMHs are seen in people in their forties (Sachdev et al., 2008). In Study I, we aimed to determine the specific contribution of PVHs and DWMHs to cognitive function in a community sample of asymptomatic participants aged 50 to 65 years. Our sample was dichotomised into low grade WMHs (participants without or with mild WMHs) and high grade WMHs (participants with moderate or severe WMHs). Analyses were performed separately in PVHs and DWMHs groups. Previous data suggest that DWMHs are distributed in a more extensive area than PVHs (Inzitari, 2000) and that their histopathological correlates may exert more severe damage to WM than PVHs (Wen et al., 2006). Therefore, our hypothesis was that high grade DWMHs would be more related to cognitive function than high grade PVHs.

Results from Study I showed that high grade DWMHs were associated with lower scores in executive functioning, attention, verbal fluency, visual memory, visuospatial skills, and psychomotor speed, whereas high grade PVHs were not associated with lower scores in any cognitive domain. Cognitive outcome in executive functioning and processing speed was related to WMHs as expected (de Carli et al., 1995; de Groot et al., 2000; Rabbitt et al., 2007; Soderlund et al., 2006; Vannorsdall et al., 2009). Verbal fluency is a frontally-mediated function that can

provide information relevant to executive control and processing speed (Hachinski et al., 2006; Strauss et al., 2006; Stuss and Levine, 2002). WMHs were not related to working memory dysfunction, which may be due to the high rate of missing data (almost 20%) for part B of the Trail Making Test, probably because of the low educational level of the sample (mean = 8 years). Associations were also found with worse visual memory and visuospatial skills, which is consistent with previous research (Leaper et al., 2001; Schmidt et al., 2005). Further analyses revealed that high grade DWMHs were also associated with a three- to fourfold increased risk of impaired scores (i.e., < 1.5 standard deviations) in executive functioning, verbal fluency, visuospatial skills, and psychomotor speed. These results support the clinical relevance of WMHs on cognitive functioning.

The specific contribution of DWMHs versus PVHs to cognitive function in this community sample confirms our hypothesis that DWMHs have a predominant role in this age group. Although most studies seem to converge on the notion that anatomical location have a specific role on cognitive functioning, previous literature has provided controversial findings on the specific role of each type of WMHs, suggesting overall a slightly stronger relation between PVHs and cognition (Bolandzadeh et al., 2012; Kloppenborg et al., 2014b). The reason for this discrepancy might be the severity of WM damage underlying PVHs and DWMHs. Kim et al. (2008) have proposed that WMHs should be divided into ischemic and non-ischemic and this new classification would include PVHs and DWMHs as well. In our sample, all the 16 participants with high grade PVHs had moderate ("smooth halo") PVHs, which reflect primarily non-ischemic changes (Kim et al., 2008; Schmidt et al., 2011a). Severe PVHs, which are related to ischemic damage in long associating tracts, were absent. On the other hand, all the 16 participants with high grade DWMHs consisted of moderate ("early confluent") DWMHs, which would be considered ischemic WMHs (Gouw et al., 2011; Schmidt et al., 2011a). The moderate correlation between PVHs and DWMHs scores described in Study I also suggests that each type of WMHs may have dissimilar pathogenic mechanisms in our sample.

In Study I, we also determined the prevalence and severity of SVD-related pathology in a community-dwelling sample aged 50 to 65 years. To our knowledge, studies using 3.0 T MRI in middle age are scarce. PVHs were present in 45 participants (46.7% from the total sample) and DWMHs were seen in 77 participants (80.2%). Seven participants (7.3%) had both high grade PVHs and high grade DWMHs, but none of the participants showed severe ("irregular") PVHs or severe ("confluent") DWMHs. Eleven LI were present across 7 participants (7.3%). Higher

magnetic fields should detect SVD-related pathology more easily (Kim et al., 2008; Scarabino et al., 2003). Nevertheless, the prevalence of WMHs in our sample was lower when compared with other studies with participants of similar age (Wen and Sachdev, 2004). Likewise, the prevalence of LI in our sample was slightly lower than seen elsewhere (Chen et al., 2009). Lifestyle (i.e., dietary patterns) or genetic factors may account for this lower prevalence (Alzamora et al., 2008; Tunstall-Pedoe et al., 1999).

Overall, Study I supports the notion that PVHs and DWMHs are specifically related to cognitive function in middle-aged healthy individuals. The predominant role of DWMHs may be attributed to underlying ischemic processes. Remarkably, most of cognitive dysfunctions were clinically relevant in that they conferred a substantial increase in risk of cognitive impairment.

WMHs and brain atrophy are concurrent findings in normal aging with potential impact on cognitive functioning. Most previous VBM studies regarding the relation of WMHs with GM volume have focused on a single measure of WMHs and only one study has distinguished between PVHs and DWMHs (Wen et al., 2006). Further, most research relating GM volume to cognitive function in participants with WMHs has either employed a ROI approach to calculate regional GM (i.e., frontal GM or hippocampus) or has applied segmentation methods to calculate a single whole brain GM volume. These approaches may overlook that regional GM atrophy related to WMHs can develop in distinct areas and the specific contribution of each area to cognition.

In Study II, we investigated the separate association of high grade PVHs and DWMHs with GM volume on a voxel-by-voxel basis. Previous VBM data have suggested that DWMHs are more related to regional lower GM volume than PVHs (Wen et al., 2006). Accordingly, we hypothesized that the spatial pattern of GM volume reduction would be found in a greater extent in participants with high grade DWMHs. In addition, we aimed to assess the predictive value to cognition of reduced GM volume within specific cortical areas related to high grade WMHs. Following data from Study I, we hypothesized that areas of reduced GM volume related to high grade DWMHs would be more associated with cognitive function than areas of reduced GM volume related to high grade PVHs.

