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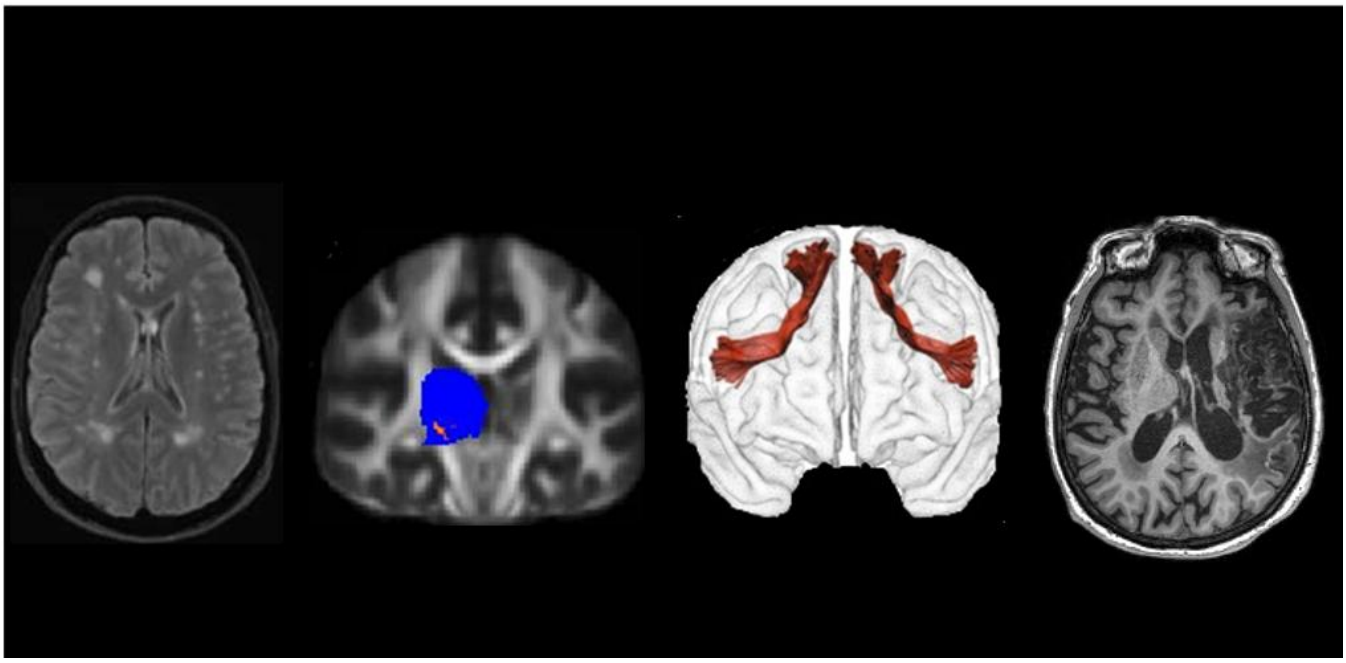

Universitat de Barcelona

Neuroimaging correlates of cognitive functioning in cerebrovascular disease

Marina Fernández-Andújar

July 2014

Department of Psychiatry and Clinical Psychobiology

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This thesis is presented by

Marina Fernández-Andújar

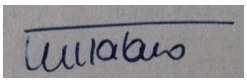
To obtain the degree of Doctor of Psychology (Medicine Doctoral program) from the University of Barcelona in accordance with the requirements of the European PhD diploma.

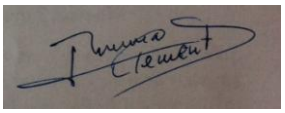
Supervised by:

Dr. Maria Mataró Serrat. University of Barcelona, Spain.

Dr. Imma Clemente Lapena. University of Barcelona, Spain.

Dr. Maria Mataró Serrat professor agregat and Dr. Imma Clemente Lapena professor titular CERTIFY that they have supervised and guided the PhD thesis entitled "Neuroimaging correlates of cognitive functioning in cerebrovascular disease" presented by Marina Fernández-Andújar. They hereby assert that this thesis meets the conditions for the defense the Doctor Degree of Psychology.





Dr. Maria Mataró Serrat

Dr. Imma Clemente Lapena

Barcelona, June 2014

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Para mi madre y Alba. Per a l'Albert.

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CONTENTS

FOREWORD

This thesis, presented to obtain the Degree of Doctor of Psychology 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. One of these three studies was also done in collaboration with the Natbrainlab, King's College, London. The studies included in this thesis are presented in the form of research articles. Two of the three presented studies have been published in international scientific journals (within the first quartile on "Neurosciences" and "Psychology") with a global impact factor of 9.67 (ISI web of knowledge, Journal Citation Reports inferred from 2012).

Study I

Fernández-Andújar, M., Soriano-Raya, J. J., Miralbell, J., Lopez-Cancio, E., Cáceres, C., Bargalló., Barrios, M., Arenillas, J.F., Toran, P., Alzamora, M., Clemente, I., Dávalos, A., Mataró, M. (2013). **Diffusion Thalamic differences related to cognitive function in white matter lesions.** *Neurobiology of Aging*, 35(5); 1103-1110. IF: 6.09.

Study II

Fernández-Andújar, M., Doornink, F., Dacosta-Aguayo, R., Soriano-Raya, J. J., Miralbell, J., Bargalló, N., Lopez-Cancio, E., Pérez de la Ossa, N., Gomis, M., Millán, M., Barrios, M., Cáceres, C., Pera, G., Forés, R., Clemente, I., Dávalos, A., Mataró, M. (2013) **Remote thalamic microstructural abnormalities related to cognitive function in ischemic stroke patients.** *Neuropsychology*, in press. IF: 3.58.

Study III

Fernández-Andújar, M., Forkel, S.J., Dacosta-Aguayo, R., Miralbell, J., Soriano-Raya, J. J., Clemente, I., Millán, M., Lopez-Cancio, E., Bargalló., Barrios, M., Cáceres, C., Toran, P., Alzamora, M., Dávalos, A., Mataró, M., Thiebaut de Schotten, M. (2013). **Disconnection of the right Frontal Aslant Tract impairs attention and response inhibition: a spherical deconvolution tractography study.** Working paper.

GLOSSARY OF ABBREVIATIONS

AD: Alzheimer's disease

CSF: Cerebrospinal Fluid

CT: Computerized Tomography

CVD: Cerebrovascular Disease

CPT: Continuous Performance Test

DWMHs: Deep White Matter Hyperintensities

DL: Dyslipidemia

DM: Diabetes mellitus

DTI: Diffusion Tensor Imaging

FA: Fractional Anisotropy

FAT: Frontal Aslant Tract

FLAIR: Fluid Attenuated Inversion Recovery

GM: Grey Matter

HTA: Hypertension

ICH: Intracerebral Haemorrhage

IFG: Inferior Frontal Gyrus

LI: Lacunar Infarcts

LVD: Large vessel disease

MBs: Microbleeds

MCI: Mild Cognitive Impairment

MD: Mean Diffusivity

MRI: Magnetic Resonance Imaging

MMSE: Mini-Mental State Examination

MoCA: Montreal cognitive assessment

Pre-SMA: Pre-supplementary Motor Area

PVHs: Periventricular Hyperintensities

ROI: Region of Interest

SAH: Subarachnoidal haemorrhage

SFG: Superior Frontal Gyrus

SD: Spherical Deconvolution

SMA: Supplementary Motor Area

SVD: Small Vessel Disease

VD: Vascular Dementia

VCI: Vascular Cognitive Impairment

VaMCI: Vascular Mild Cognitive Impairment

VRF: Vascular Risk Factors

WAIS-III: Wechsler Adult Intelligence Scale-III

WHO: World Health Organization

WM: White Matter

WMLs: White Matter Lesions

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I INTRODUCTION

1. Cerebrovascular disease: small and large vessel disease

Cerebrovascular disease (CVD) refers to a group of conditions that affect the circulation of blood flow to the brain, causing limited or no blood supply to one or many affected areas of the brain. It includes some of the most common and devastating brain disorders such as large vessel ischemic stroke and hemorrhagic stroke, as well as the pathologies that affect small brain vessels such as white matter lesions (WMLs), lacunar infarcts (LI), and microbleeds (MBs). CVD is the third most frequent cause of death and the leading cause of adult disability in the development countries (Carmichael, 2012; World Health Organization (WHO), 2004). Research and clinical efforts have been made in order to completely understand these pathologies. The present thesis particularly focuses in WMLs and ischemic stroke, to deepen the knowledge of the neurobiological bases of cognitive dysfunction through the neuroimaging correlates in these brain diseases.

1.1 Small vessel disease

The term small vessel disease (SVD) describes a group of pathological processes with various aetiologies that affect the small arteries, arterioles, venules, and capillaries of the brain. Most of these pathologies are considered clinically silent and have been associated with cognitive decline in aging and vascular cognitive impairment (VCI) ranging from mild vascular cognitive impairment (VaMCI) to dementia (Pantoni & Gorelick, 2011; Román, 2004). Age and hypertension (HTA)-related SVD and cerebral amyloid angiopathy are the most common forms. Also, SVD is mainly located in the subcortical structures such as WMLs, LI, large haemorrhages and MBs.

1.1.1 White matter lesions

Cerebral WMLs, also called white matter hyperintensities or leukoaraiosis (Hachinski et al., 1987), comprise diffuse areas of hypodensity on Magnetic Resonance Imaging (MRI) T1-weighted images and computerized

tomography (CT) and high signal intensities on T2-weighted images, proton density, and Fluid attenuated inversion recovery (FLAIR) MRI sequences. These morphological hyperintensities are considered clinically silent and HTA and old age are consistently reported to be main risk factors for these lesions (de Leeuw et al., 2002; Guo et al., 2009; Van Dijk et al., 2004). WMLs are usually divided into two groups depending on their anatomical position: those 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). Usually, DWMHs affect the anterior part of the internal capsule, the anterior part of the corona radiate, and the anterior part of the semiovale centre. WMLs are common MRI findings in normal elderly -more than half of all middle aged individuals presented it (De Leeuw et al., 2001; Enzinger et al., 2007)-, cognitively impaired individuals (Debette & Markus, 2010; Meyer et al., 1992), stroke patients (Pohjasvaara et al., 2000; Wen & Sachdev, 2004a), as well as in patients suffering from other neurological and psychiatric disorders. More specifically, WMLs can appear from the age of 30 years although the prevalence increases with aging up to the prevalence of 96% in people older than 65 years (Longstreth, 1996). A recent meta-analysis of 22 studies reported that individuals with these brain lesions also have a higher risk for stroke, dementia and vascular death (Debette & Markus, 2010).

WMLs are considered a reflection of non-necrosis SVD (Pantoni, 2002) due to incomplete white matter infarctions occurred affecting the deep penetrating arteries (Román et al., 2002) leading to an extensive demyelination and axonal loss (Fazekas et al., 1998). However, both PVHs and DWMHs also contain non-ischemic changes named “caps” and “punctuate”, respectively (Fazekas, 1998; 1993). In PVHs, “caps’’ include an affectation of the ependymal lining, myelin and axonal loss, gliosis and dilation of perivascular spaces (Schmidt et al., 2011; Udaka et al., 2002). In DWMHs, ‘‘punctate’’ findings may also reflect, among others, widening of perivascular spaces (Fazekas et al., 1993). Only ‘‘irregular’’ PVHs extending to deep white matter and ‘‘early confluent’’ and ‘‘confluent’’ DWMHs are clearly related to SVD.

Finally, hipoperfusion, inflammation and hematoencephalic barrier alteration have been proposed as other mechanisms that can influence in WMLs findings.

a) Quantification of white matter lesions

Many different approaches have been used to quantify WMLs from conventional MRI or CT scans. Many semi-quantitative visual rating scales are available for the evaluation of WMLs severity (Fazekas et al., 1987; Wahlund et al., 2001). While several scales divide WMLs into PVHs and DWMHs, as well as into different anatomical regions (de Groot et al., 2000; Fazekas et al., 1987; Wahlund et al., 2001) others divide WMLs only into normal, moderate, and severe WMLs burden (Van Swieten et al., 1991). Other methods include semi-automated volumetric approaches as well as computerised volumetric measurements and segmentation methods (DeCarli et al., 1995; Gurol et al., 2006).

b) White matter lesions and cognition

WMLs have consistently been associated with cognitive function in community-dwelling healthy participants (Pantoni et al., 2007; Schmidt et al., 2011), mild cognitive impairment (MCI) (Bombois et al., 2007), and individuals with dementia (Graham et al., 2004). For instance, *The longitudinal Leukoaraiosis and DISability (LADIS)* study collaboration showed an association between the severity of baseline WMLs and transition to global decline in a cohort of 639 elderly patients (Inzitari et al., 2009). At the end of the 3-year cognitive follow-up, 90 of them had developed dementia and 147 were diagnosed as cognitive impairment no dementia (Verdelho et al., 2010). One of the most important predictors of cognitive decline was WMLs severity independently of age, education, and medial temporal atrophy variables. Cognitive consequences 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 (Catani & Ffytche, 2005; Nordahl et al., 2006). Executive function and information processing speed deficits are the most consistently domains found to be related to WMLs (Bartrés-Faz et al., 2001; O'Brien et al., 2003; Pantoni et al., 2007).

Although previous studies have observed a relevant role of the WMLs on cognitive function, the clinical relevance of this association remains controversial (Andersson, 2010; Wallin & Fladby, 2010). Similarly, the specific contribution of PVHs and DWHMs in cognitive function is currently unknown since to date few studies have addressed this issue and also, these results are controversial (Schmidt et al., 2011).

1.1.2 Lacunar infarcts

LI are described like small ischemic strokes (no more than 15 mm) in the territory of the perforant arterioles (Fisher, 1982). Most of LI, up to 80%, are clinically silent. LI are localized predominantly in the basal ganglia, especially in the putamen, the thalamus, the internal capsule and pons, and in the centrum semiovale (Combarros, 1991). The vascular territories involved are usually the lenticulostriate branches of the anterior and middle cerebral arteries, the thalamoperforating branches of the posterior cerebral artery, and the paramedian branches of the basilar artery (Martí-Vilalta, 2004). The main etiologic risk factor of LI is HTA (Baumgartner et al., 2003; Gouw et al., 2008) as well as atherosclerosis, arteriolosclerosis, lipohyalinosis and repeated embolic events. Epidemiological data shows that LI suppose about 20-25% from all ischemic strokes (Wardlaw, 2005). However, compared with other stroke subtypes (such as ischemic or hemorrhagic stroke) the prognosis after a clinical LI is much better with almost no acute mortality, a generally good recovery and a low risk of recurrence and little or no effect on long-term survival (Clavier et al., 1994). In fact, a recent meta-analysis study suggests that only approximately 37% of patients will be cognitively impaired in the 4 years following a LI, a similar proportion to non-lacunar stroke individuals (Makin et al., 2013).

Van Zandvoort (2001; 2000) reported that, in general, clinical LI are associated with sustained attention impairment and lower processing speed information. In a recent review, Edwards et al. (2013) observed that global dysfunction, information processing speed, executive function, memory, language, attention and visuospatial skills deficits were the most cognitive domains affected after symptomatic LI. More specifically, due to presence of

concurrence WMLs, a single LI might affect notably in performance of multiple cognitive domains (McMurtray et al., 2007; Wen et al., 2004b). Moreover, cognitive impairment after multiple LI has been more specifically associated with executive dysfunction and long term cognitive impairment (Leskelä et al., 1999; Wolfe et al., 1994). Interestingly, Gold et al. (2005) and Tatemichi et al. (1992) observed a relationship between LI in the basal ganglia and thalamus regarding cognitive deficits. These impairments are probably caused by an interruption of thalamocortical connections such as prefrontal-subcortical loops disruption (Cummings, 1993; Mega & Cummings, 1994).

1.1.3 Microbleeds

MBs are defined as hemorrhagic microvascular lesions or microangiopathy in the brain. They are usually identified as small, punctuate hypointense lesions (around <10mm in diameter) in T2 MRI-images or Susceptibility-Weighted Image. There are two main mechanisms that can lead to MBs. Deep and infratentorial MBs are presumed to result from HTA and cortico-subcortical MBs seem to be related to cerebral amyloid angiopathy (Cordonnier & Van der Flier, 2011). MBs have a higher prevalence in cognitively normal elderly subjects (Poels et al., 2012; Sveinbjornsdottir et al., 2008) and are considered as a marker of future stroke (Gao et al., 2008; Jeon et al., 2007). Also, MBs have been associated with higher risk of LI (Sueda et al., 2010), WMLs (Kato et al., 2002; Poels et al., 2010; Yakushiji et al., 2010), VCI (Chen et al., 2010; Werring et al., 2010), vascular dementia (VD) (Qiu et al., 2010), and Alzheimer's disease (AD) (Pettersen et al., 2008). Although MBs had previously been considered to be clinically silent, (Kato et al., 2002; Kwa, 1998) recent studies suggest that MBs are associated with cognitive dysfunction even in healthy subjects (Takashima et al., 2011; Yakushiji et al., 2008). Deep and infratentorial MBs usually occur in brainstem, basal ganglia, and in the thalamus. It could yield fronto-subcortical circuits interruption and this can substantially explain cognitive impairment (van Norden et al., 2011; Werring et al., 2004; Yakushiji et al., 2008). MBs have been related to lower performance in processing speed, executive dysfunction and VCI global dysfunction (Gregoire et al., 2012; Qiu et al., 2010; Van Norden et al., 2011;

Werring et al., 2004), psychomotor speed (Qiu et al., 2010; Van Norden et al., 2011) and attention (Van Norden et al., 2011). Notwithstanding, these studies are hampered by a number of methodological issues (such as using only the Mini-Mental State Examination (MMSE) or the Montreal cognitive assessment (MoCA) for the global cognitive assessment or an heterogeneous samples including ischemic stroke subjects with MBs) (Lei et al., 2013; Van der Flier & Cordonnier, 2012) and more research about the specific role of MBs in cognition in both healthy participants and pathological diseases is necessary.

1.2. Large vessel disease

Large vessel disease (LVD) includes all the CVD that involve the internal and the vertebral carotids and the Circle of Willis. From a descending incidence point of view, this disease comprises atherosclerosis, vasoconstriction, aortic, carotid or vertebral artery dissection, many inflammatory pathologies of the blood vessel wall, non-inflammatory vasculopathy, Moyamoya's disease and fibromuscular dysplasia. Almost one in three people will suffer a vascular cerebral event and dementia throughout their lives (Hachinski et al., 2006) and 2-4% of the total health care costs worldwide are attributed to cerebral strokes. Stroke represents the second leading cause of death worldwide and is a major determinant of adult disability (Murie-Fernandez et al., 2012; Murphy & Corbett, 2009). Due to the high proportion of patients who suffer cognitive deficits and dementia after a cerebral stroke (Hoffman et al., 2009; Kasner et al., 2006) it is mandatory to completely understand their neurobiological basis.

1.2.1 Cerebral stroke

The current WHO defines stroke such as a focal neurological impairment of sudden onset that lasts more than 24 hours and is presumed to have vascular origin (WHO, 2006). Specifically, in ischemic stroke, blood flow is insufficient to maintain neurologic function and infarction occurs when ischemia reaches the threshold to produce cell death. Generally, cerebral strokes can be defined as >0,5-1,5 cm^3 (Thal et al., 2012).

1.2.2 Epidemiology, vascular risk factors and aetiology

Epidemiology

Stroke represents an estimated 4.5 million deaths worldwide with an approximately 9 million of survivors (Wolfe, 2000). The stroke mortality rate ranges between 50-100 per hundred thousand people every year in developing countries (Donnan et al., 2008) and the demographic current changes will increase this incidence. The risk of stroke increases with age and approximately one in four men and one in five women aged 45 years can expect to have a stroke if they reach the age of 85 years (Wolfe, 2000). Incidence rate is greater in men although fatal rates are higher in women (Heart Disease and Stroke statistics-2005 Update, 2004). Furthermore, african americans and hispanics have almost twice the risk of first-ever stroke when compared to caucasians (Sacco et al., 2001). With neurosciences and clinical advances in the acute stroke management, stroke survivors have risen from 1.5 million to 2.4 million worldwide (Muntner et al., 2002). However, it seems that an approximately a 64% of surviving patients exhibit cognitive impairments (Sahathevan et al., 2012) and a third of them will present severe cognitive deficits enough to meet criteria for dementia (Hachinski et al., 2006). Furthermore, post-stroke cognitive impairment is associated with increased mortality.

Vascular risk factors and aetiology

Stroke is caused by both ischemic and hemorrhagic mechanisms. Specifically, from the total number of strokes the vast majorities, about 87% are ischemic strokes and the 13% are hemorrhagic strokes (Gleichman & Carmichael, 2014). The role of vascular risk factors (VRF) in the initiation, progression and prevention of CVD has become a priority in basic and clinical research. Some stroke risk factors are non-modifiable factors (age, gender, ethnicity and genetics) while others are considered environmental factors modifiable by lifestyle [HTA, cardiovascular disease, diabetes mellitus (DM), dyslipidemia (DL), cigarette smoking and obesity] (O'Donnell et al., 2010; Rincon & Sacco, 2008).

1) Unmodifiable risk factors

Ethnic background, advanced age, and sex have been consistently shown to contribute significantly to the risk of stroke (Cox et al., 2006; Hajat et al., 2011; Markus et al., 2007). It is known that the lifetime risk for stroke in adults over 55 is greater than 1 in 6 (Heart Disease and Stroke Statistics-2005 Update, 2004) and doubles with each successive decade after 55 (Wolf et al., 1992). Finally, genetic susceptibility such as certain polymorphisms also represents an unmodifiable stroke risk factor.

2) Modifiable risk factors

High blood pressure is the most common modifiable VRF for both ischemic and hemorrhagic stroke (Allen & Bayraktutan, 2008; Johansson, 1992; O'Donnell et al., 2010; Whisnant, 1997). Approximately, two thirds of cerebral strokes are attributable to HTA (Lawes et al., 2004) since high blood pressure increases the risk for cerebral lesions related to stenosis and emboli by aggravating and accelerating the atherosclerosis process. HTA can induce complex pathological abnormalities in arteries and arterioles and it may represent an important precursor of LVD and SVD (Strandgaard, 1996; O'Donnell et al., 2010; Yamaguchi et al., 2014). In a meta-analysis of randomized controlled trials reported a stroke risk reduction approximately by a third with blood pressure lowering (Lawes et al., 2004). It is known that heart disease is another important risk factor for stroke (Allen & Bayraktutan, 2008; Sacco et al., 2006) and it is the major cause of larger infarct size, increased disability and mortality among surviving stroke patients (Pedelty & Gorelick, 2007). Arterial fibrillation, a cardiac arrhythmia that can result in thrombus formation, may increase the risk of stroke up to five times due to the underlying thromboemolism mechanism (Hart et al., 2004; Wolf et al., 1991). The DM relative risk for stroke has been estimated to be an increased risk between a two-to sixfold (Flemming & Brown, 2004; Goldstein et al., 2001). It is well known that DM is associated with an increased susceptibility to atherosclerosis and greater prevalence of HTA, DL and obesity (Goldstein et al., 2001). On the other hand, although DL has been investigated as stroke contributing factor, the precise contribution to stroke incidence is still controversial (Donnan, 2004; O'Donnell et al., 2010; Thrift, 2004). Tobacco

habit has long been established as an independent risk factor for stroke which contributes to atherosclerosis, alters the coagulation systems and decreases high-density lipoprotein levels (Flemming & Brown, 2004; O'Donnell et al., 2010). Specifically, smoker use increases the risk of stroke up to fourfold and increases the risk of carotid artery disease fivefold (Goldstein et al., 2001). Regarding obesity, abdominal obesity is an important risk factor for ischemic stroke across all ethnic groups, with a greater strong effect among younger people (Lu et al., 2006; Suk et al., 2003). The coexistent presence of abdominal obesity, HTA, DL and insulin resistance called "metabolic syndrome" is well-known to increase the risk of stroke (Ninomiya et al., 2004). Finally, it is well-established that high grade of alcohol consumption increases the risk of stroke whereas low to moderate alcohol consumption decrease it (Berger et al., 1999; Leys et al., 2002; O'Donnell et al., 2010).

1.2.3 Stroke pathophysiology mechanisms

Ischemic stroke pathophysiology

The cerebral ischemia etiopathogenesis results, in general, from one or more of the following five mechanisms: large vessel atherothrombosis, embolisation from the heart into brain vessels; thromboembolism of large vessels; decreasing of systemic blood pressure and decreased cardiac output. Thrombosis, an obstruction of blood flow due to a blood clot, commonly occurs in arterial vessels. Atherosclerosis process (stenosis and platelet adherence) can cause blood clots to form. Brain vasculature can be occluded by cardioembolic aetiology, mainly due to myocardial infarction or mitral valve damage, but also, by an extracranial arteries occlusion. Global decreased perfusion can also cause reduced blood flow to the brain tissue leading to brain ischemia. The most frequent cases are cardiac pump failure, myocardial infarction, arrhythmia and hypotension. Less common causes, often seen in younger patients, are cervical artery dissection, essential thrombocythaemia, polycythaemia, sickle cell anaemia, protein C deficiency and substance misuse (Carroll & Chataway, 2006).

The ischemic alteration is potentially reversible due to collateral vessels blood supply. However, if perfusion pressure drops to critical following levels,

neuronal electrical failure below 30% of the normal blood flow and failure below 10% of energy metabolism and ion pumps, brain ischemia develops (Brouns & De Deyn, 2009; Astrup et al., 1981). Finally, the breakdown of cell membrane integrity produces a final neuronal necrosis result (Kanekar et al., 2012).

Core and ischemic penumbra areas

At histological level, ischemia process comprises two zones of tissue injury, the core and the ischemic penumbra, which alter both physiology and biochemistry of the brain. The core is the ischemic primary area where cell necrosis occurs, and the ischemic penumbra is the peripheral area around the core. In the core of the focal ischemic infarct a complex pathophysiological cascade initiates resulting in excitotoxicity, peri-infarct depolarisation, inflammation and neuronal apoptosis (Patel et al., 2013). With blood flow depletion, the polarisation of cell membrane cannot be maintained and neurons and glia cells depolarise. In addition, an oedema appears and can affect both local perfusion and remote areas from the core due to increased intracranial pressure, vascular compression and herniation. Injury in enzymatic pathways and free radical production occurre which, in turn, lead to membrane disturbance, the expression of proinflammatory genes and damage to the cytoskeleton integrity. This is followed by peri-infarct spreading depolarization that facilitates the gradual expansion of the core region into the penumbra. The ischemic penumbra is an area of reduced blood flow where functional activity of neurons is suppressed although metabolic activity for maintenance (cellular homeostasis) of structural integrity of the cells is preserved (Kumar et al., 2010). The neurons within this area may remain viable for several hours after symptom onset due to the collateral supply and the area tends to decrease over time. This penumbra area is considered “time-dependent” and decreases over time by gradual recruitment into the core (Kumar et al., 2010). Information flow connectivity between the core and secondary interconnected areas via white matter tracts can be disrupted and may cause deafferentation (Haberg et al., 2009; Zhang et al., 2012). This phenomenon, known as “diaschisis” (Von Monakow, 1914) leads to structural, functional and metabolic anomalies in secondary remote areas from the ischemic lesion (Dacosta-Aguayo et al.,

2014b; Enager et al., 2004; Gold & Lauritzen, 2002). This phenomenon is responsible for clinical (Seitz et al., 1999; Whishaw, 2000) and cognitive sequels in areas remote from the location of the focal lesion.

Hemorrhagic stroke pathophysiology

Haemorrhage can be classify as intracerebral haemorrhage (ICH) which affect the brain parenchyma, and extra-axial haemorrhage -including epidural, subdural and subarachnoidal haemorrhages (SAH)- which affect the surrounding meningeal spaces. Primary ICH accounts for an estimated 10-15% of strokes, whereas SAH accounts for 5% of strokes in western countries. Briefly, ICH is the result of bleeding from an arterial source directly into the brain tissue. The main anatomical location for ICH strokes is subcortical structures and these areas are predominantly supplied by small deep arterial branches (Mohr, 2004). The principal causes of primary ICH is HTA and amyloid angiopathy, whereas secondary ICH can be caused by intracranial aneurysms, arteriovenous malformations, intracerebral tumour, arterial dissection and substance misuse among others (Carroll & Chataway, 2006; Hankey, 2007). SAH is caused by the rupture of an intracranial saccular aneurysm in 80% of cases although this abrupt event is frequently a manifestation of underlying long-standing unidentified processes (Katramados & Vareals, 2007).

