Impact of Cerebral Small Vessel Disease on Brain and Behaviour

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A thesis presented for the degree of

Doctor of Philosophy

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If anyone travels on a road in search of knowledge, Allah will cause him to travel on one of the roads of Paradise.

— Prophet Muhammad (pbuh)

Abstract

Cerebral small vessel disease (SVD) is an important contributor to the development of vascular cognitive impairment and dementia. This thesis employed multimodal magnetic resonance imaging (MRI) techniques and behavioural paradigms to investigate the effects of SVD on memory and motivation—key exemplars of the cognitive and neuropsychiatric sequelae of the condition.

Chapter 2 examined how structural, diffusion, and resting state functional MRI (rs-fMRI) measures were altered in the presence of SVD. Compared to healthy elderly control participants, people with SVD had smaller hippocampal and nucleus accumbens volumes bilaterally. Voxel-based morphometry (VBM) demonstrated the presence of grey matter atrophy in the right middle temporal gyrus, left cerebellum, left precentral gyrus, and bilateral nucleus accumbens. Diffusion-weighted imaging (DWI) data were then analysed using two approaches: diffusion tensor imaging (DTI) and neurite orientation dispersion and density imaging (NODDI). Tract-based spatial statistics (TBSS) on diffusion MRI data revealed widespread reductions in white matter microstructural integrity in SVD. However, no significant group differences were found in rs-fMRI measures after accounting for motion effects within the scanner.

Chapter 3 evaluated the impact of SVD on visual short-term memory (VSTM) using the "What was where" Oxford Memory Test (OMT), a delayed reproduction task with a continuous, analogue response space. Overall, SVD participants were less accurate and slower than controls. Mixture modelling of the behavioural data revealed that errors in the SVD group resulted from imprecision, guessing, and misbinding. Factor analysis produced two factors, Error, which was significantly higher in SVD, as well as Response Time, in which the two cohorts did not differ from each other.

Chapter 4 extended the findings from the previous chapter by investigating the association between VSTM metrics and parameters obtained from structural and diffusion MRI. Grey matter atrophy of the right occipital region, together with higher mean diffusivity (MD) in several white matter tracts such as the anterior thalamic radiation, cingulum bundle, forceps major, forceps minor, optic radiation, and superior longitudinal fasciculus, correlated with VSTM errors in SVD.

Chapter 5 focused on the impact of SVD on effort-based decision making (EBDM), a paradigm that has been used previously to study apathy. People with SVD accepted fewer offers at low effort levels and took longer to decide compared to healthy elderly controls. Applying hierarchical drift diffusion modelling (HDDM) to the behavioural data demonstrated that the SVD group had less responsiveness of drift rate to changes in effort as well as higher non-decision time.

Chapter 6 explored the neural correlates of EBDM deficits in SVD. Atrophy of the nucleus accumbens predicted higher apathy scores. VBM demonstrated two clusters, the first in the right occipital cortex correlating with decision-making threshold, and the second primarily in the left frontal lobe that was associated with apathy. TBSS indicated that higher ISOVF in several white matter tracts was associated with reduced decision-making threshold and shorter non-decision time across all participants.

Overall, these findings reveal neural correlates of short-term memory (STM) and motivation in people with SVD.

Acknowledgements

بسم الله الرحمن الرحيم

First and foremost, I praise Allah (SWT) for giving me this once-in-a-lifetime opportunity to undertake a DPhil in Clinical Neurosciences at Oxford. Blessings and salutations go to Prophet Muhammad (pbuh), his Family, and his Companions.

I would like to express my sincere gratitude to a number of parties for being part of my DPhil journey:

To my supervisors, Masud Husain and Arjune Sen, for believing in me long enough to see this project come to fruition. To Masud in particular, for all the guidance delivered in his characteristically calm, professorial, manner. More than anything, you taught me that this DPhil should be a 'labour of love'. To Arjune, for reminding me that there are more things in life than just my academic career.

To the research participants, for having the grace and patience to endure long hours of testing and scanning without expecting anything in return. I am amazed and honoured at their selflessness and dedication in the face of significant adversities.

To my friends in the lab, for helping me navigate the transition from clinical work to life as a DPhil student. To Raquel, the first person to welcome me to the lab. To Bahaa, for his patient explanation of the intricacies of behavioural and neuroimag-

ing analysis. To Sofia, who somehow finds the energy to do everything that she does. To Xin-You, for valuable DPhil and career advice.

To my friends outside the lab who made life more wholesome during my studies. There are too many of them to mention but in particular, I would like to express my utmost thanks to Azlan, Mus'ab, Muhsin, Ritzman, and their respective families, for all the help they've given.

To Yayasan Khazanah and the Oxford Centre for Islamic Studies for the Merdeka Scholarship that funded my studies. To the University of Malaya and my colleagues in the Neurology Unit, for giving me the opportunity to pursue my dream of doing a DPhil.

To my family and especially to my in-laws, Fauziah Sanad and Badaruddin Yusof, for all their support over these years. To my parents, Azian Abd Latiff and Idris Ahmad, who nurtured in me this love for knowledge in the first place. May Allah (SWT) reward you with the highest ranks of Paradise for all the sacrifices you have made.

To my children, Madeehah, Mujahid, and Muhsin: you are a constant source of joy and fulfilment. May you grow up to become pious and knowledgeable individuals who will contribute much to society.

And finally, to my dearest wife Aliyya Badaruddin, who despite her own tribulations, remained steadfast by my side, providing love and companionship as I walk these ancient corridors. Words cannot express how much it all means to me. May Allah (SWT) grant you peace, happiness, and blessings in this life and in the HereAfter.

Amin ya rabbal 'alamin.

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ACC	anterior cingulate cortex
ACE-III	Addenbrooke’s Cognitive Examination-III
AD	Alzheimer’s Disease
AES	Apathy Evaluation Scale
AMI	Apathy Motivation Index
AMICO	Accelerated Microstructure Imaging via Convex Optimization
APOE	apolipoprotein E
ARWMC	age-related white matter changes
BDI-II	Beck Depression Inventory-II
BIANCA	Brain Intensity AbNormality Classification Algorithm
BOLD	blood oxygenation level-dependent
CADASIL	cerebral autosomal dominant arteriopathy with sub-cortical infarcts and leukoencephalopathy
CSF	cerebrospinal fluid
CT	computed tomography
DAS	Dimensional Apathy Scale
DDM	drift diffusion model
DKI	diffusion kurtosis imaging
dmPFC	dorsomedial prefrontal cortex

DTI	diffusion tensor imaging
DWI	diffusion-weighted imaging
EBDM	effort-based decision making
FA	fractional anisotropy
FLAIR	fluid-attenuated inversion recovery
FLIRT	FMRIB's Linear Image Registration Tool
fMRI	functional MRI
FMRIB	Oxford Centre for Functional MRI of the Brain
FNIRT	FMRIB's Non-linear Image Registration Tool
FSL	FMRIB Software Library
GDS	Geriatric Depression Scale
GLM	general linear model
HCP	Human Connectome Project
HDDM	hierarchical drift diffusion model
ISOVF	isotropic volume fraction
LARS	Lille Apathy Rating Scale
LGA	lesion growth algorithm
LTM	long-term memory
MD	mean diffusivity
MNI152	Montreal Neurological Institute 152 brain template
MoCA	Montreal Cognitive Assessment

MRI	magnetic resonance imaging
MVPA	multi-voxel pattern analysis
NAWM	normal-appearing white matter
NDI	neurite density index
NODDI	neurite orientation dispersion and density density
NPI	Neuropsychiatric Inventory
NVC	neurovascular coupling
ODI	orientation dispersion index
OMT	Oxford Memory Test
PD	Parkinson's Disease
PVS	perivascular spaces
rs-fMRI	resting state functional MRI
STM	short-term memory
SVD	cerebral small vessel disease
TBSS	tract-based spatial statistics
TFCE	threshold-free cluster enhancement
VBM	voxel-based morphometry
vmPFC	ventromedial prefrontal cortex
VSTM	visual short-term memory
WAIS-III	Wechsler Adult Intelligence Scale Third Edition
WM	working memory

W2MHS .... Wisconsin White Matter Hyperintensities Segmentation Toolbox

1 | Introduction

1.1 Cerebral small vessel disease

SVD represents a group of clinical, radiological, and pathological phenomena affecting the small arteries, arterioles, venules, and capillaries of the brain (Pantoni, 2010). It is often diagnosed incidentally on computed tomography (CT) or MRI of the brain. Many people with the disease are unaware of the diagnosis, either because they are completely asymptomatic, or because mild signs or symptoms of neurocognitive dysfunction were wrongly attributed to 'normal aging'. Those who do develop symptoms typically present with acute stroke syndromes, cognitive impairment or dementia, mood or behavioural changes, gait problems, movement disorders, or general functional decline (Cannistraro et al., 2019).

Some of the earliest descriptions of the disease in the modern era came from the work of Fisher in the 1950s and 1960s based on post-mortem examinations of patients with lacunes (Fisher, 1965, 1982). Modern conceptions of SVD increasingly relies on neuroimaging biomarkers. However, the link between changes seen in the brain and cognitive or neuropsychological dysfunction are still poorly understood. Moreover, the association between brain pathology and cognition appears to attenuate with age (Zamboni, Griffanti, Mazzucco, Pendlebury, & Rothwell, 2019). This thesis focuses on the impact of SVD on neuroimaging biomarkers observed on MRI and the influence of the disease on behavioural measures of memory and motivation.

This chapter will first provide a brief overview of SVD. It considers the theoretical basis of the neuroimaging modalities used in the thesis, and the cognitive and neuropsychiatric features associated with SVD. It discusses concepts relevant to two key brain processes—VSTM and EBDM—that are important for cognition and behaviour, and the focus of the behavioural measures used in this work. Finally, it considers the research questions that will be answered in this thesis.

1.1.1 Classification of SVD

Pantoni proposed a classification of SVD which separates the disorder into 6 different types based on their aetiology: 1) arteriolosclerosis (or age-related and vascular risk-factor-related), 2) sporadic and hereditary cerebral amyloid angiopathy, 3) inherited or genetic small vessel diseases distinct from cerebral amyloid angiopathy, 4) inflammatory and immunologically mediated, 5) venous collagenosis, and 6) other small vessel diseases (for example post-radiation angiopathy) (**Table 1.1**) (Pantoni, 2010). Others differentiate between ‘sporadic’ SVD, and genetic causes, of which the most common is a condition known as cerebral autosomal dominant arteriopathy with sub-cortical infarcts and leukoencephalopathy (CADASIL) (Moran, Phan, & Srikanth, 2012). This thesis will focus on the sporadic form of SVD i.e., the entity related to aging and the presence of vascular risk factors.

1.1.2 Epidemiology

The increase in life expectancy across the world has brought along with it a concomitant rise in age-related issues which will impose huge demands on health services in the future (Vos et al., 2020). Dementia, one of these aforementioned age-related conditions, was estimated to affect 35.6 million people globally in 2010; this number is expected to double to 65.7 million in 2030, and 115.4 million in 2050 (Prince et al., 2013). The concept of “vascular cognitive impairment” was proposed in 1994 to describe a spectrum of cognitive impairment related to stroke or in association with otherwise ‘asymptomatic’ cerebrovascular disease

Type 1	Arteriolosclerosis (or age-related and vascular risk-factor-related small vessel diseases)
	Fibrinoid necrosis, lipohyalinosis, microatheroma, microaneurysms , segmental arterial disorganisation
Type 2	Sporadic and hereditary cerebral amyloid angiopathy
Type 3	Inherited or genetic small vessel diseases distinct from cerebral amyloid angiopathy
	For example, CADASIL, CARASIL, hereditary multi-infarct dementia of the Swedish type, MELAS, Fabry's disease, hereditary cerebroretinal vasculopathy, hereditary endotheliopathy with retinopathy, nephropathy and stroke, small vessel diseases caused by COL4A1 mutations
Type 4	Inflammatory and immunologically mediated small vessel diseases
	For example, Wegener's granulomatosis, Churg-Strauss syndrome, microscopic polyangiitis, Henoch-Schonlein purpura, cryoglobulinaemic vasculitis, cutaneous leukocytoclastic angiitis, primary angiitis of the CNS, Sneddon's syndrome, nervous system vasculitis secondary to infections, nervous system vasculitis associated with connective tissue disorders such as systemic lupus erythematosus, Sjogren's syndrome, rheumatoid vasculitis, scleroderma, and dermatomyositis
Type 5	Venous collagenosis
Type 6	Other small vessel diseases
	For example, post-radiation angiopathy and non-amyloid microvessel degeneration in Alzheimer's disease

Table 1.1: **Aetiopathogenic classification of SVD.** CADASIL = cerebral autosomal dominant arteriopathy with subcortical ischaemic strokes and leukoencephalopathy, CARASIL = cerebral autosomal recessive arteriopathy with subcortical ischaemic strokes and leukoencephalopathy, MELAS = mitochondrial encephalopathy with lactic acidosis and stroke-like episodes. Adapted from: *Pantoni et al., 2010*

(Hachinski, 1994). One of the most important causes of vascular cognitive impairment and dementia is SVD (METACOHORTS Consortium, 2016).

The features of SVD can be observed, to varying degrees, in almost everyone above the age of 60 (de Leeuw et al., 2001). The prevalence of SVD increases with age (Hilal et al., 2017) and, although early reports did not report any significant differences between the sexes, more recent studies suggest that there is a greater preponderance of males in those with moderate to severe SVD (Jimenez-Sanchez et al., 2021). There are no known differences in the racial or geographical distribution of the disease (Cannistraro et al., 2019).

Despite the fact that SVD is more closely linked with the elderly population, there is some evidence to show that early life risk factors, specifically low birth weight, low childhood intelligence quotient (IQ), and less education, are associated with more SVD burden five to eight decades later (Backhouse et al., 2021). The most important risk factor for the development and progression of SVD is hypertension (Hilal et al., 2017). Other risk factors include smoking (Khan, Porteous, Hassan, & Markus, 2007), diabetes mellitus (Gouw et al., 2008), obesity (Dearborn et al., 2015), obstructive sleep apnoea (H. Kim et al., 2013), raised triglycerides (Schilling et al., 2014), chronic kidney disease (B. Liu et al., 2018), and arterial stiffness (Riba-Llena et al., 2018).

Although once thought to be a benign accompaniment of the aging process, SVD is now known to be associated with several age-related neurological diseases. A systematic review and meta-analysis by Debette et al., for example, showed how neuroimaging markers of SVD are associated with increased risks of ischaemic stroke, intracerebral haemorrhage, dementia, Alzheimer's disease (AD), and also death (Debette, Schilling, Duperron, Larsson, & Markus, 2019). Furthermore, the presence of SVD worsens functional outcome after stroke (Ryu, Jeong, & Kim, 2020). In older individuals, the disease is associated with gait impairment (de Laat et al., 2010), falls (Sharma, Wang, McCreary, Camicioli, & Smith, 2023), and late-life depression (van Agtmaal, Houben, Pouwer, Stehouwer, & Schram, 2017).

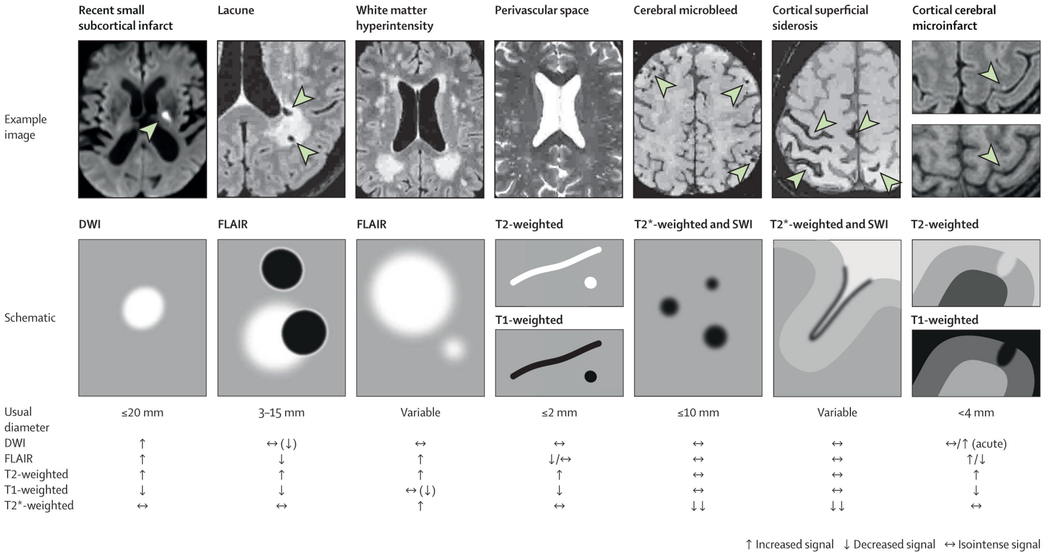
1.2 Neuroimaging biomarkers of SVD

In 2006, the US National Institute of Neurological Disorders and Stroke and the Canadian Stroke Network first proposed a set of common standards for research on vascular cognitive impairment (Hachinski et al., 2006). However, due to several problems including issues with precise definitions and measurement of SVD neuroimaging biomarkers, a new Position Paper was published in 2013 outlining what is now known as the STandards for ReportIng Vascular changes on nEuroimaging, or STRIVE-1, criteria (Wardlaw et al., 2013). According to these criteria, neuroimaging features of SVD as observed on MRI are: recent small subcortical infarct, lacune of presumed vascular origin, white matter hyperintensity (WMH) of presumed vascular origin, perivascular space, cerebral microbleed, and brain atrophy.

More recently, another Position Paper was published to provide updated guidance on neuroimaging of vascular changes for groups studying ageing and neurodegeneration, which are summarised as the STRIVE-2 criteria (Figure 1.1) (Duering et al., 2023). This built upon conventional understanding of SVD in several ways: it supported the development of a summary SVD score, defined cortical cerebral microinfarcts, described incidental lesions visible on DWI, separated such lesions from recent small subcortical infarcts, and provided an improved definition of cortical superficial siderosis (Frisoni & Van Der Flier, 2023). The authors were quick to emphasize that STRIVE-2 should be read and used in conjunction with

STRIVE-1.

The following sections will describe some of these features of SVD that can be identified on neuroimaging.



	Recent small subcortical infarct	Lacune	White matter hyperintensity	Perivascular space	Cerebral microbleed	Cortical superficial siderosis	Cortical cerebral microinfarct
Usual diameter	≤20 mm	3–15 mm	Variable	≤2 mm	≤10 mm	Variable	<4 mm
DWI	↑	↔ (↓)	↔	↔	↔	↔	↔/↑ (acute)
FLAIR	↑	↓	↑	↓/↔	↔	↔	↑/↓
T2-weighted	↑	↑	↑	↑	↔	↔	↑
T1-weighted	↓	↓	↔ (↓)	↓	↔	↔	↓
T2*-weighted	↔	↔	↑	↔	↓↓	↓↓	↔

↑ Increased signal ↓ Decreased signal ↔ Isointense signal

Figure 1.1: **Neuroimaging features of SVD according to STRIVE-2.** Example images (top), schematic representation (middle), and summary of imaging characteristics (bottom). Image courtesy: *Duering et al., 2023*

Recent small subcortical infarct

The proposed definition for the above feature is as follows: neuroimaging evidence of recent infarction in the territory of one perforating arteriole, with imaging features or clinical symptoms consistent with a lesion occurring in the previous few weeks (Wardlaw et al., 2013). Also known as lacunar infarcts, they account for about 25% of all ischaemic strokes, which is proportionally similar to ischaemic strokes due to cardioembolism or large vessel atherosclerosis (Norrving, 2008). Small subcortical infarcts are often the result of two major vascular pathologies, namely (i) thickening of the arterial media leading to narrowing of the arterial lumens and (ii) blockage of the origins of penetrating arteries due to the presence of intimal plaques on parent large intracranial arteries (Caplan, 2015). They can be clinically evident, leading to what is known as a lacunar syndrome, or be identified by chance on imaging, a condition known as silent cerebral infarction (Kang et al., 2012). Over time, recent small subcortical infarcts can evolve into lacunes, WMH without apparent cavitation, or even disappear altogether (Pinter et al., 2019). According to one report, the presence of lacunar infarcts increased the risk of vascular and nonvascular death (Conijn et al., 2011).

Lacune of presumed vascular origin

Lacunes of presumed vascular origin are round or ovoid, subcortical, fluid-filled cavity between 3-15 mm in diameter whose signal is similar to cerebrospinal fluid (CSF), reflecting their origin from a previous acute small subcortical infarct or haemorrhage in the territory of a perforating arteriole (Wardlaw et al., 2013). They are most often found in the putamen and the pallidum, although alternative locations include the pons, thalamus, caudate, internal capsule, corona radiata, and more rarely, the cerebral peduncles, pyramids, and subcortical white matter (Caplan, 2015). When seen on fluid-attenuated inversion recovery (FLAIR) sequences, they often have a central CSF-like hypointensity that is surrounded by a hyperintense rim, even though in some locations particularly the thalamus and brain stem, the central cavity fluid may not be suppressed on FLAIR making the lesion appear entirely hyperintense (Moreau et al., 2012). They are associated with an increased risk of dementia and cognitive decline, post-stroke depression, as well as gait unsteadiness and postural instability (Choi et al., 2012; Santos et al., 2009; Vermeer et al., 2003).

White matter hyperintensity of presumed vascular origin

WMH of presumed vascular origin are common findings seen especially on FLAIR images in the elderly (A. Ylikoski et al., 1995). They appear as bilateral, mostly symmetrical white matter lesions without cavitation that are hyperintense on T2-weighted sequences (such as FLAIR) and can appear as isointense or hypointense on T1-weighted sequences (Wardlaw et al., 2013). Their pathogenesis is still not well understood, with various pathogenetic mechanisms cited including ischaemia and hypoxia, hypoperfusion due to altered cerebrovascular autoregulation, blood-brain barrier leakage, inflammation, degeneration, and amyloid angiopathy (Gouw et al., 2011; Pantoni, 2002). Apart from age, their development and progression are significantly associated with major vascular risk factors like smoking, history of cardiovascular disease, hypertension, and left ventricular hypertrophy (Jeerakathil et al., 2004).

Studies have shown links between the presence and extent of WMH with cognitive impairment and dementia (Prins & Scheltens, 2015). In one systematic review and meta-analysis of 36 prospective studies, WMH at baseline elevated the risk of cognitive impairment and all-cause dementia by 14% (Hu et al., 2021). In the healthy elderly, there is also evidence to suggest that lesion location matters for cognition, with frontal WMH preferentially affecting executive function, parieto-temporal WMH impacting memory, while WMH in deep white matter regions near the corticospinal tract affecting motor processing speed (Lampe et al., 2019).

Another common observation is the co-occurrence of WMH with AD pathology (Brickman et al., 2015). For example, in one post-mortem study of brains from 132 subjects over 85 years old, neurofibrillary pathology was associated with periventricular and deep WMH in the frontal lobe (Polvikoski et al., 2010). Interestingly, progression of WMH volume in older people without dementia appears to be associated with plasma beta-amyloid circulating levels, strongly suggesting an interplay between vascular and neurodegenerative mechanisms in cerebral aging (Kaffashian et al., 2014). Additionally, high WMH burden was associated with global brain atrophy (R. Wang et al., 2014), reduction in grey matter (Wen, Sachdev, Chen, & Anstey, 2006), as well as frontal and temporal atrophy (Raji et al., 2012; Tuladhar, Reid, et al., 2015).

Perivascular spaces

Perivascular spaces (PVS) are fluid-filled spaces of similar intensity to CSF that follow the typical course of penetrating vessels, appearing as lined when seen parallel to the course of the vessel, and round or ovoid, when seen perpendicular to it (Wardlaw et al., 2013). Although one or two small perivascular spaces may be seen on MRI in healthy adults, the presence of enlarged PVS in greater numbers is pathological (Rouhl, van Oostenbrugge, Knottnerus, Staals, & Lodder, 2008). They are often seen in the basal ganglia, centrum semiovale, hippocampus, midbrain, pons, and occasionally in the cerebellar white matter (Wardlaw et al., 2020).

Cerebral microbleed

Defined as small areas of signal void with associated blooming seen on T2*-weighted MRI (or other sequences sensitive to susceptibility effects), cerebral microbleeds are often seen in the cortico-subcortical junction, deep grey or white matter in the cerebral hemispheres, brainstem, and cerebellum (Wardlaw et al., 2013). They represent focal deposition of haemosiderin, a blood breakdown product that causes T2* signal loss via magnetic susceptibility-induced relaxation (Viswanathan & Chabriat, 2006).

Cerebral microbleeds are significantly associated with incident stroke risk (Debette et al., 2019). Additionally, they are also linked to the development of dementia, with cerebral microbleed patients showing greater declines in executive function, processing speed, and Montreal Cognitive Assessment (MoCA) (X. Li et al., 2021).

Brain atrophy

Another neuroimaging feature of SVD is brain atrophy, which is defined as lower brain volumes not related to a specific macroscopic focal injury such as trauma or infarction (Wardlaw et al., 2013). Brain atrophy is a feature of normal aging but it is also seen in many disorders including SVD, AD (B. Zhang, Lin, & Wu, 2021), multiple sclerosis (Eshaghi et al., 2018), and epilepsy (Caciagli et al., 2017). It can be general or focal; Nitkunan et al, for example, showed that there was a significant difference in (total) brain volume between patients with SVD and control subjects (Nitkunan, Lanfranconi, Charlton, Barrick, & Markus, 2011). Other studies have demonstrated more focal patterns of atrophy, affecting the frontal (Y. Chen et al., 2009) or temporal lobes (Jokinen et al., 2012), cerebellum (Yoon et al., 2013), or subcortical structures like the hippocampus (Etherton et al., 2020). Furthermore, the rate of WMH growth appears to be strongly correlated with regional grey matter atrophy, which in turn is linked to global reductions in brain volume (Lambert et al., 2016).

Cortical superficial siderosis

The inclusion of cortical superficial siderosis was first suggested in STRIVE-1, but was strengthened further in STRIVE-2 (Duering et al., 2023). Cortical superficial siderosis describes neuroimaging evidence of chronic blood products in, or overlying, the superficial cortex. Possible reasons for this include convexity subarachnoid haemorrhage, superficial cortical bleeding from vascular malformations, haemorrhagic transformation of infarcts, or trauma.

Cortical cerebral microinfarct

The definition of cortical cerebral microinfarct as outlined in the STRIVE-2 criteria is as follows: small lesions appearing hypointense on T1-weighted imaging, hyperintense of T2-weighted or FLAIR sequences, and isointense on T2*-weighted MRI, that are strictly cortical in location with an upper size limit of 4 mm (Duering et al., 2023). They are a common finding at brain autopsy, as demonstrated by a systematic review of neuropathological studies in which cortical cerebral microinfarcts were detected in 62% of patients with vascular dementia, 43% of AD patients, as well as 24% of individuals 75 years or older who did not have a diagnosis of dementia before autopsy (Brundel, de Bresser, van Dillen, Kappelle, & Biessels, 2012).

1.3 Neuroimaging methods

1.3.1 Structural MRI

Although some features of SVD can be detected on computed tomography (CT) of the brain, MRI has become the *de facto* mode of investigation for diagnosing SVD. This section will cover the theory behind several of these structural MRI techniques, namely: semi-automated segmentation of WMH, subcortical brain segmentation, and VBM.

Semi-automated segmentation of WMH

Accurate WMH segmentation and quantification is crucial to improve their diagnostic utility and prognostic value in SVD. Initial attempts to do so relied on visual rating scales, the most common ones being the Fazekas scale (Fazekas, Chawluk, Alavi, Hurtig, & Zimmerman, 1987), the Scheltens scale (Scheltens et al., 1993), and the age-related white matter changes (ARWMC) scale (Wahlund et al., 2001). Indeed, these scales are still in use in clinical and research settings, but they are time consuming and suffer from inter-observer variability, which may in turn lead to inconsistencies in characterising the frequency, extent, and clinical correlates of WMH (Mantyla et al., 1997).

One way to overcome these issues is by using automated, or semi-automated, segmentation of WMH, for example with BIANCA (Brain Intensity AbNormality Classification Algorithm), a fully automated, supervised method for WMH detection (Griffanti et al., 2016). BIANCA uses the k-nearest neighbour (k-NN) algorithm, where k here represents the number of neighbouring entities examined using this approach. This algorithm provides a method for classifying objects based on the closest examples in the feature space(s) it is trained on. In this instance, the algorithm assigns a probability value that a voxel represents WMH based on the intensity and spatial features of its k nearest neighbouring voxels. It requires examples of manually segmented WMH in order to train the algorithm and has been used in large datasets like the Whitehall II imaging-sub-study and the UK Biobank (Bordin et al., 2021).

Subcortical brain segmentation

One interesting question related to SVD revolves around its impact on the volumes of subcortical grey matter structures. Automated segmentation of subcortical structures is challenging due to variabilities in intensity contrast. This thesis employed a model-based segmentation and registration tool called FIRST (Patenaude, Smith, Kennedy, & Jenkinson, 2011) which is part of the FMRIB Software Library (FSL), a library of analysis tools for MRI data (Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012; S. M. Smith et al., 2004; Woolrich et al., 2009). FIRST uses a model trained on 336 manually labelled T1-weighted MRI images to provide anatomical training information about different subcortical structures. It uses what is called the Active Shape Model to model the distribution of corresponding anatomical points before parameterizing the mean shape and its most likely variations across a training set. In addition, FIRST employs the Active Appearance Model, an extension of the Active Shape Model framework, to take advantage of intensity information when performing segmentation. The output from this model are volumetric and surface representations of the segmented structures Figure 1.2, allowing for anatomical differences between individuals (or groups of individuals) to be investigated further. The following structures were used in the analyses performed for this thesis: nucleus accumbens, amygdala, caudate, hippocampus, pallidum, putamen, and thalamus.

Voxel-based morphometry

VBM aims to detect voxel-wise differences in local grey matter volume or topography, either between several populations, or in one group in relation to a covariate of interest like disease status or neuropsychological test scores (Ashburner & Friston, 2000; Good et al., 2001). This method combines tissue-type segmentation with nonlinear registration to generate 3-dimensional images of differences in local grey matter volume over the whole brain. Briefly, each individual image is registered to a template, and in all voxels containing grey matter, measurements are taken of the expansion or contraction of the local volume need to align the im-

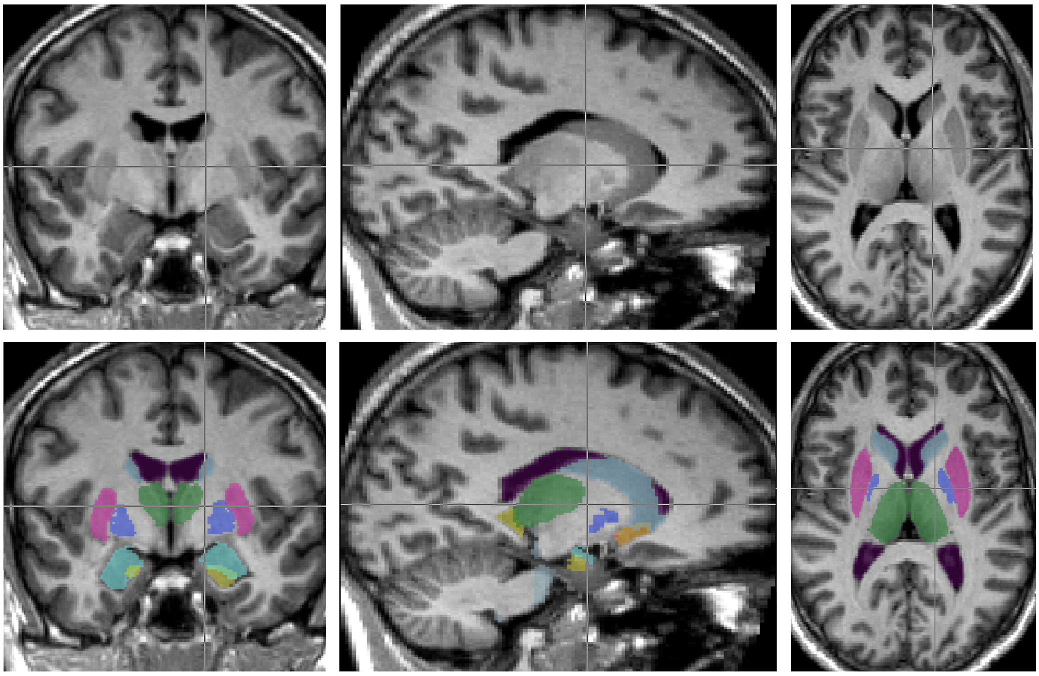


Figure 1.2: **Example of segmentation using FIRST for one individual.** Different subcortical structures are given different colours for clarity of presentation. Image courtesy: *Patenaude et al., 2011*

age with the template accurately. These measurements are then combined with the local estimate of the grey matter volume obtained from a tissue-type segmentation in a process called modulation, before applying some level of smoothing to help compensate for alignment errors, make the distribution of noise more Gaussian, and improve statistical sensitivity (Jenkinson & Chappell, 2018).

The general interpretability of results from VBM-style analysis was often criticised, at least initially, due to ambiguity as to whether the changes detected are really due to differences in grey matter density or occur due to local misalignment. In addition, VBM makes use of an arbitrary amount of smoothing to deal with residual misalignments and improve statistical sensitivity, such that the final results may depend very strongly on the amount of smoothing used in the study (Jones, Symms, Cercignani, & Howard, 2005). However, with careful application and validation, VBM has proved useful in studying changes in grey matter topography in cognitively normal elders (Raji et al., 2012) as well as in many diseases including SVD (C. Li, Du, Zheng, & Wang, 2011), schizophrenia (Douaud et al., 2007), Parkinson's disease (PD) (Mak et al., 2014), epilepsy (Santana et al., 2014), and AD (Chapleau, Aldebert, Montembeault, & Brambati, 2016).