Results from Study II showed that participants with high grade DWMHs showed reduced GM volume in different areas, whereas participants with high grade PVHs did not. The regional

pattern of reduced GM volume related to high grade WMHs included several areas, namely the superior and middle frontal gyrus, the inferior temporal gyrus, the angular gyrus, the lingual gyrus, and the insula lobe. These areas are in line with previous VBM research (Crane et al., 2015; Quinque et al., 2012; Raji et al., 2012; Rossi et al., 2006; Wen et al., 2006). Likewise, the singular association of high grade DWMHs with regional areas of GM atrophy supports previous data reporting that DWMHs have a more significant relationship with regional structural changes than PVHs (Wen et al., 2006). One of the underlying factors of the association between WMHs and brain atrophy is the variable degree of tissue destruction under WMHs (Jouvent et al., 2010). In this line, these findings suggest that tissue destruction is higher in DWMHs in our sample. This fact would be complementary to the underlying ischemic processes that may be on the basis of findings from Study I.

Several mechanisms may underlie the association between WMHs and regional GM atrophy. WMHs can disrupt anatomic pathways, leading to functional or structural alterations within the cortex (Schmidt et al., 2005; Wen et al., 2006). On the other hand, ischemia and infarction in the GM, resulting in neuronal loss and GM atrophy, can lead to WMHs through Wallerian degeneration processes (Godin et al., 2009b; Wen et al., 2006). Some lines of evidence suggest that WM damage may precede GM atrophy (Schmidt et al., 2005; Sun et al., 2014; Zhuang et al., 2012). For instance, Sun et al. (2014) exposed recently that individuals with mild WMH can exhibit microstructural and functional abnormalities without GM atrophy. However, our cross-sectional design precludes us to determine causality in our sample. Moreover, it may be that mechanisms underlying the association between WMHs and regional GM atrophy can also occur simultaneously in different degrees within different areas (Tuladhar et al., 2015).

The pattern of regional GM atrophy seen in Study II and its cognitive correlates according to the literature is congruent with the associations between WMHs and cognitive functioning reported in Study I. However, we only found a specific association of one area of reduced GM volume with cognitive outcome in Study II. Specifically, reduction of GM volume in the lingual gyrus predicted cognitive outcome in visuospatial skills. The lingual gyrus is known to be a crucial structure in visual processing (Kravitz et al., 2011). The positive relationship of GM volume in the lingual gyrus with visuospatial skills is congruent with previous research (Chechlacz et al., 2014; Ferber et al., 2007; Macaluso et al., 2000; Russell et al., 2010). In contrast with our data, a recent work has reported that reduction of cortical thickness in extensive fronto-temporal regions related to WMHs burden was associated with executive function, attention, verbal fluency, and

psychomotor speed (Tuladhar et al., 2015). Nonetheless, it should be bear in mind that VBM analysis and cortical thickness are different approaches to investigate GM atrophy (Ashburner and Friston, 2001; Hutton et al., 2009). Other methodological issues such as sample selection and size or linear regression analyses may also account for these different findings.

In summary, the main and novel finding from Study II is that one area of reduced GM volume in the lingual gyrus, associated to high grade DWMHs, has predictive value to cognitive function in a middle-aged community sample. The use of VBM allows the location of areas of regional GM atrophy in individuals with high grade DWMHs. To our knowledge, this is the first study showing a specific association of high grade DWMHs, reduced GM volume in specific cortical areas, and cognitive function.

Novel imaging techniques such as DTI are promising tools to explain cognitive dysfunction related to WMHs beyond what can be expected from conventional MRI (O'Sullivan, 2010; Seiler et al., 2012). For this reason, DTI is applied in Study III to provide novel insights into the relation of WM damage with cognition in middle-aged individuals. ROI or segmentation methods may overlook the relative contributions of major WM tracts to cognitive function, which may have some importance given the complex functional anatomy of cognitive processes (Schmahmann et al., 2008).

In Study III, we investigated the separate association of high grade PVHs and DWMHs with FA. Voxel-by-voxel FA values were compared between groups, with separate analyses for high grade PVHs and DWMHs. Following previous research (Leritz et al., 2014; Quinque et al., 2012; Sun et al., 2014), we hypothesized that participants with high grade WMHs would show a spatial pattern of lower FA throughout the whole WM compared with participants with low grade WMHs. This pattern would be found in a greater extent in participants with high grade DWMHs. We also assessed the predictive value to cognition of FA within specific WM tracts associated with high grade WMHs. Since we previously found a predominant role of high grade DWMHs in cognitive dysfunction, we hypothesized that lower FA in tracts related to high grade DWMHs would be more associated with cognitive function than lower FA in tracts related to high grade PVHs.

Our results demonstrated that participants with high grade PVHs and participants with high grade DWMHs showed lower FA in different areas of specific WM tracts. High grade

DWMHs were associated with areas of decreased FA in the right ATR, the right SLF and the bilateral frontal IFOF. High grade PVHs were associated with areas of lower FA in the left ATR, the left SLF and the left occipital and right frontal IFOF. These findings confirm our hypothesis that the spatial pattern of lower FA would be found in a greater extent in participants with high grade DWMHs (about 8,000 voxels) than in participants with high grade PVHs (about 4,000 voxels). This extensive reduction of FA also supports the increased sensitivity of DTI to detect WM damage (O'Sullivan, 2010; Schmidt et al., forthcoming). Previous research indicates that age-related SVD is a diffuse process affecting the entire brain and that WMHs are probably only the tip of the iceberg (Prins and Scheltens, 2015). Lower FA values may indicate an early pathological stage of WM pathology and WMHs may represent the extreme end of WM damage (Maillard et al., 2013), although WMHs may also contribute to decreased FA through diaschisis or Wallerian degeneration (Leritz et al., 2014).