1.2.4 Post-stroke clinical and cognitive impairment

It is well-established that cerebral stroke has many sequels including neurologic, behavioural, emotional and several cognitive impairments ranging from VaMCI to VD (Gorelick et al., 2011; Pohjasvaara, 1997; Rockwood et al., 1999; Troncoso et al., 2008). There is a certain correspondence between the neuroanatomical location of the stroke, the focal clinical symptoms and the neuropsychological deficits observed **(Table 1).** Focal infarcts may also be responsible for histological, metabolic and functional abnormalities in areas remote from the ischemic core (Dacosta-Aguayo et al., 2014b; De Reuck et al., 1995; Von Monakow, 1914) probably due to Wallerian degeneration, cortical deafferentation (Buffon et al., 2005; Haberg et al., 2009; Zhang et al., 2012) as well as, the disruption of cerebral circuit networks (Crofts et al., 2001;

Dacosta-Aguayo et al., 2014a). One of the most known cognitive cerebral networks are fronto-subcortical circuits -which connect the frontal lobe with the basal ganglia and thalamus- that are subdivided in 5 circuits which are organized in a structurally and functionally segregated way (Alexander et al., 1986). The thalamus is a crucial relay information area in these circuits (Byne et al., 2009) through extensive connections with the cerebral cortex (Alexander, 1986; Cummings et al., 1993; Leh et al., 2007). It is well-established that cortico-subcortical circuits (Byne et al., 2009) are involved in cognitive functions (Herrero et al., 2002; Sherman, 2005), but to date the specific neuroimaging correlates are still lacking.

Cognitive dysfunction frequency after stroke oscillates depending on composition of the stroke sample, the definition of cognitive impairment and the neuropsychological assessment used (Gottesman & Hillis, 2010). In general, the frequency of any cognitive impairment in the first few weeks after a stroke has been reported in several studies to be above 70% (Lesniak et al., 2008; Nys et al., 2007). Also, the risk of developing dementia five years after stroke is 9 times higher than in the healthy population (Kokmen et al., 1996). In the Pendlebury & Rockwell's (2009) meta-analysis, they reported that 1 in 10 develops new dementia soon after first stroke, and over 1 in 3 are demented after a recurrent stroke. Regarding composition of stroke samples, studies that only include symptomatic strokes might underestimate the prevalence of cerebrovascular damage, since many patients with or without clinical strokes have had other subclinical strokes or WMLs (Gottesman & Hillis, 2010). In contrast, many studies of VD involve neuropathological identification of strokes, which may or may not have been clinically apparent strokes (Launer et al., 2008). With respect to cognitive impairment frequency, in a study where cognitive impairment definition required an impairment of at least any four cognitive domains, frequency of cognitive dysfunction at three months after stroke was 35% (Tatemichi et al., 1994). The frequency of cognitive dysfunction two weeks after stroke increased until 90%, when required a Z score of -1 or lower on at least one cognitive domain (Jaillard et al., 2009).

Next are detailed the variables that can influence post-stroke cognitive dysfunction through different time phases after a vascular occurrence.

Table 1: Neuropsychological deficits according to vascular territory damage.

Anterior cerebral artery	**Left middle cerebral artery**	**Right middle cerebral artery**
○ transcortical motor aphasia ○ left unilateral ideomotor apraxia ○ left unilateral agraphia ○ humour and personality alterations	○ Broca and Wernicke aphasias and global aphasia ○ alexia with agraphia ○ ideomotor apraxia	○ hemineglect syndrome ○ constructive apraxia ○ visoperceptive and visuospatial deficits
Left posterior cerebral artery	**Right posterior cerebral artery**	**Posterior cerebral artery**
○ transcortical sensory aphasia and anomic aphasia ○ alexia ○ verbal memory impairment	○ constructive apraxia ○ visuospatial disorientation ○ visual memory alteration	○ visual agnosia ○ prosopagnosia ○ acromatopsia

Adapted from Junqué & Barroso (1999).

a) Predictors of cognitive dysfunction after stroke

Although cognitive sequels vary from person to person, it seems that some factors such as individual-level variables (age, VRF, comorbid diseases etc.) and stroke characteristics (neuroimaging volume and location of cerebral ischemic stroke, ischemia duration, ischemia penumbra area etc.) could significantly contribute to these deficits (Hankey et al., 2003; Rosso & Samson, 2014; Vogt et al., 2012). However, to date, the specific factors that explain the large variability in cognitive recovery among stroke patients have not yet been identified.

Individual-level characteristics

Demographical and medical factors such as age, sex o pre-stroke baseline cognition have been shown to influence the extent to which cognitive deficits after a vascular event are presented. It is well-established that older age is an important predictor of worse functional and cognitive outcome soon after stroke (Jehkonen et al., 2000; Klimkowicz-Mrowiec et al., 2006; Nys et al., 2007) as well as it is an important predictor of the development of cognitive impairment or dementia in the chronic period after stroke (Rasquin et al.,

2004). Specific cognitive deficits such as aphasia might also be more common in older individuals acutely after stroke (Pedersen et al., 1997; Rasquin et al., 2004). Some limitations of the study of age as a predictor of cognitive deficits after stroke have to be noted. Age variable is usually primarily confounded by higher likelihood of pre-stroke cognitive dysfunction and it is also confused by a higher frequency of cardioembolic stroke, which is more likely to lead to cortical ischemia and consequently, to yield several cognitive deficits (Gottesman & Hillis, 2010). Sex differences in the distribution of cognitive dysfunction after stroke might be attributable to differences in stroke mechanisms between men and women. Women tend to have more cardioembolic strokes, whereas men have more LI, which might explain the higher frequency of cognitive dysfunction in women than in men (Nys et al., 2007). Additionally, women tend to experience strokes at an older age than men (Reid et al., 2008), so women might have more pre-stroke cognitive dysfunction. Furthermore, pre-stroke baseline cognition, which is probably a very important factor to determine cognitive post-stroke dysfunction, is very difficult to exactly estimate although it is known that individuals with risk factors for stroke are likely to have some cognitive impairment before onset of stroke (Gottesman & Hillis, 2010). Other markers, such as fever and hyperglycaemia after stroke have been associated with worse post-stroke cognitive performance but the results are conflicting (Nys et al., 2007; Kruyt et al., 2008). Also, haemoglobin abnormal level and the presence of seizures are other intra-individual characteristics that have been related with higher risk of early post-stroke cognitive impairment (Cordonnier et al., 2007; Gottesman & Hillis, 2010). Another possible prediction factor of cognitive dysfunction post-stroke is the effect of concurrence of medication such as psychoactive medication (Gottesman & Hillis, 2010). Finally, many clinical interventions used acutely in stroke such as intravenous alteplase or cortical reperfusion might affect cognitive deficits recovery (Heiss et al., 1998; Hillis et al., 2006; 2003) and reduce disability after stroke (The NINDS rt-PA Study Group, 1995). The observed association between apolipoprotein E-Ɛ4 status and cognitive dysfunction after stroke might also be attributable to differences in baseline cognition associated with this allele (Wagle et al., 2009).

Neuroimaging correlates of post-stroke cognitive deficits

Neuroimage techniques can provide us specific information to evaluate and follow-up post-stroke cognitive deficits. Characteristics of the strokes themselves, as well as the presence of SVD and cortex atrophy, seem to affect the risk of developing cognitive deficits after stroke (Hillis et al., 2001; Jokinen et al., 2005; Nys et al., 2007; Stebbins et al., 2008). Although larger strokes seem to be related with higher rates of cognitive dysfunction (Nys et al., 2007) this association is controversial (Jaillard et al., 2010; Lazar et al., 2008). Specifically, it remains unclear whether this relation is a feature of the stroke size or just the fact that larger strokes are more likely to involve many regions (such as cortex or other important areas supporting cognition) (Gottesman & Hillis, 2010).

The influence of pre-existing brain pathological abnormalities on the development of post-stroke cognitive deficits is uncertain and controversial. Many studies, showed an association between atrophy in middle temporal area and WMLs in cognitive impairment after stroke compared to individuals with intact post-stroke cognition (Grau-Olivares et al., 2007; Jokinen et al., 2005; Stebbins et al., 2008). However, other studies have not found significant differences between the presence of WMLs, LI or cerebral atrophy and cognitive dysfunction after stroke (Jaillard et al., 2010; Nys et al., 2007). Finally, stroke patients with more presence of WMLs and cerebral atrophy are likely to have worse cognition at baseline and this might be the reason for apparent associations with cognitive function after stroke.

After 3-year follow-up study, *The longitudinal Leukoaraiosis and Disability (LADIS)* (Jokinen et al., 2012) showed that medial temporal lobe atrophy and subcortical atrophy predicted significantly steeper rate of decline in global cognitive measures and performance in psychomotor speed, executive function, and memory after adjusting for other predictors of cognitive dysfunction including LI and WMLs volume. In addition, cortical atrophy independently predicted deficits in psychomotor speed. WMLs volume remained significantly associated with cognitive decline even after controlling for atrophy scores. Therefore, significant synergistic interactions were found

between WMLs and atrophy measures in overall cognitive performance across time and the rate of cognitive decline.

Recent MRI neuroimaging techniques, such as diffusion tensor imaging (DTI), tractography and resting state technique among others, provide us specific information about microstructural abnormalities or white matter tract impairment in CVD. These MRI methods are showing promise in identifying individuals with brain abnormalities who might be at higher risk for cognitive impairment (Fazekas et al., 2005; Williamson et al., 2010).

b) Cognition in acute stroke

Although cognition is rarely assessed in detail in the acute setting (<72 hours) (Gottesmann & Hillis et al., 2010), studies that have assessed it have reported how quickly cognition can fluctuate (Hillis et al., 2002; 2001). The most common cognitive deficit after stroke is aphasia, hemispatial neglect and executive dysfunction (Engelter et al., 2006; Garret et al., 2004). Aphasia occurs from 15% to a 33% of patients with stroke (Engelter et al., 2006; Inatomi et al., 2008) and also typically occurs after a left hemispheric stroke. Similar frequencies have been reported for hemispatial neglect, with rates above 40% among patients with a right hemispheric stroke (Ringman et al., 2004). The type of language deficit presented (i.e. impairment of comprehension, grammatical sentence production, speech articulation, reading, spelling, or naming) or type of hemispatial neglect observed (whether a patient neglects the left half of objects or the left half of space) depends on the specific location of ischemia (Hillis et al., 2007; Medina et al., 2009; Verdon et al., 2010).

c) Cognition in subacute stroke

In the subacute time frame (define as within 3 months after a stroke), the estimated proportion of patients with dementia criteria was 25.5% (Pohjasvaara et al., 1997) and the aproximated rate of patients having cognitive impairment ranges from below 50% to over 90% across studies (Jaillard et al., 2009; Nys et al., 2007; 2005). These discrepancies in frequency might be partly explained by differences in the study populations and stroke subtypes. For example, Jaillard et al (2009) included large-vessel, cardioembolic strokes and

LI, and cognitive dysfunction was defined by a Z score of -1 or lower in at least one cognitive domain two weeks after stroke. The frequency of cognitive dysfunction was reported in an approximately 90% of stroke patients. In contrast, Nys et al. (2007) classified cognitive impairment separately depending on the stroke subtype and reported that fewer than 50% of patients with subcortical or infratentorial strokes had cognitive impairment compared to 74% of individuals with cortical strokes.

Notwithstanding, many of the early cognitive problems significantly improve in the first few weeks to months after a CVD. This improvement is usually spontaneous due to recanalisation, diasquisis resolution and cerebral plasticity phenomena such as a recruitment of adjacent or contralesional brain regions taking over cognitive tasks previously performed by ischemic regions (Dancause, 2006; Van Meer et al., 2012; 2010).

d) Dementia and other long-term cognitive effects

Some cognitive deficits after a vascular event resolve beyond the subacute time period and, even in the acute phase (Gottesman & Hillis, 2010) however, other cognitive impairments remain over time. Nys et al. (2005) found that over 83% of patients with early post-stroke deficits in visual perception and visuospatial construction and 78% of patients with impairment in visual memory had shown improvement in these cognitive domains by 6 months. The rate of recovery in other cognitive domains, such as executive function, abstract reasoning and neglect, was less frequent (Nys et al., 2005). At 1 year post-stroke, Lesniak et al. (2008) reported that 54% of patients still presented deficits in attention function and fewer amount of patients had impairments in language and long-term memory. In a follow-up 2 years after stroke, Hochstenbach et al. (2003) found cognitive recovery in all cognitive domains. Specifically, the biggest improvement was found in the attentional domain and the least, in the memory domain. However, the same authors conclude that the recovery of these results was due only to a subset of patients. Most patients did not show a cognitive improvement, or they even showed a decline.

It is well-established that individuals with stroke have higher prevalence of dementia (Narasimhalu et al., 2009; Troncoso et al., 2008). Individuals with VCI after stroke progress to dementia at a rate of about 8% per year (Sachdev et al., 2009). However, in a systematic review, Pendlebury & Rothwell (2009) observed that the estimated proportion of dementia at least 3 months after stroke varied depending on the stroke population included. In studies in which individuals with first-ever stroke were enrolled rate prevalence estimates were 7-12%. When participants with any (first or recurrent) stroke including pre-stroke dementia were examined, mean prevalence evaluates were even higher at 27% and were 20% when pre-stroke dementia was excluded. Also, individuals with recurrent stroke had pooled estimates of 41%.

e) The neuropsychological assessment in Vascular Cognitive Impairment

Different neuropsychological assessments have been proposed to evaluate cognitive impairment after suffering a vascular event. Hoffmann et al. (2009) have developed the Coconut test, which includes an extensive testing of language, neglect, praxis, memory and emotional responses, among other specific tests for a range of cognitive syndromes. The authors themselves concluded that this test was highly sensitive (91%), although not very specific (35%). Other shorter tests, such as Cognistat and the Screening Instrument for Neuropsychological Impairment in Stroke, have demonstrated a sensitivity of 82% and 71% respectively, in the evaluation of cognitive deficits (Nokleby et al., 2008). None of these assessments contain tests of executive function, attention and psychomotor speed. In a recent systematic review, Gottesman & Hillis (2010) suggested the importance of including these functions in order to obtain complete information on global cognitive function after a vascular event.

Both *The National Institutes of Neurological Disorders and Stroke* and *The Canadian Stroke Network* proposed an international consensus for the clinical, cognitive and conductual assessment in VCI (Hachinski et al., 2006). They included protocols of 60, 30 and 5 minutes (**Table 2**). The 60 minute protocol contains tests in 4 domains: executive/activation, language, visuospatial skills

and memory. The 30 minute protocol includes tests within the 60 minute protocol and is designed as a clinical screening instrument for suspected VCI patients. Finally, the 5 minute protocol is designed as quick clinical and cognitive screening. Finally, this group also includes MoCA test. This test takes 10-15 minutes and assesses executive function better than the traditional MMSE test.

Table 2: Neuropsychological recommended protocols

Sixty minutes protocol	
Executive/Activation ○ Semantic Fluency (Animals) ○ Phonetic Fluency ○ WAIS-III Digit Symbol-Coding ○ Trail making Test Supplemental: Strategic memory (Hopkins verbal subtest learning test-revised) and simple and choice reaction time *Language* ○ Boston Naming Test 2nd Edition, Short Form *Other* ○ MMSE *Premorbid status* Informant Questionnaire for Cognitive Decline in the Elderly, Short Form	*Memory* ○ Hopkins Verbal Learning Test or California Verbal Test Supplemental: Boston Naming Test Recognition and Digit Symbol-Coding Incidental Learning *Visuospatial skills* ○ Rey-Osterrieth Complex Figure Copy and memory *Neuropsychiatric symptoms* ○ Neuropsychiatric inventory Questionnaire Version Centre for Epidemiological Studies-Depression Scale
Thirty minutes protocol	
Executive/Activation ○ Semantic Fluency (Animals) ○ Phonetic Fluency ○ WAIS-III Digit Symbol-Coding Supplemental: Trail making Test	*Memory* ○ Hopkins Verbal Learning Test *Neuropsychiatric symptoms* ○ Neuropsychiatric inventory *Other* ○ Supplemental: MMSE
Five minutes protocol	
Executive/Activation ○ Phonetic Fluency (one letter) ○ Orientation Task (five items)	*Memory* ○ Memory task (five words)

WAIS-III (Wechsler adult intelligence scale-III); MMSE (Mini-Mental State Examination). Table adapted from Hachinski et al. (2006).

2. Vascular cognitive impairment

The term VCI refers to any degree of cognitive impairment -from VaMCI to VD or mixed dementia (AD and VD)- associated to CVD (Desmond et al., 2004; Dong et al., 2014; O'Brien et al., 2003; Román et al., 2004). The prevalence rate of VCI is 15-20% (Rockwood et al., 2000; Szatmari et al., 1999). The heterogenity of vascular and parenchymal lesions -there are more than one hundred potential causes to VCI (Chui, 2005)- can affect several important neuroanatomical regions and cerebral circuits and consequently, there are distinct neuropsychological profiles along the VCI continuum. Nonetheless, executive dysfunction is one of the main clinical manifestations in CVD, attributed to preferential damage to the prefrontal subcortical circuits observed in patients with VCI. Executive functions are involved in complex cognition processes including solving new problems, conceptual reasoning, cognitive inhibition, shifting from one task to another, information processing speed, working memory and attention abilities (Garrett et al., 2004; Nyenhuis et al., 2004; Troyer et al., 1998). Therefore, neuropsychological protocols must be emphasized in the assessment of this function.

The American Heart Association and *The American Stroke Association* (Gorelick et al., 2011) have provided a practical approach to define VCI**.** Notably, these authors have also recommended that any diagnostic criteria associated with CVD should be based on two factors:

a) Demonstration of presence of a cognitive disorder through neuropsychological examination and

b) Clinical history of CVD that demonstrates the presence of neuroimaging linking cognitive impairment and CVD.

VaMCI is defined by deficits in at least one cognitive domain with intact or mild impairment in the activities of daily living (Fischer et al., 2007; Gorelick et al., 2011). Recently, Dong et al. (2014) proposed a VaMCI classification into four subtypes: (i) amnestic single-domain; (ii) non-amnestic single-domain; (iii) amnestic multiple-domain; and (iv) non-amnestic multiple-domain. On the other hand, VD is defined by performance deficits in ≥2

cognitive domains that have enough severity to affect the subject's activities of daily living (Gorelick et al., 2011).

Due to the high prevalence and importance of VCI, new guidelines for good clinical practice for stroke suggest that individuals with risk of cognitive impairment related to vascular disease should receive a neuropsychological assessment. This should include people with HTA, DL, DM, age older than 65 years, history of stroke or neuroimaging evidence suggesting LI or WMLs, damage to other specific organs (kidneys and eyes), and vascular patients that present cognitive or functional complaints (Gorelick et al., 2011).

2.1 Vascular Cognitive Impairment and Alzheimer's disease

Traditionally, AD and VCI have been considered as separate entities, however, this dichotomy is now conceptualised as a *continuum* of overlapping syndromes. Underlying neurodegenerative and CVD pathologies often coexist (MRC CFAS et al., 2001; Saito & Murayama, 2007) and "mixed" pathology is probably the commonest substrate of cognitive impairment in older age (Fotuhi et al., 2009; Iadecola et al., 2010). It has been found that 60% of patients with AD present LI and up to 90% show WMLs. Amyloid plaques and neurofibrillary tangles have been observed in over one third of patients diagnosed of VD (Querfurth & LaFerla, 2010). Clinical pathological studies indicate that CVD and neurodegenerative pathologies interact to heighten the risk of dementia and produce more severe cognitive dysfunction than either process alone (Gorelick et al., 2011).

In a meta-analysis study, Mathias & Burke (2009) reported that, among the tests that had been used in more than one study, 12 tests may prove useful for the distinction between VD and AD. Specifically a perception (emotional recognition) and a verbal memory (delayed story recall) tests were the most sensitive tools to distinguish between these two types of dementias. It is important to take into account that all cognitive tests have limitations in their discrimination ability, for this reason these same authors suggested to be careful when using them in the diagnosis and always collect other information such as medical history, neuroimaging information and behavioural observations. Neuroimaging is an important tool to assess brain lesions possibly associated with VCI however, to date, exactly how cerebrovascular

and neurodegenerative pathologies are linked remains a critical question in understanding mechanisms of dementia.

3. Neuroimaging contributions in the vascular pathology

Nowadays, neuroimage constitutes an important tool to diagnose, follow-up assessment, and research of vascular mechanisms underlying VCI (Barber et al., 2013; Muir et al., 2006). Particularly, MRI have been accepted for decades as the choice method in the brain clinical and research assessments (Frisoni et al., 2010, Hachinski et al., 2006) due to high image resolution and timely acquisition whilst having no side effects. Moreover, this technique is considered an indicator of the underlying cerebral neuropathology (Gorelick et al., 2011; Josephs et al., 2008). It has been the significant development in recent years of new MRI techniques such as DTI, tractography, spectrography and functional MRI among others, which provide us specific and relevant information about CVD. These new MRI techniques will provide us the opportunity to study in vivo the neuroanatomical correlates regarding cognitive functioning in patients with CVD. These MRI techniques not only evaluate primary brain injury in both grey and white matter tracts but also help to investigate specifically remote brain damage not detectable with conventional MRI (Li et al., 2011; O'Sullivan et al., 2001). Integrity of microstructural tissue, cortico-subcortical loops as well as other white matter tracts has been shown to contribute to cognitive dysfunction and dementia (Chua et al., 2009; Kuczynski et al., 2010; Madden et al., 2012; Soriano-Raya et al., 2014).

3.1 Magnetic Resonance Imaging technique and sequences

The basic MRI protocol in the diagnostic work-up and follow-up of CVD includes T1 and T2 MRI weighted images **(Figure 1)**. T1-weighted images are often used to evaluate the brain structure and atrophy. On these images cerebral spinal fluid (CSF) is hypointense (i.e. dark), fat appears hyperintense (i.e. bright), grey matter (GM) has less intensity than white matter (i.e. it appears darker). In ischemic lesions, T1-weighted images look hypointense **(Figure 2)**. Specifically, T1-weighted measures allow the assessment of GM atrophy related to the loss of neurons, synapses, and

dendrite dearborisation that occurs on a microscopic level and expansion of CSF spaces. T2-weighted scans are known as “pathology” scans. On these images CSF is hyperintense, fat barely has a signal and GM looks brighter than white matter. In ischemic lesions and oedema T2-weighted image appears hyperintense. In this contrast it might be difficult to distinguish a lesion from normal CSF, especially for smaller lesions. FLAIR is a variation of a T2-weighted image where the CSF signal is nulled, the CSF signal almost entirely suppressed and it is dark on the final image, whereas lesion tissue will appear hyperintense as on the T2-weighted. This image offers a good contrast to distinguish between CSF and lesions (Hajnal et al., 2001). Particularly, this image allows the detection of lesions in border zones of different tissue types, such as cortical, PVHs or DWMHs, presumably resulting from demyelination and dying back of axonal processes (Vemuri & Jack, 2010).

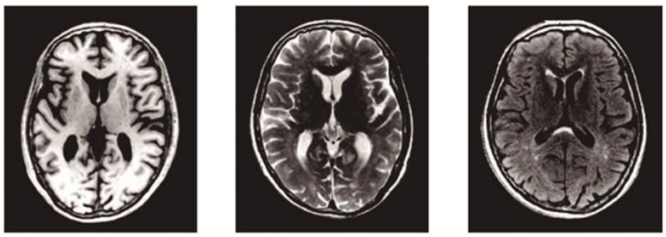

Figure 1: Basic Magnetic Resonance Imaging sequences. Images are taken from one of the healthy subjects.

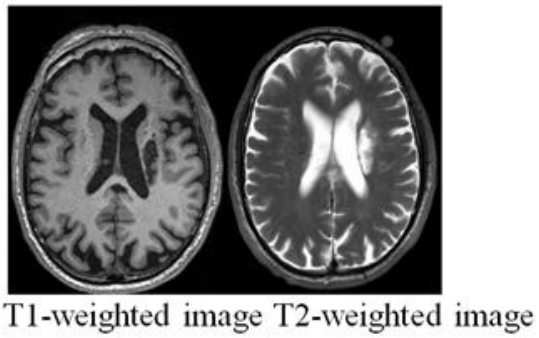

Figure 2: T1-weighted and T2-weighted images in ischemic stroke pathology. T1-weighted image appear hypointense and T2 is hyperintense in ischemic stroke lesion. Images are taken from one of the ischemic stroke patients.

3.2 Diffusion tensor imaging and tractography techniques

DTI is a MRI technique based on the measurement of the random displacements of water molecules that provides information about integrity of white matter (WM) fiber tracts (Hagmann et al., 2006; Kubicki et al., 2002; Sundgren et al., 2004) as well as information of microstructure of GM structures (Lee et al., 2013; Scanlon et al., 2013). DTI may reveal WM changes not detectable with conventional MRI (Li et al., 2011; O'Sullivan et al., 2001). Properties of diffusion water molecules depend on the underlying anatomical structure such as cell membranes and fiber structures (Le Bihan, 1995). For example, in the ventricles water can freely move in all directions; if however, the water molecules are constrained within axons diffusion is facilitated parallel to the axonal direction and hindered perpendicular to it (**Figure 3**). This diffusion property is referred to as "anisotropic" (restricted motion) and isotropic diffusion (equal motion) and forms the basis of DTI tractography. Diffusion data is more anisotropic (preferent direction of the diffusion) in the WM than in GM because of the parallel orientation of axonal membranes and myelin, which are the principal responsible for the restriction of water movements.

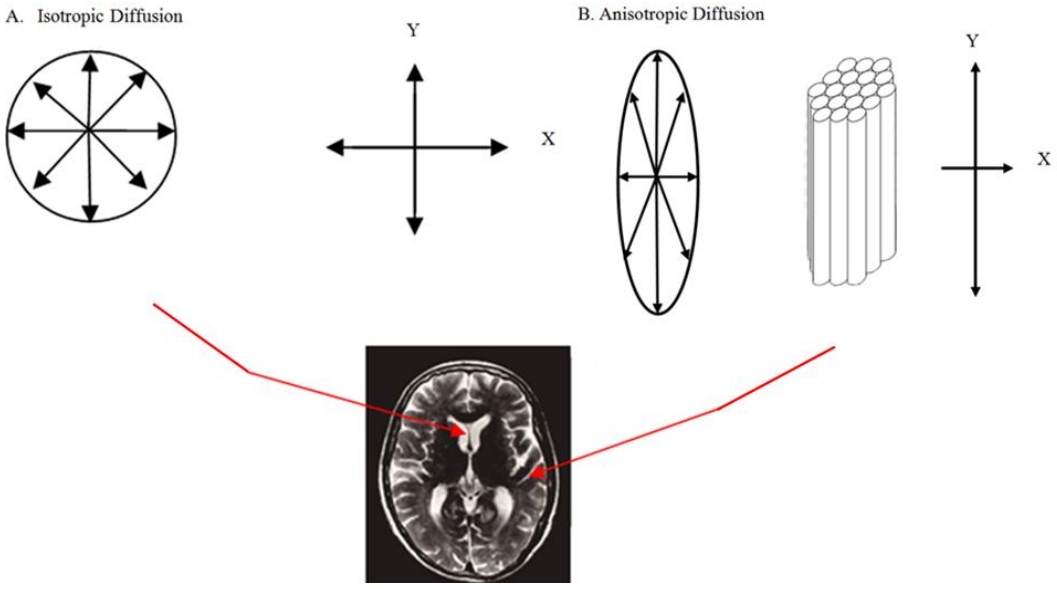

Figure 3: Concept of tissue-specific water diffusivity.
(A) Water molecules movement is unconstrained like in the large fluid-filled spaces in the brain (i.e. the ventricles, as illustrated in the MRI in the left narrow), diffusion is isotropic, which means that motion occurs equally and randomly in all directions. (B) When motion is constrained, as in white-matter tracts (illustrated in the MRI, in the right narrow), diffusion is anisotropic, meaning that motion is oriented more in one direction than another. Own elaborated figure.

There are different DTI anisotropy measures, fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity and radial diffusivity. Specifically, FA and MD, two of the most used and knowledge indexes (Basser & Pierpaoli, 1996), have been used along the three presented studies. FA is a measure of directional diffusivity (Basser et al., 1994; Le Bihan et al., 2001) and varies between 0 (isotropic diffusion / equal diffusion in all directions) and 1 (entirely anisotropic / undirectional diffusion). Lower FA values suggest loss of tissue integrity (Alexander, 2007; Basser & Pierpoli, 1996; Mori & Zhang, 2006) due to axonal damage or demyelination. MD reflects the average molecular motion considered in all directions and indicates the magnitude of diffusion. MD will typically increase when disturbance of axonal tracts occurs (Alexander, 2007; Le Bihan et al., 2001).