1.3.2 Diffusion MRI

Diffusion MRI works on the basis that water molecules are always in random motion (as described by physical diffusion processes like Brownian motion) and that this diffusion is affected by the presence of bundles of elongated axons that hinder the movement of water molecules across cell membranes (Le Bihan & Johansen-Berg, 2012). This method enables in vivo extraction of information related to the microstructure of brain tissue, for example the integrity of white matter pathways, potentially revealing abnormalities that may not be visible using conventional MRI techniques (Bodini & Ciccarelli, 2014).

One analysis model that has proven useful in interpreting the diffusion MRI signal is termed DTI (Basser, 1995). DTI is a mathematical description of the diffusion process that yields several quantities like fractional anisotropy (FA) and mean diffusivity (MD) (Jenkinson & Chappell, 2018). FA is a measure of the degree of anisotropy in the voxel, such that low FA represents almost equal diffusion in all directions, whereas high FA reflects diffusion occurring preferentially along some directions but not others. MD, on the other hand, describes average molecular motion independent of any tissue-based directionality. A major issue with using DTI-derived metrics like FA and MD is their lack of specificity for individual tissue microstructural features. For example, a decrease in FA may be caused by several processes including reduction in neurite (i.e., axons and dendrites) density as well as an increase in the dispersion of neurite orientation distribution (Beaulieu, 2009).

Despite its usefulness, therefore, DTI remains a simple model that may not accurately represent more complex biological cases like crossing fibres in the brain. This has led to the emergence of newer models, for example NODDI that provide more sophisticated descriptions of the water diffusion (H. Zhang, Schneider, Wheeler-Kingshott, & Alexander, 2012). NODDI divides the microstructural environment into 3 different compartments: intra-cellular, extra-cellular, and CSF. Doing so enables the calculation of 3 main parameters: neurite density index (NDI), a measure of the packing density of axons or dendrites, orientation dispersion index (ODI), which estimates the orientation coherence of neurite, and isotropic volume fraction (ISOVF), a metric quantifying the extent of CSF contamination in the voxel. In summary, while standard techniques like DTI and diffusion kurtosis imaging (DKI) can only produce a composite view of the multiple components existing in a voxel, NODDI may potentially enable their individualised characterisation Figure 1.3.

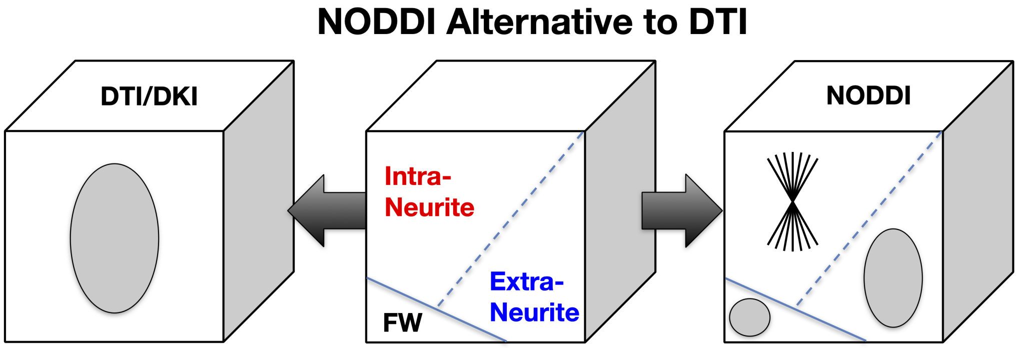


Figure 1.3: **Advantage of NODDI over DTI.** Conventional techniques like DTI/DKI only provide a summary measure of the different components making up a voxel. NODDI potentially allows the investigation of separate contributions from individual tissue components. FW = free water. Image courtesy: *UCL Microstructure Imaging Group*

Tract-based spatial statistics

An issue that arises when analysing diffusion MRI data is how best to compare the white matter tracts from multiple subjects while taking into account underlying differences in brain anatomy? More specifically, what is the optimal method to align diffusion images from multiple subjects such that valid conclusions can be drawn from the subsequent voxelwise analysis? Some researchers have opted to forgo the alignment problem altogether and simply summarised global diffusion parameters using, for example, histogram-based summary measures of fractional anisotropy (Cercignani, Inglese, Pagani, Comi, & Filippi, 2001). More recent work has attempted to introduce some spatial-localisation in the analysis of diffusion-related changes. An example of this approach is called TBSS (S. M. Smith et al., 2006), which takes its idea from VBM-style analysis (described above).

TBSS attempts to overcome the alignment and smoothing problems of VBM while being fully automated, allowing the "whole" brain to be investigated instead of requiring tracts of interest to be pre-specified. It achieves this by first estimating a group mean FA skeleton representing the centres of all fibre bundles, before projecting each subject's FA data onto the mean skeleton. Each voxel in the skeleton thus takes the FA value from the nearest relevant tract centre, allowing voxelwise statistical analyses to be carried out across subjects using the skeleton-space FA data. The same approach can be used for other diffusion parameters like MD, NDI, ODI, and ISOVF (Gharaylou et al., 2021).

1.3.3 Resting state functional MRI

While structural and diffusion MRI are concerned with the anatomy of the brain, functional MRI (fMRI) deals with changes in blood haemodynamics as a measure of neuronal activity (Matthews & Jezzard, 2004). The relationship between neuronal firing and MRI signal change is known as the blood oxygenation level-dependent (BOLD) effect (Arthurs & Boniface, 2002). To understand the BOLD effect, it is important to appreciate what happens when the cell body of a neuron receives input through dendrites and generates action potentials along axonal tracts. This triggers a localised increase in blood flow to meet the increased metabolic demand from the neuron. In fact, this increase exceeds the oxygen demand of the neuron, resulting in a local increase in blood oxygenation. The increase in blood oxygenation, a secondary and indirect measure of neuronal activity, is what is measured in functional MRI.

The normal BOLD effect relies on intact functioning of what is known as the neurovascular unit, made up of neurons and their associated cerebral vasculature (Iadecola, 2017). This relationship can be conceptualised using the term neurovascular coupling (NVC), representing the degree to which neuronal activity is associated with changes in cerebral blood flow. NVC can be impaired in people with various conditions including SVD, hypertension, diabetes, or history of stroke (Monteiro et al., 2021; Lin, Hao, Rosengarten, Leung, & Wong, 2011). A recent systematic review and meta-analysis of 29 studies demonstrated an association between SVD and reduced NVC, with endothelial dysfunction being a likely culprit (Yang & Webb, 2023). Due to the weaker NVC seen in those with SVD, the presence or absence of changes in BOLD responses in this population need to be interpreted with caution.

Functional MRI experiments can be conducted using stimuli and tasks (task fMRI) or without explicit stimuli (rs-fMRI). Rs-fMRI looks at functional connectivity, a measure of the functional relationships between different parts of the brain (Bijsterbosch, Smith, & Beckmann, 2017). This is done by checking how similar the BOLD signals are from different parts of the brain, with the assumption that regions with greater similarities also have more functional connectivity with each other. Therefore, functional connectivity in this instance can be defined as "statistical correlation between two electro- or neurophysiological measurements from different parts of the brain".

When different brain regions are connected to one another, they are said to form a network, thus a resting state network represents a group of brain regions that show similarities in their BOLD signals at rest. One of the most recognisable resting state networks is the Default Mode Network, made up of the medial prefrontal cortex, posterior cingulate cortex, precuneus, lateral temporal cortex, and inferior parietal lobule (Raichle et al., 2001). Examples of other resting state networks include the salience network, the executive control network, and the sensorimotor network (Adriaanse et al., 2014; Beckmann, DeLuca, Devlin, & Smith, 2005; Seeley et al., 2007) Figure 1.4. Resting state networks reflect how the healthy brain is organised, but they can also be affected by various neurological and psychological disorders. One useful question to ask would be if different diseases produce unique patterns of deficits amongst resting state networks. This would allow them to act as biomarkers in the diagnosis of such disorders.

1.4 Impact of SVD on brain structure and function

Using the neuroimaging methods described above, researchers have begun to characterise how brain structure and function are affected by SVD. This topic will be covered in greater detail in the Introduction to the next chapter, but before that it is useful to have a framework for understanding the multitude of ways in which SVD affects the brain Figure 1.5.

First, SVD lesions may be heterogeneous in severity and aetiology despite identical appearances on neuroimaging. A review of postmortem studies showed that

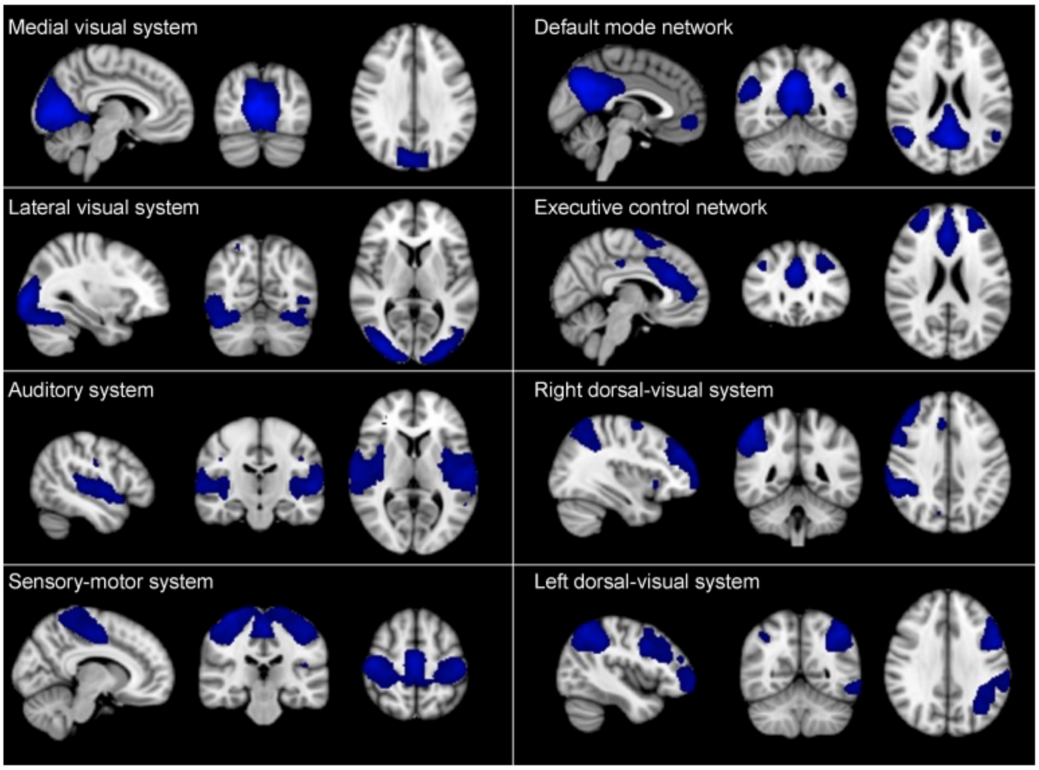


Figure 1.4: **Examples of resting state networks.** Sagittal, coronal, and axial views of different brain regions making up several resting state networks including the medial visual system, lateral visual system, auditory system, sensory-motor system, default mode network, executive control network, as well as the right and left dorsal-visual systems. Image courtesy: *Adriaanse et al., 2014*

individual WMH lesions exhibit different degrees of demyelination, gliosis, as well as loss of fibres and oligodendrocytes, with more severe and confluent lesions demonstrating more extensive pathology (Gouw et al., 2011). Second, in addition to the direct effects of lesions, SVD also exerts perilesional and remote effects on the brain. The existence of the so-called ‘SVD penumbra’—areas with altered diffusion metrics that otherwise look normal on conventional MRI—have been supported by DTI studies (Maillard et al., 2011; Maniega et al., 2015). Third, SVD lesions can alter structural and functional connectivity either by affecting the nodes of a network or the connections between them. One example of this came

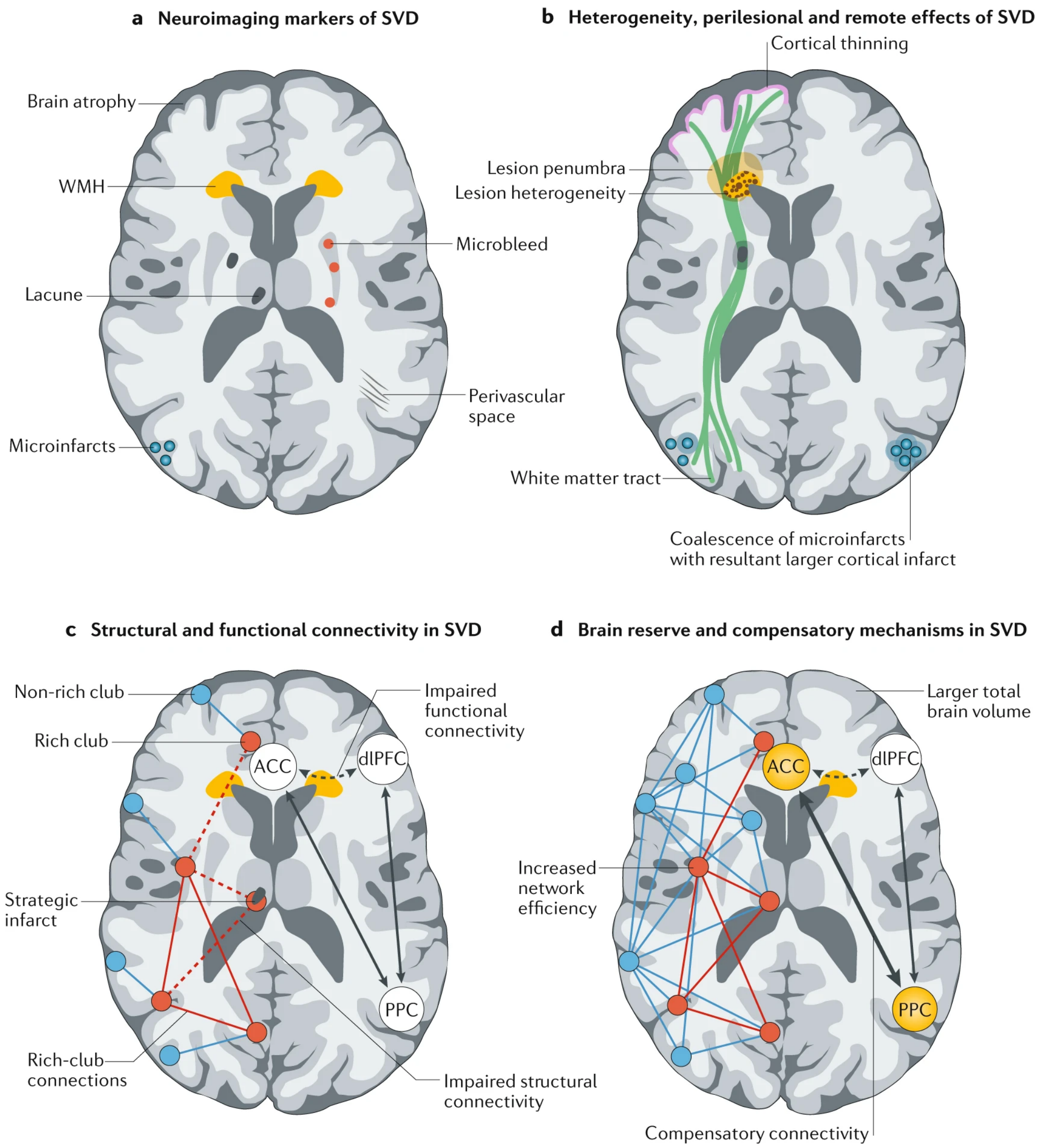


Figure 1.5: **Framework for understanding the effect of SVD on the brain. (a)** MRI markers of SVD. **(b)** SVD lesions with similar appearances on MRI may show heterogeneity in terms of underlying disease nature and severity. Moreover, lesions not only exert local but also perilesional and remote effects. **(c)** Both structural and functional connectivity can be altered in the presence of SVD. **(d)** Some of the factors that make the brain resilient to damage from SVD. ACC = anterior cingulate cortex, dlPFC = dorsolateral prefrontal cortex, PPC = posterior parietal cortex. Image courtesy: *ter Telgte et al, 2018*

from a study that applied graph-based efficiency analysis (Bullmore & Sporns, 2009) to diffusion tensor tractography data from 115 SVD patients and 50 control participants(Lawrence, Chung, Morris, Markus, & Barrick, 2014). By comparing network connectivity between the two groups, the researchers demonstrated that networks in SVD patients were less dense, with lower connection weights, and had significantly disrupted measures of network efficiency. Finally, the clinical deficits that result from SVD do not simply depend on the sum of SVD burden and brain damage but also on the degree of brain resilience, defined as the capacity of people to tolerate a certain degree of brain damage before experiencing clinical symptoms (Brickman et al., 2011) .

1.5 Cognitive and neuropsychiatric effects of SVD

To a certain extent, the effects of alterations in structural, diffusion, and rs-fMRI measures from SVD are ‘invisible’ to the individuals affected. Instead, patients may present with cognitive or neuropsychiatric symptoms that, after more detailed investigations, lead to a diagnosis of SVD. This begs the question: Why should a condition like SVD produce cognitive and neuropsychiatric symptoms in the first place? Lesions associated with SVD often occur in brain areas that traditionally are not thought to be critical for producing such deficits. However, as illustrated in Figure 1.5 above, such lesions not only cause direct damage to their immediate area but may also interfere with normal function in perilesional and remote areas of the brain (ter Telgte et al., 2018). This section will discuss two such manifestations namely the cognitive and neuropsychiatric consequences of having SVD.

Despite the importance of the topic at hand, the precise nature of cognitive impairment in SVD remains poorly characterised. Complicating matters further, vascular pathology can often be found in cognitively healthy adults, suggesting that a certain degree of vascular abnormality can be present with minimal or no cognitive consequences (Vasquez & Zakzanis, 2015). Nevertheless, current consensus statements regarding SVD-related cognitive impairment suggest that the disease predominantly affects processing speed and executive function, with relative sparing of episodic memory and language abilities (Peng, Geriatric Neurology Group, Chinese Society of Geriatrics, & Clinical Practice Guideline for Cognitive Impairment of Cerebral Small Vessel Disease Writing Group, 2019; Rosenberg et al., 2016). However, more recent reports appear to contradict this view, instead finding cognitive deficits in a broad range of domains including visuospatial abilities and delayed memory (O. K. L. Hamilton et al., 2021; Vasquez & Zakzanis, 2015).

How might we reconcile these contradictory findings? Here, it is important to remember that poor performance on a particular cognitive task may arise via many pathways. For example, testing verbal fluency by asking participants to name as many words beginning with the letter P as possible in one minute, inevitably imposes demands on multiple cognitive domains including processing speed, language, and semantic memory. Furthermore, studies on SVD patients have involved heterogeneous groups of people in terms of the aetiology of the disease (e.g., sporadic or genetic), the age of the participants (younger vs. older cohorts), as well as the degree of cognitive impairment they experienced. In the systematic review and meta-analysis by Hamilton et al. cited above, for example, the dataset included 26 cohorts with stroke presentations of SVD, 31 with either cognitive impairment or dementia, as well as 32 groups with non-clinical presentations of SVD (O. K. L. Hamilton et al., 2021).

This highlights the importance of gaining a better mechanistic understanding into the processes responsible for producing such deficits. One aspect of cognition that is conspicuously absent in many studies investigating SVD-related cognitive impairment is VSTM. Chapter 3 of this thesis will discuss the possible reasons for this absence before presenting a behavioural paradigm that may potentially offer a more sensitive method for probing the precise nature of VSTM deficits in SVD.

Another aspect of SVD that is becoming increasingly recognised is its effect on neuropsychiatric symptoms such as depression, apathy, delirium, anxiety, and fatigue (Clancy, Appleton, et al., 2021). Apathy is a neuropsychiatric syndrome that can be can be conceptualised as a loss of motivation that manifests itself as a reduction in goal-directed behaviour (Le Heron, Holroyd, Salamone, & Husain, 2019; Le Heron, Apps, & Husain, 2018). People with apathy often report that they “can’t be bothered”, or that activities they normally partake in “don’t seem worth it anymore”, or that they “just don’t know” why they are no longer interested in behaviours they used to do. Caregivers of people with apathy often report that they require prompting to do things and do not self-initiate behavioural activities when given the opportunity to do so. As with VSTM deficits, apathy may also develop due to dysfunction in several mechanisms which will be outlined further in Section 1.9 of this chapter. Apart from investigating the effects of SVD on VSTM, this thesis will also examine the relationship between SVD and apathy using a behavioural paradigm called EBDM.

1.6 Visual short-term memory

As alluded to in Section 1.1, this thesis will not just investigate the impact of SVD on the brain but also its effect on behavioural measures of memory and motivation. Any discussion of STM cannot avoid touching on a related concept which is working memory (WM). Strictly speaking, STM refers to the simple retention of small amounts of information, to be recalled immediately or after a short delay, whereas WM refers to a more complex system that enables the storing and manipulating of information (Baddeley, Eysenck, & Anderson, 2020). In practice, however, the two terms are often used interchangeably. For consistency's sake, this thesis will use the term 'short-term memory' to cover both STM itself, as well as WM.

One question that may be asked is: why study VSTM in SVD? Although VSTM deficits are not conventionally associated with SVD for reasons outlined in Section 1.5, they are nevertheless important due to their potential to exert significant adverse effects on activities of daily living. In addition, WM in particular is known to rely on a complex interplay between the prefrontal cortex and striatal circuits (D'Esposito & Postle, 2015). Cortical areas subserving VSTM may be disrupted in SVD due to several mechanisms including degeneration secondary to white matter track disruption, or from the presence of cortical microinfarcts (Markus & Erik de Leeuw, 2023).

1.6.1 Models of short-term memory

Many attempts have been made to come up with a theoretical framework for STM. One of the earliest models, termed the modal model, was proposed by Atkinson and Shiffrin (Atkinson & Shiffrin, 1968). In this model, information comes in from the environment and is first processed by sensory registers before being passed to a short-term store. This short-term store not only serves as a working memory area but is also responsible for passing information into and out of long-term memory (LTM). One prediction that arises from the modal model is that people with deficits in STM should also have impairments in LTM. This was not always the case, however, as illustrated by the existence of many patients with grossly impaired STM but relatively intact LTM (Vallar & Shallice, 1990).

Within a few years, the modal model was superseded by more complex models of STM. The most influential of these has been the multicomponent model, proposed by Baddeley & Hitch (Baddeley & Hitch, 1974). This model consisted of three components: the phonological loop, for holding sequences of acoustic or speech-based items, the visuo-spatial sketchpad, for remembering visually and spatially encoded items and arrays, and the central executive, an attentionally limited system responsible for selecting and manipulating material in the subsystems. More recently, a fourth component, the episodic buffer, was added to represent a limited capacity store with a couple of important functions namely to carry out multi-dimensional coding and to allow binding of information to create integrated episodes Figure 1.6 (Baddeley & Andrade, 2000; RepovS & Baddeley, 2006).

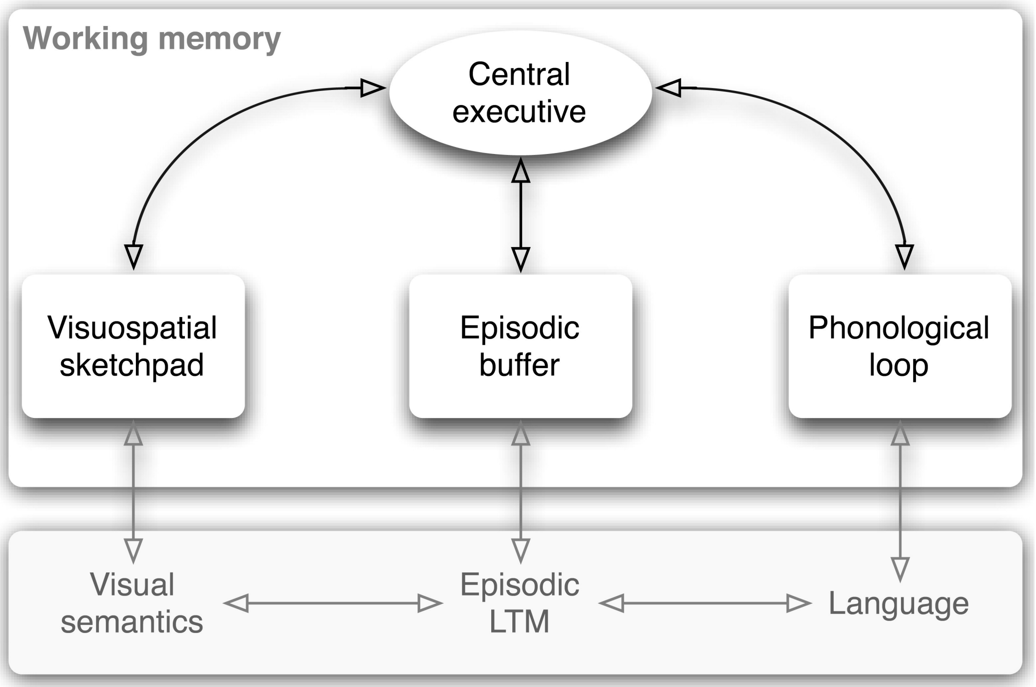


Figure 1.6: **The multicomponent model of working memory.** This model is made up of four key components: the central executive, the visuospatial sketchpad, the phonological loop, and the episodic buffer. See text for more detailed descriptions of the role played by each component. Image courtesy: *RepovS & Baddeley, 2006*

The phonological loop assumes a temporary store and a verbal rehearsal process. This begs the question: what is the function of the phonological loop? Some have hypothesized that it evolved to aid language comprehension (Vallar & Baddeley, 1987). One example of this is in situations where one must hold on to the first few words until the end of a sentence in order to understand it. Another hypothesis is that the phonological loop evolved to help us learn a language. This was demonstrated by studying the learning capacity of a patient, P.V., who was given the task of associating each of eight Russian words with their Italian equivalent (her native language) (Baddeley, Papagno, & Vallar, 1988). With auditory presentation, even after 10 trials, P.V. still did not manage to learn any of the associations, whereas all of the control participants in the experiment had managed to do so. In addition to vocabulary acquisition, it is likely that the phonological loop also aids the acquisition of grammar and reading (Ellis & Sinclair, 1996).

As mentioned before, the visuo-spatial sketchpad, another subsystem in the multi-component model, allows the storage of visual and spatial information. However, its role goes beyond simple storage and also involves manipulation of said items. Finke and Slayton gave subjects some geometric forms, lines, or alphanumeric characters, and asked them to close their eyes and imagine combining the parts to produce some type of recognizable pattern, in effect studying how spatial manipulation is carried out by the visuo-spatial sketchpad (Finke & Slayton, 1988).

An interesting experiment involving both the phonological loop and the visuo-spatial sketchpad was performed by giving participants some shapes and requiring them to create an object that they should name and afterwards draw (Pearson, Logie, & Gilhooly, 1999). Concurrent tasks were employed to try to disrupt the two subsystems, using articulatory suppression to interfere with the phonological loop, and tapping a series of spatial locations to interfere with the visuo-spatial sketchpad. Spatial tapping was shown to disrupt the capacity to create novel objects but had no effect on the recall of memorized shapes, suggesting involvement of the visuo-spatial sketchpad in imagining new objects. On the other hand, articulatory suppression disrupted the recall of names of shapes to be manipulated without affecting the ability to create new objects, implying some role of the phonological loop in this process.

STM is assumed to be directed by the central executive. This was proposed to have 2 modes of control, an automatic mode based on existing habits, and another mode that depends on an attentionally-limited executive (Norman & Shallice, 1986)).

One problem with the original three-component model was the difficulty in linking it to LTM. To illustrate this point, a study examined the vividness of visual imagery and revealed that memories for images like a familiar shopping mall environment do not depend heavily on the visuospatial or phonological subsystems but instead relies on the amount and type of information held in LTM (Baddeley & Andrade, 2000). Thus, when shown a picture of a football player and asked to recall the image later, for example, the quality of recall—how vivid the description of the remembered entity—depended principally on prior knowledge of football players i.e., elements retained in LTM. In light of this, the episodic buffer was proposed to act as a multimodal storage system capable of integrating information into coherent episodic representations.

1.6.2 Limitations to the capacity of VSTM

While attempting to demonstrate the storage capacity of VSTM, Luck and Vogel demonstrated that it was only possible to retain information about four colours or orientations at one time (Luck & Vogel, 1997). Interestingly, it was also possible to remember both the colour and the orientation of four objects, suggesting that what was stored in VSTM represented integrated objects instead of individual features. They explained their results in terms of a ‘slot’ model in which VSTM capacity is a discrete and quantised resource. Thus, a fixed number of items are represented in VSTM, irrespective of the complexity of the items (Awh, Barton, & Vogel, 2007). Subsequent work has shown that increasing the number of features in items to be remembered did not greatly affect the number of stored objects but dramatically reduced the precision of these representations in memory (Fougnie, Asplund, & Marois, 2010).

An alternative to the ‘slot’ model described above comes in the form of a ‘resource’ model which treats STM as a limited but fluid resource that can be divided flexibly between several items (Figure 1.7) (Ma, Husain, & Bays, 2014).

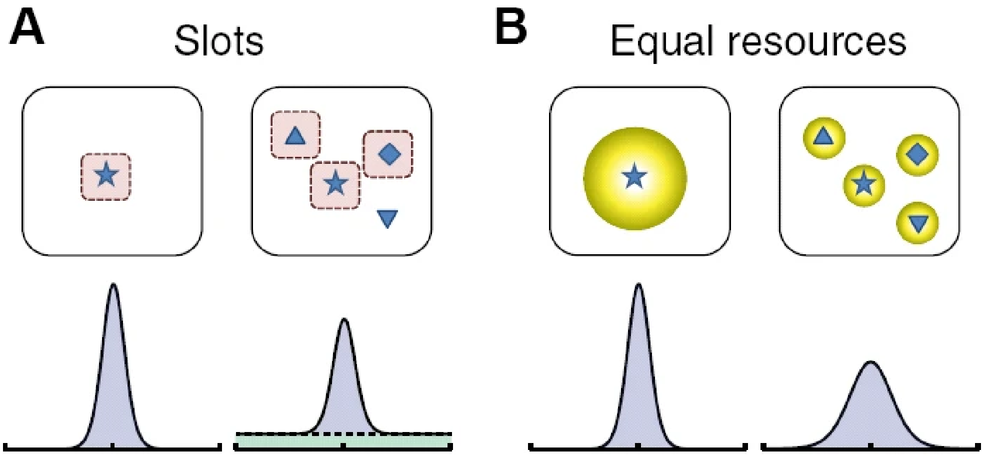


Figure 1.7: **Slot vs resource models of short-term memory.** **(A)** In the slot model, there is a fixed number of independent memory slots that can accommodate one visual item each. **(B)** In the resource model, there is a limited supply of representational medium that is divided between items. How precisely an item is remembered depends on the quantity of resource allocated to it. Adapted from: *Ma et al., 2014*

Here, it is the quality rather than the quantity of STM representations that determine performance. In the slot model, every item is either stored with high precision in memory or not at all. However, studies have shown that the precision of recall declines in a continuous manner as people are required to remember more items (Bays, Catalao, & Husain, 2009). In one such experiment in which participants were asked to remember the location and orientation of multiple visual items following a brief disappearance of the stimulus array, recall precision decreased even between one- and two-item displays. Indeed, participants' response functions were successfully fitted with cumulative Gaussian distributions, implying that the stored representations of the original stimulus were accompanied by a gaussian distribution of error (Bays & Husain, 2008). Again, this would not be consistent with the slot model, which predicts that recall performance will only begin to decline once the maximum number of items capable of being stored has been exceeded.

Many of the initial studies on VSTM employed a change-detection paradigm, one capable of interrogating the capacity or number of items that participants can recall correctly from VSTM in a binary manner. This all-or-none approach, while useful to a certain extent, might not be sensitive enough to detect changes in how well items have been retained in memory. A more recent theoretical and empirical approach makes use of a delayed reproduction paradigm whereby participants were required to reproduce the exact quality of the remembered feature in an analogue response space (Bays et al., 2009; Gorgoraptis, Catalao, Bays, & Husain, 2011). By calculating how far the response made is from the true value of the feature from the memory array, these delayed reproduction tasks are able to measure the resolution or precision of recall. This same paradigm has been implemented in the OMT which will be described in more detail in Chapter 3 of this thesis.

1.6.3 Sources of error

Many of the experiments described above that helped to advance the view of VSTM as a highly limited resource made use of delayed reproduction tasks requiring participants to reproduce the exact feature of a remembered object using a continuous, analogue response space. This paradigm provides a method to dissect out sources of error in recall performance (Fallon, Zokaei, & Husain, 2016). Here, three sources of errors can be identified (Gorgoraptis et al., 2011). First, errors can be due to some variability in how precisely memory for the probed feature is encoded. Second, errors can occur because features of non-probed items shown in the original memory array are confused with features that belong to the probed item. This type of error has been referred to as misbinding error because participants fail to correctly bind one feature of the probed item with another, instead replacing said feature with that coming from another, non-probed, item. Finally, errors can also occur randomly such as when participants are simply guessing due to, for example, failure to encode or retrieve the required item (Figure 1.8).

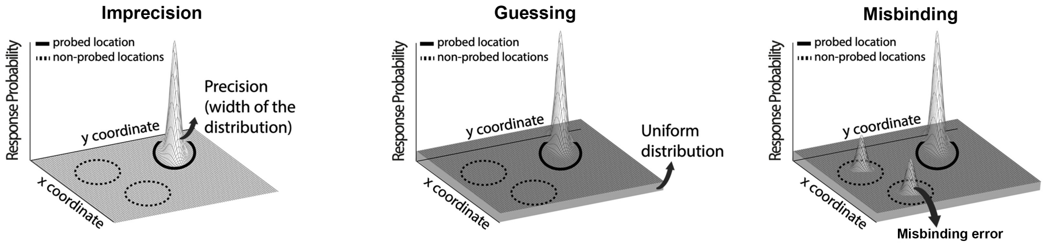


Figure 1.8: **Sources of error in VSTM.** Errors can arise from several factors including imprecision of responses centred on the probed location (left panel), random guessing (middle panel), and misbinding of one feature from the probed item with another feature from a non-probed item (right panel). Image adapted from: *Zokaei et al., 2020*

1.7 Effort-based decision making

Neurological conditions like SVD, AD, and PD often have wide-ranging effects not just on cognition but also on mood and motivated behaviour. These neuropsychiatric symptoms are often overlooked because they can be subtle, at least at the onset of the disease.