Areas showing decreased FA in high grade DWMHs predicted lower cognitive function, whereas areas with decreased FA in high grade PVHs did not. Lower FA values in the bilateral frontal IFOF were positively related to executive functioning, verbal fluency and visuospatial skills. Areas of lower FA in the right ATR were also positively associated with attention and visuospatial skills. The IFOF interconnects the frontal lobe with the posterior part of the parietal and temporal lobe, and with the occipital lobe (Wakana et al., 2004), whereas the ATR is a crucial component of the cortico-subcortical loops (Haber and Calzavara, 2009). Therefore, results from Study III provide additional evidence for the notion that cognitive dysfunction related to WMHs could be a disconnection syndrome (Geschwind, 1965, 2010; O'Sullivan et al., 2001b). In a recent work set in the same community sample, thalamic areas of lower FA were related to verbal fluency, psychomotor speed and visuospatial skills, suggesting the involvement of cortico-subcortical circuits through the thalamus in cognitive function (Fernández-Andújar et al., 2014). However, the interpretation of lower FA as a marker of WM damage should be considered with caution (Alexander et al., 2007; Chanraud et al., 2010; Mori and Zhang, 2006; Smith et al., 2006).

In conclusion, only areas of lower FA within specific WM tracts, associated to high grade DWMHs, are related to lower cognitive performance in a middle-aged community-dwelling sample. The combination of DTI and voxel-based analysis allows identifying patterns of reduced FA within WM tracts in participants with high grade WMHs. The predictive value to cognition of specific WM tracts supports the involvement of cerebral circuits in cognitive deficits only in

DWMHs. This is also the first study showing a specific association of high grade DWMHs, lower FA areas within specific WM tracts and cognitive function.

Overall results from all three studies suggest a predominant role of DWMHs in cognitive function of community-dwelling middle-aged individuals. In Study I, a characteristic cognitive profile was only related to high grade DWMHs. In Study II and Study III, only high grade DWMHs were associated with MRI structural correlates of GM and WM status, which were predictive of cognitive performance. The specific prevalence and severity of PVHs and DWMHs in this sample may account for these findings. Ischemic-related changes are usually associated with DWMHs, whereas non-ischemic age-related changes are usually related to PVHs (Fazekas et al., 1998; Gouw et al., 2011; Schmidt et al., 2011a). This highlights the importance of primary prevention and treatment of modifiable VRF, especially arterial hypertension, in middle-aged individuals.

Results from Study I also suggest a global cognitive effect specifically related to high grade WMHs that can be observed in most cognitive functions, rather than only in executive function and processing speed. This is in line with a recent meta-analysis suggesting a more global effect of WMHs on cognition than previously thought (Kloppenborg et al., 2014b). In the search for the neurobiological basis of this cognitive profile, MRI correlates of high grade WMHs were identified in Study II and Study III and were correlated with cognitive function. The pattern of lower FA areas found in Study III was more extensive than the pattern of areas with reduction of GM volume seen in Study II, probably due to the increased sensitivity of DTI technique over conventional MRI. Further, areas showing FA differences predicted cognitive performance in several cognitive domains, while areas showing GM differences were only predictive of visuospatial skills. Taken together, these results are suggestive of a predominant role of microstructural WM damage over GM atrophy in the cognitive function of middle-aged individuals. They are also converging evidence with recent studies pointing to a more relevant influence of WM status over GM volume on cognition in healthy community samples (Arvanitakis et al., forthcoming; Sun et al., 2014).

The use of a voxel-based approach in Study II and Study III allows us to identify MRI structural correlates of WMHs by applying a whole brain regional analysis of GM volume and FA values. This methodology does not only locate specific areas of reduced GM volume or lower FA between groups, but also overcomes the potential limitations of the ROI methodology, such as subjective operator-dependent placement, limited reliability and reproducibility, and partial volume

effects (Ashburner, 2009; Chanraud et al., 2010; Zhuang et al., 2010). In addition, manual tracing of WMHs for DTI analysis is not completely satisfying since the precise borders of WMHs can be difficult to delineate due also to variability in MRI signal change (Salat et al., 2009). The voxel-based approach also prevents the lack of information on a regional level characteristic of segmentation methods (Vernooij et al., 2009; Voormolen et al., 2010). Nevertheless, like all imaging analysis methods, the voxel-based approach has inherent limitations, such as the accuracy of spatial normalization, the size of the smoothing kernel and the assumption of normal signal distribution in the statistical inference (Jones et al., 2005; Ridgway et al., 2008; Smith et al., 2006). For these reasons, the FSL-VBM and TBSS procedures applied in Study II and Study III have been designed to retain the strengths of voxel-based analysis while addressing registration and smoothing issues (Douaud et al., 2007; Smith et al., 2006). Likewise, the nonparametric permutation testing used in both studies also provides a flexible and intuitive methodology for the statistical analysis of data requiring only minimal assumptions for validity (Nichols and Holmes, 2002).

WMHs are a radiological and pathological hallmark of SVD, which is thought to be possibly the most frequent cause of VCI (Pantoni, 2010). There is also increasing evidence that cerebrovascular dysfunction plays a role in neurodegenerative diseases such as AD (Iadecola, 2010). In addition to cognitive disorders, SVD also include other clinical disturbances such as slower gait, impaired balance, depressed mood, urinary dysfunction, and overall functional disability (LADIS Study Group, 2011). Neuroimaging has a central role in the diagnosis and follow-up of SVD (Román and Pascual, 2012). In this line, two important findings emerge from our data. First, the identification of areas of reduced GM volume and decreased FA in specific WM tracts related to high grade WMHs. Second, and most novel, we found that only areas of reduced GM volume and decreased FA in high grade DWMHs are related to cognitive function. Taken together, these novel results could contribute to understand the different mechanisms and clinical consequences of DWMH and PVH.