Several methods for DTI image analysis including region of interest (ROI), voxelwise analyses, tractography and histogram have been used to identify microstructural differences between groups (Berlot et al., 2014; Kanaan et al., 2014). The ROI approach is a quantitative analysis performed by

calculating the mean value of DTI indexes over a ROI in specific deep GM structures or in WM tracts. In this approach, the ROI are automatic or manually selected by an investigator, in order to carry out statistic analyses on the DTI indexes obtained from the same anatomical region across different groups. In voxelwise analysis, each subject's DTI images are registered into a standard space, and then voxelwise statistics are carried out to detect regional differences between groups (Abe et al., 2010; Smith et al., 2006).

Although this technique has been widely studied in the WM, more recently, DTI has also been used to investigate the integrity of subcortical GM structures in different cerebral pathologies (Lee et al., 2013; Müller et al., 2007; Scanlon et al., 2013), including MCI (Kantarci et al., 2001; Müller et al., 2007), AD (Stebbins et al., 2008) and ischemic stroke (Buffon et al., 2005; Hervé et al., 2005; Li et al., 2011). A DTI study showed a relationship between thalamic microstructural abnormalities and cognitive dysfunction in lacunar stroke patients with leukoaraiosis using a ROI approach (Li et al., 2012). However, to date there is no study about diffusion thalamic abnormalities related to WMLs and their association with cognitive function using a voxelwise analysis. Similarly, although previous DTI studies in stroke patients have used a general ROI approach in the thalamus (Buffon et al., 2005; Hervé et al., 2005; Li et al., 2011), to the best of our knowledge, there is no data about the relationship between thalamic DTI measures and cognitive function using a voxelwise analysis.

DTI-based tractography allow us to do "virtual dissections *in vivo*" of WM pathways (Catani et al., 2002; Wakana et al., 2004) and explore the anatomical basis of human cognition and its disorders. Especially, in the clinical area this technique has been used in the preoperative planning for brain tumors and vascular malformations (Witwer et al., 2002; Yamada et al., 2009). Tractography analysis is conceptually similar to ROI approach, but in this case, the ROIs are represented by fiber tracts that are automatically (probabilistic tractography) or manually (deterministic tractography) defined by tractography algorithms. Then, the analysis of WM measures could be by voxelwise or ROI analyses. DTI data contains information about the principal direction of diffusion in a voxel (Basser et al., 2000; Le Bihan et al., 2003). The

information of this orientation may also be used to delineate WM tracts by employing so-called tractography algorithms. The basic assumption behind these algorithms is that the principal direction of diffusion is parallel to the main direction of diffusion in every voxel (Bozzali & Cherubini, 2007). Different tractography derived variables allow us to analyze specific characteristics of WM tracts between groups (Chen & Schlaug, 2013; Jones et al., 2005) and they provide information about structural brain connectivity (Long et al., 2013). Tractography has been used to study WM anatomy in healthy populations (Catani et al., 2002; Wakana et al., 2004) and WM abnormalities in MCI and AD (Kiuchi et al., 2009; Taoka et al., 2009), epilepsy (Concha et al., 2012), schizophrenia (Jones et al., 2006; Kanaan et al., 2009) and developmental anomalies (Lee et al., 2005). Most research relating white mater tracts integrity and cognitive function in participants with WMLs has employed a ROI approach (O'Sullivan et al., 2001) or has applied other methods such as histogram (Vernooij et al., 2009). In stroke pathology, probabilistic tractography has shown to be highly sensitive to Wallerian degeneration of corticospinal tract (Kunimatsu et al., 2007; Park et al., 2013) and sensorimotor pathway (Yamada et al., 2003). More recent studies have shown that probabilistic tractography may also be used to assess patient outcomes after stroke (Konishi et al., 2005; Kunimatsu et al., 2007; Nelles et al., 2008; Zeng et al., 2011) and arcuate fasciculus tractography may predict language deficits after a vascular event (Hosomi et al., 2009; Yamada et al., 2007). Probabilistic tractography has also been used in paediatric ischemic brain injury (Koerte et al., 2011; Murakami et al., 2008) and in preterm children (Bassi et al., 2008; Berman et al., 2005). To date, there is no data about deterministic tractography abnormalities and cognitive function in both healthy and ischemic stroke subjects.

In conclusion, DTI technique not only helps us to understand the abnormalities that can occur in the primary lesion in brain disorders, but also could allow us to study secondary remote lesions in grey areas or WM tracts and their cognitive correlates in both middle-aged healthy participants and in ischemic stroke patients.

II AIMS

Executive functions are one of the most affected cognitive domains in CVD. They are crucial for human cognition since they include higher-order cognitive control processes for the attainment of a specific goal (Lezak et al., 1989). Executive dysfunction can lead to several consequences ranging from planning, monitorization, flexibility, working memory, attention and inhibition impariment to emotional, behavioural and functional deficits (Schmeichel et al., 2008; Wilson et al., 1998). In spite of a prolonged research and clinical effort, the understanding of this complex cognitive domain, its neural basis and its cognitive and behavioural sequels remains currently unknown.

The general aim of this thesis was to study the effects of direct and remote cerebrovascular lesions on cerebral circuits disruption regarding executive functions. In order to study remote abnormalities of cerebral loops and their implication in cognitive functioning, we used DTI for both SVD and LVD. We particularly focused on the study of microstructural thalamic abnormalities because thalamus is a crucial node in cortico-subcortical circuits and it is crucial for cognition, especially executive function domain. Furthermore, as attention and cognitive inhibition are some of the most important functions in the executive domain, we also addressed the relationship between a recently described frontal WM tract -called Frontal Aslant Tract, (FAT)- and these functions in healthy subjects and ischemic stroke patients.

The specific aims of this thesis were:

I. To examine remote thalamic diffusion abnormalities in healthy participants with WMLs and their relationship with cognitive function (study I).

II. To investigate remote thalamic diffusion abnormalities and cognitive dysfunction in right ischemic stroke patients 3 months after the vascular event (study II).

III. To explore the role of the right FAT in executive functions in healthy and ischemic stroke participants (study III).

III MATERIALS AND METHODS

This thesis consists of 3 studies that examine the neuroimaging mechanisms involved in executive dysfunction in CVD, using poblational and epidemiological approaches and clinic-based method. The poblational and epidemiological approaches propose a population-based frame for properly interpreting results. Particularly, in study I, the healthy middle-aged sample used was selected from primary healthcare centers, according to poblational selection criteria. Furthermore, the study design followed epidemiological criteria and this allows the results of study I to be representative of the population. The clinical approach allows obtaining valuable information of each patient's status along the cognitive follow-up assessment procedure. Poblational and epidemiological approaches and clinic-based method involve certain limitations, mainly the fact that they are by nature correlational and thus unable to determine causal relationships.

In the three presented studies we used different samples, several DTI neuroimaging analyses as well as selected neuropsychological tests. All studies have been approved by the University of Barcelona (Barcelona) and the Germans Trias i Pujol University Hospital (Badalona) Ethics committee. Informed consent was obtained for each participant in accordance with the Helsinki Declaration. The specific characteristics of the samples included in each study and the methods employed are described in detail in the included papers.

IV RESULTS

Study I

Fernández-Andújar, M., Soriano-Raya, J. J., Miralbell, J., Lopez-Cancio, E., Cáceres, C., Bargalló., Barrios, M., Arenillas, J.F., Toran, P., Alzamora, M., Clemente, I., Dávalos, A., Mataró, M. (2013). **Diffusion thalamic diffusion differences related to cognitive function in white matter lesions.** *Neurobiology of Aging*, in press doi: 10.1016/j.neurobiolaging.2013.10.087. IF: 6.09.

Study II

Fernández-Andújar, M., Doornink, F., Dacosta-Aguayo, R., Soriano-Raya, J. J., Miralbell, J., Bargalló, N., Lopez-Cancio, E., Pérez de la Ossa, N., Gomis, M., Millán, M., Barrios, M., Cáceres, C., Pera, G., Forés, R., Clemente, I., Dávalos, A., Mataró, M. (2013) **Remote thalamic microstructural abnormalities related to cognitive function in ischemic stroke patients.** *Neuropsychology journal*, accepted. IF: 3.58

Study III

Fernández-Andújar, M., Forkel, S.J., Dacosta-Aguayo, R., Miralbell, J., Soriano-Raya, J. J., Clemente, I., Millán, M., Lopez-Cancio, E., Bargalló., Barrios, M., Cáceres, C., Toran, P., Alzamora, M., Dávalos, A., Mataró, M., Thiebaut de Schotten, M. (2013). **Disconnection of the right Frontal Aslant Tract impairs attention and response inhibition: a spherical deconvolution tractography study.** Working paper.

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Thalamic diffusion differences related to cognitive function in white matter lesions

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a b s t r a c t

Cerebral white matter lesions (WMLs) are related to cognitive deficits, probably due to a disruption of frontalesubcortical circuits. We explored thalamic diffusion differences related to white matter lesions (WMLs) and their association with cognitive function in middle-aged individuals. Ninety-six participants from the Barcelona-AsIA Neuropsychology Study were included. Participants were classified into groups based on low grade and high grade of periventricular hyperintensities (PVHs) and deep white matter hyperintensities (DWMHs). Tract-Based Spatial Statistics was used to study thalamic diffusion differences between groups. Mean fractional anisotropy (FA) values in significant areas were calculated for each subject and correlated with cognitive performance. Participants with high-grade PVHs and DWMHs showed lower FA thalamic values compared to those with low-grade PVHs and DWMHs, respectively. Decreased FA thalamic values in high-grade DWMHs, but not high-grade PVH, were related to lower levels of performance in psychomotor speed, verbal fluency, and visuospatial skills. Thalamic diffusion differences are related to lower cognitive function only in participants with high-grade DWMHs. These results support the hypothesis that frontoesubcortical disruption is associated with cognitive function only in DWMHs.

1. Introduction

Cerebral white matter lesions (WMLs) comprise diffuse areas of high signal intensity on T2-weighted images in magnetic resonance image (MRI), and are common findings in normal aging (de Leeuw et al., 2001; Enzinger et al., 2007; Longstreth et al., 1996). WMLs are considered an expression of cerebrovascular small vessel disease (SVD) (Pantoni et al., 2002) and are usually divided into 2 groups: those adjacent to the ventricles (periventricular hyperintensities [PVHs]) and those located in the deep white matter (deep white matter hyperintensities [DWMHs]) (Fazekas et al., 2002).

WMLs have been consistently related to cognitive dysfunction resulting from cortico-subcortical circuit disruption (Schmidt et al., 2006; Linortner et al., 2012). However, the specific contribution of PVHs or DWHMs is still controversial (Schmidt et al., 2011).

The thalamus, which is a key structure in corticoesubcortical circuits (Byne et al., 2009), is involved in cognitive functions through extensive reciprocal connections with the cerebral cortex (Alexander et al., 1986; Cummings, 1993; Leh et al., 2007). Thalamic microstructural abnormalities have been related to cognitive dysfunction in lacunar stroke patients with leukoaraiosis (Li et al., 2012), schizophrenia (Marenco et al., 2012), and attention-deficit hyperactivity disorder (Xia et al., 2012). However, thalamic diffu-sion differences related to WMLs and their association with cognitive function remains unknown. The aims of this study were to explore thalamic diffusivity differences associated with DWMHs and PVHs, and to examine their relationship with cognitive out-comes in middle-aged, community-dwelling individuals.

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In a previous study, we found a predominant role of high-grade DWMHs in cognitive dysfunction in middle-aged individuals (Soriano-Raya et al., 2012). Accordingly, we hypothesized the following: (1) thalamic diffusion differences would be found in a greater extent in participants with high-grade DWMHs than in participants with high-grade PVHs; (2) thalamic diffusion differences related to high-grade DWMHs would be associated with lower cognitive performance; and (3) thalamic diffusion differences related to high-grade PVHs would not be associated with cognitive function.

2. Methods

2.1. Study participants

The Barcelona-AsIA (Asymptomatic Intracranial Atherosclerosis) Study is an ongoing population-based study that includes a random sample of participants more than 50 years of age without previous history of stroke or ischemic heart disease. Complete details of the Barcelona-AsIA protocol have been previously described (Lopez-Cancio et al., 2012). The Barcelona-AsIA Neuropsychology Study is a related prospective study with the following objectives: (1) to investigate the associations of vascular risk factors (VRF), asymp-tomatic cervicocerebral atherosclerosis, and MRI signs of SVD with cognition; and (2) to identify clinical and radiological features and biological mechanisms underlying these associations.

Our participants were recruited from the Peripheral Arterial Disease Study (PERART), a related ongoing population-based study that aims to determine the prevalence of peripheral arterial disease and to evaluate the predictive value of ankle-arm index in relation to cardiovascular morbidity and mortality (Alzamora et al., 2007). Details of the recruitment process have been previously described (Soriano-Raya et al., 2012). Briefly, a total of 132 participants were selected to undergo a comprehensive neuropsychological assessment and brain MRI. We included individuals 50e65 years of age. Exclusion criteria were as follows: history of stroke or transient ischemic attack (TIA), coronary heart disease, chronic neurological disease, or severe psychiatric disorder (n = 11); a Mini-Mental State Examination (MMSE) score of <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., <75% of neuropsychological assessment available) (n = 2). For the present study, we finally selected 100 participants 50e65 years of age, stratified by sex and educational level.

This study was approved by the University of Barcelona and the Hospital Germans Trias i Pujol Ethics committee. Informed consent was obtained for each participant in accordance with the Declaration of Helsinki.

2.2. Evaluation of vascular risk factors

Diagnosis of a particular vascular risk factor (arterial hypertension, dyslipidemia, diabetes mellitus, and current smoking status) was based on clinical history or use of medication for this particular condition at the time of the clinical examination.

2.3. Neuropsychological assessment

All participants completed an extensive neuropsychological assessment. Cognitive measures were grouped into 8 cognitive domains including tests that measure the same cognitive function (Lezak et al., 2004; Strauss et al., 2006): executive functioning, working memory, attention, verbal fluency, verbal memory, visual memory, visuospatial skills and psychomotor speed. 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 (Golden, 1978) were used to examine executive functioning (i.e., conceptualization, planning, and inhibition). Working memory was assessed 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). A computerized version of the Continuous Performance Test (Conners, 1995) and Digit Span Forward, Symbol Search, and Digit Symbol Coding subtests of the WAIS-III were used to measure attentional abilities. Verbal fluency was assessed with letter fluency (letters P, M, and R) (Artiola et al., 1999) and semantic category fluency (animals) (Strauss et al., 2006) in 60 seconds. Verbal and visual memory were examined using Word Lists and Visual Reproduction from the Wechsler Memory Scalee3rd edition (WMS-III) (Wechsler, 1997b), respectively. Evaluation of visuospatial skills was done by Visual Discrimination and the Copy from the Visual Reproduction subtest (WMS-III). Psychomotor speed was measured with part A of the Trail Making Test and Grooved Pegboard (Ruff and 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. The Geriatric Depression Scale 15-item version (GDS-15) (Sheikh and Yesavage,1986) was used to assess depressive symptoms.

2.4. MRI and analysis

MRI was performed on a 3T Siemens Magnetom Trio (Siemens Diagnostics Healthcare, Erlangen, Germany) at the Image Diagnosis Centre (Hospital Clínic, Barcelona, Spain). The MRI protocol included a set of 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 x 1 x 1 mm), and diffusion tensor images (DTI) acquired in 30 directions with the following echoplanar acquisition protocol matrix: 120 x120; TR: 9300 ms; TE: 94 ms; flip angle: 15º; field of view: 240 mm; no gap (2-mm thickness); voxel size: 2 x 2 x 2 mm, and b ¼ 1000 s/mm^2. Two acquisitions of DTI were averaged. Axial fluid attenuated inversion recovery (FLAIR) images (TR: 9040 ms; TE: 85 ms; inversion time [TI]: 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 x5 mm, gap: 1.5 mm) were also collected for white matter rating le-sions (see below).

Individual processing of diffusion tensor data was performed using Tract-Based Spatial Statistics (TBSS), part of the FMRIB Soft-ware Library (FSL) version 5.0.1 (Smith et al., 2004). Fractional anisotropy (FA), throughout DTI indices, has been defined as a measure of tract directionality and integrity (Mori and Zhang, 2006). First, the effects of motion and eddy currents were corrected, the registration to the reference volume (b0) was made, and non-brain voxels were removed using the Brain Extraction Tool (BET). Then, FA maps were created by fitting a tensor model to the raw diffusion data using the FMRIB Diffusion Toolbox (FDT). FA data for all participants were aligned into a common space using the higher-resolution FA standard space Montreal Neurological Institute (MNI) atlas by the nonlinear registration method. The aligned FA data for each subject was then projected onto both thalami masks provided within FSL software (Smith et al., 2004), and the resulting data were fed into voxelwise statistics. We used the thalamus FSL masks to delimitate the voxelwise analysis of FA differences between WMLs groups. FA values were extracted only from thalamic areas where we found significant differences

Table 1
Demographic, clinical, and MRI data for study sample

	Total sample (n = 96)	Low-grade PVHs (n = 80)	High-grade PVHs (n = 16)	p	Low-grade DWMHs (n = 80)	High-grade DWMHs (n = 16)	p
Age, y[a]	59.73 (3.37)	59.48 (3.48)	61.00 (2.48)	0.10	59.48(3.35)	61.00(3.25)	0.10
Sex, n (%) female)[b]	57 (59.4)	48 (60.0)	9 (56.3)	0.78	48(60.0)	9(56.3)	0.78
Education, years[c]	8 (6-9.75)	8 (6-9)	8 (6.25-10)	0.71	8(6-10)	8(6.25-8.75)	0.98
MMSE score[c]	29 (28-30)	29 (28-30)	30 (28.25-30)	0.20	29(28-30)	30(28-30)	0.71
Vocabulary (WAIS-III score)[a]	38.69 (9.04)	38.91 (8.76)	37.56 (10.56)	0.59	39.36(8.85)	37.50(9.47)	0.50
GDS-15 score[c]	1 (1-3)	2 (1-3)	1 (0-2)	0.08	2(0e3)	1(1-2.75)	0.89
Vascular risk factors, n (%)							
Hypertension[b]	45 (46.9)	38 (47.5)	7 (43.8)	0.78	34(42.5)	11(68.8)	0.04*
Dyslipidemia[b]	57 (59.4)	48 (60.0)	9 (56.3)	0.78	47(58.8)	10(62.5)	0.78
DM[d]	17 (17.7)	15 (18.8)	2 (12.5)	0.73	15(18.8)	2(12.5)	0.73
Current smoker[d]	15 (15.6)	12 (15.0)	3 (18.8)	0.71	13(16.3)	2(12.5)	1
MRI measures[a]							
GM, cm^3	582.47 (43.64)	590.82 (35.38)	580.80 (45.11)	0.41	586.12(36.22)	581.74(45.14)	0.72
WM, cm^3	546.01 (63.11)	564.90 (60.69)	542.24 (63.28)	0.19	543.56(55.53)	546.50(64.83)	0.87
BP, cm^3	1128.48 (103.18)	1155.72 (93.52)	1123.04 (104.70)	0.25	1129.68(88.42)	1128.24(106.39)	0.96
TBV, cm^3	1425.09 (127.07)	1450.51 (118.78)	1420.00 (128.76)	0.38	1424.18(109.25)	1425.27(130.96)	0.98
Ratio BP/TBV (%)	79.18 (1.56)	79.71 (2.03)	79.08 (1.44)	0.25	79.33(1.80)	79.16(1.52)	0.67
LI present, n (%)[d]	11 (7.29)	4 (5.1)	3 (18.8)	0.09	6(7.5)	1(6.3)	1

Values are mean (standard deviation) in Student t test or median (interquartile range) in Mann-Whitney test for continuous variables. Values are n (%) for categorical variables in X^2 test and Fisher exact test. The p values show statistical comparisons between participants with high-grade and low-grade white matter lesions.
Key: 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; MRI, magnetic resonance imaging; MMSE, Mini-Mental State Examination; PVHs, periventricular hyperintensities; TBV, total brain volume; WM, white matter volume.

* $p < 0.05$.
[a] Student t test.
[b] X^2 test.
[c] Mann-Whitney test.
[d] Fisher exact test.

between groups. The extracted FA values were afterwards related to cognition.

Brain tissue volumes 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).

2.5. Visual rating of WMLs

Location and severity of WMLs were estimated on T2 and FLAIR scans by a trained and blinded neuroradiologist (N.B.) using the Fazekas scale (Fazekas et al., 1987). On MRI, WMLs appear hyper-intense 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 2 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. Lacunar infarcts were defined as le-sions 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 (Fazekas et al., 2002).

Table 2
Distribution of composite z scores for cognitive domains

	Low-grade PVHs (n = 80)	High-grade PVHs (n = 16)	Low-grade DWMHs (n = 80)	High-grade DWMHs (n = 16)
EF	-0.02 (0.69)	0.18 (0.73)	0.11 (0.84)	-0.38 (0.74)
Working memory	0.06 (0.85)	-0.10 (0.81)	0.05 (0.63)	-0.19 (0.64)
Attention	0.00 (0.76)	0.01 (0.84)	0.07 (0.76)	-0.36 (0.76)
Verbal fluency	0.01 (0.80)	-0.06 (1.00)	0.12 (0.79)	-0.60 (0.81)
Verbal memory	0.00 (0.88)	0.03 (1.02)	0.04 (0.90)	-0.16 (0.89)
Visual memory	-0.02 (0.91)	0.04 (0.54)	0.07 (0.85)	-0.44 (0.78)
VS	0.03 (0.77)	-0.12 (0.68)	0.14 (0.62)	-0.67 (1.23)
PS	0.02 (0.77)	-0.14 (0.72)	0.08 (0.63)	-0.47 (1.12)

Values are mean (standard deviation) in z scores for each cognitive domain.
Key: DWMHs, deep white matter hyperintensities; EF, executive functioning; PS, psychomotor speed; PVHs, periventricular hyperintensities; VS, visuospatial skills.

2.6. Statistical analysis

We dichotomized our sample into participants with low-grade WMLs (those individuals with no lesions or mild lesions) and participants with high-grade WMLs (those individuals with moderate or severe lesions). We compared thalamic FA values between high-grade and low-grade WMLs, with separate analyses for PVH and DWMH groups. For voxelwise analyses, group differences in thalamus were estimated by applying 2 masks of left and right thalamus over all the FA normalized maps.

For the voxelwise DTI analyses, we used randomise, a permutation-based program with standard general linear model (GLM) implemented in FSL, to identify significant clusters within thalamic regions. We set the number of permutations to 5000 as recommended. This analysis was performed using the Threshold-Free Cluster Enhancement (TFCE) method (Smith and Nichols, 2009). Correction for multiple comparisons was performed using permutation-based inference with a significance level of $p < 0.05$, familywise error (FWE) corrected.

Location of specific thalamic areas with significantly lower FA values among groups was done by Harvard-Oxford Subcortical Structural Atlas (HOS) (Desikan et al., 2006), Johns Hopkins University DTI-based probabilistic WM Tractography Atlas (JHU) (Hua et al., 2008; Mori et al., 2005), and Oxford Thalamic Connectivity Probability Atlas (OTC) (Behrens et al., 2003a, 2003b) provided within the FSL. We binarized our significant results in the left and right thalamus separately, and calculated FA values within both masks of results.

Data analyses were carried out using the Statistical Package for Social Sciences (SPSS for Windows, version 18.0; SPSS Inc, Chicago, IL). A set of linear regression models were used to evaluate the specific contribution of thalamic FA values in significant regions to cognitive function (cognitive z scores). Left and right thalami were

analyzed separately. We report unadjusted and adjusted models. Model 1 was adjusted by age and sex, and model 2 was corrected for age, sex, years of education, and treatable cardiovascular risk factors associated with either WMLs or cognitive function (at $p \leq 0.1$) as previously reported (Soriano-Raya et al., 2012). Briefly, hypertensive participants had lower scores on verbal fluency, visuospatial skills, and psychomotor speed. Participants with dyslipydemia 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 nonsmoker participants.

The false discovery rate (FDR) (Benjamini and Hochberg, 1995) was used to account for multiple comparisons in all models. An FDR of $p \leq 0.006$ for the unadjusted model, and a FDR of $p \leq 0.003$ for the 2 adjusted models were used. Both uncorrected and corrected results are presented.

3. Results

Four participants were excluded from the final sample because of technical difficulties with MRI. 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 partici-pants with low-grade DWMHs (42.5%).

According to the DWMHs score, 80 participants (83.3%) were classified as having low-grade DWMHs and 16 participants (16.7%) were classified as having high-grade DWMHs. In addition, there were 80 participants (83.3%) with low-grade PVHs and 16 participants (16.7 %) with high-grade PVHs. Seven participants (7.3%) had both high-grade DWMHs and high-grade PVHs. 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 1 lacunar infarct each in the pons, internal capsule, and corona radiata.

Table 2 shows the distribution of composite z scores for cognitive domains for WMLs groups.

Table 3
Areas of decreased thalamic FA in participants with high-grade DWMHs

Region	MNI coordinates			t	p	Cluster size
	x	y	z			
Right corticospinal tract (JHU) Right posterior-parietal cortex (OTC)	19	24	2	3.67	0.02	39
Right thalamus (HOS) Right pre-motor cortex (OTC)	11	20	1	2.99	0.04	21
Left thalamus (HOS) Left anterior thalamic radiation (JHU) Left primary motor cortex (OTC)	13	21	2	3.80	0.03	49
Left thalamus (HOS) Left anterior thalamic radiation (JHU) Left pre-motor cortex (OTC)	13	20	5	3.33	0.03	15

p denotes significance level, family wise error corrected for multiple comparisons. Key: FA, fractional anisotropy; DWMHs, deep white matter hyperintensities; JHU, Johns Hopkins University DTI-based Probabilistic WM Tractography Atlas; OTC, Oxford Thalamic Connectivity Probability Atlas; HOS, Harvard-Oxford Subcortical Structural Atlas; MNI, Montreal Neurological Institute.

3.1. Thalamic diffusion differences according to high-grade DMWHs and PVHs

Participants with high-grade DWMHs showed reduced FA values in specific areas of both right and left thalamus compared to participants with low-grade DWMHs (Table 3 and Fig. 1). Specifically, decreased FA values in the right thalamus were found in the corticospinal tract projecting to the posterior parietal cortex and a small gray matter area projecting to the pre-motor cortex. In the left thalamus, decreased FA values were found in the anterior thalamic

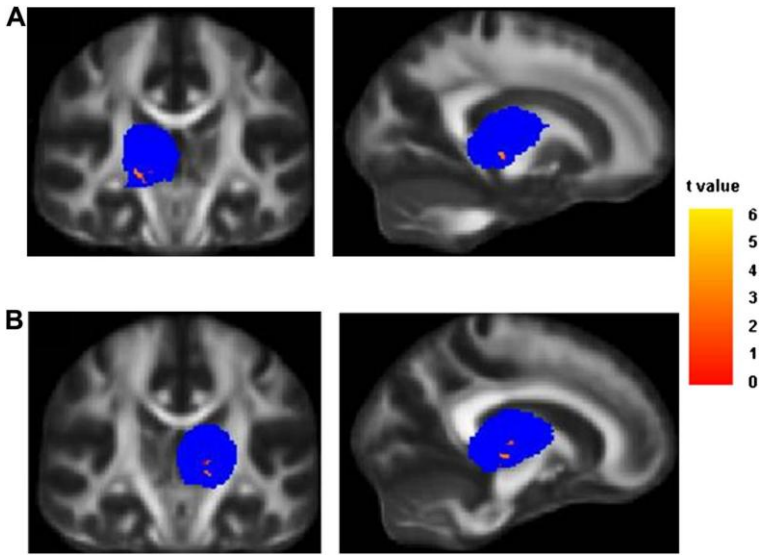

Fig. 1. The selected images illustrate the significant regions where participants with high-grade deep white matter hyperintensities (DWMHs) showed decreased fractional anisotropy (FA) values compared with participants with low-grade DWMHs. The thalamus mask used for the comparison analyses is blue. The red-yellow bar shows clusters of significantly decreased FA values related to high-grade DWMHs in the right thalamus (A) and left thalamus (B). Images are displayed in radiological convention (i.e., right side represents left side and left side represents right side of the brain).