Apathy is a multidimensional disorder involving dysfunction of various mechanisms which have been postulated to relate to option generation, option selection, anticipation, action initiation, interaction with behavioural goal, and learning (Figure 1.9) (Husain & Roiser, 2018).

Many scales have been developed to diagnose the presence of apathy. Some are unidimensional, such as the Apathy Evaluation Scale (AES) (Marin, 1991), the Neuropsychiatric Inventory (NPI) (Cummings, 1997), the Dementia Apathy Interview and Rating Scale (Strauss & Sperry, 2002), and the Structured Clinical Interview for Apathy (Starkstein, Ingram, Garau, & Mizrahi, 2005). Others take a multidimensional approach and attempt to measure cognitive, behavioural, affective, or social aspects of apathy. Examples of these scales include the Apathy Inventory (Robert et al., 2002), the Lille Apathy Rating Scale (LARS) (Sockeel, 2006), the Dimensional Apathy Scale (DAS) (Radakovic & Abrahams, 2014), and the Apathy Motivation Index (AMI) (Ang, Lockwood, Apps, Muhammed, & Husain, 2017). Using these scales, studies have demonstrated the association between apathy and many forms of dementia including vascular dementia. Kazui et al, for example, demonstrated that as dementia progresses, behavioural and psychological symptoms of dementia (which includes apathy) become more severe (Kazui et al., 2016).

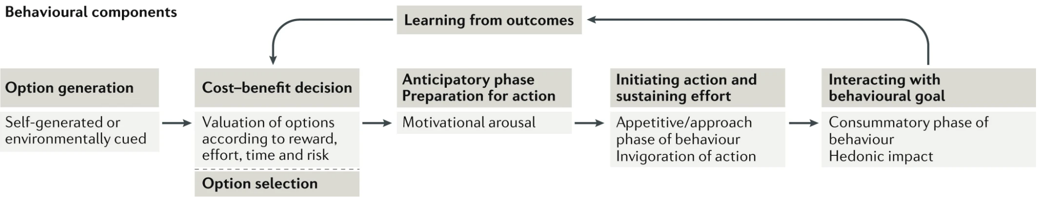


Figure 1.9: **Potential mechanisms involved in motivated behaviour and apathy as theorised using the effort-based decision making framework.** Adapted with permission from: *Husain & Roiser, 2018*

1.7.1 Behavioural approaches for studying apathy

In addition to questionnaires, several behavioural paradigms have been developed to probe the different mechanisms underlying apathy outlined in Figure 1.9. For example, option generation, which involves the ability to conceive of options for behaviour, has been tested by asking participants to generate as many option as possible for real-life scenarios. Using this approach, researchers have shown that apathy in schizophrenia patients may be related to a deficit in the generation of options for actions (Hartmann et al., 2015). The mechanism of anticipation reflects motivational arousal that typically occurs once an individual has selected an option. This can be measured using physiological parameters like heart rate or pupil dilation. This method has been employed to show that PD patients with apathy also had reduced pupillary dilation in response to potential rewards (Muhammed et al., 2016).

This thesis will focus on another one of these mechanisms namely the initiation, maintenance, and invigoration of action that form part of appetitive behaviour. A novel approach utilises performance on tasks involving EBDM to quantify this stage of motivated behaviour. Here, effort allocation can be measured physically using, for example, the number of button presses or the amount of force captured by hand-held dynamometers. Participants are often asked to choose between two options based on different combinations of reward and effort levels (Bonnelle, Manohar, Behrens, & Husain, 2016). A recent study employed this method to investigate how decision making is affected in SVD patients with apathy (Saleh, Le Heron, et al., 2021). Patients had to accept or reject offers made up of different combinations of rewards (represented by the number of apples on a tree) and effort (the amount of force generated using hand-held dynamometers). Several interesting findings emerged from this experiment. First, SVD patients with apathy rejected more offers than healthy control participants. Second, apathetic SVD patients were less responsive to low reward levels and more sensitive to high effort levels. Finally, using TBSS on diffusion MRI data (see Section 1.2.2 for details) revealed that FA in several white matter tracts such as the anterior cingulum, anterior thalamic radiation, corpus callosum, and inferior fronto-occipital fasciculus were associated with apathy.

The link between brain (e.g., diffusion MRI metrics) and behaviour (e.g., apathy score) will become an important theme in this thesis. With regards to motivated behaviour, several brain regions have been identified as key components in a network whose dysfunction leads to apathy. These include the dopaminergic projections from the ventral tegmental area to the ventral striatum (a region that encompasses the nucleus accumbens and ventral pallidum), which in turn projects to different parts of the medial prefrontal cortex such as the ventromedial prefrontal cortex (vmPFC), dorsomedial prefrontal cortex (dmPFC), and anterior cingulate cortex (ACC) (Figure 1.10) (Husain & Roiser, 2018; Kos, van Tol, Marsman, Knegtering, & Aleman, 2016; Le Heron, Apps, & Husain, 2018; Le Heron et al., 2019).

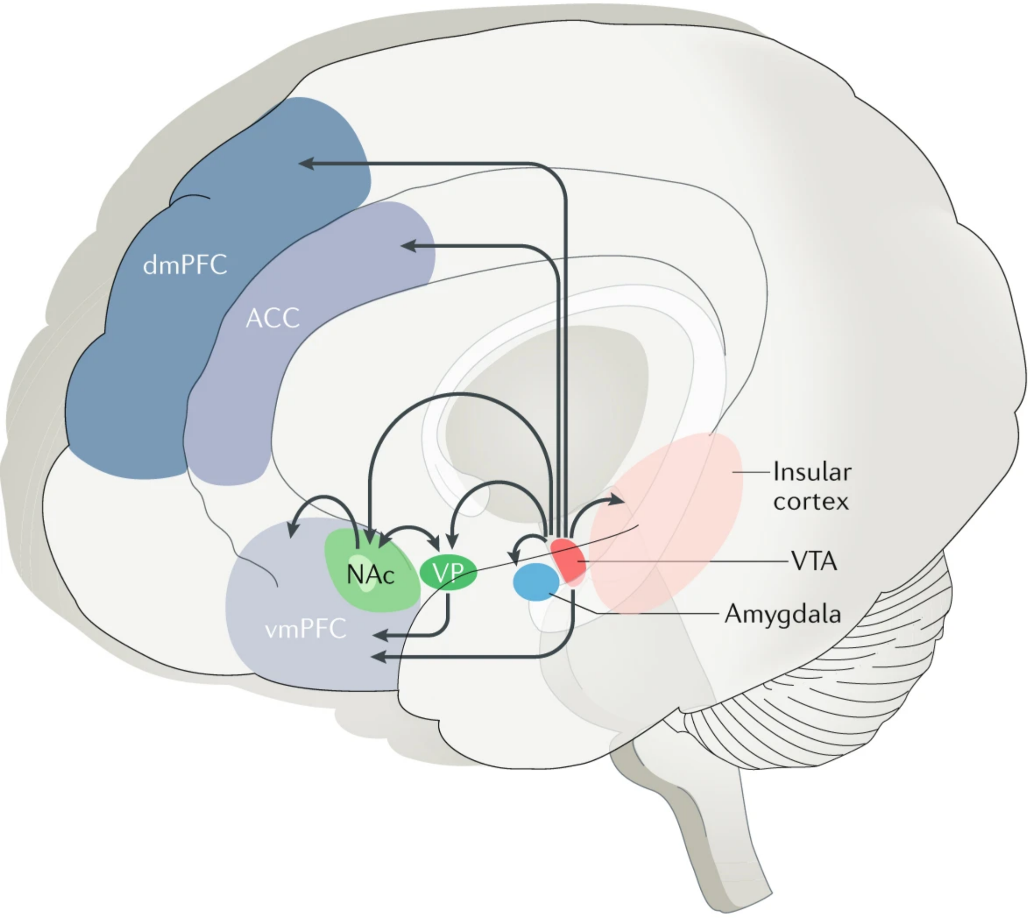


Figure 1.10: **The anatomy of apathy.** Areas involved in normal motivation include the ventral tegmental area (VTA) which sends dopaminergic projections to the ventral striatum, which comprises the nucleus accumbens (NAc) and ventral pallidum (VP). Frontostriatal circuits then connect the ventral striatum with different parts of the medial prefrontal cortex such as the ventromedial prefrontal cortex (vmPFC), dorsomedial prefrontal cortex (dmPFC), and anterior cingulate cortex (ACC). Adapted with permission from: *Husain & Roiser, 2018*

1.8 Thesis outline

This thesis aims to advance our understanding of how SVD affects the brain and influences behaviour. To that end, it will be organised into the following chapters:

Chapter 2 | Neuroimaging biomarkers of SVD

What are the neuroimaging biomarkers of SVD? By comparing SVD patients with healthy controls, this chapter will use structural MRI to investigate how the two cohorts differ in terms of their WMH burden and volume of subcortical grey matter structures. This is followed by VBM to look for voxel-wise differences in local grey matter volume. Then, two diffusion MRI diffusion models, namely DTI and NODDI, will be employed to assess how the underlying tissue microstructure is affected by SVD. Finally, the effect of the disease on various resting state networks will be compared using rs-fMRI data.

Chapter 3 | Impact of SVD on VSTM

This chapter will analyse the effect of SVD on VSTM using the OMT, a delayed reproduction task with an analogue response space. Doing so not only provides information on raw VSTM metrics like accuracy and speed, but it also allows the identification of sources of error in recall performance. This might yield important insights into the mechanism of VSTM dysfunction in SVD.

Chapter 4 | Neural correlates of VSTM in SVD

After investigating the behavioural basis of VSTM deficits in people with SVD, this chapter will probe their association with several metrics obtained from structural and diffusion MRI. Measures of VSTM performance will be correlated with total WMH volume, subcortical volume, local grey matter volume using VBM, as well as white matter microstructural integrity using TBSS.

Chapter 5 | Impact of SVD on EBDM

This chapter examines how SVD affects motivation and leads to apathy, by looking at changes in EBDM as a function of the disease. HDDM is used to integrate choice data and decision times, bringing both into a framework whereby the decision to accept or reject offers represents stochastic processes following certain drift rates to approach a decision boundary. Doing so may potentially illustrate important mechanisms for apathy in SVD.

Chapter 6 | Neural correlates of EBDM in SVD

Similar to the method used in Chapter 4, this chapter will investigate the associations between structural and diffusion MRI with behavioural data obtained from the EBDM task used in the preceding chapter.

Chapter 7 | General dicussion

Finally, the results from Chapters 2 to 6 will be summarised here, to be followed by a discussion providing a general review of their implications. This chapter will conclude by exploring areas of future work that can be carried out to build upon the findings in this thesis.

2 | Neuroimaging biomarkers of cerebral small vessel disease

2.1 Abstract

SVD is conventionally diagnosed using features detected on structural MRI. Some of these, for example WMH, are also observed in healthy ageing, albeit to a far less extent. This chapter explored the impact of SVD on structural, diffusion, and rs-fMRI. In this sample, SVD participants demonstrated smaller hippocampi and nucleus accumbens (ventral striatum) bilaterally on structural MRI. VBM indicated the presence of grey matter atrophy involving the right middle temporal gyrus, crus I of the left cerebellum, left precentral gyrus, and bilateral nucleus accumbens in SVD. Diffusion MRI analysis using two models, DTI and NODDI, demonstrated widespread reductions in white matter microstructural integrity in people with SVD. Finally, resting state functional connectivity changes that were apparent on initial analysis were all abolished by the addition of head motion as a covariate. These results shed some light into the spectrum of changes in the brain that are associated with SVD. They highlight the potential and pitfalls of different MRI modalities to act as neuroimaging biomarkers of the disease.

2.2 Introduction

SVD is often the end result of years of accumulating pathology in the aging brain (Erkkinen, Kim, & Geschwind, 2018). This has led to renewed interest in understanding the temporal and spatial sequence of changes in the brain that ultimately lead to disease (Di Luca et al., 2018). The diagnosis of SVD is often made based on features identified on MRI (Rost & Etherton, 2020). Relevant findings for lesions related to SVD have been described in two position papers, forming what are known as the STRIVE-1 and STRIVE-2 criteria (Duering et al., 2023; Wardlaw et al., 2013). Briefly, these provide standardised definitions of various neuroimaging biomarkers that can be observed in SVD, including small subcortical infarcts, WMH of presumed vascular origins, cortical superficial siderosis, and brain atrophy. One issue with diagnosing SVD is that conventional MRI, typically involving the use of 1.5 or 3 Tesla field strengths, often comes with significant limitations, chief amongst these being the inability at low field strengths to visualise the perforating arteries in which SVD pathology occurs (Benjamin, Viessmann, MacKinnon, Jezzard, & Markus, 2015). Due to this obstacle, identification of the disease often relies on detecting the sequelae of the underlying pathology such as WMH, enlarged perivascular spaces, or cerebral microbleeds, instead of direct observation of damaged blood vessels.

Structural MRI

To date, most of the widely-accepted neuroimaging biomarkers of SVD have revolved around features observed on structural MRI (Duering et al., 2023). Many of these are qualitative in nature, making them relatively straightforward to use but potentially limiting their reliability. For example, on the Fazekas scale, which is often used to classify WMH severity (Fazekas et al., 1987), the boundaries between different grades of severity are often subjective. This necessitates a judgment to be made about whether the areas of WMH observed are, for example, only beginning to show confluence (representing Grade 2) or are already confluent (i.e., Grade 3). A similar situation exists with brain atrophy, where different observers can reasonably disagree about whether one region is qualitatively showing a disproportionate amount of atrophy relative to other areas. Moreover, the significance of these qualitative findings remains debatable. In an early paper investigating the impact of WMH, no correlation was observed between neuropsychological function and the presence of WMH (Hunt et al., 1989). Since then, however, many other studies have shown a negative relationship between WMH burden and cognition (J. M. Biesbroek et al., 2016; Dufouil et al., 2009). One possible reason for these contradictory findings is the heterogeneous histopathology of WMH (Gouw et al., 2011). Different underlying pathological processes can lead to the same outcome, producing WMH. Another possible explanation has to do with lesion location. For example, Lampe et al. showed that WMH in the frontal lobe affected executive function, whereas the same feature, this time located in the parieto-temporal lobe, led to a decline in memory performance (Lampe et al., 2019).

In part due to the limitations of subjective clinical measures, attention has turned to various forms of quantitative volumetric analysis to inject some objectivity and reproducibility into the diagnostic process. Tools like BIANCA (Griffanti et al., 2016), LGA (lesion growth algorithm) (P. Schmidt et al., 2012), and W2MHS (Wisconsin White Matter Hyperintensities Segmentation Toolbox) (Ithapu et al., 2014), for example, allow automated segmentation of WMH and thus calculation of WMH volumes. These algorithms are not perfect, but they represent a step forward from the inter-rater variabilities arising from the use of visual rating scales (Vanderbecq et al., 2020).

Other than WMH, volumetric analytical approaches have also examined the impact of SVD on different subcortical structures. Most of the work have been focused on hippocampal volume, typically showing that it decreases as the burden of SVD increases (Etherton et al., 2020; M. Li et al., 2017; Small, Schobel, Buxton, Witter, & Barnes, 2011; A. G. W. van Norden et al., 2008). This is not entirely surprising because the hippocampus is vascularised by vessels with an average diameter of 0.5mm, precisely the sort of vessels affected in SVD (Perosa et al., 2020). However, the hippocampus is not the only subcortical structure whose volume is altered in SVD, with several reports demonstrating atrophy of the thalamus, caudate nuclei, and putamen (C.-H. Chen et al., 2023; Lambert et al., 2016; J. Zhao et al., 2023; W. Zhu et al., 2021). Many of these subcortical structures are involved in normal cognitive and behavioural processes. Therefore, atrophy of such structures might adversely impact domains such as memory and motivation, something that will be addressed in subsequent chapters of this thesis.

Understanding the spectrum of structural changes that occur in the brains of people with SVD need not just rely on quantifying WMH volume or the volumes of subcortical structures. An alternative approach utilises VBM to characterise voxel-wise alterations in grey matter structure (Ashburner & Friston, 2000). Using this technique, previous investigations on SVD patients attending neurology or memory clinics have reported a correlation between WMH volume and grey matter volumes in many areas including the dorsolateral prefrontal cortex, superior and middle temporal gyri, insula cortex, cingulate cortex, and superior frontal gyrus (Lambert et al., 2015; M. Li et al., 2017; Y. Li et al., 2023). What might be the explanation for this seemingly widespread involvement of different cortical regions in SVD? To a certain extent, these heterogeneous findings reflect the diversity of patient populations included in these reports. Whereas one study may recruit participants with some evidence of WMH on MRI but who are otherwise cognitively normal (J. Wang, Liang, et al., 2019), another might select to examine those who already meet the clinical threshold for (vascular) dementia (C. Liu, Li, Gui, et al., 2014). Nevertheless, in order to serve as a useful biomarker not just for diagnostic purposes but also for intervention trials, it might be prudent to emphasize testing of individuals who are at the early stages of the disease.

Diffusion MRI

Due to the complex relationship between features detected on structural MRI and cognitive decline, many researchers have turned to an alternative approach which is diffusion MRI (Nitkunan, Barrick, Charlton, Clark, & Markus, 2008). DTI is more sensitive to white matter damage and can be used to evaluate microstructural integrity within interconnected neural networks (Pasi, van Uden, Tuladhar, de Leeuw, & Pantoni, 2016). One of the most interesting findings using this approach was that damage to white matter tracts extended beyond areas that appear abnormal on structural MRI into normal-appearing white matter (NAWM) (O'Sullivan et al., 2001). The consequence of this was shown in a prospective cohort study among 444 non-demented elderly participants with SVD where loss of microstructural integrity in WMH and NAWM areas were associated with cognitive impairment (Tuladhar, van Norden, et al., 2015). Similarly, lower FA (a measure of white matter microstructural integrity) in the fronto-subcortical regions has been associated with depressive symptoms in elderly with SVD (van Uden et al., 2015). Motor impairments, too, appear to be correlated with diffusion parameters, as demonstrated in a study of 483 people with SVD in which severe loss of microstructural integrity predicted the development of mild Parkinsonian signs (de Laat et al., 2012). Throughout these, and many other DTI studies, damage to the white matter was indexed by reduced FA and increased MD (Gons et al., 2010, 2012; Pasi et al., 2015; van der Holst et al., 2013; A. G. W. van Norden, van Uden, de Laat, van Dijk, & de Leeuw, 2012).

Despite the sensitivity of DTI to tissue microstructural changes (Pierpaoli, Jezzard, Basser, Barnett, & Di Chiro, 1996), it is only able to provide a composite view representing the sum of contributions from individual compartments that make up a voxel. Hence, a reduction in FA may be due to several causes including reduced neurite density or increased dispersion of neurite orientation distribution (Beaulieu, 2009). This has led to the development of more sophisticated techniques for analysing diffusion MRI data such as NODDI, that utilise multi-component models to disentangle the contribution of each compartment (e.g., intra-neurite, extra-neurite, and free water fraction) in a voxel (H. Zhang et al., 2012).

In theory, these models should improve our understanding of microstructural alterations in SVD. Some evidence for this came from recent work by Konieczny et al. who compared the simple DTI model with two advanced, multi-shell, diffusion models namely diffusion kurtosis imaging (DKI) and NODDI (Konieczny et al., 2021). By performing standardised cognitive testing and 3T MRI which included multi-shell diffusion imaging on 50 sporadic and 59 genetically defined SVD patients, they were able to demonstrate that two DKI metrics (mean kurtosis and axial kurtosis) and one NODDI metric (extracellular volume fraction) in particular showed strong associations with processing speed performance, explaining more variance than the best performing DTI metric. To the best of our knowledge, however, no published study has directly investigated the impact of SVD on NODDI parameters relative to a healthy elderly population.

Resting state fMRI

SVD has also been associated with alterations in functional connectivity that can be detected on rs-fMRI. But the direction of change—increases or decreases in functional connectivity—has been contradictory (H. J. Kim et al., 2016; Kumar, Vipin, Wong, Ng, & Kandiah, 2020; Lawrence, Tozer, Stamatakis, & Markus, 2018; C. Liu, Li, Yin, et al., 2014). For example, in one report by Ding et al. examining changes in short- and long-range functional connectivity density, participants with SVD showed significantly decreased short-range functional connectivity in the left caudate nucleus, right middle and superior temporal gyrus, Rolandic operculum, and precentral gyrus (Ding et al., 2016). However, the same study also found increased short-range functional connectivity in the left angular and inferior parietal gyri. As for long-range connections, SVD participants had increases in the right precentral and middle frontal gyri. The authors reasonably concluded that the presence of WMH may negatively affect the efficiency of neural transmission leading to functionally reduced connectivity. However, trying to explain why connectivity can be increased in a diseased state appeared to be more challenging, requiring these changes to be interpreted as a compensatory mechanism for reductions in functional connectivity identified in other regions of the brain (Ding et al., 2016).

In addition to the direction of change in functional connectivity, one other question worth asking is which changes were reliably and consistently observed in SVD? A recent meta-analysis attempted to address this issue by analysing the reproducibility of abnormal brain regions in 20 studies (Y. Li et al., 2023). Among the included studies, patients with SVD demonstrated increased functional connectivity clustered in the left angular gyrus. Meanwhile, they also showed reduced functional connectivity clustered around the bilateral anterior cingulate cortex, left medial prefrontal cortex, and right Rolandic operculum. These regions also contain areas that are part of two important resting state networks namely the default mode network and salience network, both of which have been shown to be affected in SVD (Dey, Stamenova, Turner, Black, & Levine, 2016; Schulz, Malherbe, Cheng, Thomalla, & Schlemm, 2021; ter Telgte et al., 2018). One precautionary note regarding the rs-fMRI literature in SVD originates from a systematic review of 44 articles which concluded that current knowledge is limited by bias, confounding, and significant methodological differences particularly in data cleaning techniques (Schulz et al., 2021).

This chapter seeks to address some of the issues related to the use of imaging-derived biomarkers in SVD. After first confirming that the SVD group had a significantly higher volume of WMH compared to healthy elderly controls, it considers the following questions:

1. Is SVD associated with altered volumes of subcortical structures like the thalamus, caudate nucleus, putamen, globus pallidum, hippocampus, amygdala, and nucleus accumbens (ventral striatum)?
2. Which grey matter areas demonstrate abnormalities in volume as detected with VBM?
3. Can we apply DTI and NODDI models on diffusion MRI data to examine how SVD affects white matter microstructural integrity? If so, how do the outputs from the two models differ from each other and, perhaps more importantly, which one is better?
4. What is the impact of SVD on resting state functional connectivity?

2.3 Methods

2.3.1 Participants

Fifty-seven SVD participants aged between 50-80 years (32 males, 25 females) were recruited through the Memory Clinic at the John Radcliffe Hospital in Oxford. Patients were referred to the clinic for investigation of cognitive complaints. They were included on the basis of WMH considered radiologically to be greater than expected for age being observed on clinical (structural) MRI scans. Patients were excluded from the study if they had other clinical neurological diagnoses such as PD, AD, or epilepsy. Fifty-seven age-matched healthy controls were recruited through a volunteer database of people who were willing to be involved in research. Cognitive function screening was carried out using the Addenbrooke's Cognitive Examination-III (ACE-III) (Hsieh, Schubert, Hoon, Mioshi, & Hodges, 2013).

Permission for this study was obtained from the University of Oxford Ethics Committee (RAS ID: 248379, Ethics Approval Reference: 18/SC/0448). All subjects provided written consent in accordance with the Declaration of Helsinki and were offered monetary compensation in return.

2.3.2 MRI acquisition

Structural, diffusion, and functional MRI scans were obtained using a 3T Siemens Verio scanner at the John Radcliffe Hospital in Oxford. Structural images included: T1-weighted sequence (MPRAGE, field of view: 208 x 256 x 256 matrix, TR 2000 ms, TE 1.94 ms, TI 880 ms, flip angle 8°, voxel-size 1.0 mm isotropic) and T2-fluid attenuated inversion recovery, or T2-FLAIR, sequence (TR 5000 ms, TE 397 ms, TI 1800 ms, flip angle 120°, voxel-size 1.1 x 1.0 x 1.0 mm). Diffusion-weighted images were obtained using an echo planar sequence (TR 3600 ms, TE 92 ms, voxel size 2.0 x 2.0 x 2.0 mm) with opposite phase encoding directions (AP and PA) to allow for more robust distortion correction (AP: 104 directions, 8 b=0 s/mm2, 50 b=1000 s/mm2, 50 b=2000 s/mm2 and PA: 7 directions, 4 b=0 s/mm2). Resting-state fMRI images were acquired as follows: field of view: 88 x 88 x 64 matrix, TR 735 ms, TE 39 ms, flip angle 52°, voxel size 2.4 x 2.4 x 2.4 mm, GP-EPI with multi-band acceleration factor 8).

2.3.3 MRI pre-processing and analysis

2.3.3.1 Structural

Segmentation and quantification of WMH

Segmentation and quantification of WMH are important initial steps to verify that the two groups being compared in this study actually differ in term of their cerebrovascular disease burden. Here, I used BIANCA (Griffanti et al., 2016) described in **Chapter 1** on brain-extracted T2-FLAIR images using additional information from T1-weighted images for each participant. BIANCA requires a training dataset with pre-classified voxels and this was obtained from the UK Biobank Brain Imaging Image Processing Pipeline website (www.fmrib.ox.ac.uk/datasets/ukbiobank/bianca_class_data_labels) (Alfaro-Almagro et al., 2018). The output of BIANCA is a map representing the probability per voxel of being WMH. This was binarized using a threshold value of 0.8, generating a new map where voxels classified as WMH have a value of 1.0 and all other voxels have a value of 0. For each participant, the volume of WMH was calculated using *fslstats*, and an independent two-sample t-test was conducted to look for differences between the SVD and healthy control groups.

Calculation of subcortical volumes

Subcortical volumes were calculated by running the script *run_first_all* in FSL on brain-extracted T1-weighted images. This resulted in mesh and volumetric outputs for the following subcortical structures (with separate labels for left and right sides where applicable): thalamus, caudate, putamen, globus pallidum, hippocampus, amygdala, nucleus accumbens, and brainstem. The relevant output in this step was a single image showing all the structures that have been segmented and their separate labels. For each participant, the volume of each subcortical structures was then calculated by running *fslstats* on this output image. Group differences for the subcortical structures were then determined using independent two-sample t-tests with Bonferroni correction.

VBM

FSL-VBM was used to test for voxel-wise differences in the local grey matter volume between participants with SVD and healthy controls. This script first performs brain extraction on T1-weighted images before segmenting them into grey matter, white matter, and CSF. Grey matter partial volume images are then aligned to Montreal Neurological Institute's 152 brain template (MNI152) standard space using FLIRT (FMRIB's Linear Image Registration Tool) and FNIRT (FMRIB's Non-linear Image Registration Tool), and a study-specific grey matter template is then created by averaging the aligned images. In the next step, grey matter images from all participants are non-linearly registered to the study-specific template, taking into account the contraction or enlargement due to the non-linear component of the transformation by multiplying each voxel with the Jacobian of the warp field. Finally, all individual images are concatenated into a 4D image which is smoothed using a sigma 3 mm Gaussian kernel.

Group comparison was carried out using the *randomise* function with 5000 permutations. A general linear model (GLM) specified grey matter volume as a dependent variable, group identity as an independent variable, and age, sex, and years of education as covariates. Two different contrasts were used to test for areas where healthy controls had higher grey matter volumes than SVD participants, and vice versa. Results were corrected for multiple comparisons with Threshold Free Cluster Enhancement (TFCE) and considered significant at α = 0.05.

2.3.3.2 Diffusion

Pre-processing and fitting of diffusion models

Diffusion-weighted images were corrected for susceptibility induced distortions using *topup* in FSL (J. L. Andersson, Skare, & Ashburner, 2003). The output from *topup* was then passed into the *eddy* tool which corrects for eddy current and subject movement (J. L. R. Andersson & Sotiropoulos, 2016). Then, two different models, namely DTI and NODDI, were used to analyse the diffusion data. Fitting of the DTI model was done with *dtifit*, whereas estimation of the NODDI model was carried out using the Accelerated Microstructure Imaging via Convex Optimization (AMICO) tool (https://github.com/daducci/AMICO). AMICO provides an effective way to accelerate the fitting of biophysical models like NODDI while preserving its accuracy and precision (Daducci et al., 2015).

TBSS

Voxel-wise statistical analyses of the diffusion data from the abovementioned two models were done with TBSS. FA images from all participants were first eroded slightly and had the end slices zeroed to remove outliers. Then, all images were non-linearly aligned to a 1 x 1 x 1 mm standard space using the FMRIB58_FA standard-space image as the target. This allowed for the creation of a standard-space version of each subject's FA image. These were then merged into a 4D image, skeletonised, and thresholded with a value of 0.2. Skeletonised images for all other diffusion metrics (MD, NDI, ODI, and ISOVF) were then generated using the *tbss_non_FA* script. Finally, *randomise* was used to test for differences between the two cohorts using the same models as described for VBM.

2.3.3.3 Resting state fMRI

Resting state connectivity analysis was conducted in MATLAB 2020b using CONN Toolbox version 21.a running SPM12 (Whitfield-Gabrieli & Nieto-Castanon, 2012). The default data pre-processing pipeline was used which included realignment and unwarping, slice-timing correction, outlier detection, direct tissue-type segmentation, and MNI normalisation. Spatial smoothing with a Gaussian kernel of 8 mm full width half maximum was applied to improve signal-to-noise ratio. Denoising was carried out using linear regression of confounding effects such as noise components from white matter and CSF (8 parameters each), head motion (12 parameters i.e. 3 translation, 3 rotation, and their first-order derivatives) in addition to scrubbing of identified outliers. A temporal band-pass filter of 0.008-0.09 Hz was also applied to the data.

The next step involved running a whole-brain ROI-to-ROI analysis using 32 atlas-defined ROIs representing common resting state networks such as the default mode, salience, dorsal attention, frontoparietal, and sensorimotor networks. A GLM was employed to look for differences in resting state connectivity between SVD and healthy controls while accounting for age, sex, and crucially, subject motion. Significance testing was done with TFCE using a corrected connection threshold of $p < 0.05$.

2.4 Results

2.4.1 Demographics and WMH volume

Participants with SVD did not differ significantly from healthy controls in terms of age or sex ratio but had spent fewer years in full time education (Table 2.1). People with SVD were also more likely to be hypertensive compared to healthy controls. In terms of their cognitive status, although the mean ACE-III score for participants with SVD was statistically smaller than that for healthy controls, both these scores were still within normal limits (Beishon et al., 2019; Elamin, Holloway, Bak, & Pal, 2015; Hsieh et al., 2013; McCarthy et al., 2023).

	Control (n = 57)	SVD (n = 57)	
Measure	Mean ± std	Mean ± std	p-value
Age (years)	66.72 ± 6.83	68.93 ± 8.85	0.138
Sex (M/F)*	22 / 35	32 / 25	0.061
Education (years)	17.09 ± 6.38	14.16 ± 5.90	**0.012**
Hypertensive (Yes/No)*	6 / 51	23 / 34	**<.001**
Total ACE-III (range 0-100)**	97.21 ± 2.59	91.46 ± 8.37	**<.001**
Cantril Ladder (range 0-10)	8.02 ± 1.43	7.02 ± 1.63	**<.001**
WMH Volume (ml)	10.80 ± 7.71	39.23 ± 28.29	**<.001**

Table 2.1: **Demographic and questionnaire measures.** ACE-III = Addenbrooke's Cognitive Examination III, * Chi-square test, ** Total ACE-III score was not available for 1 Control and 1 SVD participant

As expected, WMH volume as computed by BIANCA was significantly greater in those with SVD compared to healthy controls (Table 2.1 and Figure 2.1). Crucially, however, WMHs were present in all participants, albeit to a lesser extent in healthy controls. The average volumes of WMH for Control (10.80 ± 7.71 ml) and SVD (39.23 ± 28.29 ml) participants were comparable to cohorts used in other studies. In the Radboud University Nijmegen Diffusion Tensor and Magnetic resonance Cohort (RUN DMC) study, for example, average WMH volume was 6.6 ± 3.3 ml in non-demented individuals, and 45.4 ± 23.9 ml in those with vascular dementia (van Uden et al., 2015). Similarly, in a study of non-demented UK Biobank participants, median WMH volume was found to be 2.15 ± 3.01 ml (Cox et al., 2019).

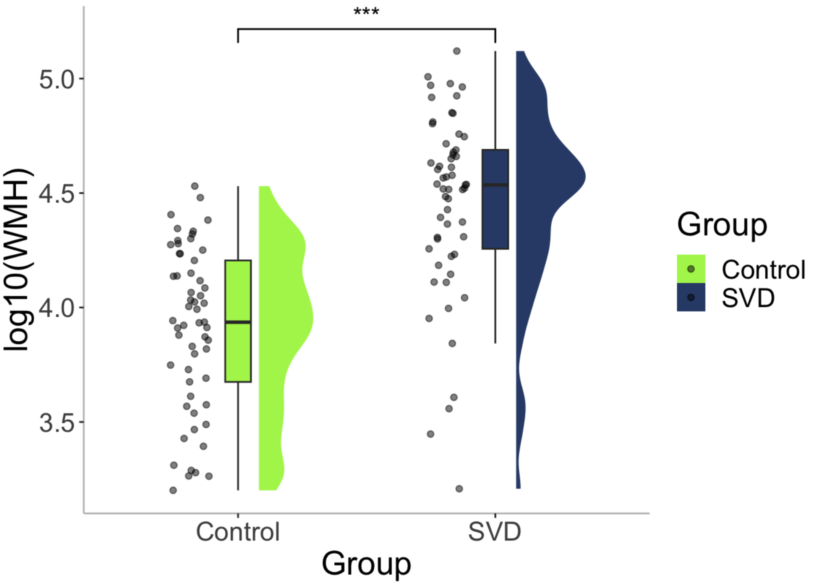


Figure 2.1: **WMH volume in healthy controls and SVD.** Significantly higher WMH volume was found in the SVD group relative to healthy controls. *** = p < 0.001

2.4.2 Smaller hippocampi and nucleus accumbens bilaterally in SVD

Comparison of subcortical volumes revealed significant differences only in the hippocampi and nucleus accumbens bilaterally between the two groups, with smaller volumes found in SVD patients (Table 2.2). However, none of these initial results survived correction for multiple comparisons using the Bonferroni method (α corrected = 0.05/14 = 0.00357).