One of the strengths of all three studies is the selection of a community-dwelling sample, clinically well-characterized without overt CVD and cognitive impairment. Other strengths are our extensive neuropsychological assessment and the use of high-resolution 3.0 T MRI to detect WMHs with an increased sensitivity and obtain high-quality T1-weighted images. Neuroimaging and regression analysis on cognitive variables were conducted with extensive adjustment for confounders. One potential weakness is the use of a visual rating scale to rate location and

severity of WMHs. Visual rating scales have some limitations, such as non-linearity of data, lack of sensitivity to small changes, and susceptibility to ceiling effects (Kim et al., 2008). Volumetric quantification of WMHs has been regarded as more reliable and robust (Gao et al., 2011; van den Heuvel et al., 2006). However, there is conflicting evidence regarding the idea that volumetric approaches for assessing WMHs may be more sensitive to clinical features than visual scores (Gouw et al., 2006). It is suggested that visual rating may be more appropriate for defining WMHs groups (van Stratten et al., 2006). Visual scales usually offer separate assessment of PVHs and DWMHs, which semi- and fully-automated quantitative methods often overlook. Other possible limitations need to be discussed. The most severe grades of WMHs are under-represented in this community-dwelling sample. The small sample size of participants with high grade DWMHs may preclude the generalization of the results. Our sample size does not allow us to study the association of cognitive function with lobar locations of PVHs and DWMHs (frontal, parietal, temporal, or occipital), which may have some importance (Debette et al., 2007; Kloppenburg et al., 2014). Finally, other unknown factors that can not be ruled out may be playing a role in these results.

Evidence from all three studies leaves several questions and challenges for future investigations. Further research is needed to more clearly elucidate whether both types of WMHs arise from dissociable forms of pathogenesis. Longitudinal data are needed to determine the temporal relation and course of the association between WMHs and regional GM atrophy, and the diagnostic value of regional GM atrophy associated with WMHs to assess cognitive function in community samples. The exact temporal relation between WMHs and FA changes should be also explored further. Additional research is also required to determine if areas of lower FA related to WMHs might have diagnostic value to assess cognitive outcome in SVD. The investigation of the role of MRI correlates of WMHs on cognitive functioning would benefit from the recruitment of larger cohorts of middle-aged participants. Larger samples would allow confirming the mediating role of MRI correlates of WMHs on cognition that is suggested in this thesis. Finally, advantages of multimodal imaging should be used to advance understanding of pathophysiology. Alternative approaches (i.e., fibre-tracking or functional connectivity) could provide additional information about composition, organization and functional status of WM networks.

In conclusion, our data suggest that DWMHs have a predominant role in cognitive function of community middle-aged individuals without symptomatic CVD and overt cognitive

impairment. It would be desirable that neuroradiologists characterize separately PVHs and DWMHs in their reports, which should be available for neuropsychologists. Given that the role of DWMHs may be attributed to underlying ischemic processes, primary prevention and treatment of modifiable VRF may be crucial to maintain cognitive function and prevent future cognitive decline during biological aging of the brain. The use of a voxel-based approach allows the identification of MRI correlates of WMHs in conventional MRI and novel neuroimaging techniques such as DTI. This novel sequence could therefore serve as an additional tool to investigate extension of WM damage. The combination of conventional MRI and DTI may be useful to predict cognitive function in SVD.

CONCLUSIONS

The main conclusions of this thesis can be summarized as follows:

1. PVHs and DWMHs are specifically related to cognitive function in middle-aged individuals without symptomatic CVD and overt cognitive impairment. High grade DWMHs are specifically associated with an extensive cognitive profile, whereas high grade PVHs are not associated with cognitive function. Remarkably, most of cognitive dysfunctions related to DWMHs are clinically relevant.

2. The use of a voxel-based approach allows the identification of MRI structural correlates of WMHs in conventional and novel MRI techniques. Individuals with high grade DWMHs show reduced GM volume in different areas, whereas participants with high grade PVHs do not. Participants with high grade PVHs and participants with high grade DWMHs show lower FA in different areas of specific WM tracts. DTI could serve as an additional tool to conventional MRI to investigate extension of WM damage.

3. Only MRI correlates of DWMHs are predictive of cognitive function, which reinforces a predominant role of these lesions in this group of age. The predictive value to cognition of lower FA within specific WM tracts supports the involvement of cerebral circuits in cognitive deficits related to WMHs.

4. The combination of conventional MRI and DTI could contribute to understand the different underlying mechanisms and clinical consequences of WMHs.

SUMMARY OF THE THESIS: SPANISH VERSION

RESUMEN DE LA TESIS

INTRODUCCIÓN

Las hiperintensidades de sustancia blanca cerebral (WMHs) son un concepto radiológico que define áreas difusas de hipodensidad en tomografía axial computerizada (TAC) e hiperintensidades en las secuencias T2, PD y FLAIR de resonancia magnética (RM). Conocidas originalmente con el nombre genérico de "leucoaraiosis" (Hachinski et al., 1987), también reciben el nombre de "white matter lesions" o "white matter changes" (Wardlaw et al., 2013a).

Las WMHs se dividen habitualmente en dos grupos según su localización anatómica: aquellas que son adyacentes a los ventrículos (periventriculares o PVHs) y aquellas situadas en la sustancia blanca subcortical o profunda (DWMHs). Por ahora, no hay otras reglas comúnmente aceptadas para clasificar los tipos de WMHs (Kim et al., 2008).

La etiología de las WMHs no se comprende por completo, probablemente porque sus mecanismos fisiopatológicos y sus correlatos histológicos no son específicos (Gouw et al., 2011; Pantoni, 2010). Sin embargo, la hipótesis más aceptada es que las WMHs están relacionadas con daño isquémico crónico debido a patología vascular de pequeño vaso (SVD). Existe una fuerte asociación epidemiológica entre las WMHs y la presencia de factores de riesgo vascular (VRF), como la edad (de Leeuw et al., 2001; Longstreth et al., 1996) o la hipertensión arterial (Basile et al., 2006; de Leeuw et al., 2002). Asimismo, las WMHs están relacionadas con un riesgo más elevado de ictus (Schmahmann et al., 2008) y de muerte vascular (Debette et al., 2010).