Table 4
Areas of decreased thalamic FA in participants with high-grade PVHs

Region	MNI coordinates			t	p	Cluster size
	x	y	z			
Left thalamus (HOS) Left prefrontal cortex (OTC)	-8	-22	2	3.60	0.04	7

p denotes significance level, family-wise error corrected for multiple comparisons. Key: FA, fractional Anisotropy; HOS, Harvard-Oxford Subcortical Structural Atlas; MNI, Montreal Neurological Institute; OTC, Oxford Thalamic Connectivity Probability Atlas; PVHs, periventricular hyperintensities.

radiation projecting to the primary motor and the pre-motor cortex. No significant results were found for the reverse contrast.

Participants with high-grade PVHs showed decreased FA values in a specific area of the left thalamus compared to participants with low-grade PVHs. This significant gray matter area projects to the prefrontal cortex (Table 4 and Fig. 2). No significant results were found for the reverse contrast.

3.2. Associations between thalamic FA values within significant regions and cognitive function

In the unadjusted model, decreased FA values in the right thal-amus, related to high-grade DWMHs, were associated with lower performance in attention (R^2 = 0.05; β = 0.22), verbal fluency (R^2 = 0.09; β = 0.31), visual memory (R^2 = 0.05; β = 0.21), visuospatial skills (R^2 = 0.08; β = 0.28), and psychomotor speed (R^2 = 0.05; β = 0.23) (Table 5). Decreased FA values in the left thalamus were associated with lower performance in verbal fluency (R^2 = 0.05; β = 0.21) and psychomotor speed (R^2 = 0.05; β= 0.21). Fig. 3 shows the positive correlations, obtained from the unadjusted model, between thalamic FA values extracted from significant areas related to DWMHs and different cognitive domains.

In model 1 (adjusted for age and sex), the relation between lower FA values in significant areas of the right thalamus and lower performance in verbal fluency (R^2 = 0.12; β = 0.28), visuospatial skills (R^2 = 0.08; β = 0.29), and psychomotor speed (R^2 = 0.12; β = 0.25) remained significant. Decreased FA values in the left thalamus in high-grade DWMHs were associated with psychomotor speed (R^2= 0.11; β = 0.22).

In model 2 (adjusted for age, sex, years of education, and treatable cardiovascular risk factors associated with cognitive function), the association between decreased FA values in significant areas of the right thalamus and lower performance in verbal fluency (R^2 = 0.23; β = 0.23), visuospatial skills (R^2 = 0.12; β = 0.27) and psychomotor speed (R^2 = 0.18; β = 0.22) remained significant.

Decreased FA values in the left thalamus in high-grade DWMHs were no longer associated with any cognitive function in the model 2 although there was a trend with psychomotor speed.

After correcting for multiple comparisons (FDR), decreased FA values in the right thalamus, related to high-grade DWMHs, remained as an independent explanatory variable for performance in verbal fluency and visuospatial skill functions (unadjusted model). The predictive power of FA values for cognitive performance in the left thalamic regions (unadjusted model) and all thalamic regions in adjusted models (models 1 and 2) were slightly attenuated and became non-significant, although the direction of the association did not change substantially.

Decreased FA values related to high-grade PVHs were not related to cognitive function in any model (results not shown).

4. Discussion

This study investigated thalamic diffusion differences related to WMLs and their association with cognitive function in a community-dwelling sample. Our main and novel finding was that participants with high-grade WMLs showed lower FA values in specific thalamic areas compared to participants with low-grade WMLs. We also found that these thalamic diffusion differences were related to lower cognitive performance in participants with high-grade DWMHs but not in participants with high-grade PVHs. Specifically, decreased FA values in the thalamus, related to high-grade DWMHs, were associated with verbal fluency, visuospatial skills, and psychomotor speed, whereas decreased FA values related to high-grade PVHs were not associated with any cognitive function. These cognitive domains have been widely related to cortico-subcortical dysfunction and WMLs (Pantoni et al., 2007; Schmidt et al., 2011).

High-grade DWMHs and high-grade PVHs were both related to diffusion differences in specific areas of both thalamus. DWMHs were associated with decreased FA values in right thalamic areas that project to the right pre-motor and right posterior parietal cortex, and in left thalamic areas that project to the pre-motor and primary motor cortex. PVHs were associated with lower FA values in a small left thalamic area projecting to the ipsilateral prefrontal cortex. To our knowledge, this is the first study to show a relationship between WMLs and thalamic diffusion differences. This finding supports the notion that cognitive dysfunction associated with WMLs is based on a cortico-subcortical circuit involvement. There are several parameters, such as myelination, axon density, axonal membrane integrity, axon diameter (Beaulieu, 2002), and intravoxel coherence of fiber orientation (Smith et al., 2007) that can influence FA values. Although lower FA values have been related

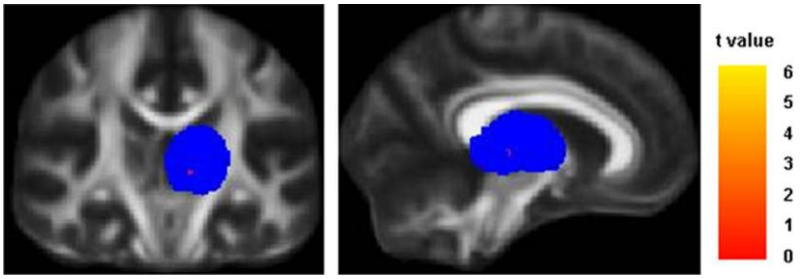

Fig. 2. The selected images illustrate the significant regions where participants with high-grade periventricular hyperintensities (PVHs) showed decreased fractional anisotropy (FA) values compared with participants with low-grade PVHs. The thalamus mask used for the comparison analyses is blue. The red-yellow bar shows clusters of significantly decreased FA values related to high-grade PVHs in the left thalamus. Images are displayed in radiological convention (i.e., right side represents left side and left side represents right side of the brain).

Table 5
Association between thalamic FA values and cognitive function

	Unadjusted model		Model 1		Model 2	
	β	p	β	p	β	p
Right thalamus						
EF	0.14	0.18	0.15	0.17	0.12	0.27
Working memory	0.13	0.25	0.10	0.39	0.12	0.34
Attention	0.22	0.04*	0.17	0.10	0.18	0.06
Verbal fluency	0.31	0.002**	0.28	0.007**	0.23	0.02*
Verbal memory	0.04	0.69	0.08	0.48	0.09	0.40
Visual memory	0.21	0.04*	0.17	0.11	0.17	0.12
VS	0.28	0.006**	0.29	0.006**	0.27	0.01*
PS	0.23	0.03*	0.25	0.02*	0.22	0.04*
Left thalamus						
EF	0.07	0.48	0.08	0.47	0.04	0.72
Working memory	0.00	0.98	0.04	0.74	0.02	0.86
Attention	0.15	0.16	0.10	0.33	0.13	0.17
Verbal fluency	0.21	0.04*	0.18	0.08	0.16	0.10
Verbal memory	0.02	0.85	0.04	0.69	0.05	0.64
Visual memory	0.11	0.30	0.06	0.56	0.07	0.53
VS	0.19	0.06	0.19	0.07	0.18	0.09
PS	0.21	0.04*	0.22	0.04*	0.19	0.07

β Values from linear regression models relating thalamic FA values within significant regions (participants with high-grade vs. low-grade DWMHs) to cognitive function. Model 1 is adjusted for age and sex. Model 2 is adjusted for age, sex, years of education, and treatable cardiovascular risk factors related to cognitive performance.

Key: β, Standardized coefficient from linear regression models; DWMHs, deep white matter hyperintensities; EF, executive functioning; FA, fractional anisotropy; PS, psychomotor speed; VS, visuospatial skills.

* $p < 0.05$; ** $p < 0.01$.

to axonal disruption (Alexander et al., 2007a), this unique interpretation should be considered with caution.

Interestingly, we also found that only the thalamic diffusion differences related to DWMHs were positively associated with verbal fluency, visuospatial skills, and psychomotor speed. An increasing amount of evidence supports the specific contribution for DWMHs and PVHs to cognitive function. Some data suggest that DWMHs are distributed in a more extensive area than are PVHs (Inzitari, 2000) and may exert more severe damage to cortico-subcortical circuits than do PVHs (Stenset et al., 2008; Wen et al., 2006). The preeminent association between DWMHs with thalamic diffusion differences and cognition in this study reinforces a predominant role for these lesions in cognitive function.

We found that verbal fluency was positively related to right thalamic cortical connections. It is known that verbal fluency is related mainly to the left hemisphere, especially to the superior longitudinal fasciculus (Peters et al., 2012; Phillips et al., 2011). However, a recent functional MRI study in epileptic patients has linked a positive modulation of thalamic cortical connectivity in the right hemisphere with verbal fluency (O'Muircheartaigh et al., 2012). We also found a positive association between diffusion differences in the left thalamus and verbal fluency, but this result did not remain significant when adjusting for age, sex, years of education, and arterial hypertension.

A positive association between thalamic diffusion differences in the right thalamus and visuospatial skills was also observed. To our knowledge, there are no studies relating diffusion differences in the thalamus with visuospatial function. This finding could be

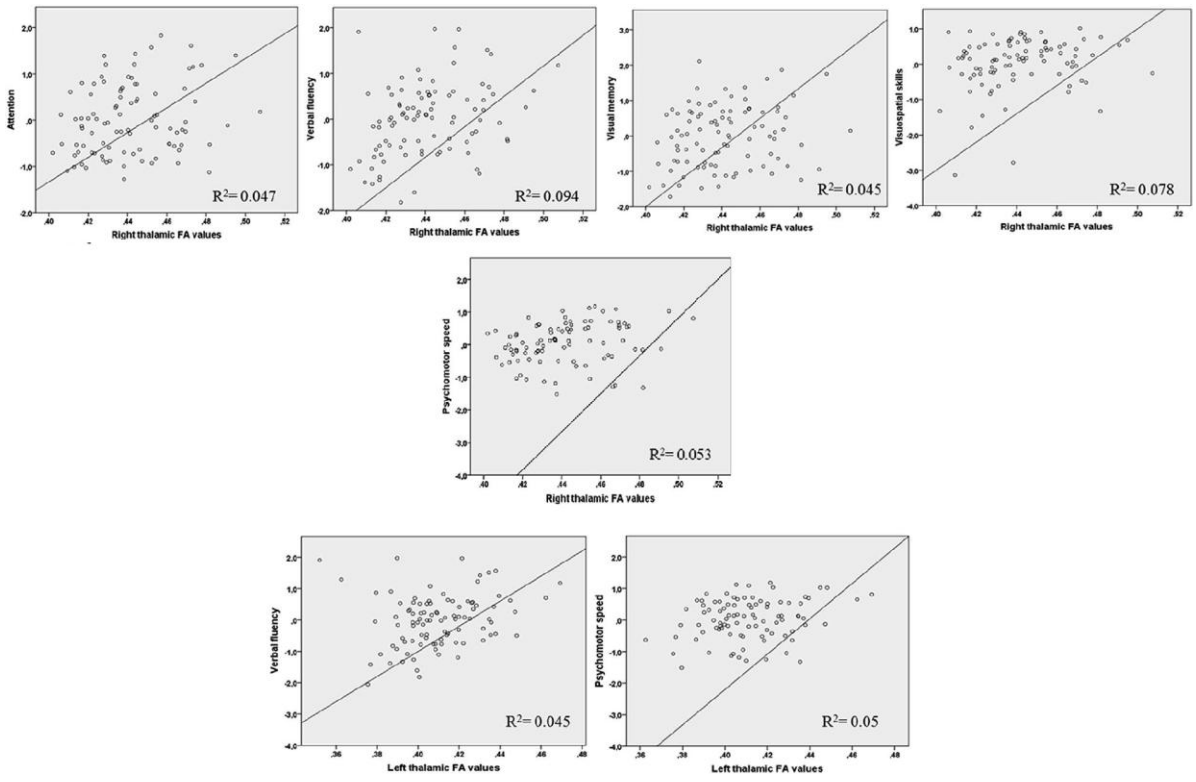

Fig. 3. The selected images illustrate positive correlations between thalamic fractional anisotropy (FA) values within significant clusters related to deep white matter hyper-intensities (DWMHs) and different cognitive domains in participants with white matter lesions (WMLs). Each cognitive domain is represented by z scores. R^2 = correlation effect size of unadjusted regression model.

explained by the fact that 1 of the significant thalamic diffusion differences was located in regions that project to the right posterior parietal cortex. The role of the right posterior parietal cortex in visuospatial skills is well known (Levin et al., 1996; Silver and Kastner, 2009). In addition, a functional MRI study has shown a positive association between right thalamic activations during a visual task (Fink et al., 2002). Our finding might help to explain the neural bases of the visuospatial deficits often found in vascular-related cognitive impairment associated with SVD.

Finally, we also found that psychomotor speed was positively associated with diffusion differences in the right thalamus. Left-side association disappeared when adjusting for age, sex, years of education, and treatable cardiovascular risk factors (hypertension, diabetes mellitus, and smoking habit). In this line, Tuch et al. (2005) reported in healthy participants a positive correlation between FA values in the right posterior thalamus among other brain structures and reaction time, strongly involved in psychomotor speed. However, a positive relation between psychomotor speed and FA values in frontal-subcortical circuits, including the left anterior thalamic radiation (Duering et al., 2012), was observed in vascular cognitive impairment (VCI) participants in concordance with our results. Furthermore, Turken et al. (2008) showed a positive association between psychomotor speed and left FA values in the middle frontal gyrus in a healthy sample.

The association of thalamic diffusion differences with cognitive function provides additional support for the notion that cognitive dysfunction associated with WMLs could be a disconnection syndrome (Geschwind, 1965, 2010; O'Sullivan et al., 2001; Schmidt et al., 2006). It is known that the thalamus allows the relay of in-formation to most areas of the cerebral cortex (Byne et al., 2009; Haber and Calzavara, 2009), and it is organized into functional regions based on their connections to the cortex (Goldman-Rakic and Porrino, 1985; Jones, 2009). Consequently, this structure can mediate sensory function, motor abilities, language, executive function, and long-term memory (Schmahmann, 2003; Stebbins et al., 2008; Tekin and Cummings, 2002).

This is the first study to show thalamic diffusivity differences in WMLs and their association with cognitive function. The main strengths of this study are an extensive neuropsychological assessment and 3T MRI to detect WMLs, which increase its sensitivity. Some limitations should also be considered. The small sample size of participants with high-grade DWMHs (n = 16) may preclude the generalizability of the results. We used the Fazekas scale (Fazekas et al., 1987), which does not allow us to localize the WMLs within a specific hemisphere. It would be interesting to study the relationship between right- or left-sided WMLs and, accordingly, right and left thalamic diffusion differences. In addition, another interesting approach would be to investigate the association of WMLs and thalamic diffusion differences related to cognitive function regarding lobar locations. Results were not adjusted for brain atrophy ratio (%) in this study, although the characteristics of the sample (i.e., age, exclusion of demented patients) suggest that degenerative changes may not emerge. The narrow age range and mid-adulthood of this community-dwelling sample allowed the examination of adult brains largely unaffected by age-related brain changes.

Although we did not adjust for the presence of silent lacunar infarcts because of the low prevalence in this sample, we reran linear regression analyses excluding the 7 participants with lacunar infarcts. Decreased FA values in the right thalamus related to high-grade DWMHs were still associated with lower performance in verbal fluency and visuospatial skills in unadjusted and adjusted models. Lower FA values in left thalamus were no longer associated with any cognitive function. The observed differences could be explained by the similar etiology between lacunar infarcts and WMLs comprehending SVD (Pantoni et al., 2002; Pantoni et al., 2007). Lacunar infarcts can also affect white matter tracts and, consequently, thalamic FA values. In this line, after excluding participants with lacunar infarcts, the relationship between FA values and cognition could be less significant. Taking into account that we have no participants with thalamic lacunar infarcts, these results can suggest Wallerian degeneration within thalamic white matter tracts. Finally, unknown confounding variables may exist that influence both WMLs and reduced thalamic diffusion differences.

In conclusion, thalamic diffusion differences are related to lower cognitive performance only in participants with high-grade DWMHs in a community-dwelling sample. These novel results support the notion that disruption of cortico-subcortical circuits may be involved in cognitive deficits associated with WMLs (Linortner et al., 2012; Schmidt et al., 2006). In addition, our data corroborate the hypothesis that PVHs and DWMHs are differentially associated with cognitive function, and suggest that the ongoing distinction between both types of WMLs is worthy. A fiber-tracking approach could provide specific information about diffusion differences of thalamic projection fibers that might be related with cognitive function in participants with WMLs. Further research is needed to determine whether thalamic diffusion differences associated with DWMHs might have diagnostic value for assessing cognitive dysfunction in community and clinical samples.

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Remote thalamic microstructural abnormalities related to cognitive function in ischemic stroke patients

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Abstract

Objective: Ischemic stroke can lead to a continuum of cognitive sequelae, ranging from mild vascular cognitive impairment to vascular dementia. These cognitive deficits can be influenced by the disturbance of cortico-subcortical circuits. The aim of this study was to explore remote thalamic microstructural abnormalities and their association with cognitive function after ischemic stroke. ***Method:*** Seventeen patients with right hemispheric ischemic stroke and seventeen controls matched for age, sex and years of education were included. All participants underwent neurological, neuropsychological and diffusion tensor image examination. Patients were assessed three months after stroke. Voxelwise analysis was used to study thalamic diffusion differences between groups. Mean fractional anisotropy (FA) and mean diffusivity (MD) values in significant thalamic areas were calculated for each subject and correlated with cognitive performance. ***Results:*** Stroke patients showed lower FA values and higher MD values in specific areas of both thalamus compared to controls. In patients, decreased FA values were associated with lower verbal fluency performance in the right thalamus (R^2 = 0.45; β = 0.74) and the left thalamus (R^2 = 0.57; β = 0.77) after adjusting for diabetes mellitus. Moreover, increased MD values were associated with lower verbal fluency performance in the right thalamus (R^2 = 0.27; β = -0.54) after adjusting for diabetes mellitus. In controls, thalamic FA and MD values were not related to any cognitive function. ***Conclusion:*** Our findings support the hypothesis that ischemic stroke lesions are associated with remote thalamic diffusion abnormalities, and that these abnormalities can contribute to cognitive dysfunction three months after a cerebrovascular event.

Introduction

Cerebral ischemic stroke can lead to motor, emotional, behavioral and cognitive sequelae. This continuum of cognitive sequelae ranges from mild vascular cognitive impairment (MVCI) to vascular dementia (VaD) (Gorelick et al., 2011, Troncoso et al., 2008).

Focal cerebral infarcts cause not only neuronal damage in the ischemic area, but may also be responsible for histological and functional abnormalities remote from the ischemic lesion (De Reuck et al., 1995; Kataoka et al., 1989; Von Monakow, 1914), probably due to Wallerian degeneration and cortical deafferentation (Buffon et al., 2005; Zhang et al., 2012).

The thalamus is a key structure in cortico-subcortical circuits (Byne et al., 2009) and is involved in cognitive functions (Herrero et al., 2002; Sherman & Guillery, 2002; Sherman, 2005) through extensive connections with the cerebral cortex (Alexander, 1986; Cummings et al., 1993; Leh et al., 2007). Thalamic abnormalities remote from the ischemic lesion, predominantly in the ipsilateral thalamus, have been reported in animal models (Abe et al., 2003; Bihel et al., 2010; Dihne et al., 2002; Kataoka et al., 1989; Persson et al., 1989) and human neuroimaging studies such as Positron Emission Tomography (PET) (Nagasawa et al., 1994), structural Magnetic Resonance Image (MRI) (Ogawa et al., 1997) and Diffusion Tensor Imaging (DTI) (Buffon et al., 2005; Hervé et al., 2005; Li et al., 2011).

DTI, a technique based on the measurement of the random displacements of water molecules, provides highly sensitive information of microstructural tissue alterations and integrity of white matter (WM) fiber tracts (Hagmann et al., 2006; Sundgren et al., 2004). More recently, DTI has also been used to investigate the integrity of subcortical gray matter (GM) structures in different cerebral pathologies (Lee et al., 2013; Müller et al., 2007; Scanlon et al., 2013), including ischemic stroke

(Buffon et al., 2005; Hervé et al., 2005; Li et al., 2011). In a previous study, we found a relationship between thalamic diffusion measures and cognitive function in community participants with white matter lesions (WMLs) (Fernández-Andújar et al., 2013). Furthermore, an association between DTI measures in the thalamus and cognitive function has also been reported in healthy participants (Piras et al., 2010; Sasson et al., 2012) and in schizophrenia patients (Marenco et al., 2012). However, the relationship between diffusion thalamic abnormalities and cognitive function after ischemic stroke remains currently unknown.

The aim of this study is twofold. Firstly, we will explore the specific localization of remote thalamic microstructural abnormalities using voxelwise analysis at three months after ischemic stroke. Secondly, we will investigate the relationship between these abnormalities and cognitive dysfunction.

Methods

Participants

This investigation is part of a prospective and longitudinal study that includes a group of ischemic stroke patients consecutively admitted in the Stroke Unit at the Germans Trias i Pujol Hospital, Badalona, Spain between September 2010 and May 2012 and a group of healthy controls.

The inclusion criteria for the potential stroke patients were the following: 1) first-ever territorial ischemic stroke in the territory of middle, anterior or posterior cerebral arteries (MCA, ACA, PCA); 2) without thalamic involvement or significant hemorrhagic transformation; 3) aged between 40 and 75 years; 4) absence of severe aphasia (Item 14 on the National Institute of Health Stroke Scale (NIHSS) ≤ 1; Brott et al., 1989); 5) no history of substance abuse, neurological or psychiatric comorbidities,

or severe sensory impairments; 6) MRI contraindications. Out of the 29 patients included in the study, we selected those with right hemispheric ischemic stroke (n=17). Seventeen paired control participants from The Barcelona-AsIA (Asymptomatic Intracranial Atherosclerosis) Study (López-Cancio et al., 2011; Miralbell et al., 2012; Soriano et al., 2012) matched by age, sex, and years of education were included.

Demographic information and clinical characteristics were collected for all participants (Table 1). Neurological, neuropsychological and MRI examinations were performed using the same protocol for both groups. For stroke patients the neuropsychological and MRI data were obtained three months after the ischemic stroke. Stroke lesion characteristics and the involved vascular territory were determined in the first 24 hours after ischemic stroke using Computed Tomography (CT) and/or MRI. Lesion volume was calculated in the subacute phase using the three largest diameters along the three orthogonal axes divided by two (AxBxC/2) (Sims et al., 2009).

This study has been approved by the University of Barcelona and the Hospital Germans Trias i Pujol ethics committee (Institutional Review Board: 00003099; Assurance number: FWA00004225). Informed consent has been obtained for each participant in accordance with the Helsinki Declaration.

Evaluation of vascular risk factors

Identification of particular vascular risk factors such as arterial hypertension, dyslipidemia, diabetes mellitus (type II) and current smoking status was based on clinical history or use of medication for this particular condition at the time of the clinical examination.

Neuropsychological assessment

All participants completed an extensive neuropsychological assessment. Cognitive measures were grouped into eight cognitive domains which include cognitive tests that measure similar cognitive function (Lezak et al., 2004; Strauss et al., 2006): executive functioning (EF), working memory, attention, verbal fluency, verbal memory, visual memory, visuospatial skills (VS) and psychomotor speed (PS). The 64-item computerized version of the Wisconsin Card Sorting Test (Kongs et al., 2000) and the interference score of the Color-Word Stroop Test (Golden, 1978) were used to examine EF (i.e., conceptualization, planning, and inhibition). Working memory was assessed 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). The Continuous Performance Test (Conners, 1995) and the Digit Span Forward, Symbol Search, and Digit Symbol Coding subtests from the Wechsler Adult Intelligence Scale (WAIS-III) were used to measure attentional abilities. Verbal fluency was assessed with letter fluency (letter P) (Artiola, Hermosillo, Heaton, & Pardee, 1999) and semantic category fluency (animals) (Strauss et al., 2006) in 60 seconds. Verbal and visual memory were examined using Word Lists and Visual Reproduction from the Wechsler Memory Scale 3rd edition (WMS-III) (Wechsler, 1997b), respectively. Evaluation of visuospatial skills (VS) was done by Visual Discrimination and the Copy from the Visual Reproduction subtest (WMS-III). Psychomotor speed (PS) was measured 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 for each group. Composite Z-scores for each participant in each cognitive domain were calculated by averaging the Z-scores of all tests within that domain. Geriatric Depression Scale 15-item version (GDS-15) (Sheikh & Yesavage, 1986) and Vocabulary test (WAIS III) (Wechsler, 1997a) were used to assess depressive symptoms and the estimated premorbid intelligence, respectively.

MRI acquisition and data processing

MRI scanning was performed on a 3T Siemens Magnetom Trio (Siemens Diagnostics Healthcare, Erlangen, Germany) at the Image Diagnosis Centre (Hospital Clínic, Barcelona, Spain). The MRI protocol included a set of 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: 1x1x1 mm], and DTI acquired in 30 directions with the following echoplanar acquisition protocol matrix: 120x120; TR: 9300 ms; TE: 94 ms; flip angle, 15°; field of view: 240 mm; no gap (2-mm thickness); voxel size: 2x2x2 mm, and b=1000 s/mm^2. Two acquisitions of DTI were averaged. 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.

Individual processing of diffusion tensor data was performed using the FMRIB Diffusion Toolbox (FDT), part of the FMRIB Software Library (FSL) version 5.0.1 (Smith et al., 2004). Fractional anisotropy (FA) and mean diffusivity (MD), two of the most used indices derived from MRI-DTI acquisitions (Basser & Pierpaoli, 1996), have been used in this study. FA measures the degree of anisotropy (Alexander, 2007; Basser et al., 1996; Mori & Zhang, 2006) and MD reflects the average molecular motion considered in all directions (Alexander, 2007; Basser et al., 1996).

The effects of motion and eddy currents were firstly corrected, the registration to the reference volume (b=0) was made, and non-brain voxels were removed using the Brain Extraction Tool (BET). Then, FA and MD maps were created by fitting a tensor model to the raw diffusion data using the DTIfit program included in FDT. FA and MD data for controls were aligned into the Montreal Neurological Institute (MNI) standard space using the higher-resolution FA template provided in FSL by the nonlinear

registration method FNIRT, (Anderson, 2007a; Anderson, 2007b) which uses a b-spline representation of the registration warp field. FA and MD data for stroke patients were first aligned each other to identify the most representative one and use this as a target image to apply an affine transformation into MNI standard space. FA and MD data for stroke patients were consequently registered into standard space by combining the nonlinear registration to the target image (FNIRT) with the affine transformation from the target image to MNI standard space. Normalized FA and MD data were fed into voxelwise statistics. We used FSL masks of left and right thalamus provided within FSL software (Smith et al., 2004) to delimitate the voxelwise analyses (Figure 1).

Brain tissue volumes 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).

Statistical Analyses

We compared thalamic voxel-by-voxel FA and MD differences between stroke patients and controls. For this voxel-wise analysis, 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 & Nichols, 2009) was used to obtain the thalamic areas showing differences between groups. Correction for multiple comparisons was performed using permutation-based inference with a significance level of $p \leq 0.05$, Family-Wise Error (FWE) corrected.

Localization of specific thalamic areas with significantly lower FA values or higher MD values between groups was done by Harvard-Oxford Subcortical Structural Atlas (HOS) (Desikan et al., 2006), Oxford Thalamic Connectivity Probability Atlas (OTC) (Behrens et al., 2003a; Behrens et al., 2003b), and Johns Hopkins University

DTI-based Probabilistic WM Tractography Atlas (JHU) (Hua et al., 2008) provided within the FSL. We binarized our significant results in the left and right thalamus separately. The mean FA and MD values were also calculated separately in the left and right thalamus within areas showing significant differences between groups for the linear regression analyses.

Two linear regression models (left and right thalamus) were used to evaluate the specific contribution of both thalamic FA and MD values in significant regions to cognitive function (cognitive Z-scores). Unadjusted and adjusted models corrected for diabetes mellitus are reported. A value of $p \leq 0.05$ was considered statistically significant. The false discovery rate (FDR) (Benjamini & Hochberg, 1995) was used to account for multiple comparisons in the unadjusted and adjusted models for linear regression analyses. The FDR procedure controls for the proportion of false positives among the cognitive domains that show significant results in this study. The FDR exerts a less strict control over false discoveries compared to other procedures such as the Bonferroni correction. For FA analyses, a FDR of $p \leq 0.003$ for the unadjusted model and a FDR of $p \leq 0.006$ for the adjusted model were used. Also, for MD analyses, a FDR of $p \leq 0.006$ for the adjusted model was used. Both uncorrected and corrected results are presented.

Statistical analyses were carried out using SPSS 18.0 for Windows (SPSS Inc., Chicago, Illinois, USA).