2.4.3 VBM reveals frontal, temporal, and bilateral nucleus accumbens atrophy

Analysis of T1-weighted images using VBM revealed five clusters where grey matter volumes differed significantly between the two groups. After including age, sex, and years of education as covariates, SVD patients exhibited more grey matter atrophy in the right middle temporal gyrus, left cerebellum crus I, left precentral gyrus, as well as the left and right nucleus accumbens (Figure 2.2 & Table 2.3).

		Control (n = 57)	SVD (n = 57)	
Structure	Side	Mean ± std	Mean ± std	p-value
Accumbens	Left	617.70 ± 134.79	549.00 ± 165.76	**0.017**
	Right	493.38 ± 147.52	424.73 ± 163.34	**0.020**
Amygdala	Left	1689.12 ± 267.50	1673.28 ± 333.29	0.780
	Right	1673.23 ± 298.84	1570.44 ± 357.54	0.099
Caudate	Left	4371.95 ± 454.94	4208.86 ± 616.09	0.111
	Right	4572.84 ± 460.77	4506.04 ± 561.98	0.489
Hippocampus	Left	4800.92 ± 596.15	4519.73 ± 755.63	**0.029**
	Right	4915.01 ± 553.48	4574.79 ± 742.35	**0.006**
Pallidum	Left	2215.12 ± 233.83	2234.838 ± 394.42	0.746
	Right	2226.37 ± 234.67	2202.99 ± 421.21	0.715
Putamen	Left	6012.83 ± 667.36	5952.59 ± 835.42	0.671
	Right	6001.50 ± 700.05	5879.99 ± 817.12	0.396
Thalamus	Left	9677.56 ± 715.99	9384.28 ± 1118.94	0.098
	Right	9480.72 ± 650.15	9186.22 ± 1004.29	0.066

Table 2.2: **Comparison of subcortical volumes between healthy controls and SVD.** Although the hippocampi and nucleus accumbens were smaller in SVD on pairwise analysis (highlighted), none of these outcomes survived correction for multiple comparisons.

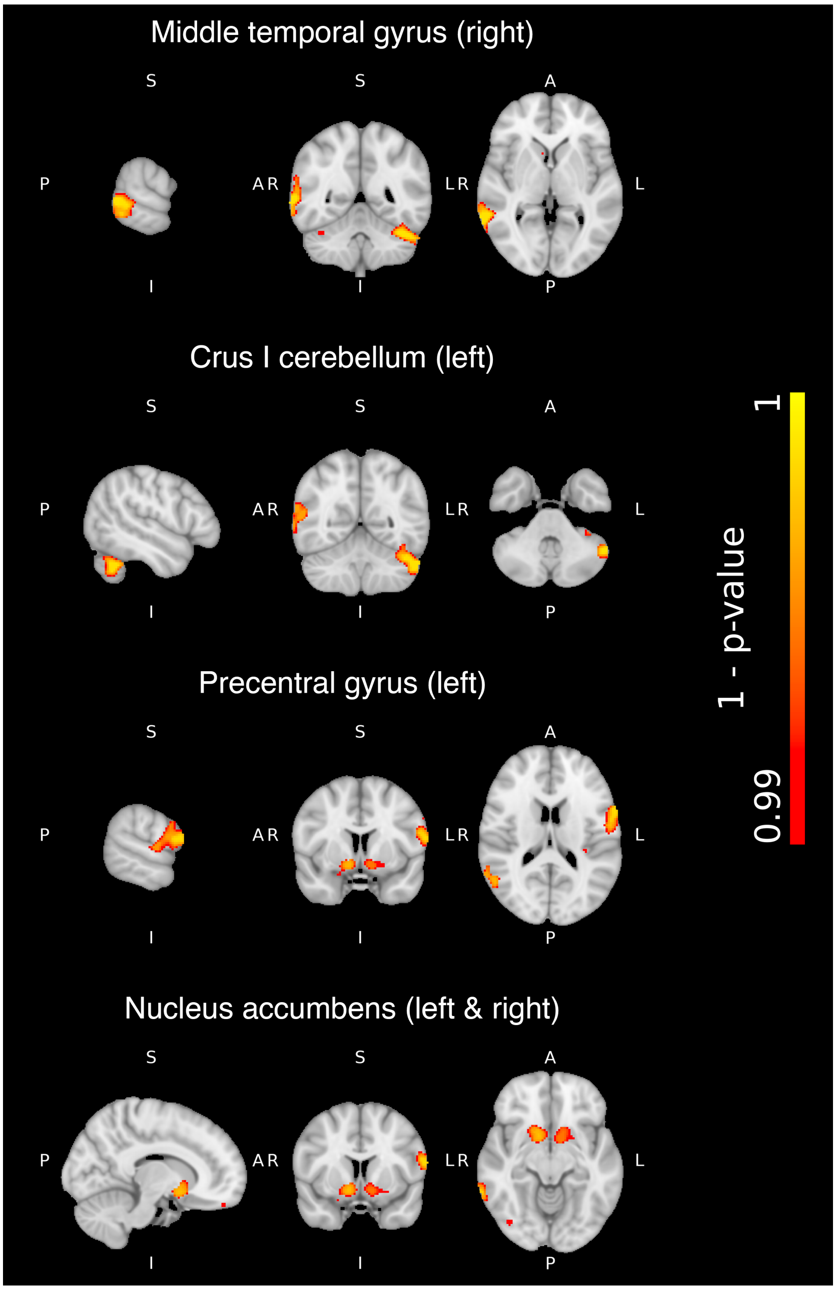


Figure 2.2: **Results of the VBM analysis showing areas where SVD participants had lower grey matter volumes compared to healthy elderly controls.** Grey matter atrophy was demonstrated in several clusters namely the right middle temporal gyrus, crus I of the left cerebellum, left precentral gyrus, and the nucleus accumbens bilaterally. Threshold for clusters set at $p < 0.01$ for clarity of visualisation.

-	No. of voxels	1 - p max	MAX X (vox)	MAX Y (vox)	MAX Z (vox)	COG X (vox)	COG Y (vox)	COG Z (vox)
Middle temporal gyrus (right)	839	0.999	12	38	37	14.2	37.7	39.8
Crus I cerebellum (left)	787	0.999	70	35	17	66.6	36.7	20.7
Precentral gyrus (left)	609	0.999	76	66	44	74.8	62.3	44
Nucleus accumbens (right)	420	0.997	39	67	31	37.1	69.1	30
Nucleus accumbens (left)	302	0.995	50	65	31	52.5	68.3	30.6

Table 2.3: **VBM cluster information.** Cluster information includes the number of voxels in the significant cluster, its significance value, X/Y/Z coordinates of the maximum intensity voxel, as well as X/Y/Z coordinates of the Centre of Gravity (COG) representing the weighted average of the coordinates by intensities within each cluster.

2.4.4 Widespread reduction in white matter tract integrity with DTI and NODDI

To investigate the impact of SVD on the microstructural integrity of white matter tracts in the brain, TBSS was performed on diffusion MRI data that were modelled using two different approaches: DTI and NODDI (see Chapter 1 for details on TBSS and the individual models).

This analysis revealed widespread reductions in white matter tract integrity in SVD participants compared to healthy elderly controls (Figure 2.3 & 2.4). Identified changes involved numerous association pathways including the arcuate fasciculus, acoustic radiation, anterior thalamic radiation, cingulum, corticospinal tract, forceps major, forceps minor, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, middle longitudinal fasciculus, optic radiation, and superior longitudinal fasciculus.

Within these white matter tracts, the direction of change was biologically plausible for most of the diffusion parameters. Specifically, with the DTI model, people with SVD had lower FA and higher MD compared to control participants (Figure 2.3A & 2.3B, respectively). Using the NODDI model revealed lower NDI and higher ISOVF in SVD (Figure 2.4A & 2.4B, respectively). One NODDI metric i.e., ODI, showed alterations in both directions. Here, SVD participants had lower ODI values than controls in the corticospinal tract, frontal aslant tract, and superior thalamic radiation bilaterally (Figure 2.4C). In contrast, they exhibited higher ODI values in the left inferior fronto-occipital fasciculus, left middle longitudinal fasciculus, and left optic radiation (Figure 2.4D).

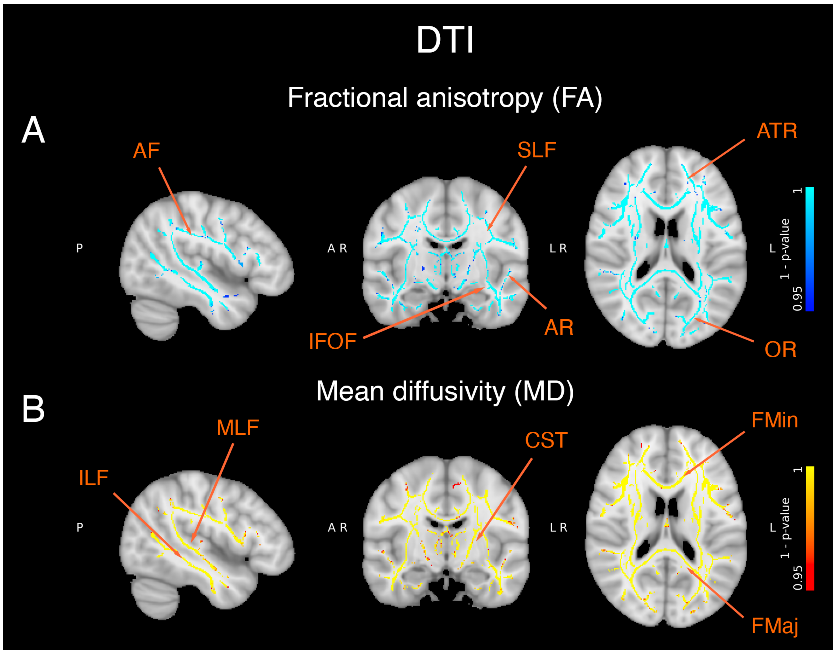


Figure 2.3: **Impact of SVD on white matter microstructural integrity as identified with DTI.** **(A)** SVD participants had lower FA (shown in blue) in several white matter tracts compared to healthy elderly controls. **(B)** Many of the same tracts also demonstrated higher MD in SVD participants (shown in red-yellow). AF = arcuate fasciculus, AR = acoustic radiation, ATR = anterior thalamic radiation, CST = corticospinal tract, FMaj = forceps major, FMin = forceps minor, IFOF = inferior fronto-occipital fasciculus, ILF = inferior longitudinal fasciculus, MLF = middle longitudinal fasciculus, OR = optic radiation, SLF = superior longitudinal fasciculus.

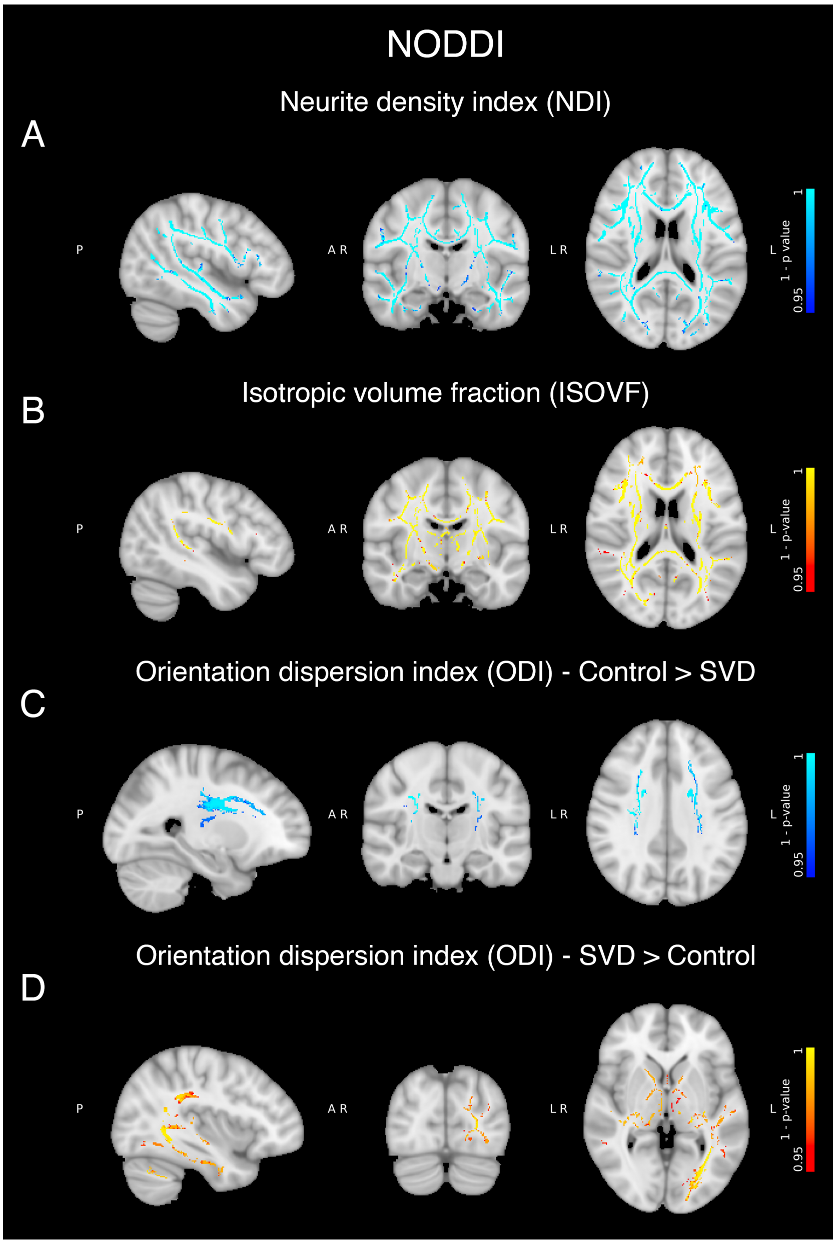


Figure 2.4: **Impact of SVD on white matter microstructural integrity as detected with NODDI.** SVD participants had lower NDI **(A)** and higher ISOVF **(B)** compared to healthy elderly controls. ODI was the only NODDI metric that showed a difference in the direction of change for different tracts. **(C)** Lower ODI in SVD was seen in the corticospinal tract, frontal aslant tract, and superior thalamic radiation. **(D)** Higher ODI in SVD was observed in the inferior fronto-occipital fasciculus, middle longitudinal fasciculus, and optic radiation, all in the left hemisphere.

To quantify the extent of changes identified on diffusion MRI, these alterations were expressed as percentages of the white matter skeleton. In total, there were 127,785 non-zero voxels that constituted the white matter skeleton. As shown in Table 2.4, FA values were significantly different between the two cohorts in 115,160 out of those non-zero voxels, representing 90.12% of the white matter skeleton. Meanwhile, MD values were altered in 113,437 voxels, or 88.77%. The corresponding values for NDI and ISOVF were 109,635 (85.80%) and 81,647 (63.89%), respectively. ODI was lower in SVD in 14,705 voxels (11.51%) but higher in 67,874 voxels, or 53.12% of the white matter skeleton.

DTI		
Diffusion metric	No. of affected voxels (out of 127,785)	Percentage of TBSS skeleton (%)
FA	115,160	90.12
MD	113,437	88.77
NODDI		
Diffusion metric	No. of affected voxels (out of 127,785)	Percentage of TBSS skeleton (%)
NDI	109,635	85.80
ISOVF	81,647	63.89
ODI (Control > SVD)	14,705	11.51
ODI (SVD > Control)	67,874	53.12

Table 2.4: **Extent of involvement of the TBSS white matter skeleton.** DTI metrics were significantly different in a higher percentage of the TBSS white matter skeleton compared to parameters obtained via NODDI.

2.4.5 Apparent changes in resting state connectivity driven by motion

Analysis of resting state fMRI data using age and sex as covariates revealed numerous regions where SVD participants had reduced functional connectivity compared to healthy elderly controls, together with a few areas where connectivity was increased in SVD (Figure 2.5A). Out of a possible 13,366 connections between 164 regions of interest (ROI), 18 clusters were formed when ROIs were sorted using hierarchical clustering. These clusters spanned multiple areas and included regions that were adjacent to each other as well as connections between remote parts of the brain. For example, cluster 1 was made up of 11 ROIs and 10 different connections involving the anterior and posterior cerebellum with the right inferior frontal gyrus, right orbitofrontal cortex, right middle temporal gyrus, and right superior temporal gyrus (Figure 2.6).

Crucially, despite the inclusion of motion correction in the pre-processing pipeline, there was still a significant difference in motion parameters between the SVD and control groups, characterised by an increase in framewise displacement in the former compared to the latter (Figure 2.7). Hence, when motion was added as a covariate to the initial analysis, all functional connectivity changes previously observed disappeared (Figure 2.5B). This strongly suggests that these apparent changes were primarily driven by group differences in motion parameters.

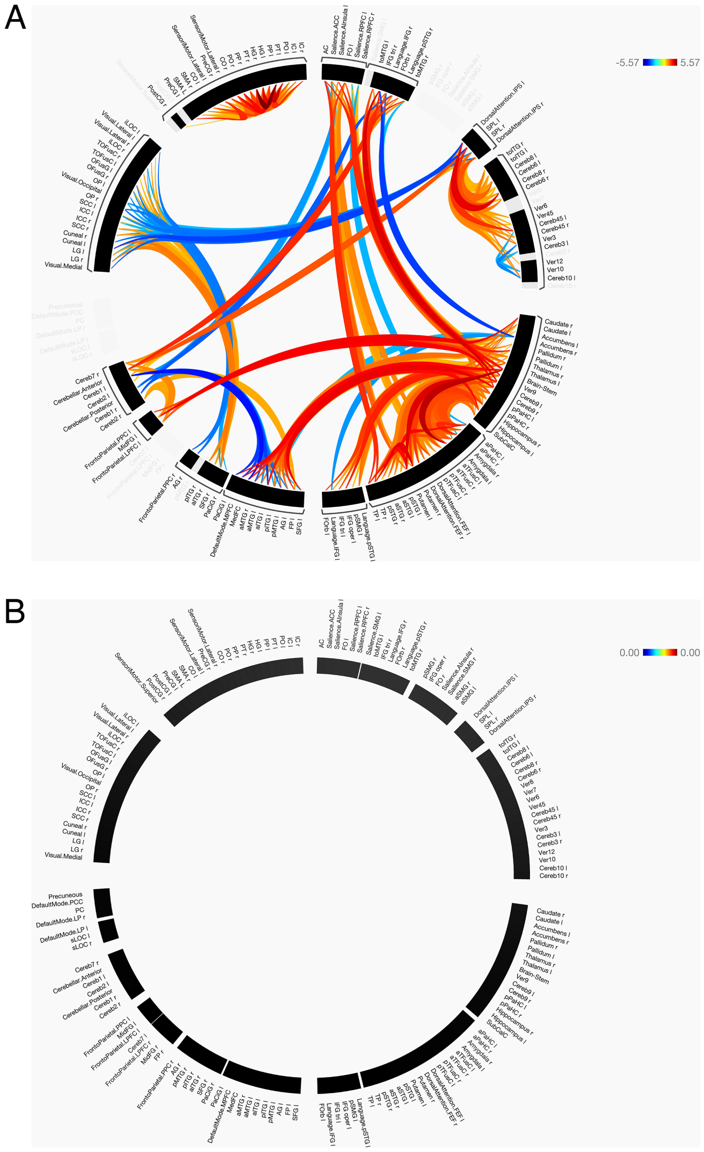


Figure 2.5: **Connectome rings showing the effect of adding motion as a covariate on functional connectivity changes. (A)** When age and sex were used as covariates, functional connectivity changes were observed in many brain regions. **(B)** Adding motion as a third covariate abolished all these apparent changes.

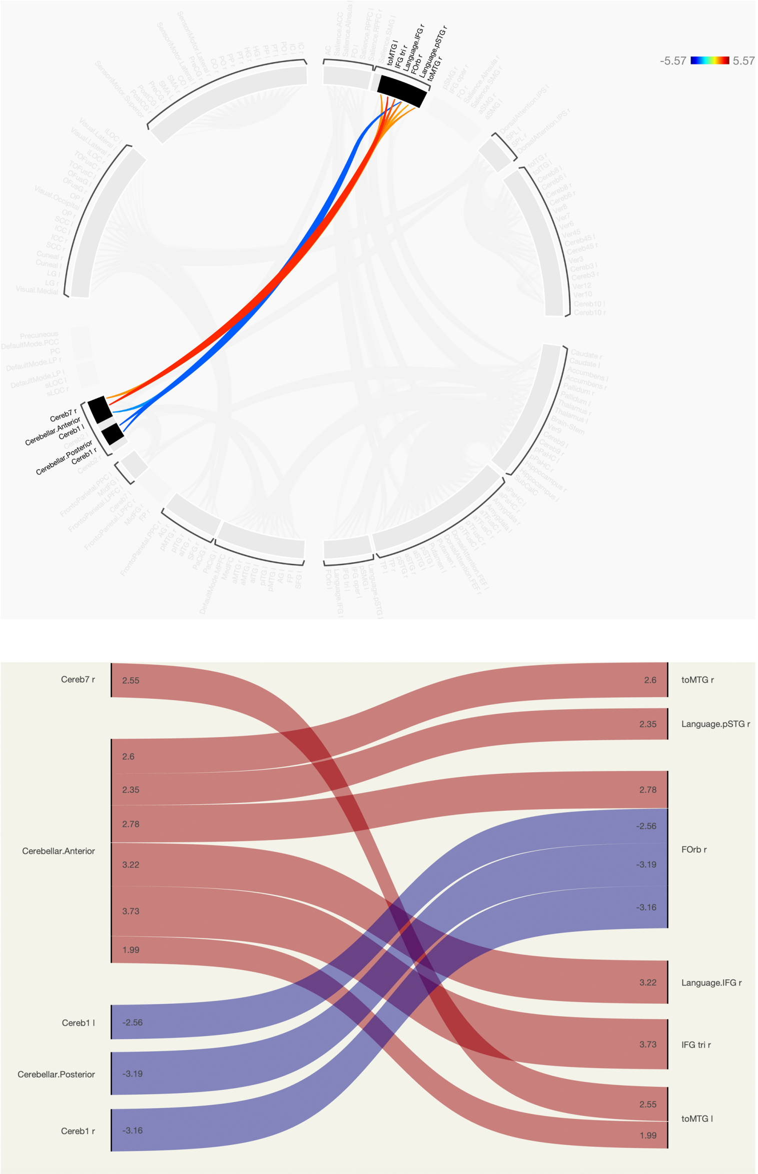


Figure 2.6: **Detail of Cluster 1 from the initial functional connectivity analysis.** The top image shows a connectome ring with ROIs that make up Cluster 1 highlighted. The bottom image gives more details about which areas were connected to each other (red = stronger connectivity in Control, blue = stronger connectivity in SVD).

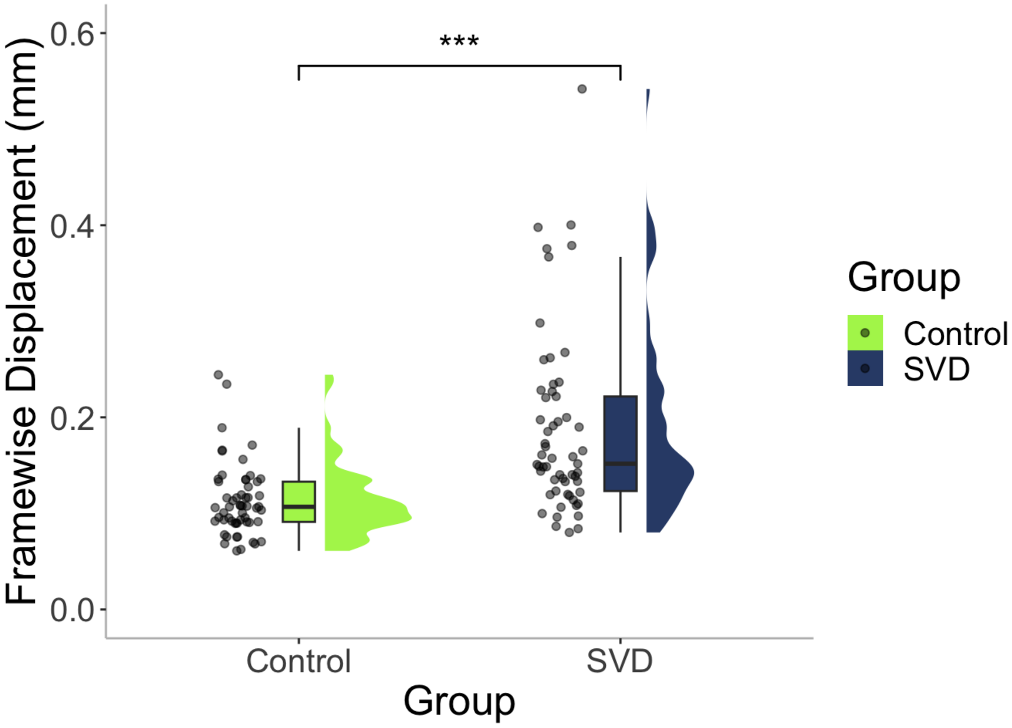


Figure 2.7: **Framewise displacement of rs-fMRI data.** Participants in the SVD group had more motion during their scans compared to those in the control group, making it necessary to include motion as a covariate in the functional connectivity analysis.

2.5 Discussion

This chapter examined the impact of SVD on the brain as detected on structural, diffusion, and rs-fMRI imaging. Structural MRI was used to determine how the two study cohorts differed in terms of WMH volume, subcortical volumes, as well as location and degree of grey matter atrophy. As expected, SVD participants had significantly larger WMH volumes as computed by BIANCA compared to healthy elderly controls. They also showed significantly smaller hippocampi and nucleus accumbens bilaterally although these set of results did not meet the threshold for statistical significance after correcting for multiple comparisons. In terms of grey matter atrophy, people with SVD had lower grey matter volumes in the right middle temporal gyrus, crus I of the left cerebellum, left precentral gyrus, and the nucleus accumbens bilaterally.

Diffusion MRI was analysed in two ways: the standard DTI model and a multi-compartment model called NODDI. In the DTI model, SVD participants demonstrated widespread reductions in microstructural integrity as evidenced by lower FA and higher MD values throughout large parts of the white matter skeleton. Affected tracts included the arcuate fasciculus, acoustic radiation, anterior thalamic radiation, cingulum, corticospinal tract, forceps major, forceps minor, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, middle longitudinal fasciculus, optic radiation, and superior longitudinal fasciculus.

A slightly more complex picture emerged when the NODDI model was used. Two of the three parameters, NDI and ISOVF, showed similar alterations to DTI, whereby people with SVD had lower NDI and higher ISOVF throughout large parts of their white matter skeleton. The ODI metric, however, exhibited differences in both directions; some tracts like the corticospinal tract, frontal aslant tract, and superior thalamic radiation showed lower values in SVD, whereas other tracts like the left inferior fronto-occipital fasciculus, left middle longitudinal fasciculus, and left optic radiation had higher values in SVD. To gain a sense of how widespread these changes were, the DTI metrics FA and MD identified significant differences in 90.12% and 88.77% of the white matter skeleton, respectively. Meanwhile, the NODDI metrics NDI and ISOVF demonstrated significant changes in 85.80% and 63.89% of the area studied. As for ODI, SVD participants had lower values in 11.51% of the white matter skeleton, and higher values in 53.12%.

In terms of rs-fMRI, the initial analysis (using age and sex as covariates) identified numerous ROIs where functional connectivity was either increased or decreased in SVD. Due to significant differences in motion between the SVD and control groups, this measure was added as a third covariate in the analysis. Addition of the motion parameter abolished all functional connectivity changes previously observed, strongly suggesting that these apparent differences were primarily driven by motion.

Significance of structural MRI changes

Although WMH are one of the features of SVD on MRI, they also exist in healthy elderly people. In routine clinical practice, the distinction between healthy aging and SVD can seem arbitrary at times, because it is difficult to know how much WMH is too much for a given person's age. This underlines the importance of finding other ways to support the diagnosis of SVD.

In this study, analysis of subcortical structures revealed smaller volumes of the hippocampi and nucleus accumbens bilaterally in SVD. The hippocampus finding agrees with some previous work showing, for example, that increased WMH burden correlated with selective degeneration of hippocampal subfields (Etherton et al., 2020). Due to the important role played by the hippocampus in memory (Fallon et al., 2016; Lisman et al., 2017; Voss, Bridge, Cohen, & Walker, 2017), it would be interesting to investigate whether these changes in hippocampal volumes in SVD are associated with poorer memory performance (explored in more detail in Chapter 3 and Chapter 4 of this thesis). The nucleus accumbens is an important part of the ventral striatum and acts as a key brain region for processing of reward and motivation signals (Salgado & Kaplitt, 2015). Dysfunction of the nucleus accumbens may theoretically lead to the development of apathy (Le Heron, Apps, & Husain, 2018), a subject that will be tackled later in Chapter 5 and Chapter 6 of this thesis.

Apart from the nucleus accumbens, VBM also demonstrated atrophy of the right middle temporal gyrus, crus I of the left cerebellum, and left precentral gyrus. The left middle temporal gyrus is postulated to subserve lexical-semantic and conceptual semantic dimensions of language (Lau, Phillips, & Poeppel, 2008; Patterson, Nestor, & Rogers, 2007). In general, the language domain is not typically considered to be affected in early stages of SVD. Of course, the significance of language extends far beyond the simple understanding and production of speech. Deficits in working memory may arise due to language impairments, as shown in a meta-analysis of 21 studies comparing visuospatial working memory performance in children with specific language impairment compared to typically developing children (Vugs, Cuperus, Hendriks, & Verhoeven, 2013).

In the cerebellum, there is some evidence that lobule crus I on the left side, in conjunction with the medial parietal cortex and right hippocampus, plays a role in place-based navigation (Igloi et al., 2015). Other studies have also demonstrated the role of the crus I lobule in cognitive and visuomotor functions (Balsters et al., 2010; Stoodley & Schmahmann, 2009; Sugihara, 2018). These reports indicate that the cerebellum is not just involved in motor processes but also cognitive ones. Meanwhile, the precentral gyrus encapsulates the primary motor cortex and serves as the origin of the corticospinal, corticobulbar, and corticorubral tracts (Lemon, 2008). Atrophy of this region may therefore affect motor performance and perhaps result in the gait impairment that can be a feature of SVD.

Impact of diffusion MRI changes

The results of the diffusion analysis revealed that damage caused by SVD extends beyond what can be captured on conventional structural MRI modalitie (O'Sullivan et al., 2001). The finding that multiple white matter tracts were affected in SVD may help to explain why SVD is associated not just with perilesional effects in the brain, but also with remote effects such as cortical thinning, possibly due to disconnection of these white matter tracts (ter Telgte et al., 2018).

Of the two models compared in this study, DTI metrics were able to detect changes in a larger percentage of the TBSS skeleton compared to NODDI measures. However, establishing what the ground truth is can be challenging. In other words, how do we confirm which white matter tracts are affected in SVD and to what extent? Are the DTI measures 'better' than NODDI because they are more sensitive to damage that is occurring in the white matter skeleton or are they the result of false positives? In theory, using a multicompartment model like NODDI should result in a better understanding of what is responsible for the changes demonstrated on diffusion MRI. To test this hypothesis, Konieczny et al. compared the performance of DTI with NODDI and diffusion kurtosis imaging (DKI), another multi-shell diffusion model, by assessing their associations with processing speed performance (Konieczny et al., 2021). Here, the strongest associations were found for DKI and NODDI metrics ($R^2 = 18\%$), with both explaining more variance in processing speed performance than the best DTI metric ($R^2 = 12\%$). Future work will be necessary to examine the reproducibility of these findings as well as the associations with other cognitive domains like executive function and working memory.

Resting state fMRI analysis

Using resting state fMRI data, numerous changes in functional in functional connectivity were identified in this study, involving different resting state networks like the default mode, frontoparietal, salience, and sensorimotor networks. However, this was only true when the analysis was carried out using age and sex as covariates. In reality, BOLD signal fluctuations that are the foundation of functional connectivity analyses may arise not just from alterations in neuronal activity, but also due to imperfections in the MRI hardware (e.g. magnetic field inhomogeneities), and more importantly, physiological noise including the effects of breathing and head motion. Head motion, in particular, has been shown to have significant, systematic effects on resting state fMRI network measures (Maknojia, Churchill, Schweizer, & Graham, 2019; Van Dijk, Sabuncu, & Buckner, 2012).

A recent systematic review examined functional connectivity changes in SVD (Schulz et al., 2021). It found 44 reports relevant to the research question, although the risk of bias and heterogeneity of results were judged to be moderate to high. Although the majority of studies indicated that SVD was associated with lower functional coupling on a global scale (J. Wang, Chen, et al., 2019; Yi et al., 2015; Y. Zhu et al., 2020), several studies found the opposite pattern i.e., higher functional connectivity in SVD (Park, Byeon, Lee, Kim, & Park, 2020; Shi et al., 2017). One reason for these conflicting findings may be the difficulty in controlling for the effects of head motion. Indeed, in this study, connectivity changes were identified involving brain regions with hitherto no known connections with each other and in different directions (both increased and decreased functional coupling). Therefore, in agreement with previous literature on the effects of head motion on resting state fMRI (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012; Satterthwaite et al., 2012), random head motion may be a plausible explanation for the above findings.