A partir de estudios histológicos, se ha realizado una distinción etiológica entre PVHs y DWMHs (Gouw et al., 2011; Schmidt et al., 2011a). La mayor parte de las PVHs reflejan esencialmente alteraciones de la pared ventricular y de las células gliales que no son isquémicas en origen, mientras que las DWMHs y las PVHs que se extienden a la sustancia blanca profunda se asocian con rarefacción difusa de la mielina, que sí refleja un mecanismo isquémico subyacente.

El uso de la neuroimagen en la práctica clínica a partir de las décadas de 1970 y 1980 ha revelado una elevada presencia de WMHs tanto en el envejecimiento normal como en muestras patológicas (Kim et al., 2008; Xiong & Mok, 2011). Más de la mitad de la población sana adulta puede presentar WMHs en RM (Enzinger et al., 2007; Longstreth et al., 1996). Esta elevada prevalencia de WMHs en población no patológica suscita un elevado interés respecto a su posible relevancia clínica (Wallin & Fladby, 2010).

La mayor parte de los estudios han revelado una asociación entre WMHs y funcionamiento cognitivo en personas sin diagnóstico de alteración cognitiva (Frisoni et al., 2007; Kloppenborg et al., 2014b; Pantoni et al., 2007; Schmidt et al., 2011b). Los problemas cognitivos se atribuyen a la disrupción de los circuitos fronto-subcorticales (Linortner et al., 2012). En muestras poblacionales sanas, las funciones ejecutivas y la velocidad de procesamiento son los dominios más consistentemente afectados (Pantoni et al., 2007; Schmidt et al., 2011b). Otras funciones relacionadas con las WMHs son la atención, la memoria, la capacidad motora y las funciones visoespaciales y visoconstructivas (Au et al., 2006; de Carli et al., 1995; de Groot et al., 2000; Leaper et al., 2001; Mosley et al., 2005; O'Brien et al., 2002).

Asimismo, estudios longitudinales han mostrado una relación de las WMHs con deterioro cognitivo (de Groot et al., 2002; Godin et al., 2010; Longstreth et al., 2005) y riesgo de demencia (Debette et al., 2010; Prins et al., 2004b) en muestras poblacionales.

En términos globales, la asociación descrita entre WMHs y función cognitiva es modesta (Frisoni et al., 2007, Debette & Markus., 2010). La relación es más fuerte cuando las lesiones son más graves (Schmidt et al., 2005; van der Flier et al., 2005), lo que sugiere un efecto 'umbral' en la relación. Por otra parte, la contribución específica de PVHs y DWMHs al funcionamiento cognitivo presenta evidencias contradictorias. Algunos estudios sostienen una mayor relevancia de las PVHs (de Groot et al., 2000; Vannorsdall et al., 2009), mientras que otros otorgan mayor importancia a las DWMHs (Sachdev et al., 2005; Silbert et al., 2008).

Pese a la abundante investigación respecto a la relación entre WMHs y funcionamiento cognitivo, el mecanismo fisiopatológico subyacente de los problemas cognitivos todavía no se comprende en su totalidad.

El uso creciente de la neuroimagen también ha revelado una presencia habitual de atrofia cerebral en el envejecimiento normal (Lockhart & de Carli, 2014). Puesto que son expresiones de SVD, tanto las WMHs como la atrofia pueden visualizarse conjuntamente. En muestras poblacionales o en personas con SVD, se ha encontrado una asociación entre WMHs y atrofia cerebral global, entendida como el conjunto de sustancia gris (GM) y sustancia blanca (WM) (Ikram et al., 2008; Jokinen et al., 2012; Schmidt et al., 2005), pero la evidencia es contradictoria cuando sólo se tiene en cuenta el volumen total de GM (Ikram et al., 2008; Wang et al., 2014). La relación es más consistente en los estudios que emplean el análisis voxel a voxel (VBM) del volumen de GM, ya que muestran un patrón regional de atrofia de GM asociado a las WMHs (Quinque et al., 2012; Raji et al., 2012; Rossi et al., 2006; Wen et al., 2006). Sólo uno de estos estudios ha distinguido entre PVHs y DWMHs (Wen et al., 2006).

La concurrencia de WMHs y atrofia cerebral podría asimismo tener algún efecto sobre el funcionamiento cognitivo. La atrofia cerebral podría amplificar o mediar los efectos de las WMHs sobre la función cognitiva (Jokinen et al., 2012; Schmidt et al., 2005). Mientras que la atrofia cerebral global ha sido asociada consistentemente con el funcionamiento cognitivo en muestras poblacionales o en personas con SVD (Godin et al., 2010; Schmidt et al., 2005), la evidencia vuelve a ser contradictoria si se tiene en cuenta sólo el volumen de GM (Raji et al., 2012; Smith et al., 2015).

La existencia de una penumbra lesional sugiere que las WMHs pueden ser incapaces de captar todo el daño existente en la WM (Maillard et al., 2013). La imagen por tensor de difusión (DTI) es una secuencia que permite una evaluación más precisa de la composición y organización de la WM (Chanraud et al., 2010). La degradación de la microestructura de la WM viene acompañada de cambios en parámetros de DTI, como un descenso en los valores de anisotropía fraccional (FA) o un aumento de la difusividad media (MD) (Neil, 2008).

La contribución relativa de medidas macroestructurales (volumen de WMHs) y microestructurales (parámetros de DTI) de daño en WM al funcionamiento cognitivo se está investigando. Se cree que ambas medidas podrían representar dos procesos relacionados que son habituales en el envejecimiento (Maillard et al., 2013; Vernooij et al., 2008; Zhuang et al., 2010). Estudios previos han relacionado las WMHs con parámetros de DTI (Muñoz-Maniega et al., 2015; O'Sullivan et al., 2004a, 2004b; Vernooij et al., 2009), aunque hay escasa evidencia de la relación entre WMHs y FA mediante VBM en envejecimiento no patológico (Leritz et al., 2014;

Quinque et al., 2012). Asimismo, diversos estudios han mostrado una asociación entre valores de FA y rendimiento cognitivo en muestras poblacionales o en personas con SVD, en dominios como funciones ejecutivas (Quinque et al., 2012), velocidad de procesamiento (Vernooij et al., 2009), fluencia verbal (Shenkin et al., 2005) o capacidad psicomotora (Vernooij et al., 2009).