Results

Sample characteristics

Demographic, clinical and MRI data of the participants are summarized in Table 1. There were no differences between groups in age, sex, years of education and

premorbid intelligence estimate. All participants were right handed. A significantly higher proportion of stroke ischemic participants (35.3%) were diagnosed with diabetes mellitus compared to controls (5.9%). Regarding MRI measures, there were differences between groups in WM and brain parenchyma volume (BP) and the ratios between BP and total brain volume (TBV). In the patient group, the mean infarct volume of stroke was 35,975 mm^3 (standard deviation: 46,044) (Table 1). Most patients had infarcts in the territory supplied by the MCA (n=14) with the exception of two patients where the stroke was located in the PCA. The cortical territory of the MCA or PCA was involved in nine patients and the lesion extended into deep regions in thirteen patients. The affected subcortical structures were the basal ganglia (n=10), corona radiata (n=6), external capsule (n=3) and extreme capsule (n=2). Other clinical and ischemic characteristics are presented in Table 2.

Thalamic microstructural abnormalities in the stroke group

The ischemic stroke group showed reduced FA values in specific areas of both right and left thalamus compared to controls (Table 3 and Figure 2). More specifically, decreased FA values were shown in two right thalamic areas (one gray matter area and the anterior thalamic radiation) and one left thalamic region (the anterior thalamic radiation), projecting to the temporal cortices, according to the HOS, JHU and OTC atlases. No significant results were observed for the reverse contrast.

Furthermore, increased MD values in two right thalamic areas (the anterior thalamic radiation and one gray matter area) projecting to the temporal cortices according to the HOS, JHU and OTC atlases, were observed in the stroke group compared with control participants (Table 4 and Figure 3). Significant results were observed neither for the left thalamus nor for the reverse contrast.

Associations between thalamic diffusion values within significant regions and cognitive function

Decreased FA values extracted from significant areas in the right and left thalamus were associated with lower verbal fluency performance in stroke patients. The relationship was observed in both the unadjusted (Right: $R^2 = 0.31$; $\beta = 0.55$; Left: $R^2 = 0.52$; $\beta = 0.72$) and adjusted model for diabetes mellitus (Right: $R^2 = 0.45$; $\beta = 0.74$; Left: $R^2 = 0.57$; $\beta = 0.77$). Lower FA values in the left thalamus were also associated with decreased working memory performance in both the unadjusted ($R^2 = 0.37$; $\beta = 0.60$) and adjusted model ($R^2 = 0.37$; $\beta = 0.60$). In addition, decreased FA values in the left thalamus were associated with verbal memory in both the unadjusted ($R^2 = 0.29$; $\beta = 0.54$) and adjusted model for diabetes mellitus ($R^2 = 0.29$; $\beta = 0.55$) (Table 5).

Higher MD values extracted from significant areas in the right thalamus were associated with lower verbal fluency performance in the stroke group in the adjusted model for diabetes mellitus ($R^2 = 0.27$; $\beta = -0.54$) (Table 6).

Figure 4 shows the correlations between thalamic FA and MD values and verbal fluency in stroke patients obtained from the adjusted model.

After correcting for multiple comparisons (FDR), decreased FA values in the left thalamus remained an independent explanatory variable for performance in verbal fluency in the stroke group (unadjusted model). Furthermore, lower FA values in both thalami remained significant for verbal fluency in the stroke group (adjusted model). Associations of lower FA values in the left thalamus with working memory and verbal memory did not remain significant after the FDR correction. In addition, increased MD values in the right thalamus were no longer associated with verbal fluency in the adjusted model after the FDR correction for multiple comparisons.

Both thalamic FA and MD values within significant areas were not related to any cognitive function in controls (data not shown).

Discussion

Remote thalamic microstructural abnormalities in patients with right hemispheric ischemic stroke were investigated in this study using a voxelwise approach. Of particular interest was that decreased FA values and increased MD values were observed in stroke patients in specific regions of both thalami that were related to lower verbal fluency performance.

The thalamus, which is a key structure in cortico-subcortical circuits (Byne et al., 2009), relays outputs to specific cortices and mediates the information flow between cortical networks (McFarland & Haber, 2002; Smith et al., 2009). Furthermore, the thalamus is involved in cognitive functions through reciprocal connections with the cortex and it is known that cortico-subcortical circuit alterations are involved in cognitive dysfunction (Linortner et al., 2012; Schmidt et al., 2006). Specifically, the thalamus is involved in executive function by cortico-thalamic loops (Schmahmann, 2003), especially through the dorsolateral prefrontal cortex (Tekin & Cummings, 2002). Therefore, cortico-subcortical circuits disruption after ischemic stroke can lead to thalamic diffusion abnormalities that could influence different cognitive functions. Previous DTI thalamic studies in stroke patients have used a general region of interest (ROI) approach to obtain a global measure of FA and MD values of the thalamus (Buffon et al., 2005; Hervé et al., 2005; Li et al., 2011). To date, microstructural thalamic abnormalities remote from the ischemic lesion have been found with MD index, but not with FA values. MD abnormalities have been reported in the ipsilateral thalamus at the first week (Li et al., 2011), one month (Hervé et al., 2005), three months (Buffon et al., 2005; Hervé et al., 2005; Li et al., 2011) and six months (Buffon et al., 2005; Hervé et al., 2005) after a cerebrovascular event. Although FA values have been studied at the same time intervals after ischemic stroke (Hervé et al., 2005; Li et al., 2011), none of these analyses yielded significant differences.

Our voxelwise DTI analyses have identified microstructural thalamic abnormalities in both FA and MD values in specific areas. The similar localization of the thalamic clusters in both FA and MD indices supports that these areas are in particular affected by the remote ischemic lesion in our sample. The amount of significant clusters in which we observed FA diffusion differences is similar between the ipsilateral and contralateral thalamus compared to controls. Nonetheless, MD abnormalities have only been observed in the ipsilateral thalamus.

FA has been defined as a measure of white matter tract directionality and integrity (Mori & Zhang, 2006) and lower FA values suggest loss of tissue integrity (Alexander, 2007; Basser et al., 1996; Mori & Zhang, 2006). MD has been considered a measure of alteration of brain tissues and higher values suggest an affectation of axonal tracts (Alexander, 2007; Basser et al., 1996). In addition, both FA and MD diffusion values are related to many factors including axonal count and density, degree of myelination, fiber organization (Beaulieu et al., 2002) and intravoxel coherence of fiber orientation (Smith et al., 2007). However, FA and MD values have been predominantly investigated in WM tracts so their interpretation remains uncertain in GM structures.

In our study, bilateral thalamic FA abnormalities and right thalamic MD abnormalities were related with verbal fluency, after adjusting for diabetes mellitus. Verbal fluency is one of the most sensitive neuropsychological tests thought to measure executive functions, and has been related with left prefrontal regions, cingulate, thalamus, cerebellum (Gourovitch et al., 2000; Noda et al., 2012; Stuss et al., 1998) and temporal cortex (Fama et al., 2000; Henry et al., 2004; Henry et al., 2005). Both left and right thalamic activations for verbal fluency tasks have also been described in healthy participants in functional MRI (Vitali et al., 2005) and PET studies (Gourovitch et al., 2000; Ravnkilde et al., 2002). In addition, impairment during verbal fluency tasks has been described after both left (Shim et al., 2008) and right (Annoni et al., 2003; Ebert et al., 1999) thalamic lesions.

Cognitive dysfunction after ischemic stroke could be mainly related to the volume and location of the cerebral lesion, the duration of ischemia, the occurrence of prior strokes, coexistence of multiple cerebral infarctions, degree of atherosclerosis and interindividual variability in the collateral supply (Hankey et al., 2003; Rosso & Samson, 2014; Vogt et al., 2012). We observed that secondary thalamic abnormalities could also contribute to cognitive impairment three months after a vascular event. However, the specific role of all these variables in cognitive dysfunction is currently unknown.

The bilateral thalamic abnormalities observed and their relation with cognitive dysfunction reinforces the idea that secondary effects from the ischemic lesion could lead to cortico-subcortical disruption not only in the ipsilateral circuits but also in contralateral circuits. The precise pathophysiological mechanisms underlying our anisotropic abnormalities remain unknown, although thalamic microstructural alterations after ischemic stroke can be caused by Wallerian degeneration of cortico-thalamic loops (Buffon et al., 2005; Hervé et al., 2005). In addition, these abnormalities can also be explained by other phenomenona such as axonal damage, neuronal swelling or shrinkage, and alterations of the tissue organization (Lim & Helpern, 2002).

In a recent DTI study, we investigated the integrity of whole brain white matter tracts in right ischemic stroke patients compared to control participants (Dacosta-Aguayo et al., 2014). Decreased FA values were observed in the right anterior thalamic radiation, among other anatomical areas. Interestingly, in both studies we found the same right anterior thalamic radiation affected but in different locations. In the present study, abnormalities were located within the thalamic region. These findings reinforce the relevant role of thalamic abnormalities and the cortico-thalamic loops disturbance in cognitive dysfunction after an ischemic stroke.

This is the first study using voxelwise analyses to show thalamic diffusivity abnormalities remote from the ischemic lesion, and the relation between these abnormalities with cognitive function three months after ischemic stroke. The main strengths of this study are the homogeneous ischemic stroke sample, the extensive neuropsychological assessment and the sensitivity of the 3T MRI to detect specific thalamic lesions. We adjusted for DM in the regression analysis due to a statistical difference in DM prevalence between stroke patients and controls. DM could be a confounding variable since its association with cognitive impairment, increased risk for dementia and diminished recovery following stroke has been extensively described (Biessels et al., 2006; Kodl & Seaquist, 2008). In addition, in recent DTI studies white matter abnormalities have been reported in DM patients without cognitive complaints (Hsu, 2012; Van Harten et al., 2006) and these abnormalities were also related to cognitive function (Kodl et al., 2008; Yau et al., 2009). Some limitations also need to be discussed. The small sample size of the stroke group (n = 17) may prevent the generalization of the results. Results were not adjusted for brain atrophy ratio (%) in this study, due to the small sample size that precludes us to adjust for it.

In conclusion, ischemic stroke lesions are related to remote thalamic diffusion abnormalities that could yield cognitive dysfunction three months after the symptoms onset. These novel results suggest that disruption of cortico-subcortical circuits can influence cognitive deficits after ischemic stroke. A fiber-tracking approach could provide more specific information about the role of diffusion abnormalities of thalamic projection fibers that might be related to cognitive dysfunction in stroke subjects. Furthermore, other neuroimaging approaches such as connectivity or functional resting state could also provide valuable information about brain neuronal networks and could help to understand cognitive deficits after ischemic stroke. Further research is needed to determine if thalamic microstructural abnormalities have diagnostic value in cognitive dysfunction and recovery after ischemic stroke.

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There are no conflicts of interest related to this study.

Table 1

Demographic, clinical and MRI data

	Control group (n=17)	**Patient group (n=17)**	**p**
Age (years)[1]	61.65 (5.40)	62.41 (9.81)	t=-0.28 (0.78)
Sex (male)[2]	13 (76.5%)	13 (76.5%)	χ^2= 0.00 (1.00)
Education (years)[1]	8.00 (3.71)	7.71 (4.96)	t= 0.20 (0.85)
Vocabulary (WAIS-III)[1]	41.18 (9.93)	34.76 (11.45)	t= 1.74 (0.09)
Vascular Risk Factors[2]			
Hypertension	7 (41.2%)	8 (47.1%)	χ^2=0.12 (0.73)
Dyslipidemia	10 (58.8%)	8 (47.1%)	χ^2=0.47 (0.49)
DM	1 (5.9%)	6 (35.3%)	χ^2=4.50 (0.03)*
Current smoker	3 (17.6%)	3 (17.6%)	χ^2= 0.00 (1.00)
Ischemic lesion volume (mm^3)[1]		35,975 (46,044)	-----
MRI measures [1]			
GM (cm^3)	612.25 (68.25)	556.40 (14.81)	t=1.41 (0.17)
WM (cm^3)	559.28 (58.85)	489.19 (76.26)	t=3.00 (0.00)**
BP (cm^3)	1155.22 (93.97)	1045.58 (14.72)	t=2.59 (0.01)*
TBV (cm^3)	1478.57 (11.27)	1393.22 (23.12)	t=1.37 (0.18)
Ratio GM / TBV	41.39 (2.83)	39.60 (4.16)	t=1.46 (0.15)
Ratio WM / TBV	37.81 (2.47)	35.76 (5.70)	t=1.36 (0.18)
Ratio BP / TBV	78.20 (3.79)	75.37 (3.38)	t=2.29 (0.03)*

Note. [1]Values are means (standard deviation). [2] values are n (%). DM = diabetes mellitus; GM = gray matter volume; WM = white matter volume; BP = brain parenchyma volume = GM+WM; TBV = total brain volume.

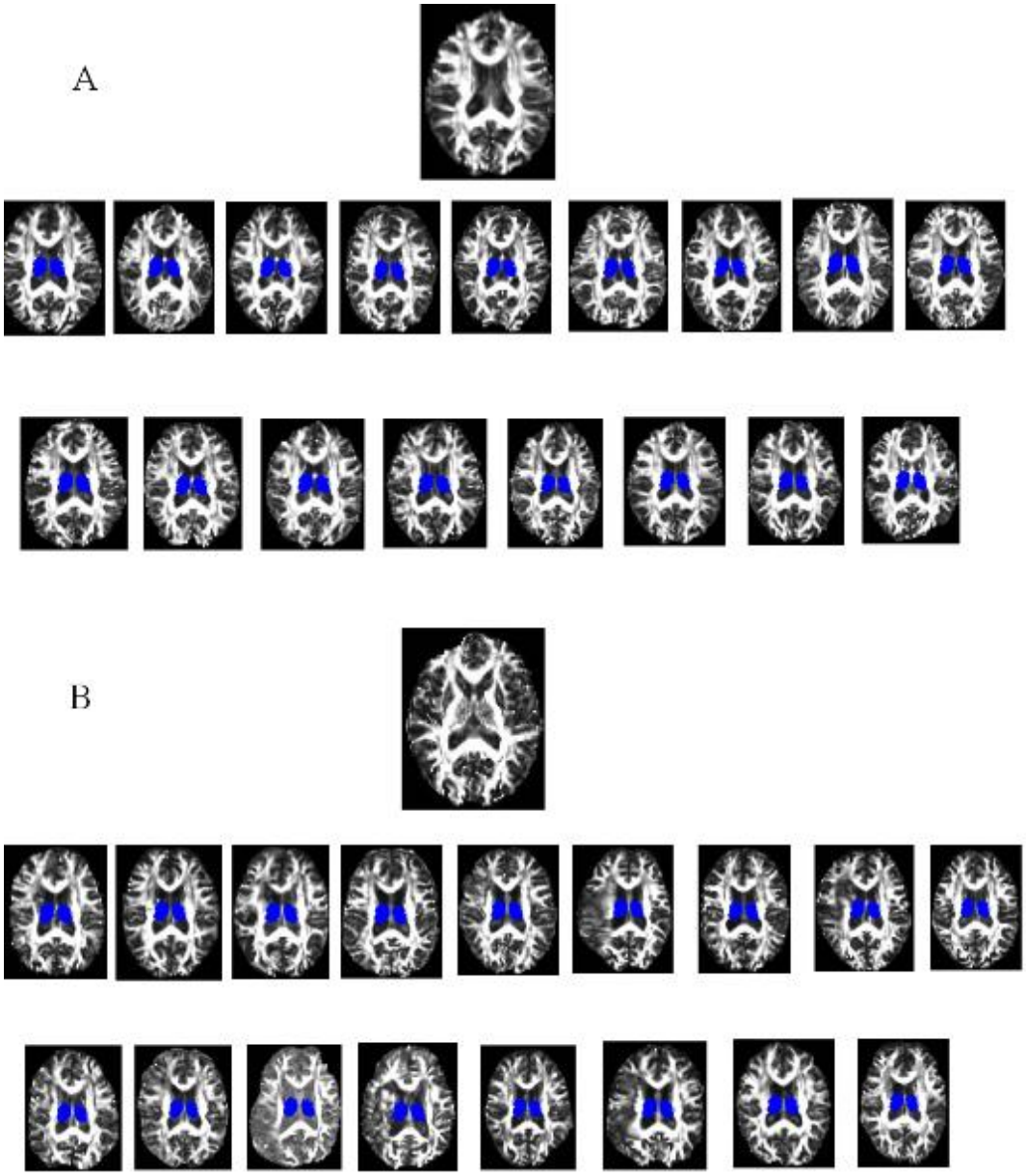

Figure 1. Panel A shows all the co-registered images for controls with the higher-resolution FA template (MNI152 target) on top of them. Panel B shows all the co-registered images for the stroke patients with the target image on top of them. Thalamus segmentations are displayed in blue. Images are displayed in radiological convention (right side represents left side and left side represents right side of the brain).

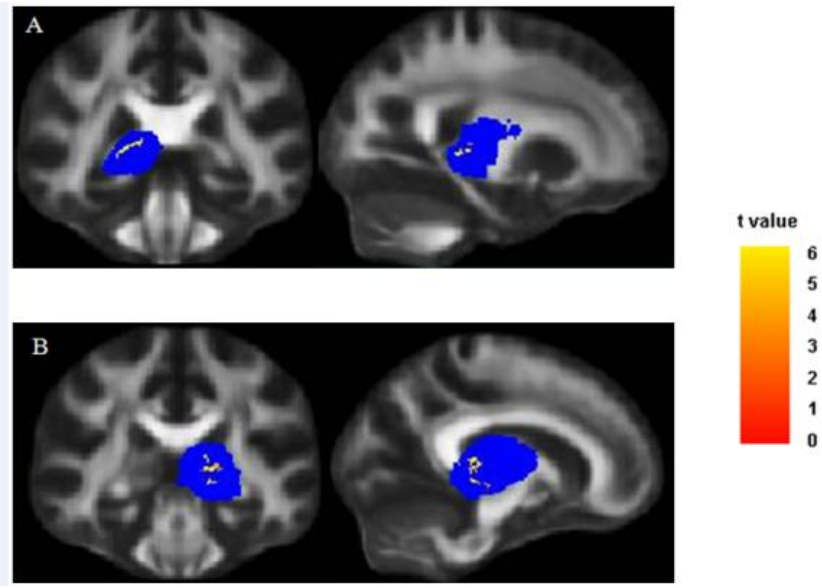

Figure 2. The selected images illustrate the significant regions where the stroke group showed decreased fractional anisotropy (FA) values compared with the control group. The thalamus mask used for the comparison analyses is blue. The red-yellow bar shows clusters of significantly decreased FA values related to stroke group in the right thalamus (A) and the left thalamus (B). Images are displayed in radiological convention (right side represents left side and left side represents right side of the brain).

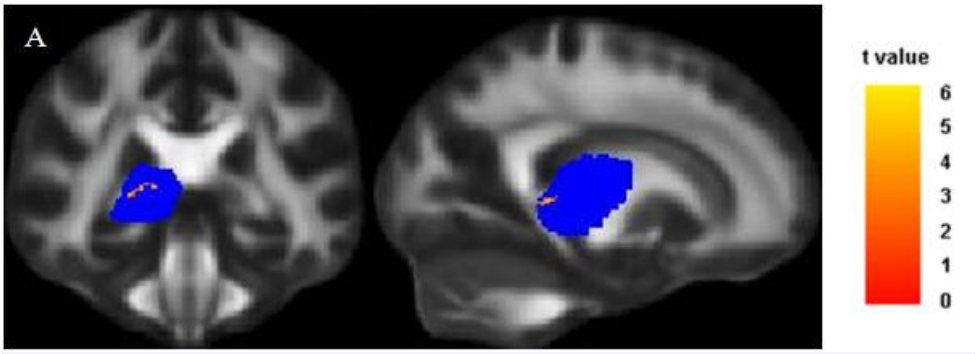

Figure 3. The selected images illustrate the significant regions where the stroke group showed increased mean diffusivity (MD) values compared with the control group. The thalamus mask used for the comparison analyses is blue. The red-yellow bar shows clusters of significantly higher MD values related to stroke group in the right thalamus

(A). Images are displayed in radiological convention (right side represents left side and left side represents right side of the brain).

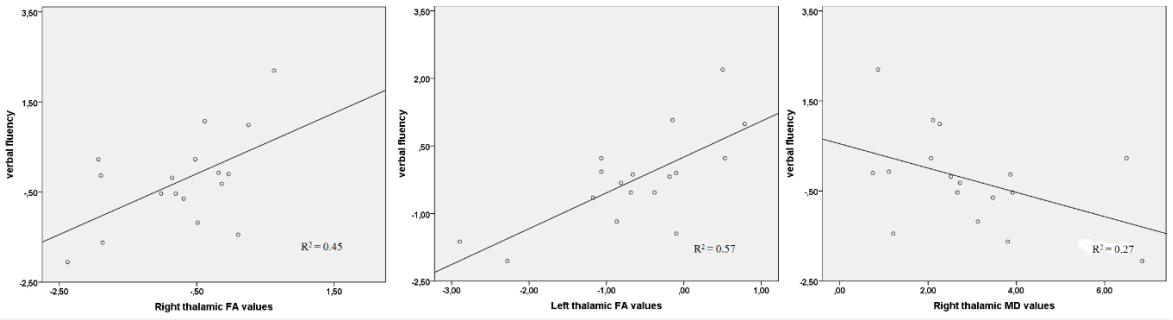

Figure 4. The selected images illustrate the correlations between thalamic fractional anisotropy (FA) and mean diffusivity (MD) values within significant clusters and verbal fluency performance in the stroke group. Each cognitive domain is represented by Z-scores. R^2 = effect size of regression model adjusted for diabetes mellitus (DM).

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Disconnection of the right FAT impairs in attention and response inhibition: a spherical deconvolution tractography study

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Abstract

Inferior frontal (IFG) and supplementary (SMA) and pre-supplementary (pre-SMA) motor areas have systematically been implicated in attention and response inhibition paradigms in functional magnetic resonance imaging studies and lesion analyses. The potential role of the interconnections between these cortical regions, however, remains almost unexplored. Using advanced diffusion weighted tractography in 96 healthy aged participants we dissected in vivo the Frontal Aslant Tract (FAT), which interconnects the pre-SMA, SMA and the IFG. We observed an association between the number of streamlines (as a surrogate of the volume) of the right FAT with the performance on attention. Stroke patients with lesions affecting the right FAT showed significant reduced response inhibition performance. Taken together, these findings suggest that the communication between IFG with the SMA and pre-SMA is essential for two components of executive functions: attention and response inhibition.

INTRODUCTION

Classical neuropsychological measures of attention and response inhibition include the Colour-Word Stroop test (Golden 1978) and the Continuous Performance Test (Conners 1995). The Colour-Word Stroop test requires the suppression of an automated response (i.e., name of the colour is perceived) to allow another response to be produced (i.e., read the colour of the word that is incongruent with the written word). The Stroop task has been associated with a variety of neuroanatomical areas, including most commonly the SMA/PreSMA and the anterior cingulate cortex in experimental and neuroimaging studies (Bush et al. 1998; Ravnkilde et al. 2002; Swick et al. 2002). The inferior frontal gyrus is been further implicated in some studies (Roberts & Hall, 2008; Grandjean et al. 2012). The Continuous Performance Test requires the detection of a target stimulus among non-targets, and an inhibition of

the response when signalled to do so (Beck et al. 1956). Similarly to the Stroop test, the Continuous Performance Test predominantly elicits activations within the SMA/PreSMA, the anterior cingulate cortex, and the posterior inferior frontal gyrus (Hampshire et al. 2010; Manly et al. 1997; Tana et al. 2010; Hilti et al. 2013). Hence, both tasks involve attention and response inhibition processes that seem to activate a network of areas involving the SMA/PreSMA, the anterior cingulate and the inferior frontal gyri.

This set of areas is interconnected in the monkey brain by a long intralobar bundle named recently the Frontal Aslant Tract (FAT, Thiebaut de Schotten et al. 2012a). In the human brain, this tract projects distinctly to the anterior supplementary and pre-supplementary motor areas and the pars opercularis and triangularis (Thiebaut de Schotten et al. 2012a; Catani et al. 2012). Considering these cortical projections, the FAT might mediate attention and response inhibition via the communication between the pre-supplementary motor area and the inferior frontal gyrus. However, the association between attention and response inhibition and the FAT in controls as well as in stroke patients have never been explored.

Hence, our first aim was to explore whether anatomical features of the FAT might correlate with attention and response inhibition in healthy participants. The second aim was to investigate if a disconnection of the FAT leads to a significant drop in these executive functions in stroke patients.

MATERIAL AND METHODS

Participants

This study has been approved by the ethics committees of the University of Barcelona and the Germans Trias i Pujol University Hospital (Institutional Review

Board: 00003099). All patients gave informed written consent to participate in the study. The study was conducted in accordance with the Declaration of Helsinki.

96 healthy participants (mean age=59.7 years; age range 50-65 years; males=39) were included as part of the Barcelona-AsIA Neuropsychology Study (López-Cancio et al. 2012; Miralbell et al. 2012; Soriano-Raya et al. 2012).

In addition, we recruited 14 stroke patients (mean age=61.6; age range 40-75 years; males=11) admitted to the acute stroke unit of the Germans Trias i Pujol University Hospital (Badalona, Spain). Inclusion criteria comprised i) first-ever ischemic stroke within the left or right middle (MCA), anterior (ACA) or posterior (PCA) cerebral artery territories, ii) no hemorrhagic transformation, iii) absence of severe aphasia (National Institute of Health Stroke Scale (NIHSS) $\leq$ 1; Brott et al. 1989), iv) no history of substance abuse, neurological or psychiatric disorders, or severe sensory impairments.

For the stroke cohort, neuropsychological assessment and neuroimaging were performed three months after symptom onset. Neuropsychological assessment for the stroke and control groups included the Colour-Word Stroop test (Golden 1978) and a computerised version of the Continuous Performance Test (CPT-II; Conners and MHS Staff 2004). For the Colour-Word Stroop test the ratio Word-Colour/Colour was used to quantify the level of inhibition of an automated response (Graf et al. 1995; Golden et al. 1999). Premorbid intelligence was assessed using the Vocabulary test (Wechsler Adult Intelligence Scale; WAIS-III); present state affect was measured with the Geriatric Depression Scale (GDS-15) (Sheikh and Yesavage 1986). For the CPT-II, the number of omission and the total number of errors were used to quantify the level of attention and inhibition of an automated response.

For the statistical analysis, stroke patients were split into two subgroups based on the presence of a disconnection of the FAT: a group of patients with a

disconnection of the right frontal aslant tract (FAT–) and a group of patients without disconnection of the right frontal aslant tract (FAT+). In the FAT– group, all patients presented with a right hemispheric lesion. In the FAT+ group, seven patients presented with a right hemispheric lesion and two patients with a left hemispheric lesion. Most of the patients (n = 12) had infarcts within the MCA territory and two patients had an infarct located within the PCA and ACA territory. Demographical information and clinical characteristics of all groups are reported in Table 1. Neuropsychological data was obtained within 94.11 days (SD=8.04) post stroke in the FAT+ group and within 96.8 days (SD=2.39) in the FAT– group.

Magnetic resonance imaging acquisition

Magnetic resonance imaging (MRI) scanning was performed on a 3T Siemens Magnetom Trio (Siemens Diagnostics Healthcare, Erlangen, Germany) at the Image Diagnosis Centre (Hospital Clínic, Barcelona, Spain). The MRI protocol included an MPRAGE T1-weighted scan with 245 axial and coronal images and 192 sagittal images, (repetition time (TR) = 2300 ms, echo time (TE) = 3 ms; flip angle = 15°; field of view = 245 mm; and voxel size = 1 mm^3). Initially two diffusion-weighted imaging (DWI) datasets were acquired and later concatenated. The following parameters were applied: each set was recorded along 30 directions with 65 axial images and 120 sagittal and coronal slices (TR = 9300 ms; TE = 94 ms; flip angle = 15°; field of view = 240 mm; no gap; voxel size = 2 mm^3 with no gap, b=1000 s/mm^2) with one additional volume for each set without diffusion weighting (b=0 s/mm^2).