Study limitations

This study had several limitations that may affect the interpretation of measured differences in MRI metrics between the two cohorts. First, the sample size was relatively small for a study on neuroimaging biomarkers. In contrast to the 57 participants per group used in this study, other projects have often involved much larger numbers of participants, for example, around 500 people in the RUN DMC cohort (A. G. van Norden et al., 2011) and 5,800 individuals in the Rotterdam Scan Study (Ikram et al., 2015). Second, the Control group used may not be truly representative of the general population, being comprised of volunteers in very good health and with high levels of education. Third, the two cohorts used were not matched in terms of the prevalence of hypertension, an important confounding factor for vascular cognitive impairment in general. Fourth, the metrics obtained from both cohorts may also have been influenced by co-existing neurodegeneration. Finally, it can be argued that the two groups did not truly differ from each other since the WMH volumes were somewhat similar between Control and SVD participants (Figure 2.1).

This last point is worth discussing further since it is fundamental to the validity of this study. Although most participants in the Control group also demonstrated some amount of WMH on structural MRI, it is arguable whether they should also be classified as having SVD given that they were completely symptom-free, in contrast to those in the SVD group who were made up of actual patients from a Memory Clinic in Oxford. In other words, SVD participants used in the study were people with subjective and, in most cases, objective evidence of cognitive dysfunction. This brings into focus a few important issues in the diagnosis of SVD, for example, whether it can be diagnosed based on the presence of WMH alone. In routine clinical practice, people may be given a diagnosis of SVD if they are deemed to have ‘too much’ WMH for their age, which begs the obvious question: how much is too much? Indeed, at what level should the threshold of WMH volume be set in order to avoid diagnosing SVD in almost every older individual in society? This underlines the importance of identifying better neuroimaging biomarkers for the condition.

2.6 Conclusion

Taken together, the results described in this study provide some additional perspective into the breadth of changes in the brain associated with SVD. In addition to conventional features like the presence of WMH, other findings using structural, diffusion, and rs-fMRI illustrate the potential (and pitfalls) of using these modalities as neuroimaging biomarkers of the disease.

3 | Impact of cerebral small vessel disease on visual short-term memory

3.1 Abstract

One of the consequences of SVD is cognitive impairment. The profile of cognitive deficits in the condition has been reported to involve deficits primarily in executive function and processing speed, with relative sparing of STM and LTM. This chapter made use of a delayed reproduction task with a continuous, analogue response space to probe VSTM. SVD participants demonstrated reduced identification accuracy and made larger localisation errors. Furthermore, they required more time to correctly identify and localise items. By applying a mixture model to the data, it was possible to further characterise the pattern of deficits observed in those with SVD, with evidence pointing to them being less precise, more likely to commit misbinding errors, and prone to random guessing. Using factor analysis, two latent factors emerged from the many behavioural variables obtained in this experiment. The first factor represented errors in memory and was significantly higher in people with SVD. The second factor reflected response times and did not show any significant differences between SVD participants and healthy elderly controls. The results provide support for the use of more sensitive measures of VSTM not just to detect the presence of memory deficits but also to delineate the sources of errors in memory.

3.2 Introduction

SVD is associated with cognitive impairment and dementia, either from the effect of the disease itself, or in concert with other neurodegenerative conditions like AD (Butt et al., 2021; Kester et al., 2014; van der Flier et al., 2005). One characteristic shared by many of these conditions is that they can develop insidiously, with pathology accumulating over many years before the diseases themselves become clinically apparent. Indeed, this is often the case in people found to have SVD on MRI incidentally, who may have early signs or symptoms of cognitive impairment that were previously thought to be part of the normal aging process (Cannistraro et al., 2019). Although SVD is conventionally diagnosed on neuroimaging, there is potential for using neuropsychological findings as a cost-effective screening strategy (Salvadori et al., 2022). This highlights the importance of gaining a better understanding of the profile of cognitive dysfunction in SVD. It also underlines the need for identifying strategies to detect any deficit as early as possible in the course of the disease.

Previous studies have attempted to shed some light on the spectrum of cognitive impairment in SVD (De Groot et al., 2002; Garde, Lykke Mortensen, Rostrup, & Paulson, 2005; Prins & Scheltens, 2015; Vermeer et al., 2003). In an early report involving participants aged 60-90 years who were free from dementia, increasing SVD burden was associated with a steeper decline in tasks indexing processing speed such as the Letter-Digit Substitution Task, as well as measures of executive function like the Stroop Colour Word Interference test (Prins et al., 2005). In contrast, tests of verbal episodic memory, for example the immediate and delayed recall of the 15-word verbal learning test, did not demonstrate any correlation with SVD burden. Another study which recruited 121 patients with MRI-confirmed lacunar stroke and leukoaraiosis found that at baseline SVD patients displayed impairments in tests of processing speed and executive function, but not in measures of working or long-term memory (Lawrence et al., 2015). Even when memory deficits were found in SVD, they appeared to be mediated by (impairments in) executive function, as shown by Jokinen et al. using mediation analysis (Jokinen et al., 2005). Current consensus statements therefore indicate that cognitive impairment in SVD primarily involves the domains of processing speed and executive function, with relative sparing of short and long-term memory (Peng et al., 2019; Rosenberg et al., 2016). However, a recent systematic review and meta-analysis appears to contradict this statement, instead demonstrating that individuals with SVD performed worse than controls in all seven cognitive domains examined: executive function, delayed memory (restricted to tasks featuring a delayed recall/recognition component in this study), processing speed, language, visuospatial ability, reasoning, and attention (O. K. L. Hamilton et al., 2021).

A few possible explanations may account for this discrepancy. First, reports of cognitive impairment in SVD may encapsulate a range of presentations of the disease, from asymptomatic individuals who were incidentally found to have WMH on brain MRI, to those with mild cognitive impairment following a stroke, all the way through to people with dementia. Second, the sample sizes used in these studies were often small, ranging between 4 to 196 participants with a median of 27 (O. K. L. Hamilton et al., 2021). Third, tests of memory themselves differ from one another in terms of their sensitivity for detecting abnormalities particularly when people only have subtle impairments in memory performance (Zokaei, Burnett Heyes, Gorgoraptis, Budhdeo, & Husain, 2015; Zokaei & Husain, 2019).

The last point above bears further scrutiny. Conventional neuropsychological tests of STM or WM often index span, by first presenting participants with increasing digit, word, or spatial location sequences, before asking them to recall or reproduce the sequence (Groeger, Field, & Hammond, 1999). An early report using this method compared the association between WMH and subcortical grey matter with scores on a series of cognitive tests including the Wechsler Adult Intelligence Scale Third Edition (WAIS-III) Digit Span indexing working memory (Marshall, Hendrickson, Kaufer, Ivanco, & Bohnen, 2006). The results demonstrated a correlation between severity of WMH and Trail Making Test B-A, a test of executive function, but not with WAIS-III Digit Span. Another approach is to employ change-detection tasks in which participants had to decide if what they were seeing in the probe array was the same as what they previously saw in the memory array (Della Sala, Parra, Fabi, Luzzi, & Abrahams, 2012; Parra et al., 2011). Typically, with this method, participants were shown memory arrays containing either single features (e.g., colour or shape), or multiple features combined in a single object (e.g. colour and shape). Most of the research work carried out using this VSTM paradigm have examined patients with AD who often show deficits in the ability to bind features together (Kozlova, Parra, Titova, Gantman, & Sala, 2021; Parra et al., 2009; Parra, Abrahams, Logie, & Della Sala, 2010). To the best of our knowledge, this binding impairment has not been specifically demonstrated in people with SVD.

What these paradigms have in common is that they dichotomize the outcome of the tests; participants are either able to recall the information or they fail to do so. This binary way of determining success or failure in memory performance overlooks the fact that failing to recall an item (using the above methods) does not mean that all the information about that item has been lost from memory. Such conventional memory tests can be less sensitive to detecting differences in memory resolution—the fidelity of recall (Zokaei et al., 2015).

As discussed in Chapter 1, a more recent approach attempts to probe the resolution with which items are retained in VSTM using a continuous response measure (Fallon et al., 2016; Ma et al., 2014). One advantage of using this approach is that it enables the use of mixture models to further understand the sources of error in memory performance (Grogan et al., 2020; Schneegans & Bays, 2016). Here, errors can occur in three ways. People can remember which features were shown but then fail to combine them together, leading to misbinding errors. They may also have forgotten the item(s) altogether and resort to random guessing. Alternatively, errors can arise due to imprecision i.e. having only an approximate memory of the required feature.

Delayed reproduction tasks that make use of a continuous, analogue response space (Bays et al., 2009; Gorgoraptis et al., 2011; Wilken & Ma, 2004) have been employed to study the quality of VSTM representation in many conditions. Liang et al. found that individuals with pathological mutations in presenilin 1 or amyloid precursor protein genes for familial AD who may have hippocampal volume loss made more misbinding errors compared to healthy controls (Liang et al., 2016). A similar study, this time in middle-aged individuals with different APOE alleles, demonstrated paradoxically that APOE $\epsilon 4$ carriers demonstrated less misbinding errors in a gene dosage-dependent manner (Zokaei et al., 2017). Likewise, patients with voltage-gated potassium channel complex antibody-associated limbic encephalitis and hippocampal involvement were impaired at binding different features together (Pertzov et al., 2013). Interestingly, PD patients who carried out the same task did not show any increase in misbinding but instead had more guessing compared to healthy controls or AD patients (Zokaei et al., 2020).

In neural terms, these different metrics may represent distinct mechanisms leading to STM impairment. In the case of misbinding, evidence suggests that it occurs due to failure of the hippocampus to perform relational binding i.e. combining different features into a coherent entity in memory (Koen, Borders, Petzold, & Yonelinas, 2017; Libby, Hannula, & Ranganath, 2014; Yonelinas, 2013). Guessing, on the other hand, may result from lapses or fluctuations in sustained attention, something that has been shown to occur in diseases linked to Lewy body pathology such as PD (C. A. Hamilton et al., 2023; O'Dowd et al., 2019). Might this also apply in people with SVD? In a survey of cohorts of neurologically healthy elderly people aged between 55-85, WMH load was found to correlate with attention deficits as measured with the Trail Making Test A (R. Ylikoski et al., 1993). Finally, imprecision may arise from noisy representations either during early sensory representations or during the maintenance stage of working memory (Fougnie, Suchow, & Alvarez, 2012; Shafi et al., 2007).

This chapter will attempt to answer the following questions:

1. Is there a VSTM deficit in a group of unselected SVD patients attending a cognitive disorders clinic?
2. If so, what is the pattern of error(s) associated with the disease? Is it akin to AD and limbic encephalitis patients who showed more misbinding, or PD patients who experienced increased guessing? Do people with SVD have a different pattern of deficit altogether?

3.3 Methods

3.3.1 Participants, demographics, and consent

Fifty-seven SVD participants aged between 50-80 years (32 males, 25 females) were recruited through the Memory Clinic at the John Radcliffe Hospital in Oxford. These were the same individuals who underwent MRI scanning as described in Chapter 2. Their performance in this study was compared to that of fifty-seven age-matched healthy controls who were also part of the cohort in the previous chapter. Demographics are presented in Table 3.1.

	Control (n = 57)	SVD (n = 57)	
Measure	Mean ± std	Mean ± std	p-value
Age (years)	66.72 ± 6.83	68.93 ± 8.85	0.138
Sex (M/F)*	22 / 35	32 / 25	0.061
Education (years)	17.09 ± 6.38	14.16 ± 5.90	**0.012**
Total ACE-III (range 0-100)**	97.21 ± 2.59	91.46 ± 8.37	**< .001**
Apathetic, AMI >1.9 (yes/no)*	0/57	8/49	**0.003**
Depressed, BDI-II >9 (yes/no)*	11/46	27/30	**0.001**
WHO-5 Well-Being Index (%)	71.58 ± 14.44	61.68 ± 23.10	**0.034**
Cantril Ladder (range 0-10)	8.02 ± 1.43	7.02 ± 1.63	**< .001**

Table 3.1: **Demographic and questionnaire measures.** ACE-III = Addenbrooke's Cognitive Examination III, AMI = Apathy Motivation Index, BDI-II = Beck Depression Inventory II, WHO = World Health Organization. * Chi-square test, ** Total ACE-III score was not available for 1 Control and 1 SVD participant

As described before, the two groups did not differ in terms of age or sex ratio. However, healthy controls had more years of full-time education compared to SVD patients. Cognitive function screening using ACE-III revealed significantly higher scores in healthy controls, although both groups had scores that were within normal limits for the general population (Hsieh et al., 2013; Mathuranath, Nestor, Berrios, Rakowicz, & Hodges, 2000). There were significantly more people with apathy and depression in the SVD cohort, as measured using the Apathy Motivation Index (AMI) and Beck Depression Inventory-II (BDI-II) respectively. Additionally, indices of subjective psychological well-being (WHO-5 Well-Being Index) and life satisfaction (Cantril Ladder) were higher amongst control participants.

Permission for this study was obtained from the local ethics committee. All subjects provided written consent in accordance with the Declaration of Helsinki and were offered monetary compensation in return.

3.3.2 Experimental setup

Participants carried out the OMT, a variant of the “What was where” experiment for testing VSTM (Pertzov, Dong, Peich, & Husain, 2012). Figure 3.1 shows a schematic of this task. They sat in front of a touch-sensitive screen (iPad Pro 11-inch, 2018 model) with a 1668 x 2388 pixel resolution. Stimuli were taken from a collection of 196 fractals and presented on a black background at a viewing distance of approximately 30 cm.

To start with, participants were presented with either 1 or 3 items and were asked to remember the identity of the object(s) shown as well as their location. The items then disappeared, and the screen stayed blank for 1 or 4 seconds. Following this, participants were presented with two fractals in the middle of the screen. One of these was taken from the array they had just seen, while the other was a foil (distractor) taken from the library of fractals used in the experiment but that had not appeared in the array to be remembered. They were then asked to identify the one they had just seen by touching the object on the screen before dragging it to its original location. Participants were allowed to adjust the final location of the item as many times as needed and were encouraged to be as precise as possible.

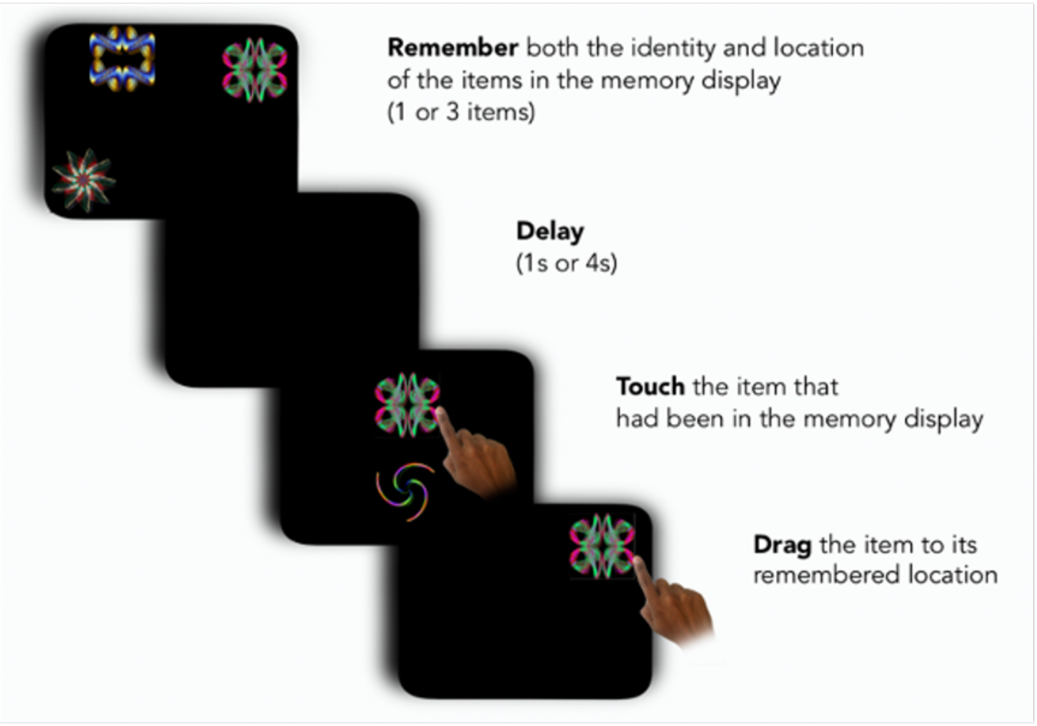


Figure 3.1: **The "What was where" Oxford Memory Test.** Participants were shown either 1 or 3 items and had to remember the identity of the objects as well as their locations. After a delay period or 1 or 4 seconds, they were shown two fractals and were asked to choose the one they had previously seen and to drag it to its original location.

This experiment involved the manipulation of 2 factors. First, the number of objects to be remembered was varied by showing either 1 or 3 items. Second, the delay period was varied by letting the screen go blank for 1 or 4 seconds. This resulted in four different experimental conditions. The experiment consisted of three blocks with each block being made up of 40 trials representing 10 trials per condition. Therefore, in total, there were 120 trials with 30 trials per condition.

3.3.3 Behavioural analysis and mixture modelling of error

Several metrics were obtained in this experiment. **Identification Accuracy** represented the proportion of trials in which participants touched the correct shape when given a choice between two fractals. **Localisation Error** was calculated using the Euclidian distance between the centre of the original location of the probed item and the centre of the final location of the chosen object. **Identification Time** was the time it took participants to touch the correct object following the appearance of two shapes on the screen. **Localisation Time** was defined as the delay from first touching an item to confirmation of its final location.

As described above, the use of a delayed reproduction task with a continuous, analogue response space enabled the precision of memory representations to be analysed further. This was done using MemToolbox2D, an extension of the MATLAB package MemToolbox which employed two-dimensional mixture models to isolate sources of spatial error (Bays et al., 2009; Grogan et al., 2020). Here, three more parameters were obtained: imprecision, misbinding, and guessing. **Imprecision** corresponded to the width of response distributions around the target object. **Misbinding** referred to the proportion of 3-item trials in which participants succeeded in identifying the correct fractal but dragged it to the location of another item in the original array, in effect swapping the two locations. **Guessing** represented the proportion of trials in which participants randomly report the final location of a correctly identified item.

The mixture model metrics were calculated as follows: for each trial in which the correct object was identified, the distance between the response location (i.e., the final position of the item chosen by the participant), and three other items were calculated. The three items corresponded to:

1. Target
2. Distractor (non-target in that trial)
3. Another distractor taken from a randomly chosen trial

Depending on which of the three distances was the shortest, the participant's response was classified as either (1) target, (2) misbinding i.e., aiming for a distractor, or (3) guessing i.e., random response. This procedure was repeated 5,000 times per trial, using a randomly chosen distractor each time. Doing it this way enabled the proportions for these three sources of error to be quantified (absolute amount of response type/5,000). Introducing a randomly chosen distractor allowed for the differentiation between errors that were systematically linked to a distractor in that specific trial vs errors that could be accounted for even by a randomly chosen distractor that was not present in the actual trial.

3.3.4 Statistical analysis

To examine how SVD impacts measures of VSTM, a 2x2x2 factorial ANOVA was conducted for all the above metrics apart from misbinding. The number of items (1 item versus 3 items) and delay (1 second versus 4 seconds) were "within-subjects" factors, whereas group membership (healthy controls versus SVD) was selected as the "between-subjects" factor. For misbinding specifically, only the delay period was used as a "within-subject" factor as there can be no misbinding when only 1 item was shown in the original array to be remembered.

Since performance on this task can be measured in terms of different metrics (see section 3.3.3), a factor analysis was performed using all the variables obtained in the experiment. These were first standardised i.e., scaled, by applying the *prcomp* function to place them on a common scale and ensure that they have equal weight in the subsequent analysis. A scree plot was then utilised to determine the number of factors to extract from the data. With this information, factor analysis was carried out using the *factanal* function and specifying promax as the method of rotation. The promax rotation is an oblique rotation which allows factors to be correlated, something that was theoretically likely for certain variables like Identification Time and Localisation Time in OMT. All statistical analyses were carried out in R Studio version 2023.06.0 Build 421.

3.4 Results

3.4.1 SVD participants had lower accuracy compared to healthy controls

There was a main effect of group on identification accuracy (F(1, 448) = 36.82, p <.001) indicating that SVD patients had significantly lower accuracy compared to healthy controls (SVD: M = 0.89, SE = 0.01, control: M = 0.93, SD = 0.01). There was also a main effect of the number of items (F(1,448) = 447.06, p <.001) such that participants performed worse when there were 3 items to be remembered compared to only 1 item (3 items: M = 0.85, SE = 0.01, 1 item: M = 0.98, SE = 0). In addition, there was a significant effect of delay (F(1,448) = 14.03, p <.001) due to lower accuracy when the delay was 4 seconds compared to 1 second (4 seconds: M = 0.90, SE = 0.01, 1 second: M = 0.92, SE = 0.01).

A significant interaction was also observed between group and number of items (Figure 3.2) (F(1,448) = 10.09, p <.01) whereby the decline in performance was worse in SVD patients compared to healthy controls when the number of items increased from 1 to 3.

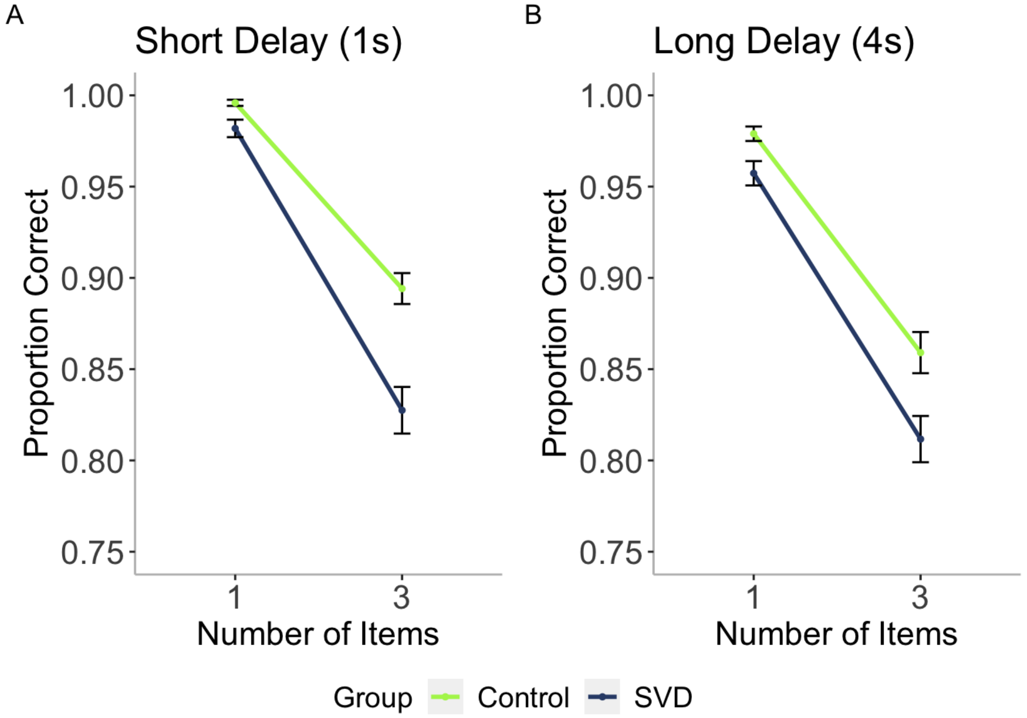


Figure 3.2: **Identification accuracy.** SVD patients (blue) correctly identified the required item in a lower proportion of trials compared to healthy controls (green) regardless of whether the delay period was short **(A)** or long **(B)**. In contrast, they experienced a greater decline in performance when the number of items was increased from 1 to 3. Error bars show ± SEM.

Localisation error was significantly larger in SVD patients than healthy controls as per a significant effect of group (F(1,448) = 67.04, p <.001, SVD: M = 131.14, SE = 5.62, control: M = 96.17, SE = 3.98). There were also main effects of number of items and delay on localisation error (F(1,448) = 701.46, p <.001 and F(1,448) = 12.48, p <.001 respectively). Moreover, there was a significant interaction between group and number of items (F(1,448) = 15.57, p <.001) such that increasing the number of items from 1 to 3 led to a larger increase in localisation error for SVD patients than healthy controls (Figure 3.3).

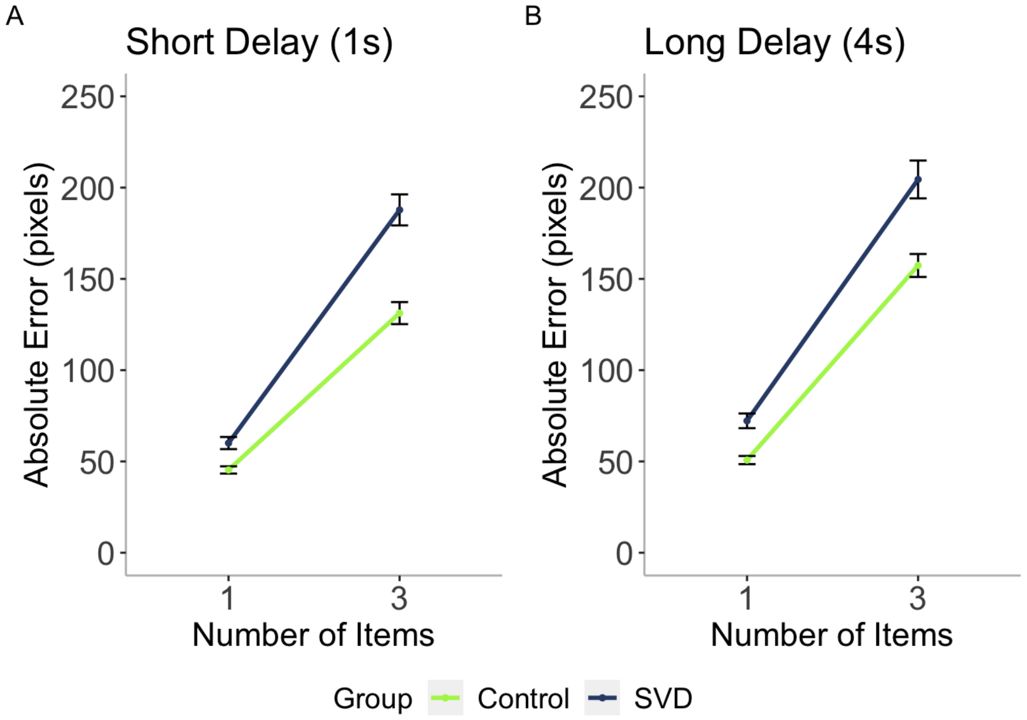


Figure 3.3: **Localisation error.** SVD patients (blue) made a higher degree of error (measured in pixels) compared to healthy controls for both short **(A)** and long **(B)** delays. In both delay conditions, changing from 1 to 3 items resulted in a larger increase in absolute error for SVD patients. Error bars show ± SEM.

3.4.2 SVD participants required more time to identify and localise items

Apart from accuracy, participants were also measured on how long they took to perform the objectives of the experiment. Here, there were significant main effects of group, number of items, and delay on identification time (group: F(1,448) = 26.70, p <.001, number of items: F(1,448) = 244.45, p <.01, delay: F(1,448) = 20.32, p <.001) (Figure 3.4A & B). In particular, significantly more time was required by SVD patients (M = 2.32, SE 0.09) to identify the correct item compared to healthy controls (M = 1.89, SE 0.06). No significant interaction was observed between any of the factors.

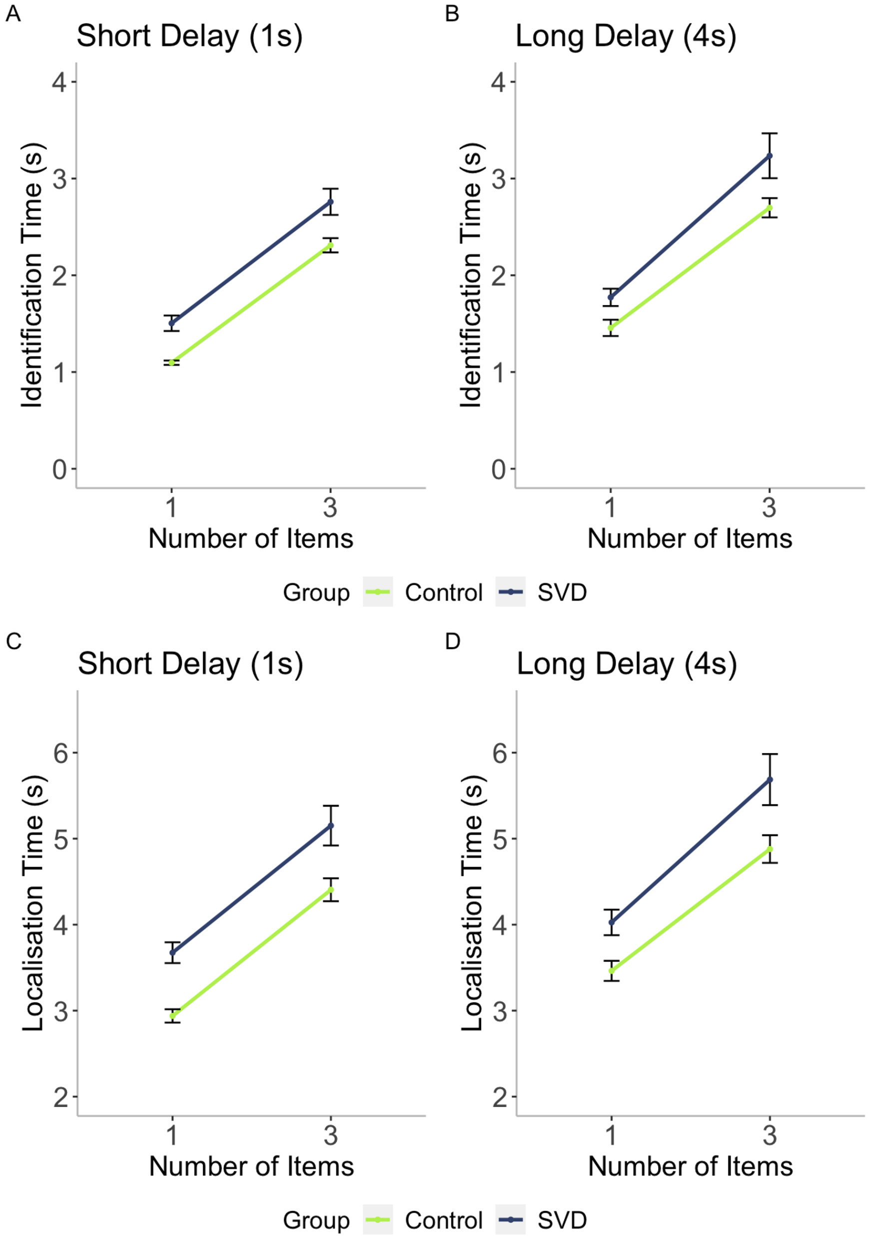


Figure 3.4: **Identification and localisation times.** SVD patients (blue) needed more time to identify items irrespective of whether the delay period was short **(A)** or long **(B)**. Localisation time was also increased in the SVD group in comparison to healthy controls for both delay periods (**(C)** and **(D)**). Error bars show ± SEM.

Similarly, there were also significant main effects of group, number of items, and delay on localisation time (group: F(1,448) = 33.69, p <.001, number of items: F(1,448) = 150.13, p <.001, delay: F(1,448) = 14.71, p <.001), with SVD patients needing longer to localise their chosen object compared to healthy controls (SVD: M = 4.63, SE = 0.12, control: M = 3.92, SE = 0.08) (Figure 3.4C & D). There were no significant interactions between factors.

3.4.3 Sources of error

Localisation performance appears to be poorer in SVD patients, but what is responsible for this? To examine the nature of the deficit, a mixture model (see section 3.3.3) was applied to further break down the error metric into its components.

The first potential explanation for error is **imprecision** in localisation. Here, there was a significant main effect of group (F(1,448) = 72.78, p <.001) due to SVD patients being more imprecise than healthy controls (SVD: M = 74.08, SE 1.80, control: M = 57.17, SE = 1.18) (Figure 3.5). There were also significant main effects for number of items and delay (number of items: F(1,448) = 74.13, p <.001, delay: F(1,448) = 8.83, p <.01). No interaction effect was observed between any of the factors.

VSTM errors can also be caused by **random guessing**. For this metric, significant main effects were observed for group, number of items, and delay period (group: F(1,448) = 72.50, p <.001, number of items: F(1,448) = 70.17, p <.001, delay: F(1,448) = 6.79, p <.01) (Figure 3.6). Relevant to the research question, the main effect of group was driven by an increase in the proportion of guessing amongst SVD patients compared to healthy controls (SVD: M = 0.18, SE = .01, control: M = 0.13, SE = 0.00).