La mayor parte de los estudios anteriores han empleado una metodología basada en la región de interés (ROI) o la segmentación de áreas específicas (como todo el tejido de WM o de WMHs) para calcular el valor medio de FA. Esta metodología podría obviar la contribución relativa de los grandes tractos de WM a la función cognitiva.

OBJETIVOS

El objetivo general de esta tesis es estudiar las asociaciones entre las WMHs, sus correlatos estructurales en RM y el funcionamiento cognitivo en personas de mediana edad, entre 50 y 65 años, sin diagnóstico de alteración cognitiva ni de patología vascular de gran vaso. Con ese fin, los participantes se seleccionaron de la muestra de un estudio poblacional, se les aplicaron diferentes técnicas de RM y se les realizó una exhaustiva evaluación cognitiva.

Los objetivos específicos de la tesis son:

- Determinar la contribución específica de las PVHs y las DWMHs al rendimiento cognitivo en personas de mediana edad (Estudio I)
- Examinar la presencia y la gravedad de marcadores de SVD (Estudio I)
- Investigar la asociación específica de las PVHs y las DWMHs con el volumen de GM mediante VBM (Estudio II)
- Evaluar el valor predictivo para la cognición de las áreas con atrofia de GM específicamente relacionadas con las PVHs y las DWMHs (Estudio II)
- Investigar la asociación específica de las PVHs y las DWMHs con los valores de FA mediante VBM (Estudio III)
- Evaluar el valor predictivo para la cognición de los valores de FA en los tractos de WM específicamente relacionados con las PVHs y las DWMHs (Estudio III)

MATERIALES Y MÉTODOS

Cien individuos sin historia de ictus ni demencia fueron seleccionados, estratificados por sexo y nivel educativo, de un estudio poblacional sobre arteriopatía vascular periférica (Alzamora et al., 2007). Se incluyeron personas entre 50 y 65 años con una puntuación de Mini-Mental State Examination (MMSE) ≥ 25; sin enfermedades médicas que pudieran afectar el examen de RM y/o el funcionamiento cognitivo; sin contraindicaciones para realizar un examen de RM (como claustrofobia, prótesis o implantes metálicos), y sin anormalidades incidentales detectadas en la RM (Vernooij et al., 2007). Por problemas técnicos en la adquisición de las imágenes de RM, se excluyeron 4 participantes, por lo que finalmente la muestra quedó reducida a 96 sujetos.

El protocolo de RM incluyó las secuencias T1, T2, FLAIR y DTI. Los participantes se clasificaron como "sin lesiones" (0 puntos), "leves" (1 punto), "moderados" (2 puntos) y "graves" (3 puntos) según las puntuaciones PVHs y DWMHs de la escala visual de Fazekas (Fazekas et al., 1987) obtenidas de las secuencias T2 y FLAIR. Los infartos lacunares (LI) fueron identificados como hiperintensidades en T2 e hipointensidades en T1 y FLAIR, con un diámetro entre 5 y 15 mm (Fazekas et al., 2002).

La evaluación cognitiva se realizó mediante una exhaustiva batería de pruebas neuropsicológicas. Las distintas pruebas se agruparon en los siguientes dominios cognitivos: planificación e inhibición ejecutiva; memoria de trabajo; atención; fluencia verbal; memoria verbal; memoria visual; funciones visoespaciales y visoconstructivas, y velocidad y coordinación psicomotora.

RESULTADOS

Estudio I

Soriano-Raya, J. J.; Miralbell, J.; López-Cancio, E.; Bargalló N; Arenillas, J. F.; Barrios, M.; Cáceres, C.; Toran, P.; Alzamora, M.; Davalos, A.; Mataró, M. (2012). **Deep *versus* Periventricular White Matter Lesions and Cognitive Function in a Community Sample of Middle-Aged Participants.** *Journal of the International Neuropsychological Society, 18*, 874-885. IF: 2,96 (primer tercil de las categorías Clinical Neurology y Psychology)

Estudio II

Soriano-Raya JJ, Miralbell J, López-Cancio E, Bargalló N, Arenillas JF, Barrios M, Cáceres C, Toran P, Alzamora M, Dávalos A, Mataró M (2015). **Regional cortical atrophy in lingual gyrus predicts visuospatial skills in a community sample of participants with white matter lesions.** Working paper

Estudio III

Soriano-Raya JJ, Miralbell J, López-Cancio E, Bargalló N, Arenillas JF, Barrios M, Cáceres C, Toran P, Alzamora M, Dávalos A, Mataró M. **Tract-specific fractional anisotropy predicts cognitive outcome in a community sample of middle-aged participants with white matter lesions.** *J Cereb Blood Flow Metab* 2014;34(5):861-9. IF: 5,41 (primer cuartil de la categoría Neurosciences)

RESUMEN DE LOS RESULTADOS Y DISCUSIÓN

Los resultados de los estudios incluidos en esta tesis aportan nuevos conocimientos sobre la relación entre WMHs, sus correlatos estructurales de RM y función cognitiva en personas de mediana edad sin historia de ictus ni de alteración cognitiva.