Diffusion-weighted imaging (DWI) preprocessing

Data were corrected for head-motion, eddy current and geometrical distortions using ExploreDTI (http://www.exploredti.com). Spherical deconvolution (SD) (Tournier et al. 2004; Alexander 2006) was then estimated using a modified version of the Richardson-Lucy algorithm for SD (Dell'Acqua et al. 2010). Algorithm parameters were chosen as described in Dell'Acqua et al. (2012). The high signal to noise ratio (SNR) of the data allowed us to apply a relatively low regularisation threshold equal to η=0.02 without an excessive increase of spurious components in the fibre orientation distributions (FODs). The other parameters for the deconvolution algorithm were: i) fibre response function equivalent to a tensor of [1.5 0.3 0.3] x 10^{-3} mm^2/s; ii) 200 algorithm iterations and iii) regularisation geometric parameter of ν=8. Fibre orientation estimates were obtained by selecting the orientation corresponding to the peaks (local maxima) of each FOD profile. To exclude spurious local maxima, we applied an absolute and a relative threshold. A first "absolute" threshold was used to exclude small local maxima due to noise or isotropic tissue. This threshold is three times the amplitude of a spherical FOD obtained from a grey matter isotropic voxel. A second "relative" threshold of 5% of the maximum amplitude of the FOD was applied to remove the remaining local maxima with values greater than the absolute threshold (Dell'Acqua et al., 2009).

Tractography algorithm

A Modified Fibre Assignment by Continuous Tracking (M-FACT) algorithm was used to propagate the streamlines from each brain voxel (Descoteaux et al. 2009). Streamlines were reconstructed by sequentially piecing together discrete, shortly-spaced estimates of fibre orientation to form continuous trajectories. In regions with crossing white matter bundles, the algorithm followed the orientation of least

curvature as described by Schmahmann et al. (2007). Streamlines were halted when a voxel without fibre orientation was reached or when the curvature between two steps exceeded a threshold of 45°. The software estimating and reconstructing the orientation vectors and the trajectories from diffusion MRI was written in Matlab 7.8 (http://www.matwork.com) (Dell'Acqua et al. 2010, 2012).

Tractography dissections

Virtual dissections were performed in TrackVis (www.trackvis.org) using a two-regions of interest (ROIs) approach. ROIs were manually defined bilaterally on the superior frontal gyrus and the inferior frontal gyrus to isolate the FAT bilaterally as described by Thiebaut de Schotten et al. (2012a) and Catani et al. (2012). ROIs were delineated around areas that represent "compulsory regions" along the course of a tract (Thiebaut de Schotten et al. 2012a; Catani et al. 2012; Catani et al. 2013). We extracted the number of streamlines reconstructed for each tract as a surrogate of the volume of the FAT.

FAT atlas based on aged participants and variability maps

For each participants SD maps (Dell'Acqua et al. 2010) were registered to the Montreal Neurological Institute (MNI152) template provided within the FMRIB Software Library package (FSL, http://www.fmrib.ox.ac.uk/fsl/) using Advance Normalisation Tools (ANTs, http://www.picsl.upenn.edu/ANTS/), which combine affine with diffeomorphic deformations (Avants et al. 2007).

A binary map of the FAT was created for each participant by assigning each voxel a binary value of either 1 or 0 depending on whether this voxel was intersected by the streamlines of the tract. The transformation matrix derived from the previous

normalisation was applied to each individual FAT binary map. Normalised FAT maps were then averaged to produce left and right FAT percentage maps. This method produces probability overlap maps by summing up at each point in the MNI space the FAT normalised maps from each participant; hence, the overlap of the FAT maps varies according to inter-subjects anatomical variability (Lawes et al. 2008; Thiebaut de Schotten et al. 2008).

Lesion normalisation and analysis

For each patient, lesions were delineated on native axial T1-weighted images using manual lesion tracing in MRICro software (Rorden and Brett 2000). A binary lesion mask was obtained for every participant by setting all voxels within the lesion to 1 and the background to 0. This lesion mask was used to estimate the size of the lesion.

In order to allow for the use of the atlas created from the 96 healthy control participants, native T1-weighted images of patients had to be normalised to MNI space using linear and non-linear image registration tools (FLIRT/FNIRT) as implemented within FSL (fMRIB software library; http://www.fmrib.ox.ac.uk/fsl/). Hereafter, the FAT atlas was superimposed onto the normalised ischemic stroke brains. When a patient's lesion overlapped on a voxel where the probability to contain the right FAT was above 50% (above chance level), we considered this tract to be disconnected (Thiebaut de Schotten et al. 2012b).

Statistical Analysis

Kolmogorov-Smirnov test for normality did not confirm a Gaussian distribution for all variables. Hence, the relationship between the volume of the FAT

(number of streamlines) in each hemisphere and attention and response inhibition performance at the Colour-Word Stroop test and Continuous Performance Test in healthy participants was assessed with Spearman ranking correlation analyses.

Statistical comparison of the neuropsychological performances between FAT+ and FAT– groups was calculated using univariate analyses of covariance (ANCOVA) as provided in the SPSS 18 (http://www-01.ibm.com/software/analytics/spss/). The ANCOVA was carried out with the Word-Colour/Colour or Continuous Performance Test omission error and total errors as dependent variable (i.e., behavioural outcome). The presence of damage to the right FAT was defined as independent variable (defined as 0=no right FAT damage, 1=right FAT damage). Years of education and age at symptom onset were defined as covariates. Within ANCOVA effect size was calculated using partial eta-squared (η^2_p) conventionally interpreted as small ($\eta^2_p \geq 0.01$), medium ($\eta^2_p \geq 0.06$), or large ($\eta^2_p \geq 0.14$) (Cohen 1988). We calculated *post hoc* power (1-β) given the probability level α, the sample size of our recruited cohort and the minimum expected effect size using G*power software (http://www.psycho.uni-duesseldorf.de/abteilungen/aap/gpower3/; Thomas et al. 1997).

RESULTS

FAT atlas in aged participants

The left and the right FAT percentage maps are shown in Figure 1. The FAT probability maps show a concentric distribution with a descending gradient from the central portion (overlap more than 90%) to the most peripheral areas (overlap below 50%) (Thiebaut de Schotten et al. 2011). The FAT projected to the SMA/Pre-SMA (equivalent to BA6 / BA8, respectively) and the posterior portion of the inferior frontal gyrus (equivalent to BA47 and BA44).

FAT volume and cognitive performance

In healthy participants, the right FAT volume (number of streamlines) correlated with the Continuous Performance Test performance (Continuous Performance Test omission error: Spearman $\rho = -0.268$; $P = 0.009$; Continuous Performance Test total errors: Spearman $\rho = -0.235$; $P = 0.022$) with a statistical power ($1-\beta$) of 0.69 for the Continuous Performance Test omission errors and 0.75 for the Continuous Performance Test total errors (Figure 1). The Continuous Performance Test did not correlate with the volume of the left FAT (Continuous Performance Test omission error: $\rho = -0.013$; $P = 0.904$; Continuous Performance Test total errors: $\rho = -0.029$; $P = 0.78$) (data not shown). Similarly, no correlations were observed between the Colour-Word Stroop interference performance and the left ($\rho = 0.155$; $P = 0.134$) and right ($\rho = 0.127$; $P = 0.22$) FAT volume, respectively (data not shown).

FAT disconnection and Inhibition in stroke

The FAT– group presented with a marginally higher level of education compared to the FAT+ group ($t_{(1;11)} = -2.1$; $P = 0.06$) and a tendency to be younger ($t_{(1;11)} = 1.93$; $P = 0.11$), hence those two variables were included as covariate of no interest. No further differences were observed between the two stroke groups in demographic, clinical and MRI characteristics. Also, there was no significant difference in the size of the lesions between the two groups ($t_{(1;11)} = -1.06$; $P = 0.31$).

A group difference in response inhibition performance was observed in the ANCOVA examination between the FAT+ and FAT– groups (Figure 3). The FAT+ group showed highly significantly impaired interference performance compared to the FAT–

group ($F_{(1,11)}$= 12.16; p = 0.006, η^2_p =0.55) with a statistical power of 0.95 (Figure 3). Both groups did not differ in their performance at the Continuous Performance Test measures (Continuous Performance Test omission error: ($F_{(1,11)}$= 0.65; p = 0.440, η^2_p = 0.06); Continuous Performance Test total errors: ($F_{(1,11)}$= 0.92; p = 0.360, η^2_p = 0.08) (data not shown).

DISCUSSION

In this study we investigated the relation between the FAT and attention and response inhibition, two of the most relevant executive components, in healthy participants and in a group of first-ever ischemic stroke patients using spherical deconvolution tractography.

FAT dissections in aged participants were consistent with previous post-mortem dissections (Lawes et al. 2008; Catani et al. 2012) and tractography studies (Lawes et al. 2008; Thiebaut de Schotten et al. 2012a). The observed heterogeneity of the FAT in our tractography-based maps was also consistent with the white matter heterogeneity reported in histology-based studies (Rademacher 1993, 2001; Bürgel et al. 2006).

Part of this heterogeneity (i.e., the volume of the right FAT) correlated with the CPT attention performance in aged participants. With aging, neuronal loss and small vessel alteration lead to progressive white matter damage associated with cognitive decline in the elderly (Pantoni 2010; Xiong & Mok 2011; O'Sullivan et al. 2005; Metzler-Baddeley et al. 2011). Cognitive decline affects predominantly executive functions and the distribution of these brain changes seems to be heterogeneous. Nonetheless, the frontal lobe regions are

predominantly affected (Good et al. 2001; Raz 2000). Hence, progressive damage of the FAT with advanced aging might be partly responsible amongst other factors (i.e., demyelination, decreased blood perfusion) for the observed decreased attentional habilities in the elderly. On the other hand, decreased response inhibition by the Stroop test was observed when the communication between the right inferior frontal gyrus and the right pre-supplementary motor area, which are connected via the FAT, was interrupted by an ischemic stroke. Stroop paradigm is considered a typical clinical test (Stuss & Levine 2002), so it might be easier to find results in lesioned patients than in healthy ones. The fact that stroke sample presented lesions in different white matter tracts that could affect attention and the small stroke sample size might have precluded finding significant differences in the CPT attentional task.

Some limitations of this study should be considered. The small sample size of stroke participants may preclude the generalisation of the results. However, the stroke participants were consecutively admitted in a tertiary stroke center and this may partially help to mitigate our sampling bias. Although we used the number of streamlines as a surrogate of FAT volume, there are some factors such as length, volume, and curvature that may also affect the number of streamlines count (Vos et al. 2011; Szczepankiewicz 2013). In line with is, it would be interesting to investigate the association between FAT tract and attention and response inhibition with apparent fibre density or the hindrance modulated orientational anisotropy (HMOA) among other diffusion metrics in future studies.

These results complement previous findings reporting the involvement of the inferior frontal gyrus (Garavan et al. 1999; Aron et al. 2003) and the pre-

supplementary motor area (Rushworth et al. 2002; Rushworth et al. 2004; Nachev, Kennard, and Husain 2008) in attention and response inhibition. Our results suggest that cortical areas are not operating independently but rather rely on an intact interaction via the FAT.

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Table 1 Demographic, clinical and magnetic resonance imaging (MRI) data of the healthy and stroke groups

	Healthy group	Stroke sample (n=14)	
		Right FAT+	Right FAT-
	(n = 96)	(n=9)	(n=5)
Age (years)	59.73 ± 3.37	65.33 ± 4.82	55 ± 11.40
Sex	39M:57F	7M:2F	4M:1F
Education (years)	8 ± 3.23	7 ± 4.12	12.20 ± 5.02
MMSE	29 (28-30)	27.89 ± 1.45	28.60 ± 0.89
Laterality	95RH:1LH	9RH:0LH	4RH:1LH
WAIS III (vocabulary test)	38.69 ± 9.04	29.67 ± 9.19	45 ± 10.1
GDS	1 (1-3)	2.11 (1.9)	4.20 (1.92)
Lesion volume (mm^3)	-	3597 (200-9200)	5920 (2400-14520)
Time Testing post-stroke	-	94.11 (8.04) days	96.8 (2.39) days

MMSE, Mini-Mental State Examination; WAIS III, Wechsler Adult Intelligence Scale; GDS, Geriatric Depression Scale;

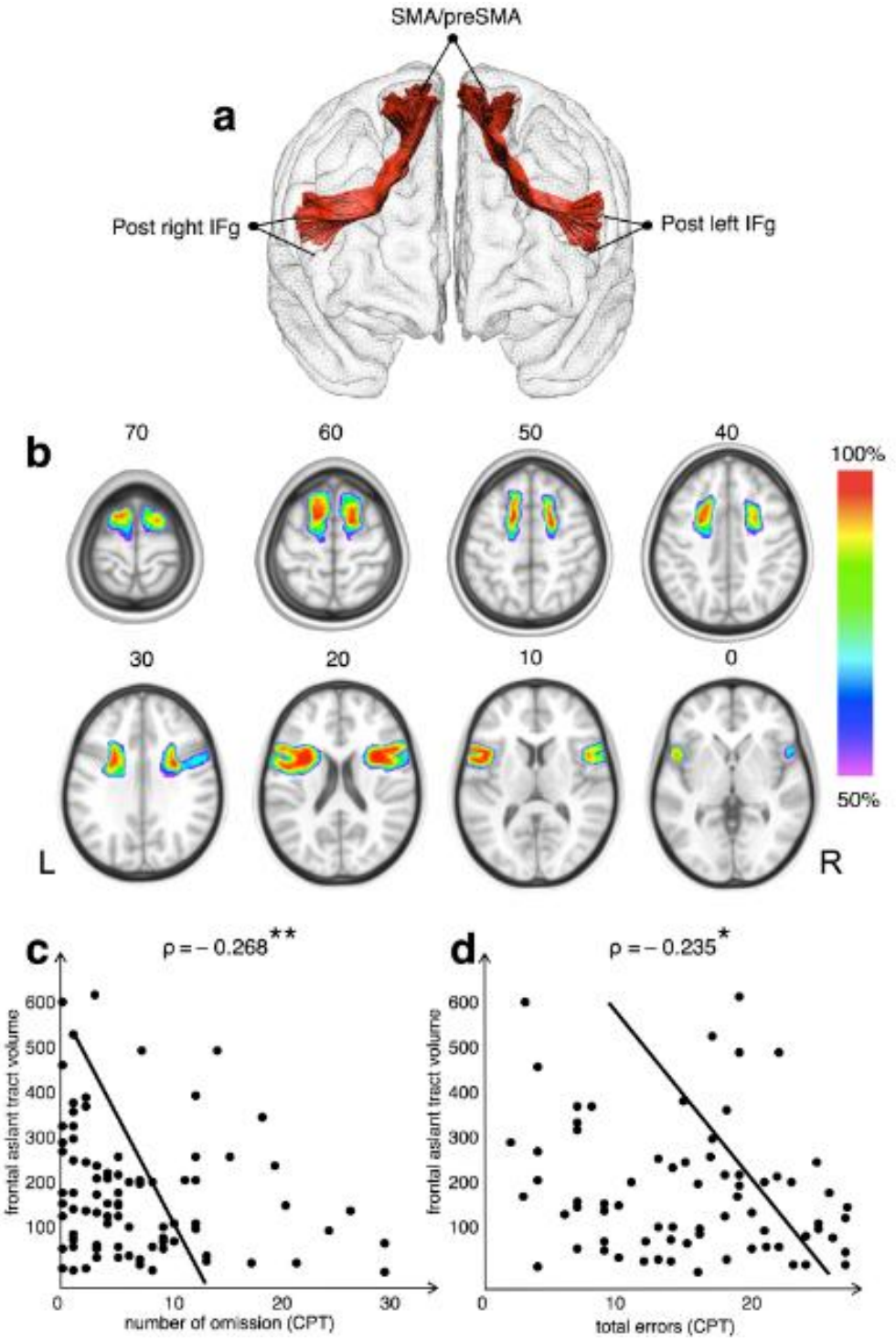

Figure 1 FAT variability in healthy controls and its behavioural correlates. (a) Frontal view of the left and right FAT (visualised in radiological convention). (b) Percentage overlap maps of the FAT in the MNI152 space. (c, d) Behavioural correlation between the size of the FAT in the right hemisphere and attention performance. Post IFg = posterior part of the inferior frontal gyrus

***** $p < 0.05$; ****** $p < 0.01$

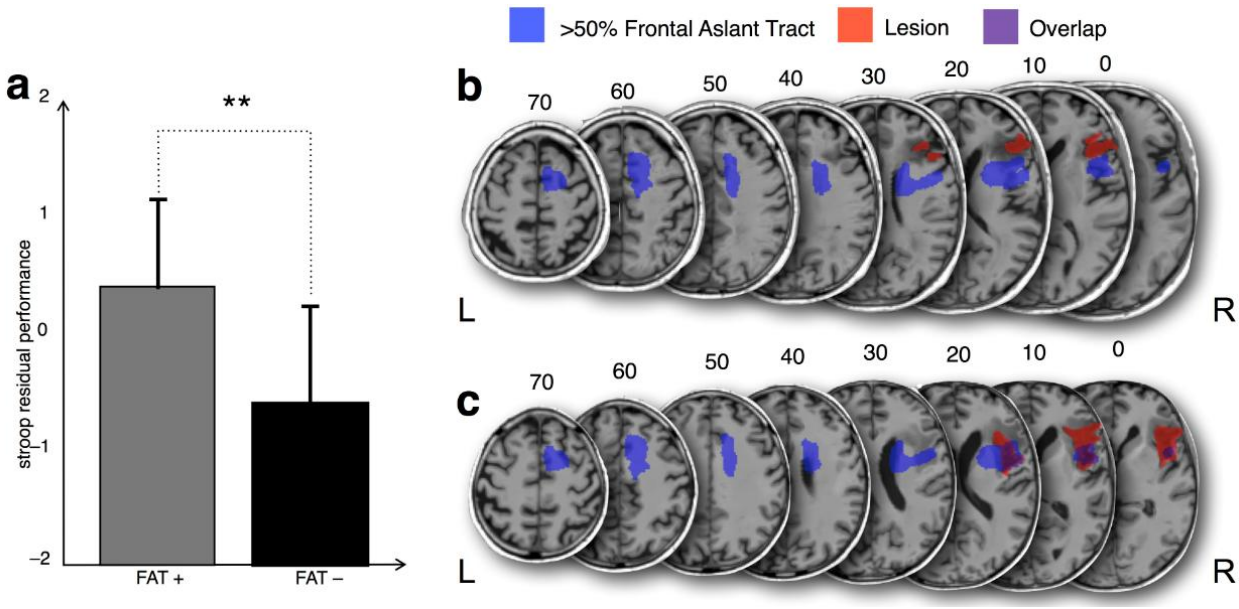

Figure 2 Clinical neuroanatomical correlation between the FAT and response inhibition. (a) Average response inhibition performance in stroke patients with a spared (FAT+) or disconnected (FAT–) FAT. (b) Stroke patient with spared right FAT. (c) Single case stroke patient with a right FAT disconnected

** $p < 0.01$

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V SUMMARY OF THE RESULTS AND DISCUSSION

The present thesis comprises three studies which addressed the investigation of cognitive and microstructural effects of cerebral circuits disruption, in both hemispheres (ipsilateral and contralateral), in SVD and LVD. These studies contribute into the understanding of the neurobiological mechanisms underlying VCI and executive dysfunction by using DTI technique. In the first two studies, we emphasised on the role of microstructural thalamic abnormalities remote from cerebrovascular lesions -WMLs or ischemic stroke lesions- and their relation to cognitive dysfunction. In the third study, we investigated the role of one specific frontal tract (the right FAT) in attention and response inhibition function in healthy middle-aged participants. In addition, we explored the cognitive deficits by FAT disturbance due to an ischemic stroke lesion.

WMLs have been consistently related to executive dysfunction (DeCarli et al., 1995; Gunning-Dixon & Raz, 2003; O'Brien et al., 2003; Pantoni et al., 2007; Tullberg et al., 2004), which is thought to be caused by a cortico-subcortical circuit disruption (Linortner et al., 2012; Schmidt et al., 2006). It is known that the thalamus is a crucial structure in these circuits (Byne et al., 2009) and widely implicated in multiple cognitive functions (Schmahmann, 2003; Stebbins et al., 2008; Tekin & Cummings, 2002). In the first study, we aimed to explore thalamic microstructural abnormalities related to WMLs and their association with cognitive function in middle-aged individuals. The results of the study I demonstrated that participants with high grade DWMHs and PVHs showed lower FA thalamic values compared to those with low grade. The role of thalamic microstructural abnormalities in cognition has been previously observed in lacunar stroke patients with leukoaraiosis (Li et al., 2012), schizophrenia (Marenco et al., 2012), and attention-deficit hyperactivity disorder (Xia et al., 2012). Therefore, these studies demonstrate that DTI is regarded as a highly sensitive technique to detect thalamic microstructural abnormalities.

Interestingly, we observed that only decreased FA thalamic values in high grade DWMHs (but not high grade PVHs) were related to cognition. The fact that high grade DWMHs effects were related to cognitive performance is

in concordance with a recent study of our group with the same middle-aged community sample (Soriano-Raya et al., 2012). Although there is increasing evidence about the specific contribution of PVHs and DWHMs in cognitive function, this issue is still controversial (Schmidt et al., 2011). For example, De Groot et al. (2000) showed that PVHs has a predominant role in global dysfunction, verbal memory and psychomotor speed, whereas Sachdev et al. (2005) reported a stronger relation between DWMHs with motor deficits and slowed information processing speed in community-dwelling samples. These inconsistencies have been explained by differences in anatomical locations, severity and aetiology of WMLs (Desmond, 2002; Pantoni et al., 2007). The preeminent association between DWMHs with thalamic diffusion differences and cognition in our study reinforces a predominant role for these lesions in cognitive function in middle-aged healthy individuals.

In the study I, we specifically found that microstructural thalamic abnormalities in high grade DWMHs were related to lower levels of performance in verbal fluency, psychomotor speed and visuospatial skills. These three cognitive domains have been widely related to cortico-subcortical dysfunction in WMLs (Pantoni et al., 2007; Schmidt et al., 2011; Soriano-Raya et al., 2012). In our study, verbal fluency was positively related to right thalamic cortical connections. Verbal fluency is considered as one of the most sensitive tests of executive functions (Baddeley, 1996; Baldo et al., 2001; Stuss & Levine, 2002; Warbuton et al., 1996) and, it is particularly involved in initiation, self-monitoring, cognitive inhibition and efficient organisation of retrieval and verbal recall (Crawford & Henry, 2005; Roher et al., 1999; Rosser & Hodges, 1994). Verbal fluency task consists of producing as many words -beginning with a certain letter or belonging to a particular category- as possible in 1 min (Basso et al., 1997; Frith et al., 1991; Ruff et al., 1997). It has been mainly related to the left hemispheric function, especially to the dorsolateral prefrontal cortex and the superior longitudinal fasciculus (Okada et al., 2003; Peters et al., 2012; Phillips et al., 2011). Both left and right thalamic activations in verbal fluency tasks have been observed in functional MRI studies in healthy participants (Vitali et al., 2005) and epileptic patients (O'Muircheartaigh et al., 2012). Furthermore, impairment during verbal fluency tasks has been described after both left (Shim et al., 2008) and right

thalamic lesions (Annoni et al., 2003; Ebert et al., 1999). Regarding psychomotor and visuospatial skills results, they are considered cognitive domains generally associated with frontal lobe systems and fronto-striatal circuits (Au et al., 2006). In our study, psychomotor speed was associated with diffusion differences in the right thalamus (specifically in the thalamic corticospinal tract projecting to the posterior parietal cortex and a small gray matter area projecting to the pre-motor cortex). A positive correlation between FA values in the right posterior thalamus, among other brain structures, and reaction time has previously been observed in healthy participants (Tuch et al., 2005). Left anterior thalamic radiation FA values were related to psychomotor speed in another DTI recent study in VCI participants (Duering et al., 2012). Finally, Turken et al. (2008) reported a positive association between psychomotor speed and left FA values in the middle frontal gyrus in a healthy sample. We also found an association between thalamic diffusion differences in the right thalamus and visuospatial skills. To the best of our knowledge, there are no studies relating diffusion differences in the thalamus with visuospatial function. This finding could be explained by the fact that one of the significant thalamic diffusion differences was located in regions that project to the right posterior parietal cortex. The role of the right posterior parietal cortex in visuospatial skills is well established (Levin et al., 1996; Silver & Kastner, 2009). In addition, a functional MRI study showed an association between right thalamic activations during a visual task (Fink et al., 2002). Our finding might help to explain the neural bases of the visuospatial deficits that are frequently found in vascular-related cognitive impairment associated to SVD (Au et al., 2006; Delano-Wood et al., 2008; Soriano-Raya et al., 2012).

Our cognitive results provide novel neuroimaging data about the neurobiological basis of executive dysfunction in healthy participants with WMLs. They support the notion that cognitive dysfunction associated with WMLs could be a disconnection syndrome (Geschwind, 2010; 1965; O'Sullivan et al., 2001; Schmidt et al., 2006). However, WMLs are only a part of the spectrum of SVD. Other cerebrovascular processes could also be involved in cognitive dysfunction in healthy middle aged community-dwelling participants (Pantoni et al., 2007). Thus, SVD-related lesions, such as LI or MBs, should be also considered in the cognitive evaluation. Furthermore,

cognitive status of elder participants is not only associated with SVD, but also with degenerative changes that often coexist.

The sample used in our study consisted of middle-aged participants (aged between 50-65 years) without a history of cardiovascular disease and/or dementia. The thalamic microstructural abnormalities and their association with cognitive function represent an important advance with respect to the clinical implications of WMLs. Our results suggest that the ongoing distinction between both types of WMLs is worthy and corroborate the hypothesis that DWMHs are predominantly associated with cognitive function.

We used the Fazekas scale to assess the location and severity of WMLs (Fazekas et al., 1987). The Fazekas scale is a visual semi-quantitative rating scale which is widely used in clinical practice (De Groot et al., 2000; Longstreth et al., 1996; Pantoni et al., 2005) and it is considered to have a good rate of reproducibility (Scheltens et al., 1998). Although WMLs semi-automated quantitative scales are more reliable and more robust, visual semi-quantitative scales are considered more appropriate for differentiating DWMHs and PVHs (Van Straaten et al., 2006). Given that visual scales are easy to use and PVHs and DWMHs have distinct repercussions on cognitive function, neuroradiologists should characterize PVHs and DWMHs separately which should be available for neuropsychologists.

In conclusion, in the study I we showed, for the first time, an involvement of cortico-subcortical circuits through the thalamus regarding cognitive function in middle-aged participants with WMLs. The existence of remote thalamic abnormalities and their relevant role in cognition represents an advance in the understanding of cognitive functioning in healthy middle aged community-dwelling participants.

In the study II, we investigated thalamic microstructural abnormalities remote from the ischemic lesion and their association with cognitive function three months after a right cerebrovascular event. It is known that cerebral infarcts can cause not only neuronal damage in the primary ischemic area, but also histological, metabolic and functional abnormalities remote from the ischemic lesion (Achard et al., 2006; Dacosta-Aguayo et al., 2014b; De Reuck et al., 1995; Haberg et al., 2009; Kataoka et al., 1989). Processes such as

Wallerian degeneration or cortical deafferentation (Buffon et al., 2005; Haberg et al., 2009; Hervé et al., 2005; Pierpaoli et al., 2001; Werring et al., 2000; Von Monakow, 1914; Zhang et al., 2012) and cerebral circuit networks disturbance (Crofts et al., 2001; Dacosta-Aguayo et al., 2014a; Kaiser et al., 2007) could explain these remote effects. Other phenomenona as axonal damage, neuronal swelling or shrinkage and alterations of the tissue organization could also explicate remote microstructual abnormalities (Lim & Helpern, 2002).

Thalamic abnormalities remote from the ischemic lesion, predominantly in the ipsilateral thalamus, have been previously investigated in animal models (Abe et al., 2003; Bihel et al., 2010; Dihne et al., 2002; Kataoka et al., 1989; Persson et al., 1989) and human neuroimaging studies such as Positron Emission Tomography (Nagasawa et al., 1994), structural MRI (Achard et al., 2006; Ogawa et al., 1997) and DTI (Buffon et al., 2005; Hervé et al., 2005; Li et al., 2011). The results of the study II, demonstrated that right ischemic stroke patients presented lower FA values and higher MD values in specific areas in both ipsilateral and contralateral thalamus. Both DTI FA and MD indices were related to post-stroke cognitive dysfunction.

Previous DTI thalamic studies in stroke patients used a general ROI approach to obtain a global measure of FA and MD values of the thalamus (Buffon et al., 2005; Hervé et al., 2005; Li et al., 2011). To date, microstructural thalamic abnormalities remote from the ischemic lesion have been found with MD index, but not with FA values (Buffon et al., 2005; Hervé et al., 2005; Li et al., 2011). MD abnormalities have been reported in the ipsilateral thalamus at the first week (Li et al., 2011), one month (Hervé et al., 2005), three months (Buffon et al., 2005; Hervé et al., 2005; Li et al., 2011) and six months (Buffon et al., 2005; Hervé et al., 2005) after a cerebrovascular event. Although FA values have been studied at the same time intervals after ischemic stroke (Hervé et al., 2005; Li et al., 2011), none of these analyses yielded significant differences. The results of the study II showed a similar localisation of thalamic clusters in both FA and MD indices, supporting the concept that these areas are particularly affected by the remote ischemic lesion in the studied sample.