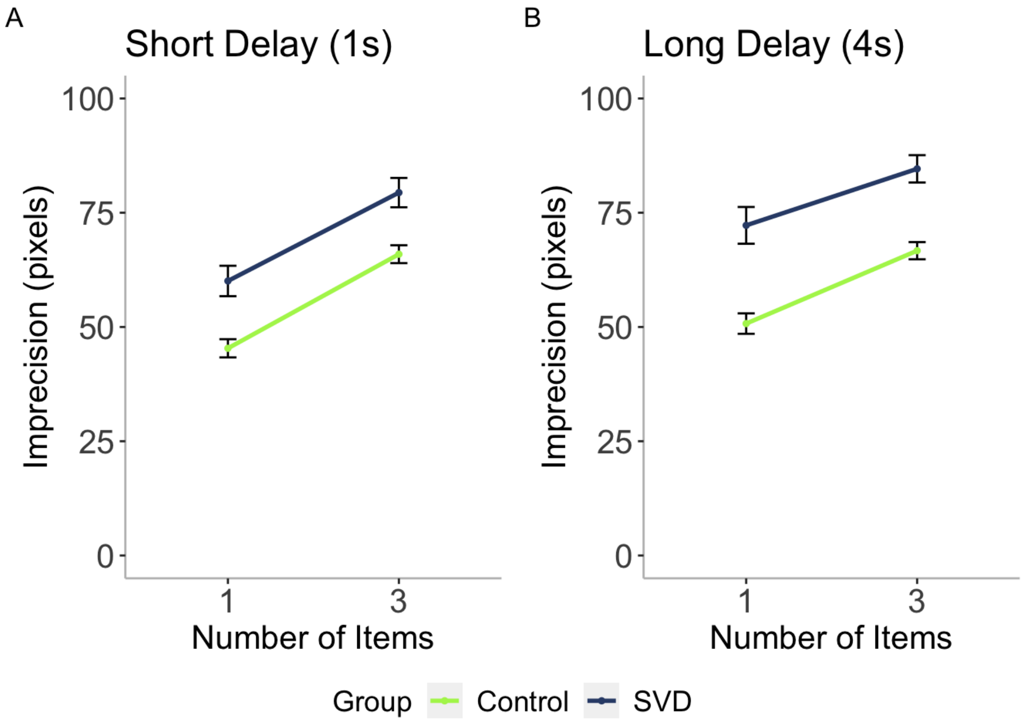


Figure 3.5: **Degree of imprecision when participants were aiming for the location of the original item.** SVD patients (blue) were more imprecise compared to healthy controls (green) regardless of the number of items (1 versus 3) or whether the delay was short **(A)** or long **(B)**. Error bars show ± SEM.

Another source of error comes in the form of **misbinding** features belonging to different objects when more than one item was shown in the original array. Interestingly, here there was a main effect of group but no significant effect of delay on this metric (group: F(1,224) = 13.14, p <.001, delay: F(1,224) = 0.29, p = 0.59) (Figure 3.7). Furthermore, there was a significant interaction between group and delay (F(1,224) = 5.52, p <.05). Post-hoc t-tests revealed that SVD patients committed more misbinding errors than healthy controls after a delay of 1 second (p <.001) but did not differ in performance with the control group after 4 seconds (p = 0.80). Thus their misbinding deficit was present only at the short delay.

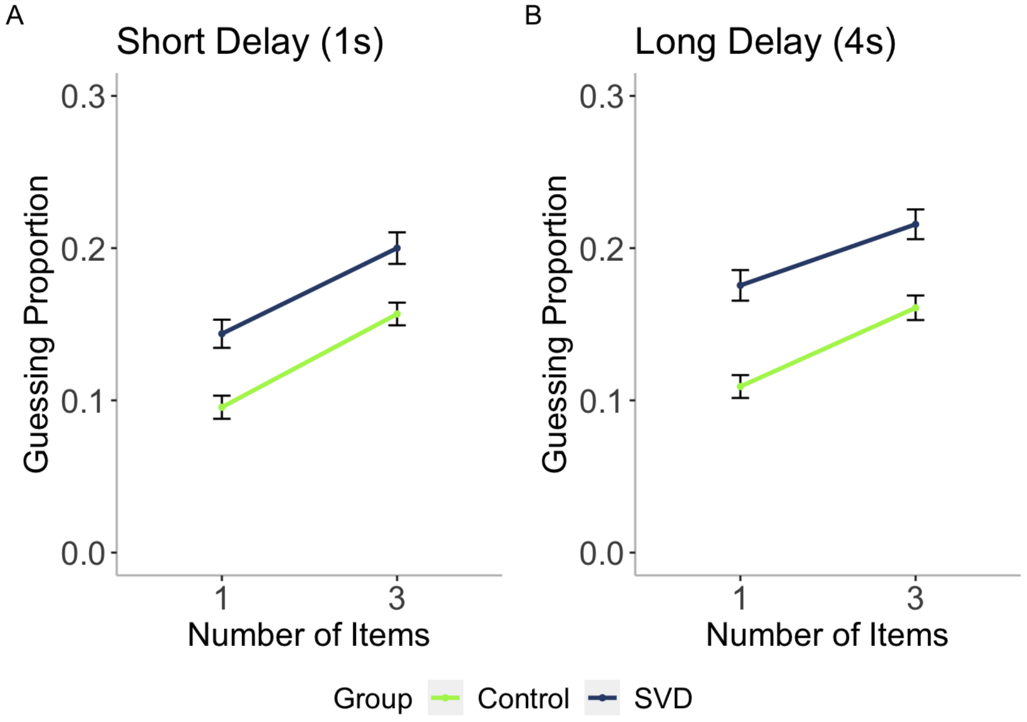


Figure 3.6: **Proportion of trials in which participants committed guessing errors.** SVD patients (blue) made more guessing errors irrespective of the number of items for both short **(A)** and long **(B)** delay periods. Error bars show ± SEM.

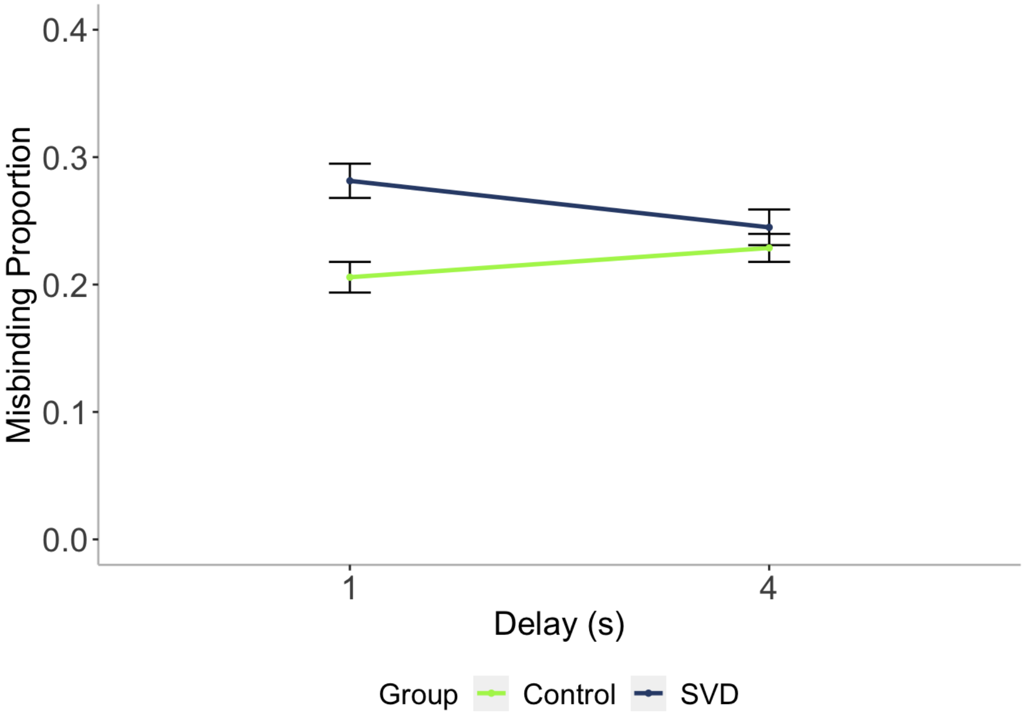


Figure 3.7: **Proportion of trials involving binding errors.** SVD patients (blue) made more misbinding errors after a delay of 1 second but did not differ significantly from healthy controls (green) after 4 seconds. Error bars show ± SEM.

3.4.4 VSTM performance can be fractionated into two factors

To determine if the metrics obtained in this experiment reflect some underlying structure than can be made apparent using fewer variables, a factor analysis was conducted using all the performance metrics described above. After scaling the data appropriately, principal components analysis was conducted, and the results plotted using a scree plot. Deciding how many factors to include in the final analysis can be performed in several ways, one of them being Kaiser's rule, which states that all components with eigenvalues greater than 1 should be retained. Using the scree plot below (Figure 3.8), it was apparent that two factors met the threshold for inclusion.

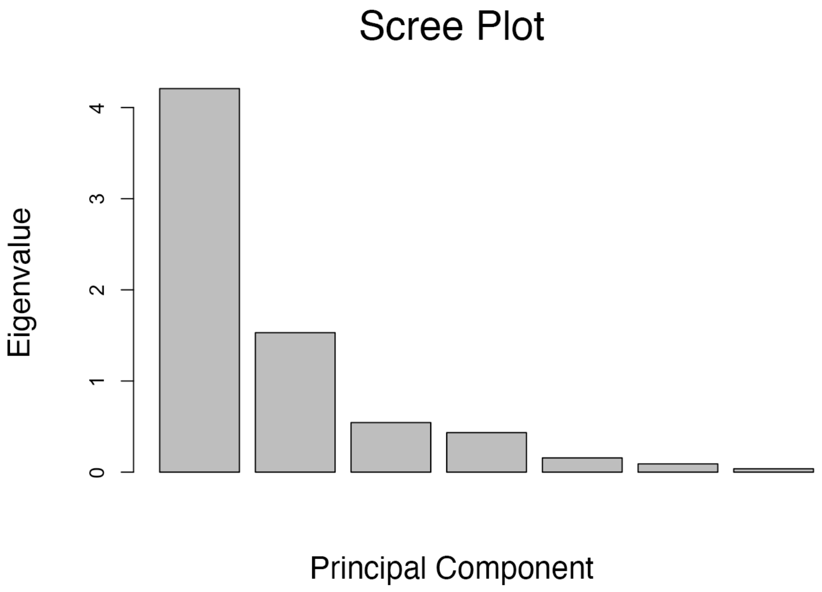


Figure 3.8: **Scree plot of principal components** Two components had eigenvalues greater than 1 and thus were kept for the purpose of this analysis.

The nature of these two factors can be surmised by looking at how individual metrics load onto each factor. As shown in Figure 3.9, the first factor was made up primarily of metrics reflecting errors in memory (namely Identification Accuracy, Absolute Error, Imprecision, Guessing, and Misbinding), whereas the second factor was predominantly composed of metrics indicating response times (i.e., Identification Time and Localisation Time). Crucially, the error factor was significantly higher in SVD participants than healthy controls, whereas the two groups did not differ in terms of the response time factor (Figure 3.10).

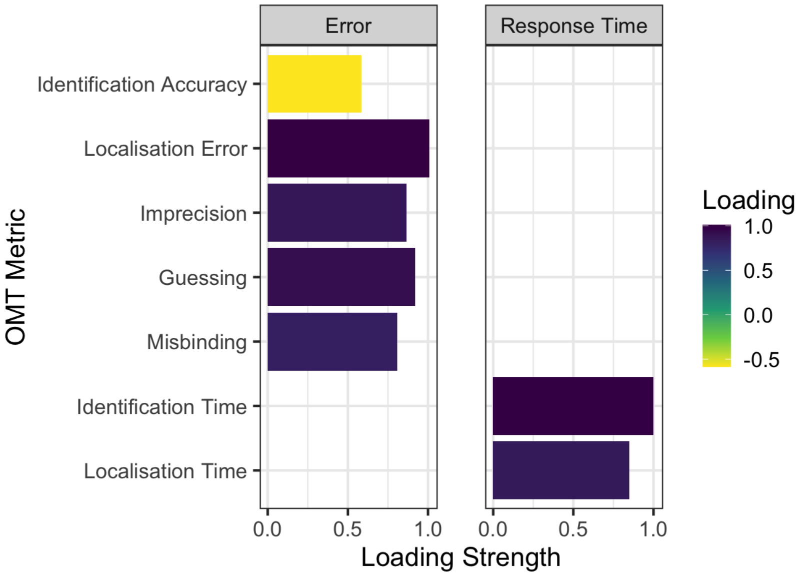


Figure 3.9: **Loadings for the two factors responsible for 76% of variance in the behavioural experiment.** The first factor representing error (**left column**) was made up of identification accuracy, absolute error, imprecision, guessing, and misbinding. Meanwhile, the second factor reflecting response times (**right column**) was derived from identification and localisation times. The colour bar on the right indicates the magnitude of loading from negative (yellow) to positive (purple).

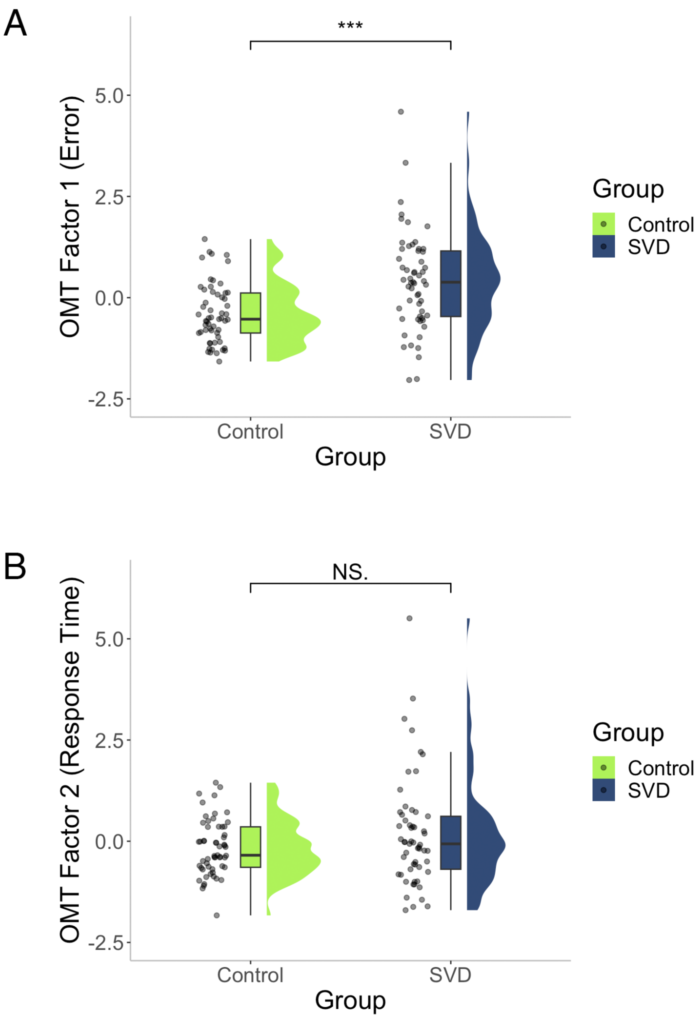


Figure 3.10: **Group differences in OMT factors.** **(A)** The first factor, composed mostly of error metrics, was significantly higher in SVD participants compared to healthy controls. **(B)** No differences were observed in the second factor corresponding to response times.

3.5 Discussion

This chapter examined VSTM performance in participants with SVD and healthy controls using a delayed reproduction task with a continuous, analogue response space (Liang et al., 2016). Overall, SVD patients showed significantly worse memory for identifying and localising the correct item. For both these measures, increasing the number of items from 1 to 3 affected SVD patients to a larger extent than control participants. Comparing the length of time required to identify and localise the correct item in this experiment revealed that participants with SVD spent longer to accomplish both tasks. Moreover, even when they managed to identify the correct object, SVD patients were more imprecise, committed more binding errors, and resorted to random guessing in a larger proportion of trials. Performance in this experiment could be described in terms of two key factors reflecting memory error and response time. While memory error was significantly higher in SVD, the second factor representing response time did not differ significantly between the two cohorts.

The primary objective of this chapter was to ask if there exists a VSTM deficit in SVD. Two of the metrics described above, namely identification accuracy and localisation error, reveal that such a deficit does exist in this patient population. Traditionally, the profile of cognitive impairment in SVD primarily involves deficits in executive function and processing speed (Peng et al., 2019; Rosenberg et al., 2016) with relative sparing of short and long-term memory. However, this may have been due to the use of relatively insensitive tests involving memory span (Legdeur et al., 2019; Marshall et al., 2006; Sachdev, Wen, Christensen, & Jorm, 2005). The digit span test, for example, involves asking participants to recite an increasingly lengthy sequence of numbers forwards or backwards. Forwards span typically only measures STM storage, whereas backwards span imposes some manipulation of information (Groeger et al., 1999). Delayed reproduction tasks such as the one used above have the advantage of being able to assess memory recall precision instead of just investigating memory span (Zokaei et al., 2015). This is crucial because, in a cohort of patients with early-stage disease and relatively mild cognitive impairments, tests involving memory span may fail to find any deficits.

One aspect of the results presented here that is consistent with current knowledge of SVD-related cognitive impairment is the finding that identification time and localisation time were longer in SVD. Previous reports using a variety of tasks like the Digit Symbol subtest of the WAIS-III, TMT-A, reading subtask of the Stroop test, for example, have indicated that this is a common finding in this patient population (de Groot et al., 2000; Hotz et al., 2021; R. Schmidt et al., 1993; van Dijk et al., 2008). One such study demonstrated that psychomotor speed, measured using a combination of the reading subtask of the Stroop test, one-letter subtask of the Paper-and-Pencil Memory Scanning Test, and the Letter-Digit Substitution Task, in participants with the most severe periventricular WMH assessed with a rating scale on 1.5-T MRI were nearly 1 standard deviation below average (de Groot et al., 2000). A longitudinal study by van Dijk et al. recruited 668 people for repeated MRI scanning and neuropsychological testing during a 3-year period. They demonstrated that lesion progression as detected on MRI correlated with a decline in global cognition and in particular, with a decrease in processing speed indexed using a compound score made of the same three tests used by de Groot et al. (van Dijk et al., 2008).

The second objective of this chapter was to characterise the nature of VSTM deficits in SVD. In this behavioural task, participants with SVD were more imprecise, had more misbinding, and carried out more guessing compared to healthy controls. To place these results in context, it is worth looking at the findings of similar studies performed on other (healthy and patient) populations. Pertzov et al. showed in a small cohort of 7 limbic encephalitis patients with hippocampal lesions that they exhibited more misbinding errors (Pertzov et al., 2013). The authors hypothesized that this specific deficit may be due to damage to the medial temporal lobe in these patients. Indeed, hippocampal volume has been shown to exhibit a negative correlation with misbinding, but not with object identity or localisation, suggesting a specific role for the hippocampus in relational binding (Liang et al., 2016). In a more recent study, Zokaei et al. carried out the same behavioural task on AD and PD patients, and compared their performance to two control populations: healthy age-matched controls and individuals with subjective cognitive impairment (SCI) (Zokaei et al., 2020). Different patterns of deficits were found in the patient groups. Specifically, AD patients demonstrated more misbinding errors whereas PD patients showed more guessing responses. It is interesting to note that the SVD cohort tested in this chapter showed increases in both types of error. This suggests that the cognitive impairment in SVD involves multiple components perhaps due to more widespread pathology involving multiple white matter regions of the brain in these patients. Thus there was no specific source of error associated with SVD.

One interesting finding concerns the nature of misbinding errors in SVD. Here, patients committed more misbinding errors than healthy controls following a short delay period of 1 second but not after the longer delay of 4 seconds. In the case of misbinding errors, at least, increasing the delay period had a beneficial effect on memory performance in SVD patients. This may reflect an interaction between the cognitive domains of memory and processing speed. One might speculate that due to their slower speed of information processing, SVD patients made more misbinding errors after a short delay, but increasing the delay period gave them additional processing time which allowed their performance to be commensurate with that of healthy controls. One implication of this is that the maintenance period is when most of the information processing takes place.

This begs the question: Why is this pattern not observed in the other metrics? Two factors may account for this. First, SVD patients may genuinely be worse at identifying or localising the correct item. Alternatively, the delay period of 4 seconds may have been inadequate to allow them to process all the information presented in the original memory array. One implication of this for cognitive testing purposes is that SVD patients may simply require more processing time to achieve the same level of memory accuracy as healthy elderly controls. It should be noted, however, that although exposure times and delays between sample and test stimuli were fixed, there was no restriction in time taken to respond in this study.

How did the number of items affect memory performance in SVD? Increasing set size i.e. the number of items from 1 to 3, effectively adds to the load of information that must be retained in, and subsequently recalled from, memory. Both groups experienced a deterioration in memory performance in all metrics (apart from misbinding which only applies to the 3-item trials) when set size was increased. This is in concordance with previous reports indicating the negative effect of increasing set size on VSTM performance (Fallon, van Rhee, Kienast, Manohar, & Husain, 2023; Pertzov et al., 2012; Tabi et al., 2021). However, participants with SVD were disproportionately more affected by this increase in two of the metrics obtained, namely identification accuracy and localisation error. These findings suggest a reduced ability to cope with increased memory load as a function of the disease. The same interaction effect was not observed when the delay period was increased from 1 to 4 seconds. In other words, although memory performance was poorer for longer delays, both cohorts exhibited the same degree of reduction in their performance.

Understanding the exact nature of the memory deficits in SVD is important for a few reasons. First, it might potentially help to differentiate SVD from other neurological diseases if there were a unique cognitive pattern or fingerprint of the disease. This could then be combined with the results from testing other domains of cognition in order to build a more comprehensive profile of the spectrum of cognitive deficits found in different conditions. However, as we have seen here, SVD patients appeared to be globally impaired across all performance metrics.

Second, these tests have the potential to act as a more sensitive marker of disease and thus provide a better way to differentiate SVD from healthy aging. This is especially important because many people with early signs of SVD on neuroimaging may not yet experience any noticeable change in their cognitive abilities (Libon et al., 2008).

Third, by allowing comparisons to be made between the patterns of deficits identified in different neurological conditions with their respective pathologies, behavioural tasks like the one used in this chapter may help shed some light into the underlying mechanism of VSTM. Diseases affecting the hippocampus, for example, appear to be associated with binding deficits in STM, regardless of whether they are neurodegenerative, autoimmune, or vascular in nature (Liang et al., 2016; Pertzov et al., 2013). This last point bears further elaboration: in this study, although initial analysis revealed smaller hippocampi in SVD participants compared to healthy controls (see section 2.4.2), this finding did not survive correction for multiple comparisons. Nevertheless, hippocampal arteries are themselves small arteries that are potentially affected in SVD, and the link between vascular supply of the hippocampi with cognitive performance has been explored previous using high-resolution 7 Tesla time-of-flight angiography (Perosa et al., 2020).

In the last part of this chapter, I used factor analysis to reduce the number of variables obtained in this behavioural task into a few latent factors. Two factors emerged out of this analysis, that together account for approximately 76% of the variance in memory performance. One factor was termed ‘Error’ as it received contributions from identification accuracy, localisation error, imprecision, guessing, and misbinding. The other factor represented ‘Response Time’, being made up of identification time and localisation time. Memory error increased in SVD. Intriguingly, the two cohorts did not differ in terms of the Response Time factor. This suggests that the apparent differences in Identification and Localisation Times from among the original behavioural performance variables may have been driven by an underlying deficit in STM. In other words, SVD participants were slower to respond because of difficulties recalling the precise details of the item tested, not due to any inherent slowing down of processing speed.

This study had some limitations. First, the sample size was relatively small for the purposes of detecting changes in cognition in SVD patients. However, previous reports using similar VSTM experimental setups have shown its ability to detect memory impairments in similar numbers for other groups of patients (Liang et al., 2016; Zokaei et al., 2020). Second, people in the SVD group recruited for this study were mostly in the earlier stages of this condition and were mostly non-demented. Therefore, the findings in this study may not necessarily be applicable for all SVD patients particularly those with more advanced stages of the disease. Third, the study cohort was recruited from a Memory Clinic which predominantly sees patients aged less than 65 years old who complaint of memory impairment. Although not tested specifically in this study, these participants may have co-existent AD pathology, which may in turn influence the finding that memory impairment is an early feature of SVD.

3.6 Conclusion

The results described in this chapter provide support for the presence of VSTM deficits in SVD patients who were mostly non-demented. They also shed some light into the pattern of deficits associated with this condition, whereby participants with SVD were less precise, committed more misbinding errors, and had to guess more than healthy elderly controls. One important question that can be asked is: how do these behavioural metrics relate to changes identified on neuroimaging? In the next chapter, I will attempt to address this question using behavioural data from this experiment, and neuroimaging data from the preceding chapter, in order to examine the neural correlates of VSTM and how these are affected by SVD.

4 | Neural correlates of visual short-term memory in cerebral small vessel disease

4.1 Abstract

VSTM deficits are a common occurrence in many neurological conditions, including SVD. However, most studies involving the neural correlates of VSTM have relied on data from cognitive or neuropsychological tests that are often dichotomized into showing either the presence or absence of deficits. This chapter made use of behavioural data obtained from the VSTM experiment with a continuous response space reported in the previous chapter to first identify correlations of VSTM performance with WMH and subcortical volumes. Then VBM and TBSS analyses were performed to determine if grey matter atrophy and white matter microstructural integrity parameters predicted VSTM performance. Neither WMH volume nor the volumes of various subcortical structures were significantly associated with VSTM error or response times. In contrast, grey matter atrophy in the right occipital region, as well as disruptions in the white matter microstructural integrity of several tracts including the anterior thalamic radiation, dorsal subsection of the cingulum bundle, forceps major, forceps minor, optic radiation, and superior longitudinal fasciculus demonstrated significant correlations with error in VSTM. These findings provide important clues for understanding the neurobiology of VSTM impairments in SVD.

4.2 Introduction

The previous chapter provided evidence for the presence and nature of VSTM deficits in SVD. VSTM is a crucial component of cognition, allowing for the encoding, maintenance, and subsequent retrieval of important pieces of visual information over brief periods of time (Jonides et al., 2008). Early reports observed a distinction between memory for the spatial location of objects (where) and memory for object identity (what), with the former being considered to rely upon more dorsal areas of the brain, and the latter associated with more ventral brain regions (Kosslyn et al., 1993; Kosslyn, Thompson, Kim, Rauch, & Alpert, 1996; Mishkin, Ungerleider, & Macko, 1983; E. E. Smith & Jonides, 1997). Since then, work on the neural correlates of VSTM, as well as its closely-related counterpart, visual WM, have provided a more nuanced view, suggesting that different brain regions might subserve VSTM/WM in unique ways depending on whether they retain low-level or more abstract sensory information (Christophel, Klink, Spitzer, Roelfsema, & Haynes, 2017).

Most of this research, at least in the initial stages, came from electrophysiological recordings in non-human primates. In an influential paper, monkeys with lesions in the prefrontal cortex (PFC) demonstrated impairments in the ability to maintain task-relevant information across brief delays, with preservation of their capability to perform tasks that did not require memorisation (Jacobsen, 1936). The precise nature of this task-relevant information is subject to ongoing debates, but subsequent electrophysiological studies have provided support for the existence of delay-period activity that is content-specific i.e., reflecting a diverse range of sensory features like objects, numerosity, colour, and frequency of tactile vibrations (Buschman, Siegel, Roy, & Miller, 2011; Meyer, Qi, Stanford, & Constantinidis, 2011; Miller, Erickson, & Desimone, 1996; Nieder, Freedman, & Miller, 2002;

Romo, Brody, Hernandez, & Lemus, 1999). In addition to the PFC, further recordings in non-human primates have also revealed persistent stimulus-selective activity in other brain regions like the sensory cortices, frontal eye fields, and even subcortical areas like the mediodorsal nucleus of the thalamus (Armstrong, Chang, & Moore, 2009; Super, Spekreijse, & Lamme, 2001; Watanabe & Funahashi, 2012).

Similar identification of the neural correlates of STM in human brains is made more difficult due to the inability to conduct electrophysiological recordings (outside of highly specialised instances like epilepsy surgery) and the limited spatial resolution of conventional neuroimaging techniques. The advent of multivoxel pattern analysis (MVPA) (Haxby et al., 2001; Haynes & Rees, 2006; Kamitani & Tong, 2005) and the application of inverse encoding models (Brouwer & Heeger, 2009; Ester, Anderson, Serences, & Awh, 2013), however, have identified content-specific delay period activity not just in sensory cortical regions, but also in frontal areas like the frontal eye field and lateral prefrontal cortex (Ester, Sprague, & Serences, 2015; Jerde, Merriam, Riggall, Hedges, & Curtis, 2012). Taken together, the findings from non-human primates and humans highlighted above indicate that STM/WM representations are widely distributed across sensory, parietal, temporal, and prefrontal cortices. This distributed representation confers some benefits like increasing the robustness of STM contents against distraction (Bettencourt & Xu, 2016) and allowing for different levels of abstraction in memory representation (D'Esposito & Postle, 2015), but it also creates multiple points of failure for STM.

Previous reports have attempted to link SVD burden, often in the form of WMH, with cognitive dysfunction (J. M. Biesbroek et al., 2016; Coenen et al., 2022; Dufouil et al., 2009; R. Schmidt et al., 1993). Although WMH appear to be associated with cognitive impairment in general, it is often difficult to determine the extent to which lesions seen on MRI contribute towards clinical symptomatology, something that is termed the *clinicoradiological paradox* in one review (Prins & Scheltens, 2015). One reason for this may be the heterogeneous histopathology of WMH, as shown by correlative MRI and post-mortem studies reporting a range of tissue damage from slight disentanglement of the matrix to varying degrees of myelin and axonal loss (Gouw et al., 2011). Various approaches have been tried to account for this heterogeneity e.g., by distinguishing between periventricular and deep WMH (Soriano-Raya et al., 2012), or by using voxel-based lesion-symptom mapping (J. M. Biesbroek et al., 2016), but despite these attempts the clinicoradiological paradox remains an issue.

Although VBM has been used to investigate group differences between healthy elderly controls and people with SVD (Grau-Olivares et al., 2010; Lambert et al., 2015), relatively little is known about the association between VBM metrics and VSTM in SVD. One study recruited three groups: patients with subcortical vascular mild cognitive impairment (svMCI), patients with subcortical vascular dementia (SVaD), and healthy controls. The authors investigated the relationship between cognitive deficits and cerebral grey matter volume reduction as detected using VBM (M. Li et al., 2017). In the brain regions where significant atrophy was detected compared to healthy controls, mean cerebral grey matter volume was significantly correlated with performance on tests of verbal memory (the Auditory Verbal Learning Test). Another group utilised the Rey-Osterrieth complex figure to test VSTM, measured cortical thickness using automated 3-D image processing, but did not relate the two directly (Seo et al., 2010). Given that SVD is associated with alterations in grey matter volume as shown in Chapter 2, and that VSTM is known to depend on a distributed network of brain regions, it would be interesting to see if it is possible to relate atrophy of the grey matter directly with measures of VSTM.

Diffusion MRI makes it possible to investigate the impact of altered white matter microstructural integrity on VSTM. Traditionally, studies have focused on using the DTI model rather than NODDI (Charlton, Barrick, Lawes, Markus, & Morris, 2010; Y. Chen et al., 2015; Metoki et al., 2017; Zeng et al., 2020). For example, Charlton et al. analysed a community sample of 84 middle-aged and elderly adults to investigate the effect of WMH volume and changes in DTI parameters on WM after 2 years (Charlton, Schiavone, Barrick, Morris, & Markus, 2010). They revealed that alterations in MD normalised peak height frequency, skewness, and kurtosis, correlated with declining scores in the Digit Span backwards and Letter-Number Sequencing tests of WM. Analysis of the tracts involved in this process came from work by Metoki et al. who found that worsening verbal WM performance was correlated with reducing FA and increasing MD in the uncinate fasciculi and cingulum bundle bilaterally (Metoki et al., 2017). This was supported by a report from Biesbroek et al. indicating that MD of the left uncinate fasciculus explained an additional 2.1% of variance in models of verbal WM performance on top of demographics and conventional MRI markers (J. M. Biesbroek et al., 2017). In one of the few experiments investigating visuospatial WM specifically, no significant associations were found for FA or MD (Tuladhar, van Norden, et al., 2015).

This chapter will explore the relationship between SVD features seen on neuroimaging with measures of VSTM obtained in Chapter 3. Specifically, it will investigate the correlation between the two factors representing error and response times obtained in the previous chapter with the following:

1. Total WMH volume
2. Volume of several subcortical structures
3. Grey matter volume (using VBM)
4. White matter microstructural integrity (using TBSS to analyse DTI and

NODDI parameters)

4.3 Methods

4.3.1 Participants and clinical measures

This study included 57 patients with a clinical diagnosis of SVD (age: M = 68.93, SD = 8.85, 25 females) and 57 healthy elderly controls (age: M = 66.72, SD = 6.83, 35 females) who completed the Oxford Memory Test (OMT) described in Chapter 3. Participants were evaluated cognitively using the ACE-III and Digit Span tests. ACE-III measures cognitive performance in 5 domains namely attention, memory, verbal fluency, language, and visuospatial abilities (Hsieh et al., 2013). Digit span is a standard conventional measure of verbal working memory. It involves repeating a series of numbers of increasing length either forwards or backwards. The forward version asks participants to repeat the numbers in the same order in which they first heard them, assesses simple attention. The backward version requires participants to repeat the numbers in reverse order and is therefore considered to be a test of executive function (Hale, Hoeppner, & Fiorello, 2002). Demographics of the study groups are shown in Table 4.1.

Permission for the study was obtained from the Ethics Committee at the University of Oxford (RAS ID: 248379, Ethics Approval Reference: 18/SC/0448). All participants agreed to take part in the study and were offered monetary compensation in return.

4.3.2 Experimental paradigm and behavioural analysis

All participants completed the OMT as described in Chapter 3. In brief, this was a “What was where” task in which participants were shown either 1 or 3 items followed by a delay period of 1 or 4 seconds. They were then presented with 2 fractals in the middle of the screen and were asked to choose the one they had seen previously and to drag it to its original location. Behavioural metrics obtained from this experiment included identification accuracy, localisation error, identification time, localisation time, imprecision, misbinding, and guessing. A factor analysis was applied to the raw behavioural data resulting in 2 factors representing 'Error' (Factor 1) and 'Response Time' (Factor 2).