En el estudio I, la presencia de DMWHs moderadas se asoció con un menor rendimiento cognitivo en función ejecutiva, atención, fluencia verbal, memoria visual, funciones visoespaciales y visoconstructivas, y velocidad y coordinación psicomotora. La presencia de PVHs moderadas no se asoció con un menor rendimiento en ningún dominio cognitivo. Desde un punto de vista clínico, las DWMHs moderadas se asociaron además con un mayor riesgo de alteración cognitiva en función ejecutiva, fluencia verbal, funciones visoespaciales y visoconstructivas, y velocidad y coordinación psicomotora. Las PVHs moderadas tampoco se hallaron relacionadas con un mayor riesgo de alteración.

El perfil cognitivo asociado específicamente con las DWMHs es consistente con los estudios previos sobre la relación entre WMHs y funcionamiento cognitivo (Kloppenborg et al., 2014b; Pantoni et al., 2007; Schmidt et al., 2011b). Estos resultados también corroboran la hipótesis de que las PVHs y las DWMHs están relacionadas de forma diferente con el funcionamiento cognitivo en personas de mediana edad y apoyan la distinción entre ambos tipos de WMHs (Sachdev & Wen, 2005; Schmidt et al., 2011b). Asimismo, nuestros resultados recomiendan la caracterización separada de ambos tipos de WMHs en los informes radiológicos, puesto que es una información con potencial relevancia clínica.

En el estudio I, la prevalencia de PVHs alcanzó el 46,9%, mientras que las DWMHs estuvieron presentes en el 80,2% de la muestra. Uno de cada seis participantes (16,7%) presentó DWMHs moderadas. También uno de cada seis participantes (16,7%) presentó PVHs moderadas. Ningún participante mostró DWMHs o PVHs graves. Once LI fueron identificados en 7 de los participantes (7.3% del total). La presencia de marcadores radiológicos de SVD es menor que en otros estudios poblacionales, lo que podría explicarse por variables relacionadas con el estilo de vida, como la dieta, o con factores genéticos.

En el estudio II, los participantes con DWMHs moderadas mostraron una reducción localizada de volumen de GM en áreas frontales, temporales, parietales y occipitales, y en el

lóbulo de la ínsula, en comparación con los participantes sin DWMHs o con DWMHs leves. Por su parte, los participantes con PVHs moderadas no mostraron reducciones localizadas de GM comparados con los participantes sin PVHs o con PVHs leves. El volumen de GM en las áreas con atrofia del giro lingual se halló asociado con el rendimiento cognitivo en capacidades visoespaciales y visoconstructivas.

Estos resultados sugieren que la asociación entre WMH y el patrón regional de atrofia cortical depende del tipo de lesión. También confirman estudios previos con VBM en los que el mayor grado de reducción del volumen de GM se localiza en áreas frontales (Quinque et al., 2012; Raji et al., 2012). La novedosa relación entre DWMHs moderadas, atrofia cortical en la circunvolución lingual y funciones visoespaciales y visoconstructivas apoya el papel predominante de las DWMHs en la cognición que también se desprende del estudio I, aunque la falta de relación del resto de áreas con otras funciones cognitivas sugiere que otros mecanismos subyacentes podrían ser más relevantes en este grupo de edad.

En el estudio III, los participantes con DWMHs moderadas mostraron un valor de FA reducido en áreas del fascículo fronto-occipital inferior (IFOF) bilateral, la radiación talámica anterior (ATR) derecha y el fascículo longitudinal superior (SLF) derecho, comparados con los participantes sin lesiones o con DWMHs leves. Los sujetos con PVHs moderadas también mostraron un valor de FA reducido en diferentes áreas del IFOF, la ATR y el SLF, comparados con los participantes sin lesiones o con PVHs leves. Sólo el valor medio de FA en las áreas relacionadas con DWMHs moderadas se asoció con función ejecutiva (IFOF), atención (ATR), fluencia verbal (IFOF) y funciones visoespaciales y visoconstructivas (IFOF y ATR), mientras que el valor medio de FA en las áreas relacionadas con PVHs moderadas no predijo rendimiento cognitivo.

El estudio III muestra que la combinación de DTI y VBM permite localizar áreas de reducción de FA en personas con WMHs moderadas, lo que sugiere la presencia de un daño microestructural en la WM más extenso que el daño macroestructural (visible como WMHs) presente en las secuencias más convencionales de RM. Este hecho apoya el uso de la DTI como técnica adicional para investigar la extensión del daño en WM. Las áreas asociadas a DWMHs moderadas fueron más numerosas, más extensas y de mayor predominio frontal que las áreas asociadas a PVHs moderadas. El novedoso valor predictivo del valor de FA en tractos específicos apoya el papel de los circuitos cerebrales en los problemas cognitivos asociados con

WMHs. Estos resultados también pueden contribuir a una explicación más precisa de los mecanismos subyacentes a la relación entre WMHs y función cognitiva.

Los resultados de los tres estudios sugieren en su conjunto un papel preponderante de las DWMHs en el funcionamiento cognitivo de personas de mediana edad sin antecedentes de ictus ni diagnóstico de alteración cognitiva. La prevalencia y gravedad específica de PVHs y DWMHs en esta muestra podría explicar estos resultados. El papel preponderante de las DWMHs podría atribuirse a procesos isquémicos subyacentes localizados en áreas con potencial relevancia funcional (Gouw et al., 2011; Kim et al., 2008; Schmidt et al., 2011a), lo que subraya la importancia de la prevención y el tratamiento de los VRF en este grupo de edad.

Los resultados del primer estudio también sugieren un efecto de las WMHs que puede observarse en la mayor parte de las funciones cognitivas. Este hallazgo es congruente con un reciente meta-análisis que también sugiere que las WMHs podrían tener un efecto más global sobre la cognición, más allá de las funciones ejecutivas y la velocidad de procesamiento (Kloppenborg et al., 2014b). Asimismo, las asociaciones entre correlatos de RM y funcionamiento cognitivo encontrados en el segundo y el tercer estudio apoyan un papel más relevante del daño microestructural de WM que de la atrofia de GM en la función cognitiva de personas de mediana edad. Este hecho coincide con investigaciones recientes que también hallan una mayor asociación de la integridad de WM con funcionamiento cognitivo en muestras poblaciones sanas (Sun et al., 2014).