We observed both decreased FA and increased MD values associated with lower verbal fluency performance in the ipsilateral thalamus. In addition,

decreased FA values were also related with lower verbal fluency performance in the contralateral one. This finding might be explained by the strong implication of the left hemisphere in this function. Overall, these results suggest an involvement of cortico-subcortical circuits through the thalamus regarding cognitive dysfunction three months after a right ischemic stroke.

Post-stroke cognitive outcome is significantly influenced by several factors such as individual-level variables (age, VRF, comorbid diseases etc.) and stroke characteristics (neuroimaging volume and location of cerebral ischemic stroke, ischemia duration, ischemic penumbra area etc.) (Hankey et al., 2003; Rosso & Samson, 2014; Vogt et al., 2012). All these factors, including remote thalamic abnormalities, can contribute to explain the cognitive and clinical variability sequels observed among stroke patients.

Previous thalamic DTI studies used heterogeneous stroke samples regarding hemispheric lesion location, the sample size was very small and the implication of thalamic abnormalities in cognitive function was not addressed (Buffon et al., 2005; Hervé et al., 2005; Li et al., 2011). In our study the stroke sample was homogeneous since we only included right lesion patients. The sample size, although was relatively small, was larger than previous DTI studies (Buffon et al., 2005; Hervé et al., 2005; Li et al., 2011).

To conclude, this study is the first DTI work that showed the effects of cerebral circuits disruption, in both ipsilateral and contralateral thalamic regions, related to executive function due to a remote right ischemic lesion three months after the vascular event.

In both studies I and II, we used a voxelwise DTI analyses that allow identifying microstructural thalamic abnormalities in specific thalamic areas using FA and MD indices. Voxelwise approach has been used in a wide range of cerebral and psychiatric pathologies to study diffusion differences between groups (Abe et al., 2010; Smith et al., 2006). This technique does not only allow to localise specific areas of diffusion differences between groups by different FSL atlas (Behrens et al., 2003a, 2003b; Desikan et al., 2006; Hua et al., 2008; Mori et al., 2005), but also circumvents the need to make a priori hypothesis concerning the location of differences (Jones et al., 2005). It is semi-automated and is not dependent of the neuroanatomical knowledge of the investigator (such as the manually placement of the ROI). Finally, voxel-wise

analysis is available and time-efficient (Yang et al., 2012). The DTI voxel-based approach that we used in the study I and II prevent the potential limitations of obtaining a global measure through ROI methodology, such as subjective operator dependent placement, limited reliability and reproducibility and partial volume effects (Chanraud et al., 2010; Zhuang et al., 2010). However, as all MRI techniques, voxel-based approach has issues regarding the accuracy of spatial normalization, the size of the smoothing kernel and the statistical analysis using general linear model inferring the normal signal distribution (Jones et al., 2005).

In both studies, we observed statistical significant differences with FA and MD indices. Traditionally, lower FA values suggest loss of tissue integrity (Alexander, 2007; Basser & Pierpoli, 1996; Mori & Zhang, 2006) and higher MD values suggest an affectation of axonal tracts (Alexander, 2007; Basser & Pierpoli, 1996). However, both FA and MD diffusion values are related to many parameters such as axonal count and density, axonal membrane integrity, axonal diameter, degree of myelination, fiber organization (Beaulieu et al., 2002) and intravoxel coherence of fiber orientation (Smith et al., 2007). The interpretations of FA and MD indices have been predominantly investigated in WM tracts, so their explanations in GM remain still uncertain. Finally, in both studies we demonstrated a relationship between remote thalamic microstructural abnormalities and verbal fluency. It is well-established that verbal fluency is one of the most sensible tests to evaluate executive deficits and it is widely used in clinical and neuropsychological assessments.

It is noteworthy that much of the current cognitive brain knowledge is based on the modular paradigm, in which brain regions are considered to work as independent areas for specific complex cognitive functions. This paradigm, although it has helped to build some of the present understanding of brain functioning, has important limitations when applied to explain cognitive dysfunction and clinical variability in CVD. In both studies, cognitive function seems to be related to secondary anatomical abnormalities involving cerebral circuits dysfunction. This process can extend days, weeks, or months after vascular event and could significantly influence in the clinical and functional outcome of patients (Viscomi & Molinari, 2014).

In the study III, we introduced another DTI approach to address the relationship between a recent described frontal WM tract, called FAT, and cognition in healthy and ischemic stroke subjects. We focused on two cognitive processes that participate in executive function: attention and response inhibition. We observed an association between the right FAT volume and the performance on attention in 96 healthy participants. In patients, only those with stroke lesions encroaching the right FAT showed lower performance in response inhibition.

The FAT tract connects the pars opercularis of the inferior frontal gyrus (IFG) with the anterior part of the supplementary (SMA) and pre-supplementary motor area (pre-SMA) of the superior frontal gyrus (SFG). FAT cognitive correlates are so far unknown, however, it seems to be involved in frontal cognition and language (Catani et al., 2012; Vassal et al., 2014).

Although the IFG has been consistenly associated in response inhibition and maintaining goals (Cardillo et al., 2004; Dosenbach et al., 2006), more general roles have been subsequently proposed, namely the fast adaptation of response (Dodds et al., 2011) and/or attentional control (Hampshire et al., 2010). Pre-SMA seems to be implicated in sustained attention (Hilti et al., 2013), however, its precise role in response inhibition remains still unclear.

Widely used measures of attention and response inhibition include the Continuous Performance Test (CPT) (Conners, 1995) and the Stroop Color-Word Stroop test (Golden, 1978). These tasks have consistently been associated with a large bilateral fronto-parietal network but more predominantly in the right hemisphere including the medial frontal area, the dorsolateral prefrontal cortex, the IFG, the anterior cingulate cortex, the inferior and superior parietal cortex and the insula (Grandjean et al., 2012; Laird et al., 2005; Nee et al., 2007; Olsen et al., 2013; Ogg et al., 2008; Roberts & Hall, 2008). In the study III, we did not find the same results in CPT and Stroop tests in both groups. Whereas right FAT was implicated in attention in healthy participants, right FAT lesion was related to worse response inhibition function in ischemic stroke patients. Since Stroop paradigm is considered a typical clinical test (Stuss & Levine 2002), significant results could be easier established in lesioned pathological brains than in healthy ones. The fact that stroke sample presented lesions in different WM tracts that could affect

attention and the small stroke sample size might have precluded finding significant differences in CPT attentional task. To the best of our knowledge, this is the first correlational study that adress the implication of the FAT in executive function. Further research is needed to confirm our cognitive results and deepen in the characterisation of its cognitive correlates and its relation to other tracts and circuits that sustained executive functions.

To analyse the FAT, we used the novel spherical deconvolution (SD) tractography technique that partially overcomes the limitations of fibre crossing and false negative reconstructions of WM pathways (Dell'Acqua et al., 2010; 2007; Tournier et al., 2004). This can facilitate the properly visualization of those connections that are not visible with conventional tractography (Thiebaut de Schotten et al., 2011a; 2011b). The specific SD tractography variable that we used to measure right FAT was the number of streamlines. As a limitation, we have to take into account that some factors such as length, volume and curvature may affect the number of streamlines count (Szczepankiewicz, 2013; Vos et al., 2012).

In the three presented studies in this PhD thesis, brain MRI was performed with a 3T scanner instead of 1.5T scanners used so far. The sensitivity of 3T MRI (Kim et al., 2008; Scarabino et al., 2003) allow us to examine with precision the severity and location regarding WMLs, primary ischemic area and potential specific thalamic lesions. Others main strengths of these studies are the extensive neuropsychological assessment and the adjustment for possible confounders, such as age, sex, years of education and VRF regarding the association between DTI measures and cognitive function.

There are few limitations along the three presented studies that should be considered. The small sample size of ischemic stroke (study II n=17; study III n=14) may also decrease the sensitivity and may preclude the generalisation of our results. However, the inclusion criterion for patients was very strict and the stroke participants were consecutively admitted in a tertiary stroke center. This may partially help to mitigate our sampling bias. Similarly, in all the presented studies, results were not adjusted for brain atrophy ratio. In the study I, the characteristics of our community-dwelling sample (i.e. age, exclusion of demented patients) suggest that major degenerative changes did not emerge. In

study II and III the small stroke sample size precluded us to adjust for brain atrophy ratio. Therefore, although our results are novel and promising, they should be taken as preliminary.

The studies included in this PhD thesis leave several questions open and pose future challenges to be explored. The role of neuroimaging correlates of cognitive functioning in CVD would benefit from the development of multicenter studies that allow the recruitment of larger cohorts of healthy and ischemic stroke participants. Such investigations would allow studying the generalisation of the results reported in this thesis. Finally, further studies that combine multimodal techniques, such as structural and functional techniques, are needed to establish the sensitivity of neuroimaging correlates in the cognitive follow-up evaluations in small and large vessel CVD.

In conclusion, our results suggest that SVD and LVD can affect cortico-subcortical circuits involved in executive functions through remote thalamic microstructural abnormalities, in both ipsilateral and contralateral hemispheres. In addition, the recent described FAT is also implicated in executive functions. Novel DTI neuroimaging technique can have a relevant role in the knowledge of cognitive functioning in both SVD and LVD. The concomitant use of conventional MRI and novel techniques may be useful to follow-up cognitive evaluation in CVD.

VI CONCLUSIONS

The main conclusions of this thesis derived from the three studies developed, can be summarized as follows:

1. Secondary thalamic microstructural abnormalities remote from the cerebrovascular lesion may occur in both ipsilateral and contralateral thalamus in healthy subjects with WMLs and in stroke patients.

2. Remote thalamic abnormalities may be related to cerebral circuits disruption that are associated to executive dysfunction in both SVD and LVD.

3. Verbal fluency has been the most sensitive cognitive function related to remote thalamic diffusion abnormalities.

4. In healthy middle-aged individuals, thalamic diffusion differences in high grade DWMHs, but not in PVHs, are associated to lower cognitive function.

5. In healthy and in ischemic stroke subjects, the right FAT is implicated in attention and response inhibition, two of the most important components of the executive functions.

6. DTI neuroimage technique provides valuable information of cognitive functioning in CVD.

ANNEX: SPANISH VERSION

RESUMEN DE LA TESIS

I INTRODUCCIÓN

Los accidentes cerebrovasculares (AVD) hacen referencia a un grupo de enfermedades que afectan la circulación del flujo sanguíneo cerebral, causando un suministro de sangre limitado o nulo que afecta a una o muchas áreas del cerebro. Los ACV incluyen algunos de los trastornos cerebrales más comunes y devastadores como son la enfermedad de grande vaso (EGV) que incluye por ejemplo, el infarto cerebral o la hemorragia y las patologías que afectan a los pequeños vasos (EPV) tales como las lesiones de sustancia blanca (LSB) o los infartos lacunares (IL) entre otros. Los ACV son la tercera causa más frecuente de muerte y la causa principal de discapacidad en adultos en los países desarrollados (Carmichael, 2012; Organización Mundial de la Salud (OMS), 2004). Por este motivo, es importante abordar el estudio de esta patología así como sus consecuencias en la cognición. En la presente tesis, nos hemos centrado en las LSB y en el ictus isquémico para tratar de profundizar en el conocimiento de las bases neurobiológicas de la disfunción cognitiva de estas enfermedades a través de sus correlatos de neuroimagen.

1. Las lesiones de sustancia blanca

Las LSB comprenden áreas difusas de hipodensidad en la secuencia de T1 de Resonancia Magnética Nuclear (RMN) e hiperintensidad en imágenes de T2 y FLAIR de la RMN (Hachinski et al., 1987). Estas LSB se consideran clínicamente asintomáticas y la hipertensión arterial (HTA) y la edad son los factores de más riesgo para estas lesiones (de Leeuw et al., 2002; Guo et al., 2009; Van Dijk et al., 2004). En general las LSB se dividen en dos grupos en función de su localización anatómica: aquellas situadas cerca de los ventrículos [hyperintensidades periventriculares o (HPVs)] y aquellas localizadas en la sustancia blanca profunda [hiperintensidades de la sustancia blanca profunda (o HSBPs)] (Fazekas et al., 2002). Las LSB son hallazgos comunes en la RMN de gente mayor sana -más de la mitad de todos los individuos de mediana edad las presentan (De Leeuw et al., 2001; Enzinger et al., 2007)-, en individuos con

deterioro cognitivo (Debette & Markus, 2010; Meyer et al., 1992), en pacientes con ACV (Pohjasvaara et al., 2000; Wen & Sachdev, 2004a) o con otros trastornos neurológicos y psiquiátricos. Las LSB se consideran EPV no necróticas (Pantoni, 2002) debido a la ocurrencia de infartos incompletos en la sustancia blanca (SB) que afectan a las arterias penetrantes del cerebro (Román et al., 2002). Esto conlleva una extensa desmielinización y pérdida axonal cerebral (Fazekas et al., 1998). Sin embargo, tanto las HPVs como las HSBPs también contienen alteraciones no isquémicas (Fazekas, 1998; 1993).

1.1 Cuantificación de las lesiones de sustancia blanca

Se han planteado diferentes maneras de cuantificar las LSB en las imágenes de RMN. Por ejemplo, las escalas semicuantitativas visuales evalúan la gravedad de las LSB cerebrales (Fazekas et al., 1987; Wahlund et al., 2001). Mientras unas dividen las LSB en HPVs y HSBPs, así como en diferentes regiones anatómicas (De Groot et al., 2000; Fazekas et al., 1987; Wahlund et al., 2001) otros dividen las LSB en normal, moderado, y alto grado de LSB (Van Swieten et al., 1991). También se han propuesto otros métodos cuantitativos como son los métodos semiautomáticos volumétricos, las mediciones volumétricas digitalizadas y los métodos de segmentación (DeCarli et al., 1995; Gurol et al., 2006).

1.2 Lesiones de sustancia blanca y cognición

Las LSB se han relacionado consistentemente con la cognición en sujetos sanos de la comunidad (Pantoni et al., 2007; Schmidt et al., 2011), en individuos con deterioro cognitivo leve y en personas con demencia. Por ejemplo, el estudio colaborativo *The longitudinal Leukoaraiosis and DISability (LADIS)* mostró una asociación entre la gravedad de LSB basales y el deterioro cognitivo global en una cohorte de 588 sujetos de edad avanzada (Inzitari et al., 2009). Al final de los 3 años de seguimiento de evaluación cognitiva, 90 de ellos habían desarrollado demencia y 147 fueron diagnosticados de deterioro cognitivo sin demencia (Verdelho et al., 2010). Uno de los predictores más importantes de deterioro cognitivo fue la gravedad de las LSB independientemente de la edad, la educación, y otras variables relacionadas con la atrofia temporal. Los déficits cognitivos en sujetos con LSB se han atribuido

principalmente a una disrupción en los circuitos fronto-subcorticales (Linortner et al., 2012; Schmidt et al., 2006) y afectación de las fibras de asociación corticales y de proyección (Catani & Ffytche, 2005; Nordahl et al., 2006). Los dominios cognitivos más consistentemente relacionados con las LSB han sido las funciones ejecutivas y la velocidad de procesamiento de la información (Bartrés-Faz et al., 2001; O'Brien et al., 2003; Pantoni et al., 2007).

Aunque estudios previos han observado que las LSB tienen un papel notable en la cognición, la relevancia clínica de esta asociación sigue siendo controvertida (Andersson, 2010; Wallin & Fladby, 2010). Del mismo modo, la contribución específica en la cognición de las HPVs y las HSBPs actualmente todavía no se conoce con certeza (Schmidt et al., 2011) dado que hasta la fecha pocos estudios han abordado este tema y los resultados son controvertidos.

2. El infarto cerebral isquémico

La Organización Mundial de la salud (OMS) define el infarto como un daño neurológico focal de inicio brusco y de duración de más de 24 horas y de presunto origen vascular (OMS, 2006). En concreto, en el infarto cerebral isquémico el flujo de sangre es insuficiente para mantener la función neurológica y el infarto se produce cuando la isquemia alcanza el umbral necesario para producir muerte celular. En general, los infartos cerebrales se pueden definir como > 0,5-1,5 cm^3 (Thal et al., 2012).

2.1 Epidemiología

Se estima que los ACV representan 4,5 millones de muertes en el mundo y 9 millones de sobrevivientes anualmente (Mathers et al., 2009; Wolfe, 2000). El riesgo de ACV aumenta con la edad y aproximadamente, uno de cada cuatro hombres y una de cada cinco mujeres de más de 45 años, sufrirá un ictus si llega a la edad de 85 años (Wolfe, 2000). Con el progreso en el conocimiento de las neurociencias y los avances clínicos en el tratamiento del ACV agudo, los sobrevivientes de ACV han aumentado de 1,5 millón a 2,4 millones en todo el mundo (Muntner et al., 2002). Sin embargo, parece ser que aproximadamente un 64% de los supervivientes presentará alteraciones cognitivas (Sahathevan et al., 2012) y un tercio de ellos presentará déficits

cognitivos graves compatibles con criterios de demencia (Hachinski et al., 2006).

2.2 Factores de riesgo vascular y etiología

Los ACV son causados por mecanismos isquémicos y hemorrágicos. Alrededor del 87% de los ACV son isquémicos y el 13% son hemorrágicos (Gleichman & Carmichael, 2014). El papel de los factores de riesgo vascular (FRV) en el inicio, la progresión y la prevención de los ACV se ha convertido en una prioridad en la investigación básica y clínica. Algunos factores de riesgo de los ACV se consideran factores no modificables (edad, género, etnia y genética), mientras que otros se creen factores ambientales modificables por el estilo de vida [HTA, diabetes mellitus (DM), dislipemia (DL), consumo de cigarrillos, obesidad y consumo de alcohol] (O'Donnell et al., 2010).

2.3 La zona primaria isquémica y el área de penumbra

A nivel histológico, el proceso de isquemia comprende dos zonas, la zona de la lesión primaria o core y la zona de penumbra isquémica. Las dos zonas alteran la fisiología y la bioquímica del cerebro. La zona primaria isquémica es donde se ha producido necrosis celular y, la zona de penumbra isquémica, es el área periférica alrededor del área primaria isquémica. En el núcleo del infarto isquémico focal tiene lugar una compleja cascada fisiopatológica que incluye excitotoxicidad, despolarización de la zona adyacente a la lesión, inflamación y apoptosis neuronal (Patel et al., 2013). Además suele aparecer un edema cerebral que puede afectar tanto a la perfusión local como a zonas remotas a ésta. Esto va seguido de una expansión de la despolarización neuronal que induce la transformación de la zona de penumbra inicial isquémica en área necrótica. La zona de penumbra isquémica es una zona con reducción de flujo sanguíneo en la cual se suprime la actividad funcional de las neuronas aunque la actividad metabólica se mantiene y la integridad estructural de las células se conserva (Kumar et al., 2010). Las neuronas de esta área pueden permanecer viables durante varias horas después de la aparición de los síntomas del ictus pero se considera un área "dependiente del tiempo", de tal manera que esta área va disminuyendo y transformándose en core a medida que pasa el tiempo (Kumar et al., 2010). La conectividad de

los tractos de sustancia blanca entre la zona primaria y las zonas secundarias a la lesión pueden lesionarse y causar desaferentación (Haberg et al., 2009; Zhang et al., 2012). Este fenómeno, conocido como "diasquisis" (Von Monakow, 1914) conlleva anomalías estructurales, funcionales y metabólicas en áreas remotas secundarias a la lesión isquémica (Dacosta-Aguayo et al., 2014b; Enager et al., 2004). Este fenómeno es responsable de déficits clínicos y cognitivos en zonas remotas a la lesión focal más allá de las consecuencias directas que se esperarían del área primaria de la lesión (Seitz et al., 1999; Whishaw, 2000).

2.4 Consecuencias clínicas y cognitivas después de un ictus

El ictus cerebral conlleva secuelas neurológicas, deterioro cognitivo y alteraciones conductuales y emocionales. Los déficits cognitivos pueden oscilar desde el deterioro cognitivo vascular leve (DCVL) a la demencia vascular (DV) (Gorelick et al., 2011; Troncoso et al., 2008). Hay una cierta correspondencia entre la localización neuroanatómica del ictus, los síntomas neurológicos y los déficits neuropsicológicos observados **(Tabla 1)**. Como mencionamos anteriormente, los infartos cerebrales pueden ser responsables de alteraciones histológicas, metabólicas y funcionales en zonas remotas a la zona primaria de la lesión isquémica (Dacosta-Aguayo et al., 2014b; De Reuck et al., 1995). Estos cambios, probablemente, son debidos a degeneración Walleriana, desaferentación cortical (Haberg et al., 2009; Zhang et al., 2012) y disrupción de circuitos cerebrales (Crofts et al., 2001; Dacosta-Aguayo et al., 2014a). Uno de los circuitos cerebrales más importantes para la cognición son los circuitos fronto-subcorticales que conectan el lóbulo frontal con los ganglios basales y el tálamo (Alexander et al., 1986). El tálamo es una estructura clave en estos circuitos (Byne et al., 2009) y está involucrado en muchas funciones cognitivas (Herrero et al., 2002; Sherman, 2005) a través de amplias conexiones con la corteza cerebral (Alexander, 1986; Cummings et al., 1993; Leh et al., 2007). Aunque se sabe que los circuitos cortico-subcorticales están implicados en las funciones cognitivas, hasta la fecha sus correlatos de neuroimagen se desconocen.

2.5 Predictores de disfunción cognitiva después de un accidente cerebrovascular

Aunque las secuelas cognitivas pueden variar según las personas, parece ser que factores individuales (edad, FRV, enfermedades concomitantes etc.) y las características propias del ACV (volumen y localización del ictus, duración de la isquemia, área de penumbra isquémica etc.) pueden contribuir significativamente (Rosso & Samson, 2014; Vogt et al., 2012). Sin embargo, hasta la fecha no se han identificado los factores específicos que explican la variabilidad de la recuperación cognitiva entre aquellos pacientes que han sufrido un ACV.

2.6 Los déficits cognitivos en la fase subaguda tras un ictus cerebral isquémico

El término subagudo se refiere al periodo de tiempo que abarca hasta los 3 meses después de haber sufrido un ictus cerebral. La proporción de pacientes con demencia en la fase subaguda se estima del 25,5% (Pohjasvaara et al., 1997) y la estimación de pacientes con deterioro cognitivo oscila entre el 50% y el 90% según los diferentes estudios (Jaillard et al., 2009; Nys et al., 2007). Esta variabilidad podría explicarse, en parte, por las diferencias en las muestras de estudio y los subtipos de ictus incluidos en ellas. Despúes de un ACV, los dominios cognitivos donde más se han observado déficits son el lenguaje (afasia), la función visuoespacial (heminegligencia espacial) y las funciones ejecutiva.

3. Deterioro cognitivo vascular

El término deterioro cognitivo vascular (DCV) se refiere a cualquier grado de disfunción cognitiva -desde DCVL a DV o mixta [Enfermedad de Alzheimer (EA) y VD]- asociado a ACV (Dong et al., 2014; Román et al., 2004). La tasa de prevalencia del DCV es del 15-20% (De Rockwood et al., 2000). La heterogeneidad de las lesiones vasculares y del parénquima puede afectar a varias regiones neuroanatómicas y circuitos cerebrales importantes para la cognición. En consecuencia, se pueden observar distintos perfiles neuropsicológicos a lo largo del continuo del DCV (Chui, 2005). Sin embargo, como ya se ha mencionado después de un ACV es muy frecuente observar

déficits en las funciones ejecutivas. Las funciones ejecutivas están involucradas en una gran variedad de procesos cognitivos complejos. Estas funciones incluyen la resolución de nuevos problemas, el razonamiento conceptual, la inhibición cognitiva, la alternancia, la velocidad de procesamiento de la información, la memoria de trabajo y la atención (Garrett et al, 2004; Nyenhuis et al, 2004). Por lo tanto, los protocolos de evaluación neuropsicológicos deberían hacer hincapié en la evaluación de estas funciones, entre otros dominios cognitivos.

Recientemente, *The American Heart Association and The American Stroke Association* (Gorelick et al., 2011) han proporcionado un enfoque práctico para la definición del DCV. Estos autores recomiendan que cualquier criterio diagnóstico relacionado con un ACV debería basarse en dos factores:

a) Demostración de alteración cognitiva mediante una evaluación neuropsicológica y que
b) La historia clínica del ACV demuestre que los correlatos de neuroimagen puedan vincular la disfunción cognitiva y el ACV.

Finalmente, el DCVL se define por un déficit de al menos un dominio cognitivo con un deterioro leve o nulo en las actividades de la vida diaria (Fischer et al, 2007; Gorelick et al., 2011). Por otra parte, la DV se define por la existencia de un rendimiento inferior en al menos 2 o más dominios cognitivos, los cuales producen una afectación funcional en las actividades de la vida diaria (Gorelick et al., 2011).

4. Imagen por tensor de difusión y tractografía

La imágen por tensor de difusión (ITD) es una técnica de RMN que se basa en la cuantificación del movimiento de las moléculas de agua en el tejido cerebral. Esta técnica nos proporciona información acerca de alteraciones en la microestructura cerebral no detectables con la RMN convencional (Li et al., 2011; O'Sullivan et al., 2001). Concretamente, la ITD nos proporciona información acerca de la integridad de los tractos de SB (Hagmann et al., 2006; Sundgren et al., 2004) así como información acerca de la microestructura de las estructuras de sustancia gris (SG) (Lee et al., 2013; Scanlon et al., 2013). La difusión de las moléculas de agua depende de la estructura anatómica subyacente, como por ejemplo las membranas celulares y los axones (Le

Bihan, 1995). Existen diferentes medidas de la ITD, la anisotropía fraccional (AF), la difusividad media (DM), la difusividad axial y la difusividad radial. La AF y la DM, dos de los índices más conocidos y utilizados (Basser & Pierpaoli, 1996), se han usado a lo largo de los estudios presentados. La AF es una medida de la dirección de la difusividad (Basser et al., 1994; Le Bihan et al., 2001) y varía entre 0 (difusión isotrópica / difusión igual en todas las direcciones) y 1 (difusión anisotrópico / difusión no direccional). Valores bajos de AF sugieren pérdida de la integridad del tejido cerebral (Alexander, 2007; Mori & Zhang, 2006) debido a daño axonal o desmielinización. La DM refleja el movimiento molecular promedio en todas las direcciones e indica la magnitud de la difusión. La DM normalmente aumenta cuando se produce una interrupción de los tractos axonales (Alexander, 2007; Le Bihan et al., 2001). Existen varios métodos de análisis de la ITD que incluyen la región de interés (RI), el análisis vóxel a vóxel, la tractografía y el histograma. Todos ellos se han utilizado para identificar diferencias microestructurales entre grupos de interés (Berlot et al., 2014; Kanaan et al., 2014). En el análisis vóxel a vóxel, las imágenes de DTI de cada sujeto se registran en el espacio estándar, y luego un análisis vóxel a vóxel se llevan a cabo para detectar diferencias estadísticas regionales entre los grupos (Abe et al., 2010).

Aunque esta técnica ha sido ampliamente estudiada en SB, recientemente, la ITD se ha utilizado para investigar la integridad de las estructuras de SG en diferentes patologías cerebrales (Lee et al., 2013; Scanlon et al., 2013) incluyendo el ACV isquémico (Buffon et al., 2005; Hervé et al., 2005; Li et al., 2011). Li et al. (2012) llevó a cabo un estudio de ITD donde relacionó microstructura del tálamo con la disfunción cognitiva en pacientes con ictus lacunares con leukoaraiosis utilizando la técnica de la RI. Sin embargo, hasta la fecha no existe ningún estudio sobre anomalías de difusión talámicas relacionadas con LSB y su relación con la función cognitiva mediante un análisis vóxel a vóxel. Del mismo modo, aunque existen estudios previos de ITD que han estudiado el tálamo con un análisis de RI en ictus cerebral isquémico (Buffon et al., 2005; Hervé et al, 2005; Li et al., 2011), hasta la fecha no hay datos sobre la relación entre las medidas de ITD en el tálamo y la función cognitiva mediante un análisis vóxel a vóxel.