4.3.3 MRI acquisition and pre-processing

Structural and diffusion MRI scans were obtained using a 3T siemens Verio scanner at the John Radcliffe Hospital in Oxford. Structural images included: T1-weighted sequence (MPRAGE, field of view: 208 x 256 x 256 matrix, TR 2000 ms, TE 1.94 ms, TI 880 ms, flip angle 8°, voxel-size 1.0 mm isotropic) and T2-fluid attenuated inversion recovery, or T2-FLAIR, sequence (TR 5000 ms, TE 397 ms, TI 1800 ms, flip angle 120°, voxel-size 1.1 x 1.0 x 1.0 mm). Diffusion-weighted images were obtained using an echo planar sequence (TR 3600 ms, TE 92 ms, voxel size 2.0 x 2.0 x 2.0 mm) with opposite phase encoding directions (AP and PA) to allow for more robust distortion correction (AP: 104 directions, 8 b=0 s/mm2, 50 b=1000 s/mm2, 50 b=2000 s/mm2 and PA: 7 directions, 4 b=0 s/mm2).

Pre-processing of the MRI data was described in further detail in Chapter 2. The following is a summary of the important steps:

Segmentation and quantification of WMH were carried out using BIANCA (Griffanti et al., 2016). The output from BIANCA was a binary map whereby voxels classified as WMH had a value of 1.0 and all other voxels were given a value of 0. The command line tool *fslstats* was then used to determine the actual volume of WMH per participant.

Calculation of subcortical volumes was done using the script *run_first_all* in FSL on brain-extracted T1-weighted images. This script resulted in an image with separate labels for the following seven subcortical structures: thalamus, caudate, putamen, globus pallidum, hippocampus, amygdala, and nucleus accumbens. Again, *fslstats* was used to calculate the volume of each segmented subcortical structure for every participant.

For the VBM analysis, a study-specific grey matter template was first created using the tool FSL-VBM. This template was then used as a target for non-linear registration of the grey matter images from individual participants. All non-linearly registered images were then concatenated into a 4D image which was smoothed using a sigma 3 mm Gaussian kernel.

Diffusion-weighted images first underwent corrections for susceptibility-induced distortions, eddy currents, and subject movement with the tools *topup* and *eddy* in FSL. Pre-processed diffusion data were then analysed using the following 2 models: DTI and NODDI. For each voxel, the diffusion metrics obtained from DTI included FA and MD, whereas applying the NODDI model resulted in values representing NDI, ODI and ISOVF. TBSS was then used to create 5 different skeletons (one for each diffusion metric) prior to voxel-wise statistical analyses.

4.3.4 Statistical analysis

Linear regression was used to investigate the relationship between WMH and subcortical volumes with OMT Factors 1 & 2 (Error and Response Time, respectively). All models controlled for age, sex, and years of education. In addition, an interaction term was introduced to determine if the association between the two variables of interest was modified by the presence of SVD.

For the VBM analysis (Ashburner & Friston, 2000; Good et al., 2001), a GLM was used to identify areas of grey matter atrophy showing positive or negative correlations with OMT metrics across the whole cohort. Age, sex, and years of education were included as covariates. A separate GLM was then used to check for differences in the slope of the linear relationship between grey matter atrophy and OMT metrics between Control and SVD participants. Where differences were observed, separate GLMs were run for each group to determine the nature of this association. All comparisons were carried out using the *randomise* function with 5000 permutations. Results were corrected for multiple comparisons using TFCE and were considered significant at $\alpha = 0.05$.

TBSS-style analysis (S. M. Smith et al., 2006) employed the same GLMs used for VBM to first identify associations between diffusion metrics and OMT measures across the whole cohort before looking specifically for group differences. As before, all comparisons were carried out using the *randomise* function with 5000 permutations. Results were corrected for multiple comparisons using TFCE and were considered significant at $\alpha = 0.05$.

4.4 Results

4.4.1 Relationship between WMH and VSTM metrics

After controlling for age, sex, and years of education, linear regression analysis revealed no correlation between Error and WMH volume ($\beta = +0.25$, t = 0.61, p = 0.54) (Figure 4.1A). The slope of the relationship between WMH volume and Error did not differ significantly between Control and SVD participants. ($\beta = +0.42$, t = 0.83, p = 0.41). Similarly, no association was found between Response Time and WMH volume ($\beta = -0.16$, t = -0.37., p = 0.71) across the whole cohort (Figure

4.1B). Having a diagnosis of SVD did not alter the slope of this relationship (β = +0.36, t = 0.65., p = 0.52).

4.4.2 Relationship between subcortical volumes and VSTM metrics

The volumes of seven subcortical structures were used for this analysis: nucleus accumbens, amygdala, caudate, hippocampus, pallidum, putamen, and thalamus. After controlling for age, sex, and years of education, linear regression revealed that subcortical volumes did not correlate significantly with Error across all participants (Figure 4.2). Here, the presence of SVD did not change the slope of the relationship between subcortical volumes and Error ($p > 0.05$ for all beta coefficients).

Response Time also did not show any significant association with subcortical volumes across all participants. As seen in Figure 4.3, although the slope of the relationship between globus pallidum volume and Response Time appears to differ between Control and SVD participants, this finding did not survive correction for multiple comparisons ($p > 0.05$ for all beta coefficients).

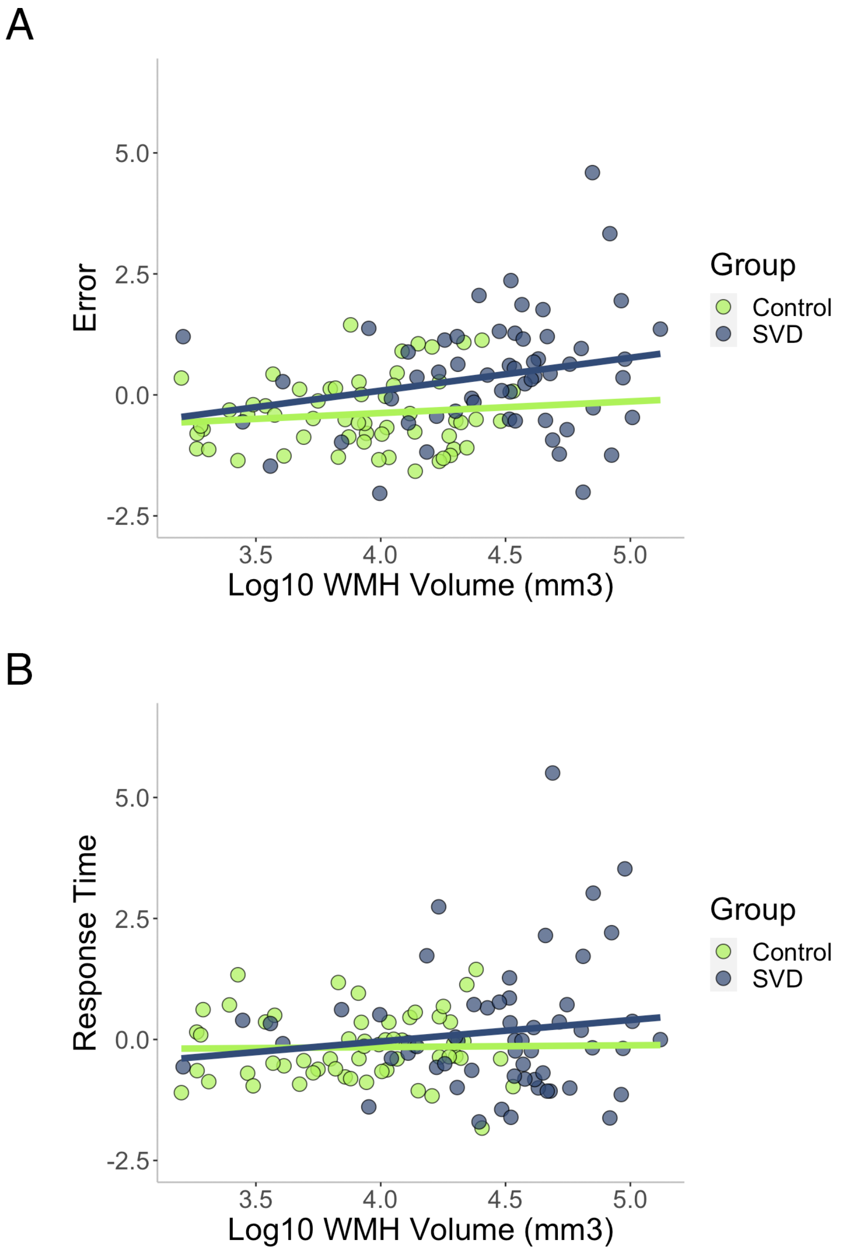


Figure 4.1: **WMH volume did not correlate with Error or Response Time.** Plot of relationship between $\log_{10}$ of WMH volume and VSTM metrics representing Error **(A)** and Response Time **(B)** as measured in the OMT. No significant association was found between WMH volume and both of these metrics across the whole cohort. Control and SVD participants also did not differ in the (lack of a) relationship between WMH volume and VSTM metric.

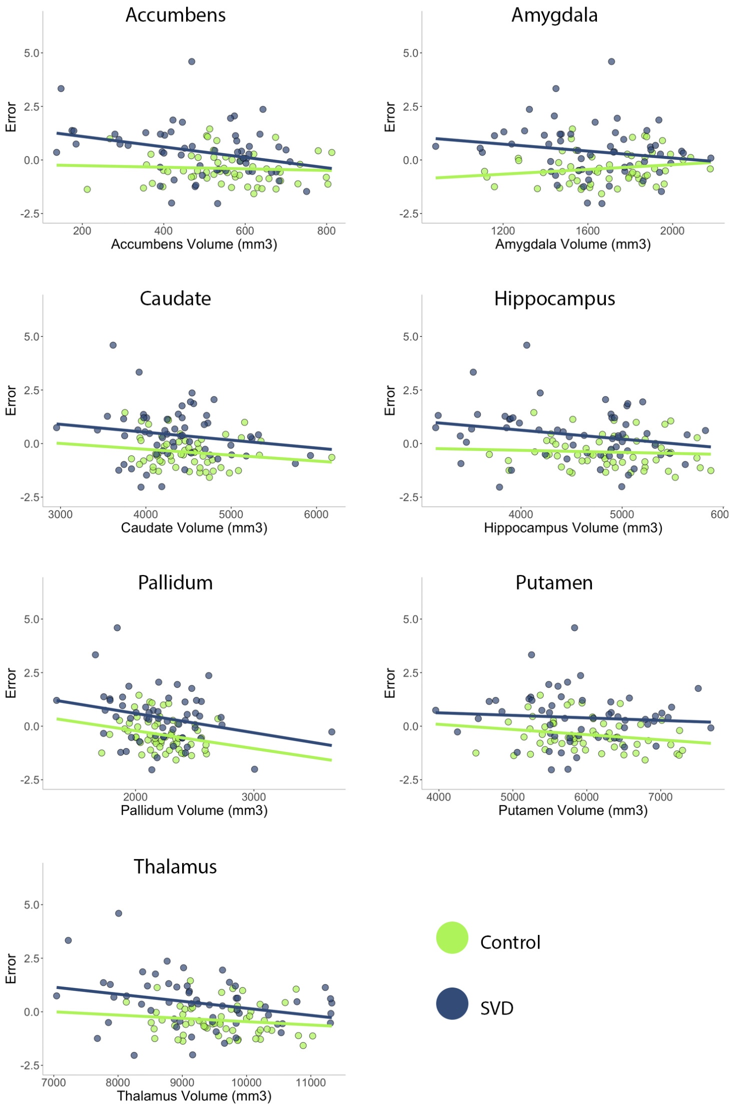


Figure 4.2: **Subcortical volumes did not correlate with error in memory performance.** Scatterplots showing how the volumes of several subcortical structures vary as a function of the OMT factor termed Error. No significant correlations were detected between all of the examined variables.

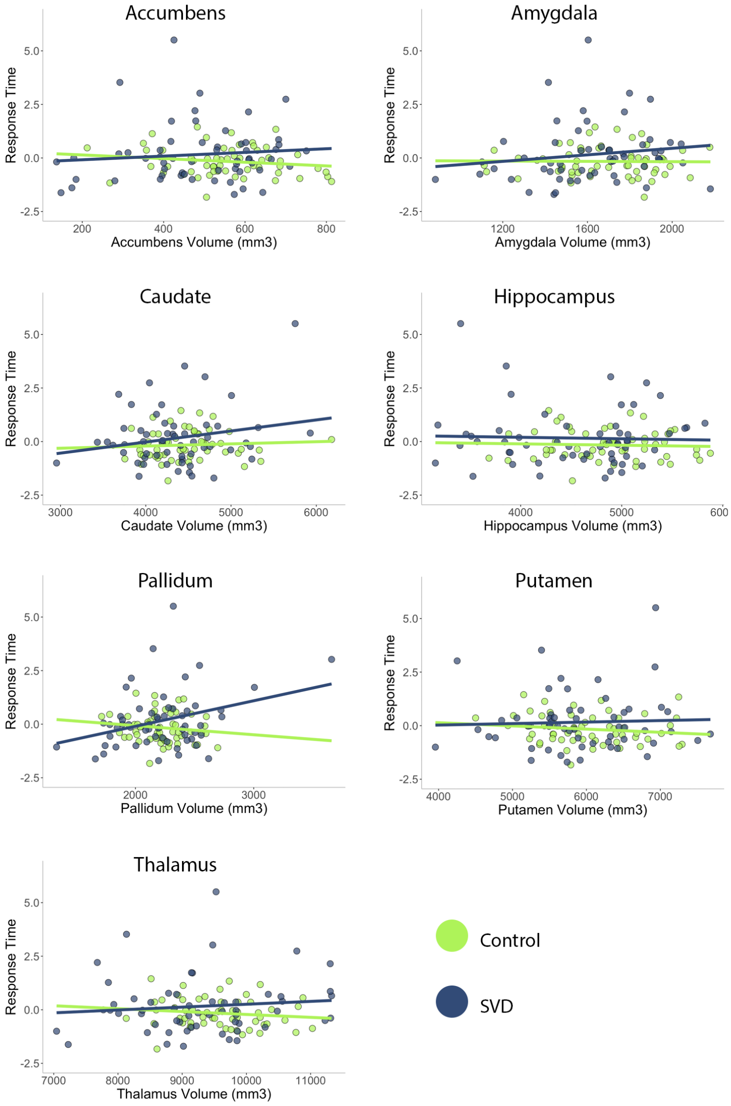


Figure 4.3: **Subcortical volumes did not correlate with response times.** Scatterplots of subcortical volumes and how they vary based on response time. Of note, for the relationship between volume of the globus pallidum and response time, the difference in slopes for Control and SVD participants did not survive correction for multiple comparison.

4.4.3 Correlation between grey matter volume and VSTM metrics

VBM-style analysis was used to look for correlations between local grey matter volume and VSTM metrics across the whole cohort, and separately within the Control and SVD groups. When considering the whole cohort, using $\alpha = 0.05$ and after correcting for multiple comparisons with TFCE, atrophy of the right occipital cortex was associated with greater Error (Figure 4.4A). Was this equally true for both groups, or was it specific to Control or SVD participants in particular? Here, there was a difference between Control and SVD in the slope of the relationship between right lingual grey matter volume and Error (Figure 4.4B). Tests of individual group slopes revealed that in SVD participants, atrophy of an area involving the right lingual gyrus as well as lobules V and VI of the right cerebellum was associated with greater VSTM Error, whereas Control participants did not exhibit the same relationship (Table 4.1, Figure 4.4C). No significant association was found between Response Time and local grey matter volume.

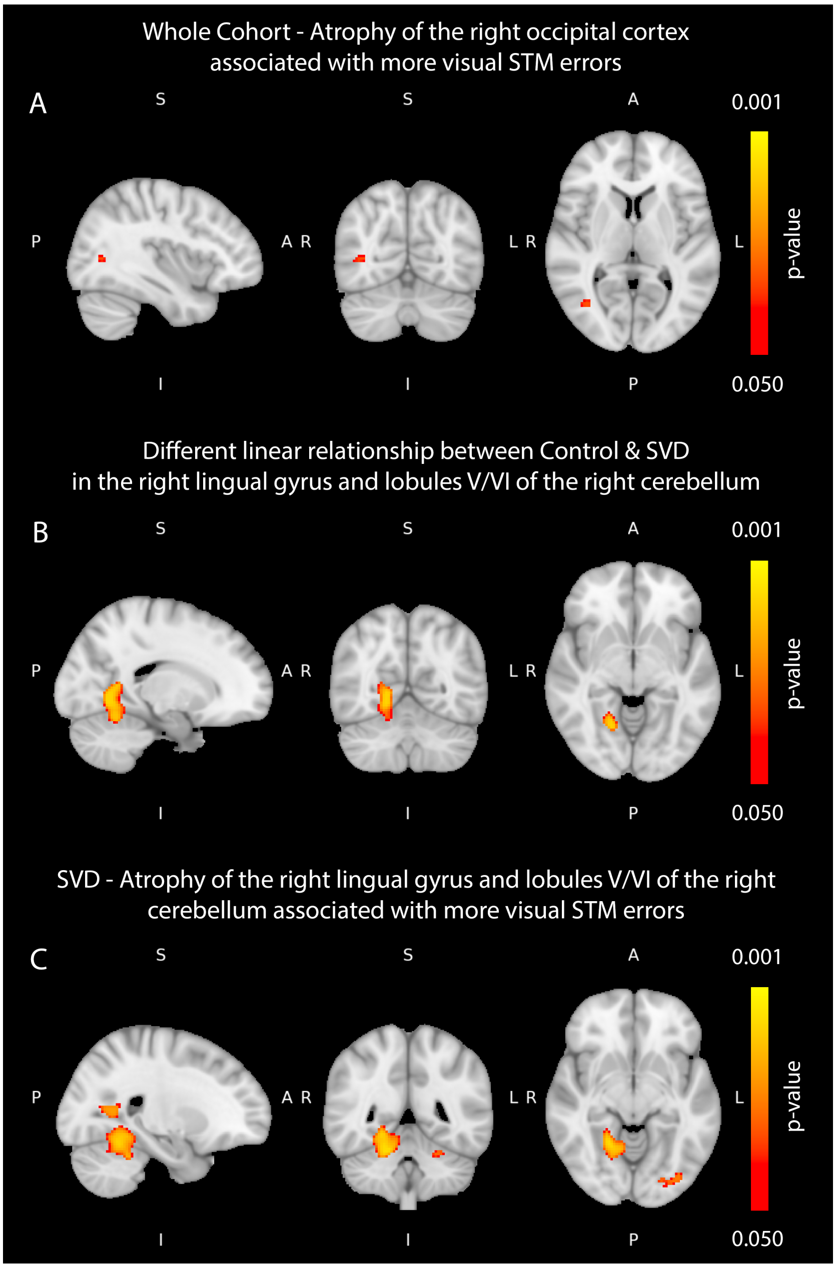


Figure 4.4: **Results of VBM-style analysis.** **(A)** In the whole cohort, atrophy of the right occipital cortex was associated with higher rates of VSTM errors. **(B)** The linear relationship between Error and grey matter volume in the right lingual gyrus as well as lobules V/VI of the right cerebellum was different between Control and SVD participants. **(C)** In SVD participants, atrophy of the same areas outlined above were correlated with more Error, whereas no such relationship existed in Control participants.

-	No. of voxels	1 - p max	MAX X (vox)	MAX Y (vox)	MAX Z (vox)	COG X (vox)	COG Y (vox)	COG Z (vox)
Right lingual gyrus & lobules V/VI of right cerebellum	2251	0.997	37	35	26	43.7	34.2	29.6

Table 4.1: **VBM cluster information.** Cluster information includes the number of voxels in the significant cluster, its significance value, X/Y/Z coordinates of the maximum intensity voxel, as well as X/Y/Z coordinates of the Centre of Gravity (COG) representing the weighted average of the coordinates by intensities within each cluster.

4.4.4 TBSS

TBSS analysis, with $\alpha = 0.05$ and correcting for multiple comparisons with TFCE, using the DTI model on the whole cohort demonstrated that lower FA and higher MD values were associated with more VSTM Error across large parts of the white matter skeleton (Figure 4.5A & 4.5B). These changes were most prominent in the anterior thalamic radiation bilaterally, dorsal subsection of the cingulum bundle bilaterally, forceps major, forceps minor, and superior longitudinal fasciculus bilaterally.

To investigate whether these findings were true for both Control and SVD participants, or only specific to one group in particular, differences were sought in the slope of the relationship between DTI measures and OMT metrics (Figure 4.6).

Using this approach, it was possible to show that there was a change in the linear relationship between MD and Error in parts of the white matter skeleton namely the anterior thalamic radiation, dorsal subsection of the cingulum bundle, forceps major, forceps minor, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, middle longitudinal fasciculus, optic radiation, superior longitudinal fasciculus, and vertical occipital fasciculus (Figure 4.6A). Specifically, in these white matter tracts, SVD participants showed a stronger positive association between MD and Error compared to Control participants (Figure 4.6B).

Application of the NODDI model, again with a threshold of $\alpha = 0.05$ and correcting for multiple comparisons with TFCE, revealed that alterations in NDI and to a lesser extent, ODI and ISOVF, parameters were associated with Error (Figure 4.7). All changes were in the directions that were most biologically plausible. That is, higher Error was associated with lower NDI, higher ODI and increased ISOVF. No significant differences were found in the slope of the relationship between NODDI parameters and OMT metrics, indicating that these associations were general in nature and not disease specific.

As for Response Time, no significant associations were found between this factor and any of the DTI or NODDI parameters.

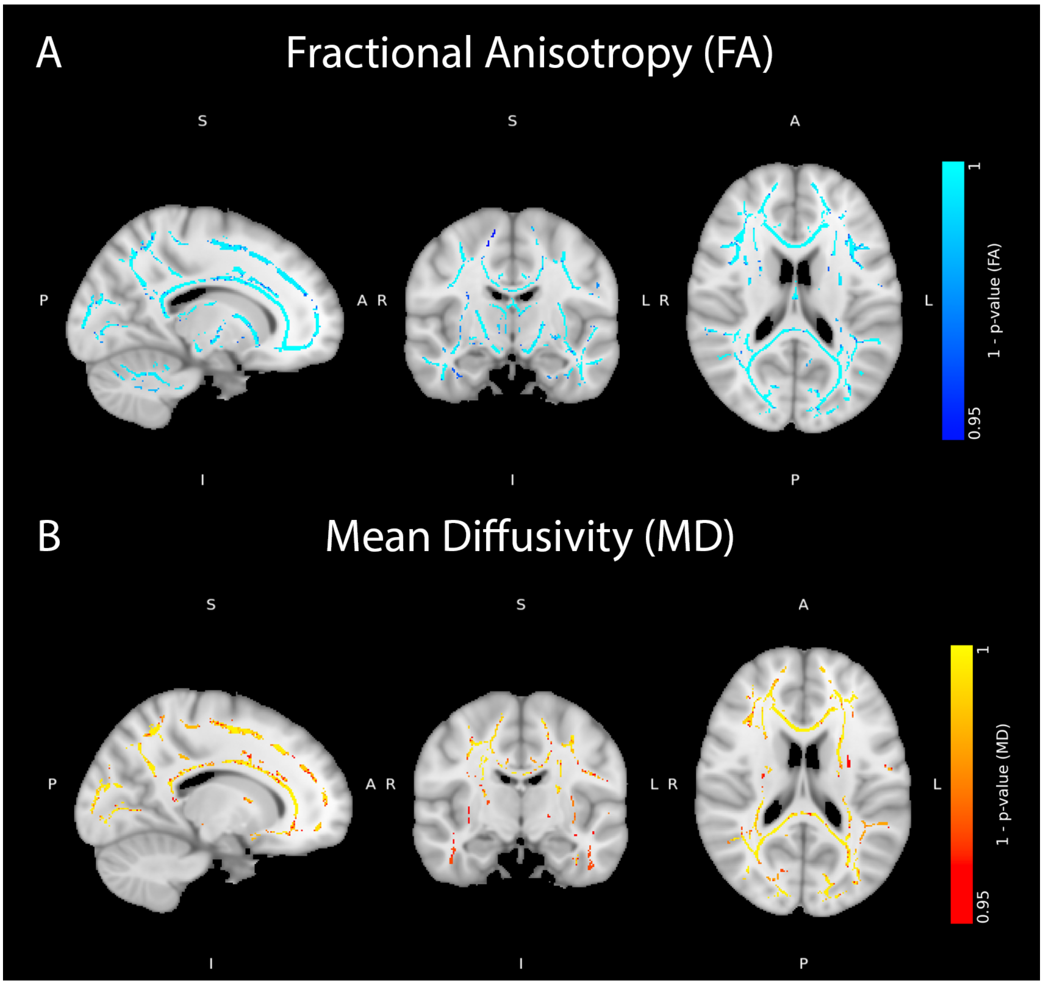


Figure 4.5: **TBSS analysis using the DTI model.** **(A)** VSTM errors were associated with reduced FA across many areas of the white matter skeleton. **(B)** Similar white matter tracts were involved where higher MD correlated with more VSTM errors.

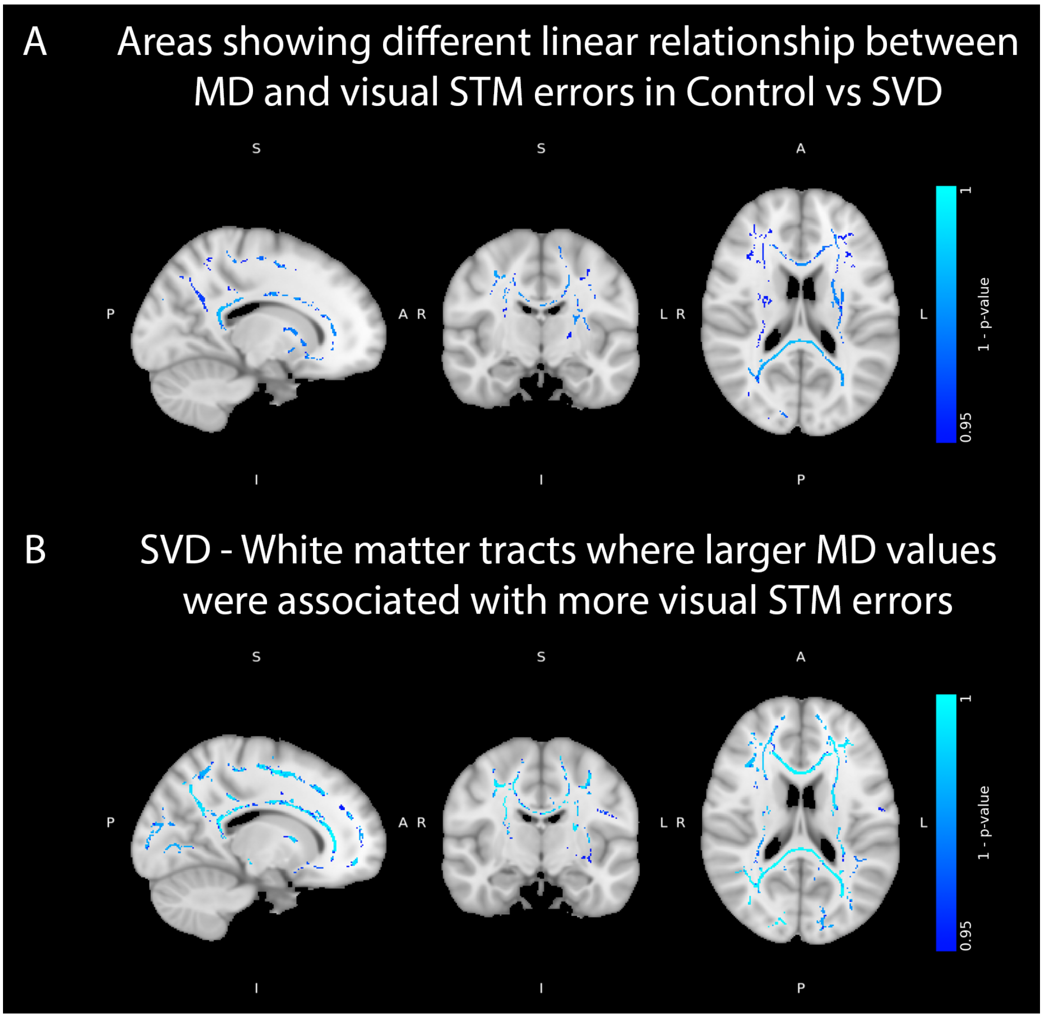


Figure 4.6: **Group differences in the association between MD and VSTM errors. (A)** Differences were found in the linear relationship between MD and Error in these white matter tracts. **(B)** In SVD, larger MD values in these tracts were associated with more VSTM errors. The same correlation was not demonstrated in Control participants.

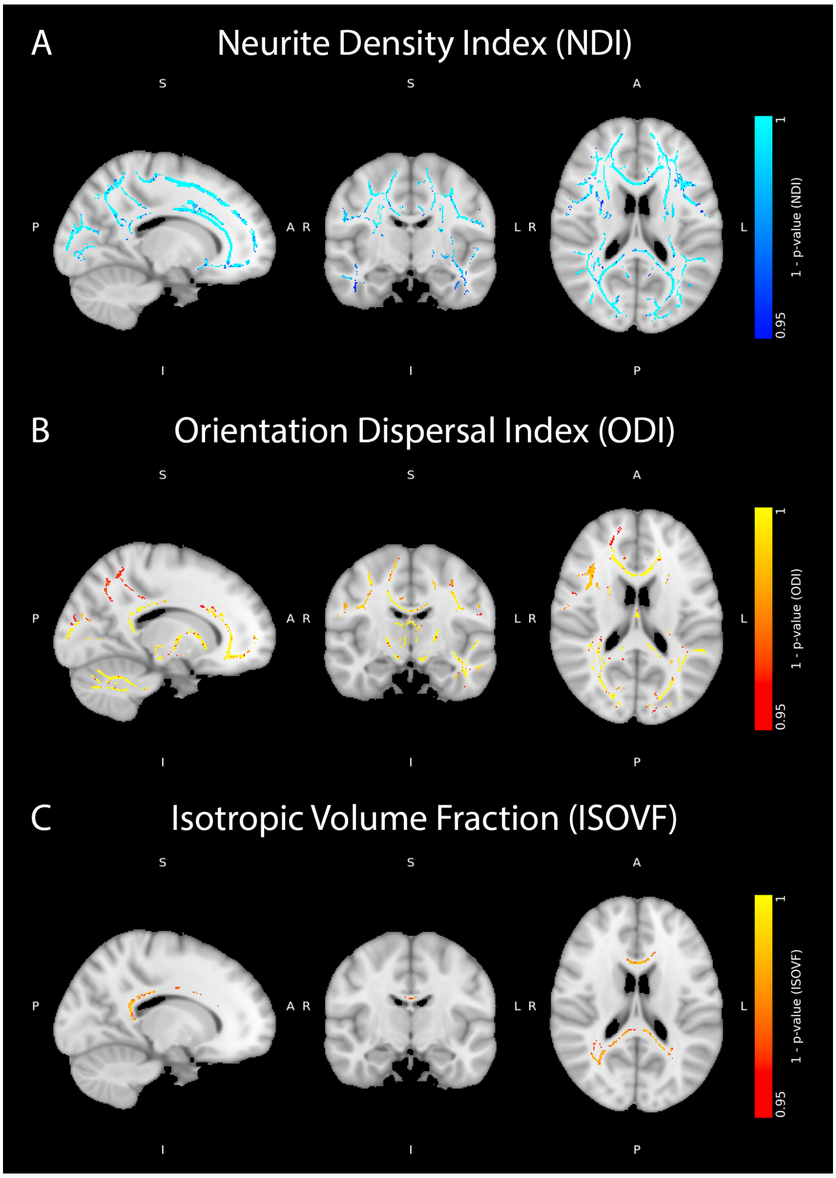


Figure 4.7: **TBSS analysis using the NODDI model.** **(A)** Lower NDI was associated with more VSTM errors in many parts of the white matter skeleton. **(B)** Higher ODI correlated with poorer memory performance. **(C)** The same changes were seen, albeit to a lesser extent, for ISOVF across the whole cohort.

4.5 Discussion

In this chapter, several different MRI modalities were used to investigate the neural architecture of VSTM in a cohort of healthy elderly and SVD participants. The analyses examined whether any neural correlates of memory performance were applicable across the whole cohort or were specific to the presence of disease. Several important findings emerged. First, neither WMH burden nor subcortical volumes predicted VSTM metrics representing error or response time in VSTM performance. Second, atrophy in the right occipital region, specifically the right lingual gyrus correlated with how well participants did in the VSTM task. Finally, a performance error in VSTM was associated with diffuse changes in the white matter skeleton with a particular emphasis on certain tracts: anterior thalamic radiation, dorsal subsection of the cingulum bundle, forceps major, forceps minor, and superior longitudinal fasciculus. Although most of these changes occurred throughout the whole cohort, some were more specific for SVD.

VBM revealed that grey matter atrophy in the right occipital region correlated significantly with making more errors involving VSTM. The occipital lobe contains primary and association visual cortices, and its role in visual perception and processing is well-known. On its medial surface, the calcarine sulcus divides that part of the brain into the cuneus (superior to the calcarine sulcus) and the lingual gyrus (inferior to it). In an early study, bilateral ischaemic necrosis of the lingual gyri was associated with impaired visual learning (Bogousslavsky, Miklossy, Deruaz, Assal, & Regli, 1987). The same investigation also highlighted the potential role of visuo-limbic disconnection in explaining visual memory dysfunction. This was supported by a more recent report showing how cortical atrophy especially in the posterior part of the right cerebral hemisphere correlated with worse attention as well as immediate and delayed visual memory performance (Peterson et al., 2009).

One question that arises from the VBM finding is whether this relationship is equally true for both control and SVD participants. In people with SVD, atrophy of the right lingual gyrus predicted greater error in VSTM performance, whereas no such association was present in healthy elderly participants. Why is this the case when the main pathology of SVD, at first glance at least, appears to be distributed in periventricular and deep white matter regions? One likely reason is that the ranges of VSTM performance in control participants were very small in this study (see Figure 3.10A from the previous chapter), therefore making it more difficult to identify subtle relationships between grey matter atrophy and performance on the OMT. Another possible explanation is that lesions in SVD do not just exert perilesional effects but may also have remote manifestations including cortical thinning via the disconnection of white matter tracts (ter Telgte et al., 2018). Further supporting this view, several studies have shown negative associations between WMH and the volumes of cortical regions far from the site of lesions (Dickie et al., 2016; Lambert et al., 2015; Tuladhar, Reid, et al., 2015).