El uso de un análisis basado en el vóxel en los estudios II y III permite la identificación de los correlatos estructurales de las WMHs, bien como áreas específicas de reducción de volumen de GM o como áreas específicas con valores reducidos de FA. Esta metodología permite asimismo solucionar las limitaciones de otros métodos como la ROI (Ashburner, 2009; Chanraud et al., 2010; Zhuang et al., 2010). Además, el trazado manual de las WMHs característico de las ROI en los análisis de DTI puede ser poco satisfactorio dada la dificultad añadida para delimitarlas de forma precisa por la variabilidad de la señal de RM (Salat et al., 2009).

Se considera que las WMHs son una expresión radiológica de SVD, que probablemente es la causa más frecuente de alteración cognitiva vascular (VCI) (Pantoni, 2010). La neuroimagen juega un papel fundamental en el diagnóstico y el seguimiento de la VCI (Román & Pascual, 2012). En este sentido, dos hallazgos importantes están presentes en esta tesis. En

primer lugar, la identificación de áreas de atrofia cortical y de áreas con un valor reducido de FA en tractos específicos de WM que se encuentran asociadas con las WMHs. Y en segundo lugar, lo que es más novedoso, que sólo las áreas asociadas con las DWMHs están asociadas con función cognitiva. En su conjunto, estos resultados podrían contribuir a explicar los diferentes mecanismos y las diferentes consecuencias clínicas de ambos tipos de WMHs.

Uno de los puntos fuertes de esta tesis es la selección de una muestra poblacional, bien caracterizada desde un punto de vista clínico, sin antecedentes de accidente vascular sintomático ni diagnóstico de alteración cognitiva, que ha sido explorada mediante una completa batería neuropsicólogica. Además, se ha utilizado una campo magnético de RM de 3.0 T, con una mayor capacidad para detectar las WMHs y obtener imágenes T1 de alta calidad. Un posible punto débil es el uso de una escala visual para evaluar la localización y gravedad de WMHs (Gao et al., 2011; Kim et al., 2008; van den Heuvel, et al., 2006). Otras limitaciones son que la muestra no incluye WMHs graves y que su tamaño es reducido, lo dificulta la generalización de los resultados o el estudio de la localización de las WMHs en función del lóbulo donde se encuentran (Debette et al., 2007; Kloppenburg et al., 2014).

En resumen, los resultados de la presente tesis sugieren un papel relevante de las DWMHs en el funcionamiento cognitivo de personas de mediana edad sin ictus ni diagnóstico de alteración cognitiva. Por lo tanto, la prevención primaria y el tratamiento de los VRF podrían ser cruciales para el mantenimiento de la función cognitiva y la prevención del deterioro cognitivo durante el envejecimiento biológico cerebral. El uso de una metodología basada en el vóxel permite la identificación de correlatos de las WMHs en RM convencional y en nuevas técnicas de neuroimagen como la DTI. Esta nueva secuencia podría servir como herramienta adicional para investigar la extensión del daño en WM. Los resultados de esta tesis también sugieren que el uso multimodal de RM convencional y de técnicas más avanzadas como la DTI puede ser útil para predecir la función cognitiva en SVD.

CONCLUSIONES

Las principales conclusiones de la presente tesis se resumen a continuación:

1. Las PVHs y las DWMHs están específicamente relacionadas con la función cognitiva en personas de mediana edad sin historia de ictus ni demencia. Las DWMHs moderadas están asociadas con un extenso perfil cognitivo, mientras que las PVHs no se relacionan con el rendimiento cognitivo en ninguna función. Además, la mayor parte de disfunciones cognitivas asociadas con las DWMHs moderadas tienen relevancia clínica.

2. El uso del análisis vóxel a vóxel permite la identificación de correlatos estructurales de las WMHs mediante técnicas convencionales y avanzadas de RM. Las personas con DWMH moderadas presentan un patrón localizado de atrofia en diferentes áreas, mientras que las personas con PVHs moderadas no presentan patrón de atrofia. Las personas con PVHs y DWMHs moderadas presentan un patrón específico de valores reducidos de FA en diferentes áreas de tractos de WM. La DTI podría ser útil como herramienta adicional para investigar la extensión del daño de WM.

3. Sólo los correlatos estructurales de las DWMHs moderadas tienen capacidad predictiva, lo que refuerza el papel preponderante de dichas lesiones en la función cognitiva de personas de este grupo de edad. El valor predictivo de las áreas con FA reducida en diferentes tractos apoya la implicación de los circuitos cerebrales en los problemas cognitivos relacionados con WMHs.

4. El uso multimodal de diferentes secuencias de RM puede contribuir a explicar los mecanismos subyacentes en la relación entre WMH y cognición y a predecir la función cognitiva en la SVD.

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Over the past three decades, the amount of data on the clinical and pathological correlates of white matter hyperintensities (WMHs) has vastly increased. Most research about WMHs has involved participants who are older than 65 years. However, these abnormalities are also seen commonly in middle-aged individuals in their 50s and early 60s.

The general aim of this thesis was to study the association between WMHs, their related magnetic resonance imaging (MRI) structural correlates, and cognitive function in a community sample of stroke- and dementia-free individuals aged 50 to 65 years old.

Our data suggest that deep white matter hyperintensities (DWMHs) have a predominant role in cognitive function of community middle-aged individuals without symptomatic cerebrovascular disease and overt cognitive impairment.

The use of a voxel-based approach allows the identification of MRI correlates of WMHs in conventional MRI and novel neuroimaging techniques such as diffusion tensor imaging (DTI). This novel sequence could therefore serve as an additional tool to investigate extension of white matter damage. The combination of conventional MRI and DTI may be useful to predict cognitive function in small-vessel disease (SVD).