La técnica de la tractografía se basa en la ITD y nos permite hacer "disecciones virtuales en vivo" de los tractos de SB (Catani et al., 2002; Wakana et al., 2004). Esta técnica nos permite explorar las bases anatómicas de la cognición humana y sus trastornos y nos proporciona información acerca de la conectividad del cerebro. El análisis de tractografía es conceptualmente similar a un análisis de RI, sin embargo, en este caso, las RI están representadas por tractos de SB que son definidos automáticamente (tractografía probabilística) o manualmente (tractografía determinista) por algoritmos de tractografía. El análisis posterior de los tractos de SB puede estar basado en las medidas extraídas de los propios tractos, por análisis vóxel a vóxel o por la técnica de la RI. La mayoría de investigaciones que han abordado la relación entre la integridad de la SB y la cognición en los participantes con LSB han empleado un enfoque por RI (O'Sullivan et al., 2001) o han usado otros métodos de análisis como el histograma (Vernooij et al., 2009). En el ACV, la tractografía probabilística ha demostrado ser altamente sensible a degeneración Walleriana del tracto corticoespinal (Park et al., 2013) y de la via sensoriomotora (Yamada et al., 2003). Estudios más recientes han demostrado que la tractografía probabilística también puede ser utilizada para evaluar el resultado cognitivo tras un ACV (Nelles et al., 2008; Zeng et al., 2011). Hasta la fecha, no hay datos sobre anomalías estructurales y su relación con la función cognitiva usando la tractografía determinística en participantes sanos y en ictus cerebral isquémico.

En conclusión, la ITD no sólo nos aporta información sobre anomalías que pueden producirse en la lesión primaria de las enfermedades cerebrales, sino que también nos permite estudiar alteraciones secundarias a la lesión tanto en estructuras de SG o en tractos de SB y sus correlatos cognitivos en sujetos sanos y en pacientes con un ACV isquémico.

II OBJETIVOS

Las funciones ejecutivas son uno de los dominios cognitivos más afectados después de un ACV e incluyen procesos de control cognitivo de orden superior para la consecución de un de un objetivo específico (Lezak et al., 1989). La disfunción ejecutiva puede provocar déficits en la planificación, la monitorización, la flexibilidad, la memoria de trabajo, déficits en la atención

y la inhibición cognitiva pero también déficits emocionales, conductuales y de adaptación funcional del individuo (Eliot et al., 2003; Schmeichel et al., 2008). A pesar de los esfuerzos que se han hecho en investigación básica y clínica, todavía se desconoce en la actualidad las bases neurales y las secuelas cognitivas y conductuales de este complejo dominio cognitivo.

El objetivo general de esta tesis ha sido estudiar los efectos de una interrupción en los circuitos cortico-subcorticales debido a una lesión directa o remota en las funciones ejecutivas. Para el estudio de las anomalías remotas en los circuitos cerebrales y su implicación en el funcionamiento cognitivo, usamos la técnica de la ITD, tanto para la EGV como para la EPV. Concretamente, nos centramos en el estudio de las anomalías microstructurales talámicas dado que el tálamo es una estructura clave en los circuitos cortico-subcorticales y es crucial para la cognición, sobre todo en las funciones ejecutivas. Además, dado que la atención y la inhibición cognitiva son una de las funciones más importantes de las funciones ejecutivas, estudiamos la relación entre un tracto de SB recientemente descrito -llamado Frontal Aslant Tract (FAT)- y estas funciones en sujetos sanos y en pacientes que habían sufrido un ictus isquémico.

Los objetivos específicos de esta tesis fueron:

I. Examinar anomalías de difusión talámicas remotas y su relación con la cognición en sujetos sanos con LSB (estudio I).

II. Investigar la relación entre estas anomalías de difusión talámicas remotas y la disfunción cognitiva en pacientes que han sufrido un ACV isquémico derecho 3 meses después del evento vascular (estudio II).

III. Abordar el papel del FAT derecho en las funciones ejecutivas en individuos sanos y en sujetos que han sufrido un ACV isquémico (estudio III).

III MATERIALES Y MÉTODOS

Esta tesis consta de 3 estudios que examinan los mecanismos de neuroimagen implicados en la disfunción ejecutiva en los ACV, usando un

enfoque poblacional y epidemiológico y un método basado en la clínica. El enfoque poblacional y epidemiológico propone un marco explicativo basado en la población de tal manera que permite una adecuada interpretación de los resultados obtenidos. En particular, en el estudio I, la muestra de sujetos sanos de mediana edad fue obtenida a partir de centros de atención primaria siguiendo criterios de selección poblacional. Además, el diseño del estudio I siguió criterios epidemiológicos y esto permite que los resultados del estudio sean, en cierta manera, representativos de la población. Por otro lado, el enfoque clínico permite obtener información valiosa de cada paciente a lo largo de las evaluaciones cognitivas de seguimiento. Los enfoques poblacionales y epidemiológicos y el método basado en la clínica implican ciertas limitaciones. Una limitación importante es que todos estos enfoques son de naturaleza correlacional y, por lo tanto, no se puede determinar relaciones causales entre las variables estudiadas.

En los tres estudios presentados se utilizaron diferentes muestras, distintos análisis de la ITD, así como diferentes pruebas neuropsicológicas. Todos los estudios fueron aprobados por los comités éticos de la Universidad de Barcelona y el Hospital Universitario Germans Trias y Pujol de Badalona. Se obtuvo de cada participante el consentimiento informado de acuerdo con la Declaración de Helsinki. Las características específicas de las muestras incluidas y los métodos empleados en cada estudio se describen en detalle en los artículos incluidos en esta tesis.

IV RESULTADOS

Estudio I

Fernández-Andújar, M., Soriano-Raya, J. J., Miralbell, J., Lopez-Cancio, E., Cáceres, C., Bargalló., Barrios, M., Arenillas, J.F., Toran, P., Alzamora, M., Clemente, I., Dávalos, A., Mataró, M. (2013). **Diffusion thalamic differences related to cognitive function in white matter lesions.** *Neurobiology of Aging*, 35(5); 1103-1110. IF: 6.09.

Estudio II

Fernández-Andújar, M., Doornink, F., Dacosta-Aguayo, R., Soriano-Raya, J. J., Miralbell, J., Bargalló, N., Lopez-Cancio, E., Pérez de la Ossa, N., Gomis, M., Millán, M., Barrios, M., Cáceres, C., Pera, G., Forés, R., Clemente, I., Dávalos, A., Mataró, M. (2013) **Remote thalamic microstructural abnormalities related to cognitive function in ischemic stroke patients.** *Neuropsychology journal*, in press. IF: 3.58

Estudio III

Fernández-Andújar, M., Forkel, S.J., Dacosta-Aguayo, R., Miralbell, J., Soriano-Raya, J. J., Clemente, I., Millán, M., Lopez-Cancio, E., Bargalló., Barrios, M., Cáceres, C., Toran, P., Alzamora, M., Dávalos, A., Mataró, M., Thiebaut de Schotten, M. (2013). **Disconnection of the right Frontal Aslant Tract impairs attention and response inhibition: a spherical deconvolution tractography study.** Working paper.

V RESUMEN DE LOS RESULTADOS Y DISCUSIÓN

Las LSB han sido consistentemente relacionadas con la disfunción ejecutiva (Pantoni et al., 2007; Tullberg et al., 2004) probablemente causado por un interrupción en los circuitos cortico-subcorticales (Linortner et al., 2010; Schmidt et al., 2006). El tálamo es una estructura crucial en estos circuitos (Byne et al., 2009) y está ampliamente involucrado en múltiples funciones cognitivas (Schmahmann, 2003; Stebbins et al., 2008). El objetivo del estudio I fue explorar anomalías microestructurales talámicas relacionados con LSB y su asociación con la cognición en personas sanas de mediana edad. Los resultados del estudio I mostraron que participantes con alto grado de HPVs y HSBPs tenían valores inferiores de FA talámicos en comparación con aquellos sujetos con un bajo grado de HPVs y HSBPs. El papel de las alteraciones microestructurales tálamicas en la cognición se ha observado previamente en pacientes con ictus lacunares y leukaraiosis (Li et al., 2012), esquizofrenia (Marenco et al., 2012) y déficit de atención e hiperactividad (Xia et al., 2012). Estos estudios han demostrado que la técnica de la ITD es

altamente sensible para detectar anomalías microestructurales talámicas (Deo et al., 2006; Taylor et al., 2007).

Interesantemente, encontramos que sólo valores talámicos inferiores de FA en pacientes con alto grado de HSBPs (pero no en sujetos con alto grado HPVs) se relacionaban con la cognición. El hecho que un alto grado de HSBPs se asociara con la cognición está en concordancia con un estudio reciente de nuestro grupo con la misma muestra comunitaria de mediana edad (Soriano-Raya et al., 2012). Aunque cada vez hay más evidencia sobre la contribución específica de las HPVs y las HSBPs en la cognición, este tema sigue siendo controvertido (Schmidt et al., 2011). Por ejemplo, De Groot et al. (2000) mostró que las HPVs tienen un papel relevante en la disfunción cognitiva global, la memoria verbal y la velocidad psicomotora en una muestra sana comunitaria. Por otro lado, Sachdev et al. (2005) describió una relación entre las HSBPs y déficits motores y en la velocidad de procesamiento también en una muestra sana de mediana edad. Estas inconsistencias han sido explicadas por diferentes localizaciones anatómicas, gravedad y etiología de las LSB (Desmond, 2002; Pantoni et al., 2007). La asociación encontrada en nuestro estudio entre las diferencias de difusión talámicas en las HSBPs y la cognición refuerza el papel predominante de estas lesiones en la disfunción cognitiva en individuos sanos de la comunidad.

Específicamente, en el estudio I, encontramos que anomalías talámicas microestructurales en alto grado de HSBPs se asocian con un rendimiento inferior en fluidez verbal, velocidad psicomotor y habilidades visuoespaciales. Estos tres dominios cognitivos han sido ampliamente relacionados con una disrupción en los circuitos cortico-subcorticales en las LSB (Schmidt et al., 2011; Soriano-Raya et al., 2012). En nuestro estudio, la fluidez verbal se asoció positivamente con conexiones corticales tálamicas derechas. La fluidez verbal es considerada una de las pruebas más sensibles de las funciones ejecutivas (Baldo et al., 2001; Stuss & Levine, 2002) y, particularmente, está implicada en iniciación, autocontrol, inhibición cognitiva y organización eficiente de recuperación y recuerdo verbal (Crawford & Henry, 2005; Roher et al., 1999). La fluidez verbal se ha relacionado principalmente con el hemisferio izquierdo, especialmente con la corteza prefrontal dorsolateral y el fascículo longitudinal superior (Okada et al., 2003; Peters et al., 2012; Phillips et al., 2011).

Activaciones del tálamo izquierdo y derecho en tareas de fluidez verbal se han observado en estudios de resonancia magnética funcional en sujetos sanos (Vitali et al., 2005) y pacientes epilépticos (O'Muircheartaigh et al., 2012). Además, déficits en la fluidez verbal se han sido descrito después de lesiones tanto en el tálamo izquierdo (Shim et al., 2008) como en el derecho (Annoni et al., 2003). La velocidad psicomotora y las habilidades visuoespaciales también son dominios cognitivos que generalmente se han relacionado con el lóbulo frontal y con los circuitos fronto-estriatales (Au et al., 2006; Cummings et al., 2003). En nuestro estudio, la velocidad psicomotora se asoció con diferencias de difusión en el tálamo derecho. En esta línea, Tuch et al. (2005) publicó, en participantes sanos, una correlación entre los valores de FA en el tálamo derecho, entre otras estructuras cerebrales, y el tiempo de reacción durante la realización de una tarea cognitiva. En otro estudio reciente de ITD, valores de AF de la radiación talámica izquierda se han relacionado con la velocidad psicomotora en participantes con DCV (Duering et al., 2012). Los resultados de nuestro estudio también mostraron una asociación entre diferencias de difusión en el tálamo derecho y el rendimiento en habilidades visuoespaciales. Hasta la fecha no existen estudios que relacionen alteraciones microstructurales talámicas y la función visuoespacial. Este hallazgo encontrado en el estudio I podría explicarse por el hecho que una de las diferencias significativas de difusión talámica se encuentra en regiones que proyectan a la corteza parietal posterior derecha. En este sentido, el papel de la corteza parietal posterior derecha en las habilidades visuoespaciales está bien establecido (Levin et al., 1996; Silver & Kastner, 2009). Además, un estudio de resonancia magnética funcional ha demostrado que existe una asociación entre activaciones talámicas derechas durante la realización de una tarea visual (Fink et al., 2002). Nuestro hallazgo podría ayudar a explicar las bases neurales de los déficits visuoespaciales que a menudo se encuentran en el DCV asociado con ACV (Delano-Wood et al., 2008; Soriano-Raya et al., 2012).

En resumen, nuestros resultados aportan novedosa información de las bases neurobiológicas de la disfunción ejecutiva en participantes sanos de mediana edad con LSB. Además, estos resultados apoyan la idea que la disfunción cognitiva asociada a las LSB podría ser un síndrome de desconexión cerebral (Geschwind, 2010; Schmidt et al., 2006). Sin embargo,

dado que las LSB son sólo una parte del espectro de la EPV, otros procesos cerebrovasculares podrían estar involucrados en la disfunción cognitiva en individuos sanos de la comunidad (Pantoni et al., 2007). Por otra parte, el estado cognitivo de los participantes de mediana edad no sólo está asociado con EPV, sino que también parece estar relacionado con cambios degenerativos que a menudo coexisten con la EPV.

La muestra utilizada en nuestro estudio consistió en sujetos de mediana edad (de entre 50-65 años) sanos sin historia de ACV y/o demencia. El hecho de que en esta franja de edad ya se observen anomalías microestructurales talámicas y su asociación con la cognición representa un avance importante en relación a las implicaciones clínicas de las LSB. Nuestros resultados corroboran la hipótesis de que las HPVHs y las HSBPs afectan de manera diferente a la cognición a través del tálamo en individuos sanos de la comunidad.

En conclusión, en el estudio I hemos mostrado, por primera vez, una implicación de los circuitos cortico-subcortical a través del tálamo en la función cognitiva en participantes de mediana edad sanos con LSB. La existencia de anomalías talámicas remotas y su papel relevante en la cognición, representa un avance en la comprensión de la función cognitiva en individuos sanos de la comunidad.

En el estudio II, investigamos alteraciones microestructurales talámicas remotas a una lesión isquémica y su asociación con la cognición tres meses después de un evento vascular derecho. Se sabe que los infartos cerebrales pueden causar daño neuronal no solo en el área isquémica primaria sino también producir anomalías histológicas, metabólicas y funcionales en áreas remotas a la lesión isquémica (Achard et al., 2006; Dacosta-Aguayo et al., 2014b; Haberg et al., 2009). Como explicaciones de estos efectos remotos se han propuesto, entre otros, la degeneración Walleriana, los procesos de desaferentación cortical (Buffon et al., 2005; Haberg et al., 2009; Zhang et al., 2012) y la disrupción de los circuitos cerebrales (Dacosta-Aguayo et al., 2014a; Kaiser et al., 2007). Otros fenómenos tales como daño axonal, inflamación, daño neuronal y alteraciones de la organización del tejido cerebral también podrían explicar estas anomalías microstructuales remotas (Lim & Helpern, 2002).

Anomalías talámicas remotas a la lesión isquémica, mayoritariamente en el tálamo ipsilateral, han sido previamente investigadas en modelos animales (Abe et al., 2003; Bihel et al., 2010) y en estudios de neuroimagen en humanos tales como tomografía por emisión de positrones (Nagasawa et al., 1994), RMN estructural (Achard et al., 2006; Ogawa et al., 1997) e ITD (Buffon et al., 2005; Hervé et al., 2005; Li et al., 2011). Los resultados del estudio II, mostraron que pacientes con un ACV isquémico tenian valores inferiores de AF y valores superiores de DM en áreas del tálamo específicas, en ambos hemisferios (tálamo ipsilateral y contralateral). Ambos índices de AD y DM estuvieron relacionados con la disfunción cognitiva tras un ictus cerebral isquémico derecho.

Estudios previos de ITD talámicos en pacientes con ictus han utilizado un enfoque general de región de interés (RI) para obtener una medida global de los valores de FA y MD del tálamo (Buffon et al., 2005; Hervé et al., 2005; Li et al., 2011). Hasta la fecha, anomalías microestructurales talámicas remotas a una lesión isquémica se han encontrado con el índice de MD, pero no con valores de AF (Buffon et al., 2005; Hervé et al., 2005; Li et al., 2011). Los resultados del estudio II mostraron una localización similar de las diferencias de difusividad en la AF y en la DM. Estos resultados apoyan el hecho que estas áreas están particularmente afectadas por una lesión isquémica remota en la muestra estudiada.

Hemos observado una asociación entre valores bajos de AF y valores altos de DM con un menor rendimiento de la fluidez verbal en el tálamo ipsilateral. Además, valores bajos de AF también se relacionaron con un menor rendimiento de la fluidez verbal en el hemisferio contralateral. Este hallazgo podría explicarse por la fuerte implicación del hemisferio izquierdo en esta función cognitiva. En general, estos resultados sugieren una relación entre los circuitos cortico-subcorticales a través del tálamo y la disfunción cognitiva tres meses después de un ACV isquémico derecho.

Algunas variables individuales (edad, FRV, enfermedades coexistentes etc.) y características del ACV (volumen de la lesión, localización del ictus, duración de la isquemia, área de penumbra isquémica etc.) se sabe que contribuyen de una manera significativa en la cognición después de un ACV (Hankey et al., 2003; Rosso & Samson, 2014; Vogt et al., 2012). Todos estos

factores, incluyendo las anomalías talámicas remotas, pueden ayudar a explicar la variabilidad clínica y cognitiva que se observa en pacientes que han tenido un ictus cerebral isquémico.

Los estudios talámicos previos de ITD han usado muestras de sujetos con ictus muy heterogéneas con respecto a la ubicación hemisférica de la lesión, el tamaño de las muestras era muy pequeño y no se abordó la implicación de las alteraciones talámicas en la cognición (Buffon et al., 2005; Hervé et al., 2005; Li et al., 2011). En nuestro estudio, la muestra de ictus isquémico fue homogénea dado que sólo se incluyeron pacientes con lesión en el hemisferio derecho. El tamaño de la muestra, aunque fue relativamente pequeño, fue más grande que en los estudios anteriores (Buffon et al., 2005; Hervé et al., 2005; Li et al., 2011).

En conclusión, el estudio II es el primer trabajo de ITD que muestra los efectos de la interrupción de los circuitos cerebrales, en ambas regiones del tálamo ipsilateral y contralateral, en relación con la función ejecutiva debido a una lesión isquémica remota derecha.

En ambos estudios I y II, se utilizó un análisis por ITD vóxel a vóxel que permite la identificación de anomalías microestructurales en áreas talámicas específicas mediante los índices de AF y DM. Esta técnica no sólo permite localizar áreas específicas donde hay diferencias de difusión mediante distintos atlas del FSL (Behrens et al., 2003a; Desikan et al., 2006; Hua et al., 2008), sino que también evita la necesidad de hacer hipótesis a priori sobre la ubicación de estas diferencias (Jones et al., 2005). Esta técnica es semi-automatizada y no depende del conocimiento neuroanatómico del investigador (como sería el caso de la colocación manual de una RI). Por último, el análisis vóxel a vóxel es fácilmente accesible y es eficiente en relación al tiempo (Yang et al., 2012). El enfoque de la ITD basado en el vóxelwise que hemos usado, evita las limitaciones de la obtención de una medida global a través de la metodología de la RI, tales como la colocación subjetiva de la RI, una limitada fiabilidad y reproducibilidad y los efectos del volumen parcial de la RI (Chanraud et al., 2010; Zhuang et al., 2010). No obstante, como todas las técnicas de RMN, el análisis vóxel a vóxel tiene limitaciones con respecto a la exactitud de la normalización espacial, el tamaño del proceso de suavizado y el

análisis estadístico usando el modelo lineal general que presupone una distribución normal de los datos (Jones et al., 2005).

En ambos estudios, encontramos resultados estadísticamente significativos con los índices de AF y DM. Tradicionalmente, valores bajos de AF han sugerido una pérdida de integridad del tejido cerebral (Alexander, 2007; Mori & Zhang, 2006) y valores superiores de DM han sido explicados por una interrupción de los tractos axonales (Alexander, 2007; Basser & Pierpoli, 1996). Hay muchos otros factores tales como la densidad axonal, la integridad de la membrana axonal, el diámetro axonal (Beaulieu, 2002) y la coherencia intravóxel de la orientación de las fibras (Smith et al., 2007) que pueden influir en los valores de difusión de FA y MD. También es importante señalar que la FA y la MD se han investigado sobre todo en tractos de SB y su interpretación en las estructuras de SG aún no se sabe con certeza. Por último, en ambos estudios se demostró una relación entre anomalías microestructurales talámicos remotas y la fluidez verbal. Se conoce bien que la fluidez verbal es una de las pruebas más sensibles para evaluar los déficits ejecutivos y es ampliamente utilizada en las evaluaciones clínicas y neuropsicológicas.

Vale la pena mencionar que la mayor parte del conocimiento actual sobre la cognición humana se basa en el paradigma modular, en el cual se considera que distintas regiones del cerebro trabajan de manera independiente para llevar a cabo funciones cognitivas complejas. Este paradigma, aunque ha aportado conocimiento sobre el funcionamiento del cerebro y la cognición, tiene importantes limitaciones cuando se trata de explicar la disfunción cognitiva y la variabilidad clínica y cognitiva tras una ACV. En ambos estudios, la función cognitiva parece estar relacionada con anomalías microstructurales secundarias a la lesión que incluyen la disrupción de circuitos cerebrales.

En el estudio III, abordamos la asociación entre un tracto de SB descrito recientemente llamado FAT y la cognición en sujetos sanos y en pacientes con un ictus isquémico, utilizando la tractografía por deconvolución esférica (DE). Específicamente, nos centramos en dos procesos cognitivos que intervienen de manera crucial en la función ejecutiva: la atención y la inhibición de respuesta. Los resultados de este estudio mostraron una asociación entre el volumen del FAT derecho y la atención en 96 sujetos sanos. Asimismo, encontramos que

aquellos pacientes con una lesión que involucraba el FAT derecho mostraban un rendimiento inferior en la inhibición de respuesta en comparación con aquellos pacientes que habían sufrido un ACV pero que tenían intacto el FAT derecho.

El tracto del FAT conecta la parte opercularis del giro frontal inferior (GFI) con la parte anterior del área motora suplementaria y el área pre-motora suplementaria (pre-AMS) del giro frontal superior. Hasta la fecha los correlatos cognitivos del FAT no se saben con certeza, sin embargo, recientemente, se ha sugerido que este tracto está involucrado en el lenguaje y la cognición y el comportamiento frontal (Catani et al., 2012; Vassal et al., 2014).

Aunque el GFI se ha asociado consistentemente con la inhibición de respuesta y la capacidad de lograr metas (Cardillo et al., 2004; Dosenbach et al., 2006), también se ha relacionado esta área con funciones más generales como una rápida adaptación de respuesta (Dodds et al., 2010) y / o control de la atención (Hampshire et al., 2010). La pre-AMS parece estar implicada en la atención sostenida (Hilti et al., 2013), sin embargo, su papel exacto en la inhibición de la respuesta se desconoce.

La prueba del Continuous Performance Test (CPT) (Conners, 1995) y la tarea del Stroop (Golden, 1978) han sido muy utilizadas para evaluar la atención y la inhibición de respuesta. Estas tareas se han relacionado con una amplia red fronto-parietal bilateral, predominantemente con áreas del hemisferio derecho, incluyendo el área medial frontal, la corteza prefrontal dorsolateral, el GFI, la corteza cingulada anterior, la corteza inferior y superior parietal y la ínsula (Grandjean et al., 2012; Olsen et al., 2013; Roberts & Hall, 2008). En este estudio, no se encontraron los mismos resultados en las pruebas del CPT y el Stroop en ambos grupos. Mientras que en participantes sanos el FAT derecho se encontró relacionado con atención, en pacientes con un ACV isquémico una lesión en el FAT derecho se asoció con un peor rendimiento en inhibición de respuesta. Una posible explicación para estas diferencias podría ser que la prueba del Stroop se considera una prueba típicamente clínica (Stuss & Levine, 2002) y probablemente es más fácil obtener resultados significativos en cerebros patológicos que no en cerebros sanos. Además, en el grupo de pacientes que han sufrido un ACV seguramente también están afectados otros tractos de SB que puede afectar a

la tarea de atención. Finalmente, la muestra de pacientes con un ictus isquémico es pequeña y esto puede explicar el hecho de no encontrar resultados en la prueba del CPT. Este es el primer estudio correlacional que aborda la relación entre el FAT y la función ejecutiva en gente sana de la comunidad y en patología vascular. Se necesita más investigación para confirmar nuestros resultados cognitivos del FAT así como estudiar su relación con otros tractos que sustentan también las funciones ejecutivas.

Para el análisis del FAT utilizamos la técnica de la DE que supera, en parte, las limitaciones de los cruces de tractos de SB y las reconstrucciones falsas de los tracto de SB (Dell'Acqua et al., 2010; 2007). Esto facilita la visualización correcta de estos tractos de SB, no visibles con tractografía convencional (Thiebaut de Schotten et al., 2011a; 2011b). La variable específica que utilizamos para medir el FAT derecho fue el número de axones del tracto. Sin embargo, debemos tener en cuenta que otros factores como la longitud, el volumen y la curvatura del FAT pueden afectar a la cantidad de axones del tracto (Szczepankiewicz, 2013; Vos et al., 2012).

En los tres estudios presentados en esta tesis se ha usado una RMN de 3T en lugar de 1.5T ampliamente utilizada. La sensibilidad de la RMN de 3T (Kim et al., 2008; Scarabino et al., 2003) nos ofrece examinar con precisión la gravedad y la ubicación de las LSB, el área primaria isquémica, así como posibles lesiones talámicas. Otros puntos fuertes de estos estudios son la extensa evaluación neuropsicológica y la covariación de los análisis por posibles factores de confusión tales como la edad, el género, los años de educación y los FRV con respecto a la asociación entre las medidas de ITD y la cognición.

Hay unas pocas limitaciones a lo largo de los tres estudios presentados que deben ser consideradas. El tamaño pequeño de las muestra de pacientes que han sufrido un ACV isquémico (estudio II n=17; estudio III n=14) disminuye la sensibilidad e impide la generalización de nuestros resultados. Sin embargo, el criterio de inclusión de los pacientes fue muy estricto y los participantes con ACV fueron admitidos de forma consecutiva en un centro terciario de ictus. Esto puede ayudar a mitigar parcialmente el sesgo en nuestras muestras. Del mismo modo, en todos los estudios presentados, los resultados no fueron corregidos por la atrofia cerebral. Sin embargo, en el

estudio I, las características de la muestra de sujetos sanos de la comunidad (como por ejemplo la edad o la exclusión de pacientes con demencia) no sugirieron que hubiese cambios degenerativos. Asimismo, en el estudio II y III debido al tamaño pequeño de la muestra de pacientes con ACV no corregimos los resultados por atrofia cerebral. Por lo tanto, aunque nuestros resultados son nuevos y prometedores se deben tomar como preliminares.

En conclusión, nuestros resultados sugieren que tanto la EPV como la EGV pueden afectar los circuitos cortico-subcortical a través de anomalías microstructurales talámicas, en ambos hemisferios ipsilateral y contralateral. Además, el reciente descrito FAT también está implicado en funciones ejecutivas. La novedosa técnica de neuroimagen ITD puede tener un papel relevante en el conocimiento del funcionamiento cognitivo tanto en EPV como en EGV. El uso concomitante de la RM convencional y las nuevas técnicas puede ser útil para la evaluación cognitiva de seguimiento de los ACV.

VI CONCLUSIONES

A continuación se resumen las principales conclusiones de esta tesis derivadas de los tres estudios presentados:

1. Anomalías secundarias microestructurales talámicas remotas a la lesión cerebrovascular pueden ocurrir tanto en el tálamo ipsilateral como en el tálamo contralateral, en sujetos sanos con LSB y en pacientes con un ictus cerebral isquémico.

2. Anomalías talámicas remotas pueden estar relacionadas con una disrupción en los circuitos cortico-subcorticales asociado con disfunción ejecutiva tanto en EPV como en EGV.

3. La fluencia verbal ha sido la función cognitiva más sensible relacionada con anomalías talámicas microstructurales remotas.

4. En individuos sanos de mediana edad, diferencias de difusión talámicas en alto grado de HSBPs, pero no en HPVs, están asociadas con un peor rendimiento en la cognición.

5. En sujetos de la comunidad y con un ictus isquémico, el FAT derecho está implicado en atención e inhibición de respuesta, dos de los componentes más importantes de las funciones ejecutivas.

6. La técnica de neuroimagen de la ITD ofrece información valiosa del funcionamiento cognitivo en el ACV.

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