The results from TBSS-style analyses give the clearest impression yet of how lesions seemingly focused in relatively small areas of the white matter may be predictive of more widespread pathology. Reductions in microstructural integrity of the white matter skeleton were observed in several tracts across both Control and SVD participants. In these tracts, lower FA and NDI were consistently associated with more errors; the same was true for higher MD, ODI, and ISOVF values. Tracts that were frequently involved include the anterior thalamic radiation, dorsal subsection of the cingulum bundle, forceps major, forceps minor, optic radiation, and all branches of the superior longitudinal fasciculus.

The anterior thalamic radiations connect anterior and midline nuclei in the thalami with the frontal lobe (Yuan et al., 2016). Previous studies have identified their involvement in executive dysfunction (J. M. Biesbroek et al., 2013, 2016). For example, in the 2013 report by Biesbroek et al., voxel-based lesion-symptom mapping was used to demonstrate a significant correlation between white matter lesions in the anterior thalamic radiation and tests of executive function. A subsequent study from the same group found that in a cohort of SVD patients attending memory clinics, region of interest-based analyses revealed inverse associations between WMHs located in the anterior thalamic radiation and executive function (J. M. Biesbroek et al., 2016). The anterior thalamic radiation has also been identified as a potential tract involved in processing speed deficits (Duering et al., 2011, 2013, 2014) in both sporadic and genetic SVD.

The cingulum bundle is a complex structure linking not just frontal, parietal, and medial temporal sites with each other but also subcortical nuclei to the cingulate gyrus (Bubb, Metzler-Baddeley, & Aggleton, 2018). It is thought to play a role in cognitive control and executive function, as demonstrated in a study by Bettcher et al. who used latent variable modelling to show that FA changes in the dorsal cingulum independently predicted executive function as measured by tasks involving mental set shifting, information updating, and inhibition of pre-potent responses (Bettcher et al., 2016). Further support for this concept came from the demonstration that FA in the posterior cingulum tract is associated not just with attention/executive function, but also with verbal and visual memory, language, and visual-spatial processing domains (Kantarci et al., 2011). In addition, cingulum bundle MD has also been shown to inversely correlate with working memory (Charlton, Barrick, et al., 2010).

The forceps major is formed by fibres running backwards from the splenium of the corpus callosum into the occipital lobe. A longitudinal DTI study of 148 healthy children by Krogsrud et al. demonstrated the importance of forceps major integrity for verbal and visuospatial WM (Krogsrud et al., 2018). The forceps minor is made up of fibres running forwards from the genu of the corpus callosum into the frontal lobes. Microstructural integrity of the forceps minor has been shown to differentiate between vascular dementia and mild cognitive impairment or AD (Zarei et al., 2009; Y. Zhang et al., 2022). Furthermore, the forceps minor has been identified as one of many strategic white matter tracts subserving processing speed, executive function, as well as verbal and visual memory (J. Biesbroek, Weaver, & Biessels, 2017; Duering et al., 2011, 2014).

The optic radiations are made up of axons travelling from the lateral geniculate nucleus to the primary visual cortex. They relay visual information originating from the retina to the visual cortex. The superior longitudinal fasciculus (SLF) is an association bundle composed of three distinct branches (Catani, 2016). The most relevant branch as for as VSTM processing is concerned is the second branch (SLF II). In the right hemisphere, this branch of the SLF participates in attention, visuospatial processing, and spatial working memory (Catani, 2016).

From the descriptions of these various white matter tracts, one can speculate that they play a crucial role in various aspects of cognition including VSTM. Therefore, reductions in their microstructural integrity may result in disruption of functional connections between key regions of the brain subserving VSTM and thereby have adverse effects on recall performance.

Additionally, it is important to highlight how the presence of SVD potentially imposes an extra burden on these white matter tracts. In this study, SVD altered the linear relationship between MD values and VSTM error. However, as with VBM, the absence of a similar relationship in healthy elderly participants may be due to the limited spread of diffusion values in the Control group, rather than any pathological effects of SVD *per se*.

In this study, no relationship was found between WMH volume and VSTM performance. This is not entirely surprising, given that the link between WMH and cognitive dysfunction or dementia has been inconsistent, partly due to heterogeneity in study parameters such as population characteristics, disease stage, and WMH characteristics (Hunt et al., 1989; Jokinen et al., 2016; Longstreth et al., 2005; Mungas et al., 2005; van den Heuvel et al., 2006; Y.-L. Wang et al., 2020). Furthermore, there is evidence to indicate that the link between WMH and cognition becomes more attenuated in older people (Zamboni et al., 2019). One key issue with using WMH, either qualitatively or quantitatively, is that their presence alone does not automatically imply a diagnosis of SVD.

One way to solve this conundrum is to identify better ways to characterise WMH, for example, by distinguishing between deep and periventricular WMH. Using this approach, Soriano-Raya et al. demonstrated that deep WMH, but not periventricular WMH, was associated with lowers scores in executive functioning, attention, verbal fluency, visuospatial skills (using Visual Discrimination and Copy from the Visual Reproduction subtests from the Wechsler Memory Scale 3rd edition), and psychomotor speed (Soriano-Raya et al., 2012). In contrast, a recent systematic review and meta-analysis found that periventricular WMH increased the risk of all-cause dementia (Hu et al., 2021). As described in the Introduction to this chapter, another strategy is to quantify the volume of WMH and relate that to cognitive dysfunction, although in this study, no associations were found between the two.

Differences in the volumes of various subcortical structures offer an alternative way of understanding the mechanisms responsible for cognitive dysfunction in SVD. In the SVD cohort recruited for this study, although the volumes of some subcortical structures were smaller compared to Control participants, no associations were found between these and VSTM metrics indexing error or response time. This, despite some of the structures like the pulvinar nuclei in the thalamus being important for vision (Benarroch, 2015). One explanation for this may be that these volume changes in SVD are too small to provide enough sensitivity to demonstrate a relationship with VSTM performance. Indeed, as demonstrated in Chapter 2 of this thesis, although volume reductions were initially identified in the hippocampi and accumbens bilaterally, none of these findings survived correction for multiple comparisons. Decreases in the volumes of subcortical structures may therefore be a relatively late stage in the pathogenesis of cognitive impairment in SVD.

4.6 Conclusion

In conclusion, the data in this chapter demonstrate that VSTM deficits in SVD are not associated with the volumes of WMH or subcortical structures. Instead, atrophy of the right occipital region as well as widespread reductions in the microstructural integrity of several white matter tracts serve as predictors of errors in memory performance. In the next chapter, I switch from memory to motivation, looking at the relationship between SVD and apathy using an effort-based decision-making paradigm.

5 | Impact of cerebral small vessel disease on effort-based decision making

5.1 Abstract

EBDM is a framework that has been used to investigate mechanisms underlying apathy across neurological conditions. This chapter investigated how the presence of SVD affected EBDM and related any deficits found to measures of apathy and depression. Participants with SVD were more sensitive than healthy controls to low effort levels and took longer to decide when considering offers. Combining offer acceptance and reaction time data into a HDDM revealed a significant difference in two parameters namely (i) the influence of effort on drift rate and (ii) non-decision time, i.e., time required for decision-independent processes such as visual perception, motor planning and movement execution. Neither the raw behavioural results nor the parameters obtained from HDDM showed any significant correlations with clinical measures of apathy or depression. The results demonstrate the presence of EBDM deficits in SVD but raise the possibility that these may occur independently of clinical neuropsychiatric diagnoses such as apathy and depression. The findings may have implications for how we understand and treat cognitive and neuropsychiatric symptoms in SVD.

5.2 Introduction

SVD is a slowly progressive disease that manifests itself clinically in several ways, including cognitive impairment, urinary symptoms, gait abnormalities, and mood disturbances (Rost & Etherton, 2020). As our understanding of the clinical manifestations of SVD continues to develop, increasing attention has been paid to the spectrum of mood and motivational disturbances that can afflict people with the condition (Carnes-Vendrell, Deus, Molina-Seguin, Pifarre, & Purroy, 2019; Cosin et al., 2015; Douven et al., 2020; Staekenborg et al., 2010). These neuropsychiatric symptoms can be debilitating for patients and constitute a significant source of stress and burden for their caregivers (Ferro, Caeiro, & Figueira, 2016). A recent systematic review and meta-analysis of 45 studies involving 8,120 participants revealed significant associations between WMH severity and neuropsychiatric outcomes such as apathy, fatigue, and delirium (Clancy, Gilmartin, et al., 2021).

Apathy can be defined as a syndrome involving loss or reduction of motivation resulting in impairments in goal-directed behaviour, cognitive activity, emotion, as well as interest in interacting with other people (Husain & Roiser, 2018). When asked to describe their symptoms, apathetic individuals often say that they just “can’t be bothered”, that they “don’t know why activities no longer interest them”, or that such behaviours “don’t seem worth it” anymore (Le Heron et al., 2019). Apathy can occur without depression, and vice versa, but some patients can fulfil the criteria for both diagnoses (Hollocks et al., 2015; Lanctot et al., 2023). Efforts to characterise apathy have led to the development of self-report and clinician administered measures such as the Lille Apathy Rating Scale (LARS), Dimensional Apathy Scale, and Apathy-Motivation Index (AMI)(Ang et al., 2017; Radakovic & Abrahams, 2014; Sockeel, 2006).

Several previous reports have demonstrated an association between SVD and apathy (Hollocks et al., 2015; Lohner, Brookes, Hollocks, Morris, & Markus, 2017; van der Mast et al., 2008; H. Zhao, Liu, Xia, Xie, & Huang, 2021). For example, in a study of 196 SVD patients, apathy, measured using a subset of the Geriatric Depression Scale (GDS), was present either on its own in 15.8% of participants, or together with depression in a further 11.8% of them (Lohner et al., 2017) Overall, across studies, the prevalence of apathy in SVD is estimated to be between 15-30% (Le Heron et al., 2019). To put this in context, apathy is also prevalent in a broad range of neurological and psychiatric conditions, affecting approximately 30% of PD patients, 50% of AD patients, and >50% of frontotemporal dementia patients (Pagonabarraga, Kulisevsky, Strafella, & Krack, 2015; Lanctot et al., 2017; Lansdall et al., 2017).

As the link between SVD and apathy has become clearer, focus has shifted away from simply demonstrating the presence of apathy in SVD to attempting to deconstruct its underlying mechanisms. One approach that has been used is to examine apathy from a behavioural perspective using a framework of EBDM for rewards (Husain & Roiser, 2018). Early theories of decision-making often attempted to explain behaviour in terms of the influence of goal value and strength of reinforcement, with less emphasis placed on how the cost of an action contributes towards the final decision to act (Kurniawan, Guitart-Masip, & Dolan, 2011). EBDM overcomes this limitation by addressing how a choice is made after integrating the value of goals with the cost of actions. EBDM can be decomposed into several constituent mechanisms including option generation, option selection, anticipation, initiation of action, interaction with the behavioural goal, as well as learning from outcomes (Husain & Roiser, 2018). In theory, dysfunction in any one of these processes might potentially lead to the development of apathy.

In deciding whether or not to spend some effort to obtain a reward, several mechanisms may contribute towards impaired decision-making in apathy. These include changes in sensitivity to reward or effort, global reduction in engagement on the task at hand, or some combination of these factors. Saleh et al. examined 82 patients with MRI evidence of late-onset SVD by offering them monetary rewards in return for physical effort (Saleh, Le Heron, et al., 2021). On a trial-by-trial basis, participants were asked to either accept or reject the offer of some (virtual) apples on a tree for a specific amount of effort indicated by a horizontal line across the tree trunk. If an offer was accepted, participants then had to squeeze a handheld device in proportion to the effort level required by the offer. SVD patients with apathy as measured using the Apathy Evaluation Scale (AES) rejected more offers compared to patients who did not have apathy. Furthermore, not only were SVD patients with apathy less motivated by low levels of reward, they were also more sensitive to high levels of effort in the experiment.

One way to conceptualise performance on the EBDM task is to view it as a two-alternative forced choice experiment in which participants must choose either to accept or reject an offer. Using this perspective allows the application of well-validated two-alternative forced choice modelling approaches like the drift diffusion model (DDM) that can offer clearer mechanistic insights into the presence of latent psychological processes responsible for cost-benefit evaluation in EBDM (Bogacz, Brown, Moehlis, Holmes, & Cohen, 2006; Ratcliff, 1978; Ratcliff & McKoon, 2008).

DDM assumes an internal accumulation of evidence in a noisy manner towards one of two decision boundaries (upper and lower), corresponding to the two available responses (accept or reject). This model can be described using four parameters: (i) the bias, z, representing the starting point for evidence accumulation such that a completely non-biased starting point would be equal to 0.5; (ii) the drift rate, v, reflecting how quickly evidence is accumulated; (iii) the threshold, a, measuring the distance between the two decision boundaries; and (iv) the non-decision time, t, composed of the time needed for decision-independent processes such as perception and execution of physical movement.

In the abovementioned study on apathetic vs. non-apathetic SVD patients by

Saleh et al., drift rate increased (and the time to reach decision threshold reduced) as reward increased and effort decreased (Saleh, Le Heron, et al., 2021). The EBDM framework has also provided notable findings in CADASIL, the early onset, monogenic, form of the disease (Le Heron, Manohar, et al., 2018). When given the choice to accept or reject varying levels of monetary reward in return for spending physical effort by squeezing handheld dynamometers on the same task as deployed by Saleh and colleagues (Saleh, Le Heron, et al., 2021), apathetic CADASIL patients (assessed using the LARS and the AES) exhibited reduced incentivization by rewards and therefore rejected more offers overall compared to non-apathetic CADASIL patients or healthy controls (Le Heron, Manohar, et al., 2018). Thus, in both late-onset and early-onset SVD with apathy there is evidence for impaired EBDM.

Although deficits in EBDM have been linked previously with apathy, they may also arise independently of it. One example of this comes from a study performed in a group of patients with PD where apathy and being ON or OFF dopaminergic medication were found to have distinctly different effects on EBDM (Le Heron, Plant, et al., 2018). Specifically, apathetic patients ended up rejecting more offers with low reward, whereas dopamine increased acceptance of high effort, high reward offers regardless of the underlying apathy status, i.e. across all PD patients. A more complex picture, therefore, emerges with regards to how factors may affect EBDM in different forms of neurological diseases.

This chapter will attempt to answer the following questions:

1. Do SVD participants have a deficit in EBDM compared to healthy controls? If so, what is the nature of this impairment?
2. Can HDDM be used to investigate the possible mechanism(s) behind any EBDM deficits detected in this experiment?

3. How do the raw behavioural parameters and HDDM metrics correlate with scores on the AMI (a self-report measure of apathy) and BDI-II (an instrument for measuring depression)?

5.3 Methods

5.3.1 Participants

The study included 51 participants with SVD (Age: μ = 68.9, SD = 9.03, 26 males) and 51 age- and gender-matched healthy controls (Age: μ = 66.7, SD = 6.25, 20 males). Both cohorts were subsets of the SVD and healthy elderly control groups used in Chapters 2-4. Comparable previous work in healthy participants and patients was used to determine the appropriate sample size (Chong et al., 2015; Le Heron, Manohar, et al., 2018; Saleh, Le Heron, et al., 2021). Permission for this study was obtained from the University of Oxford Ethics Committee (RAS ID: 248379, Ethics Approval Reference: 18/SC/0448). All participants provided written consent and were offered monetary compensation for taking part in the study.

Participants from both groups were required to complete the AMI and BDI-II, self-report questionnaires measuring apathy (Ang et al., 2017) and depression (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) respectively. The AMI is a brief, self-report index of apathy and motivation that covers three domains of apathy namely behavioural activation, emotional sensitivity, and social motivation. Proposed cut-offs for total AMI score are $\geq$ 1.91 for moderate apathy and $\geq$ 2.38 for severe apathy, representing scores that are more than 1 standard deviation and more than 2 standard deviations, respectively, from mean scores in a healthy population (Ang et al., 2017). The BDI-II is made up of 21 items corresponding to symptoms of depression that are grouped into several categories such as somatic, affective, cognitive, and vegetative symptoms (Beck et al., 1961). Each item is given a rating between 0-3 depending on their intensity or severity. The final score ranges from 0-63 and is obtained by adding up the individual ratings for all 21 items. Proposed cut-off scores are as follows: 0-9 indicating no or minimal depression, 10-18 for mild to moderate depression, 19-29 reflecting moderate to severe depression, and 30-63 for severe depression (Butcher, Taylor, & Cynthia Fekken, 1998).

5.3.2 EBDM paradigm

The EBDM task employed a setup similar to ones used in previous studies involving healthy participants as well as patients with PD, genetic SVD (CADASIL) and sporadic SVD (Bonnelle et al., 2016; Chong et al., 2015; Le Heron, Plant, et al., 2018; Saleh, Le Heron, et al., 2021). Participants were asked to make a decision after weighing potential rewards against the effort required to obtain those rewards. Here, reward was depicted as apples on trees whereas effort levels were shown as bars on the tree trunks. Five different reward levels were used in this experiment, represented by 1, 4, 7, 10, and 13 apples, respectively.

Effort in the task was measured using hand-held dynamometers. At the start of the test, participants were asked to squeeze the handle as hard as they could in order to establish their maximal voluntary contraction (MVC). Then, to give participants some idea of what the 5 different effort levels entailed, they were asked to squeeze the dynamometer while receiving feedback in the form of a red bar drawn on the tree trunk. As soon as the desired effort level was reached, this bar turned yellow and participants were allowed to relax their grip. The 5 effort levels corresponded to 16, 32, 48, 64, and 80% of MVC, with each effort level experienced twice (Figure 5.1).

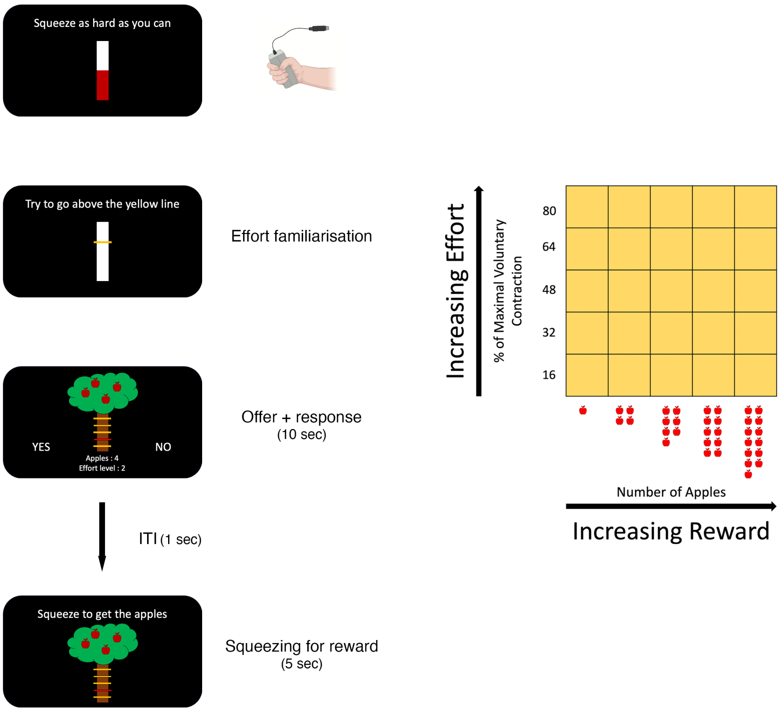


Figure 5.1: **Effort-based decision making task.** First, calibration of the handheld dynamometer was done according to the maximum voluntary contraction (MVC) for each participant. Then, participants were familiarised with the different effort levels used in the task by asking them to squeeze the handles up to the effort level corresponding to 16, 32, 48, 64, and 80% of their MVC. Next, they were required to decide whether the reward on offer (apples) were worth the effort assigned to it. Finally, they were told that at the end of the experiment, 10 of their decisions would be randomly selected and that they would have to carry out their choice by squeezing to the required effort level if they had said yes to the original offer. The matrix on the right provides a representation of the different effort and reward levels used in the experiment.

Participants then moved on to the decision-making part of the experiment, in which they were shown different combinations of reward and effort levels and were asked the following question: Is it worth spending the amount of effort indicated on the display to obtain the number of apples shown on the screen? They could then accept or reject the offer by selecting the word “Yes” or “No” displayed on the screen using either the left or right arrow keys (on a standard keyboard). To reduce the likelihood of participants simply pressing the same key without evaluating the offer on display, the positions of “Yes” and “No” were changed randomly between trials. At the end of the experiment, participants were told that 10 of their decisions would be selected randomly and that they would have to follow through with their decision i.e. by squeezing the handles to the required effort level if they had said “Yes” to the original offer.

5.3.3 Statistical analyses

Statistical analyses and modelling were performed in MATLAB version R2023a and Jupyter Notebook running Python version 3. Mixed-effect models were fitted using the *fitglme* function in MATLAB. Linear regression was carried out in R Studio using the *lm* function, part of the stats package in R. Post hoc analyses were carried out in R using either the student t-test or Wilcoxon rank-sum test depending on whether parametric assumptions were met.

5.3.4 Application of HDDM

Based on the design of this experiment, the following parameters were fixed across conditions: threshold (a), bias (z), and non-decision time (t). The drift rate (v) however, was allowed to vary with reward and effort, producing four further subcomponents, namely: (i) the average drift rate across all trials, v0; (ii) the effect of reward on drift rate, vr; (iii) the effect of effort on drift rate, ve; and (iv) the interaction between reward and effort on drift rate, vr*e. For each segment within the decision space, the actual drift rate (Vr*e) was therefore assumed to have a linear relationship with reward, effort, and their interaction such that:

$$Vr * e = v0 + vr - ve - vr * e$$

All parameters described above were obtained by employing a hierarchical Bayesian estimation procedure to fit the model to the response and reaction time data. This was done using a well-validated hierarchical DDM (HDDM) toolbox (https://github.com/hddm-devs/hddm; version 0.9.8; Python 3).

5.4 Results

5.4.1 Demographics

Demographics are summarised in Table 5.1. The two groups did not differ in terms of age or sex ratio. SVD participants had significantly lower total ACE-III scores compared to healthy controls, although the scores for both groups were still within normal limits for the general population (Hsieh et al., 2013; Mathuranath et al., 2000). Using the AMI as a measure of apathy revealed higher scores in all domains (behavioural, social, emotional, and total) for people with SVD (Ang et al., 2017). When participants were dichotomised into apathetic versus non-apathetic groups based on their total AMI as proposed by Ang et al., none of the healthy controls were found to be apathetic, whereas 8 out of 51 SVD participants met the criterion for apathy. In addition, people in the SVD group were more likely to be depressed and demonstrated lower scores on the WHO-5 Well-Being Index and Cantril Ladder questionnaires (Cantril, 1965; Topp, Ostergaard, Sondergaard, &

Bech, 2015; Y.-P. Wang & Gorenstein, 2021).

	Control (n = 51)	SVD (n = 51)	
Measure	Mean ± std	Mean ± std	p-value
Age (years)	66.7 (6.25)	68.9 (9.03)	0.153
Sex (M/F)*	20/31	26/25	0.233
Total ACE-III (range 0-100)	97.20 (2.65)	92.20 (7.05)	**< .001**
Total AMI	1.08 (0.38)	1.53 (0.48)	**< .001**
AMI Behavioural	1.16 (0.55)	1.62 (0.71)	**< .001**
AMI Social	1.23 (0.61)	1.86 (0.89)	**< .001**
AMI Emotional	0.86 (0.43)	1.10 (0.59)	**0.021**
Apathetic, AMI >1.9 (yes/no)*	0/51	8/43	**0.003**
Depressed, BDI-II >9 (yes/no)*	8/43	25/26	**< .001**
WHO-5 Well-Being Index (%)	71.22 (14.90)	60.86 (23.00)	**0.024**
Cantril Ladder (range 0-10)	8.02 (1.46)	7.02 (1.61)	**< .001**

Table 5.1: **Demographic, cognitive, and neuropsychological measures.** * Chi-square test

5.4.2 Proportion of offers accepted and reaction time

As shown in Figure 5.2A, overall SVD participants and healthy controls did not differ in terms of the total proportion of offers accepted throughout the experiment (Control: $\mu = 0.67$, SD = 0.13, SVD: $\mu = 0.63$, SD = 0.15, $t_{100} = 1.18$, p = 0.24). However, participants in the SVD group took longer to make a decision compared to healthy controls (Control: $\mu = 2.51$, SD = 0.55, SVD: $\mu = 2.96$, SD = 0.62, $t_{100} = -3.91$, $p < 0.001$).

To investigate if these metrics were related to apathy as indexed by total AMI scores, linear regression models controlling for age, sex, and years of education were performed. The results did not reveal any significant associations between either proportion of offers accepted or reaction time with scores on the AMI questionnaire ($p > 0.1$ for both) (Figure 5.2B). Similarly, no relationship was found between the two behavioural metrics and depression (BDI-II) ($p > 0.1$ for both; figure not shown).

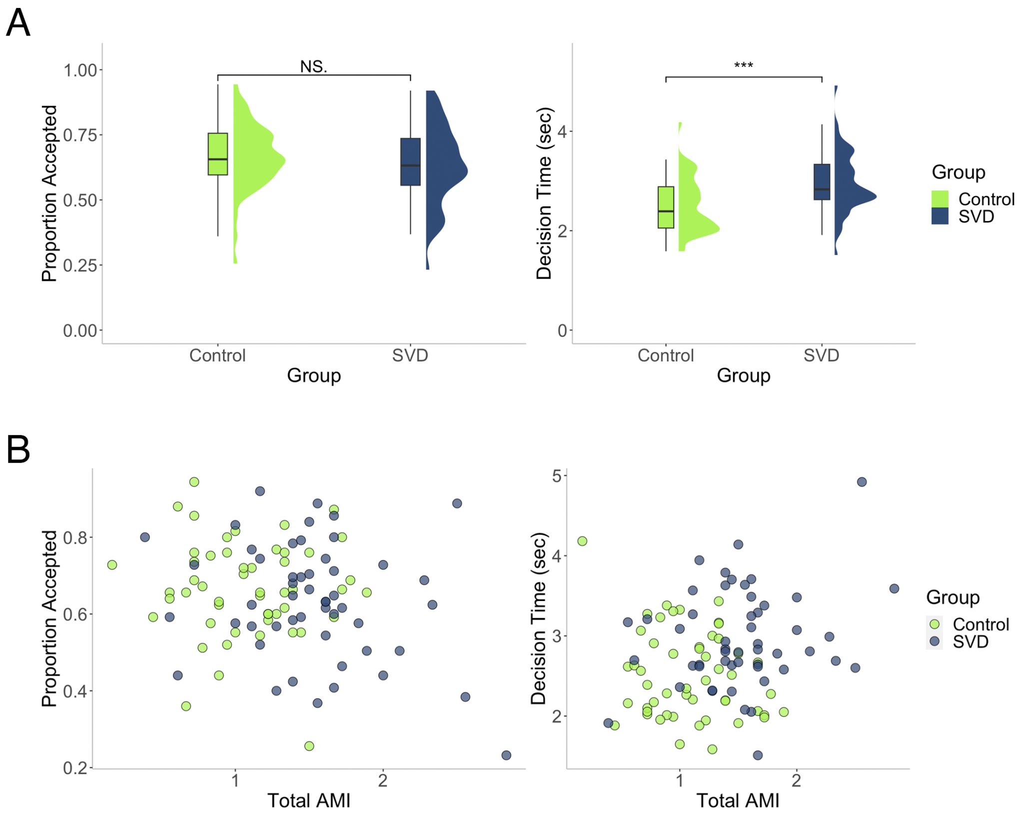


Figure 5.2: **Raw results for proportion of offers accepted and reaction time.** **(A)** Participants from the two groups did not differ in terms of the proportion of offers accepted. However, SVD participants took longer to come to a decision overall compared to healthy controls. **(B)** No significant associations were found between offer acceptance or reaction time with apathy.

5.4.3 Effect of reward and effort on offer acceptance

To investigate how the proportion of offers accepted varied as a function of group, reward, and effort, a generalised linear mixed-effects model was performed. The model used quadratic transformation of effort, consistent with the methodology employed by previous reports investigating EBDM using an approximately similar paradigm (Le Heron, Manohar, et al., 2018; Saleh, Le Heron, et al., 2021).

As expected, participants accepted more offers when reward increased as well as when the effort required decreased (main effect of reward on acceptance: β = 0.033, SE = 0.012, t_{12742} = 2.79, $p < 0.01$; main effect of effort on acceptance: β = -1.76, SE = 0.22, t_{12742} = -7.89, $p < 0.001$) (Table 5.2, Figure 5.3A). There was no main effect of group (p = 0.08) but there was a significant interaction between group and effort; SVD participants were more sensitive—that is they accepted fewer offers—at low effort levels, compared to healthy controls (group x effort: β = 0.40, SE = 0.14, t_{12742} = 2.85, $p < 0.01$) (Figure 5.3B). In addition, the interaction between reward and effort was significant, suggesting that the aversive effect of efforts became less pronounced when countered by increasing rewards (reward x effort: β = 0.078, SE = 0.025, t_{12742} = 3.17, $p < 0.01$). No three-way interaction was found between group, reward, and effort (p = 0.28).

Offer Acceptance				
Name	Estimate	SE	t_{12742}	p-value
(Intercept)	0.81	0.12	6.61	**<0.001**
Group	-0.13	0.078	-1.73	0.084
Reward	0.033	0.012	2.79	**<0.01**
Effort	-1.76	0.22	-7.89	**<0.001**
Group * Reward	0.0033	0.0074	0.44	0.66
Group * Effort	0.40	0.14	2.85	**<0.01**
Reward * Effort	0.078	0.025	3.17	**<0.01**
Group * Reward * Effort	-0.017	0.016	-1.09	0.28

Table 5.2: **Generalised linear mixed-effects models examining the effect of group, reward, and effort on offer acceptance.** Models were specified as follows: choice 1 + group * reward + group * effort + reward * effort + group * reward * effort + (1 + reward * effort | participant)

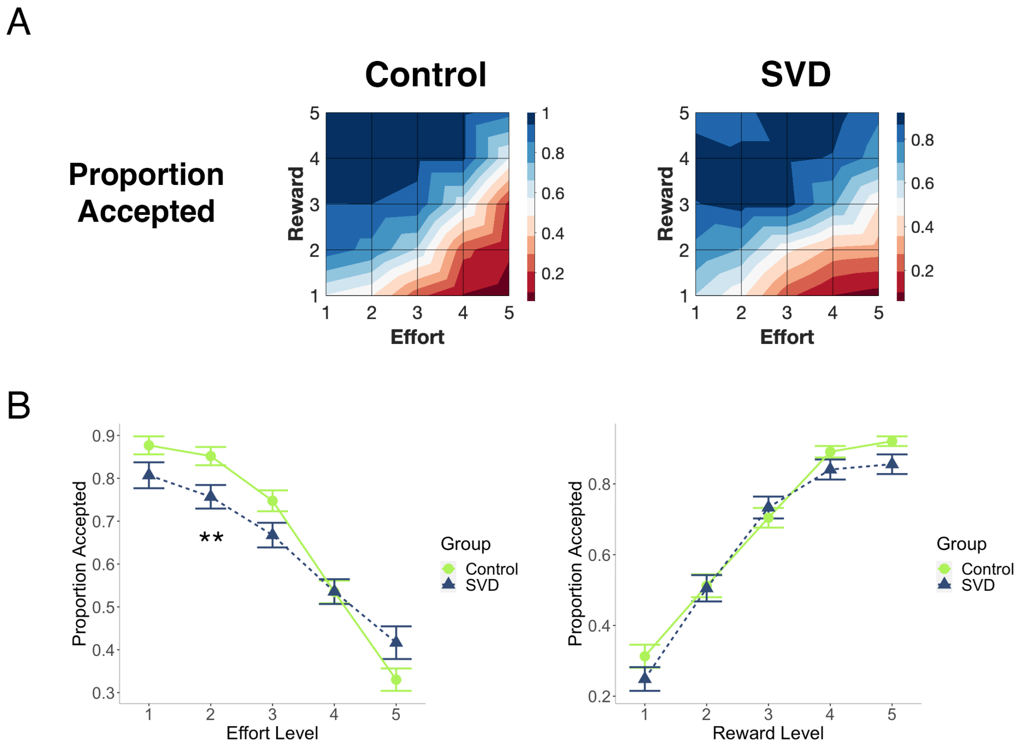


Figure 5.3: **Effect of reward and effort on offer acceptance.** **(A)** Participants from both groups accepted more offers (darker shade of blue) when reward increased and fewer offers (darker shade of red) when effort increased. **(B)** SVD participants accepted fewer offers at low effort levels (denoted by the two asterisks ** in the line graph on the left) compared to healthy controls. Error bars show ± SEM.

5.4.4 Effect of reward and effort on reaction time

Another metric obtained from the experiment was the amount of time taken to process the available information (number of apples *vis-a-vis* effort required) before deciding to accept or reject the offer. As above, a generalised linear mixed-effects model was used to investigate how reaction times were influenced by group, reward and/or effort.

The results indicate that SVD participants were slower in making decisions compared to healthy controls (main effect of group on reaction time: β = 0.47, SE = 0.157, t_{12742} = 2.30, p < 0.01) (Figure 5.4A, Table 5.3). Participants in both groups were quicker to decide when reward increased (main effect of reward on reaction time: β = -0.056, SE = 0.019, t_{12742} = -2.95, p < 0.01), but did not show any significant changes in reaction times with different effort levels (p = 0.150) (Figure 5.4B). However, in high conflict situations where both reward and effort increased, participants took longer to make their decisions (reward x effort: β = 0.17, SE = 0.044, t_{12742} = 3.89, p < 0.001).

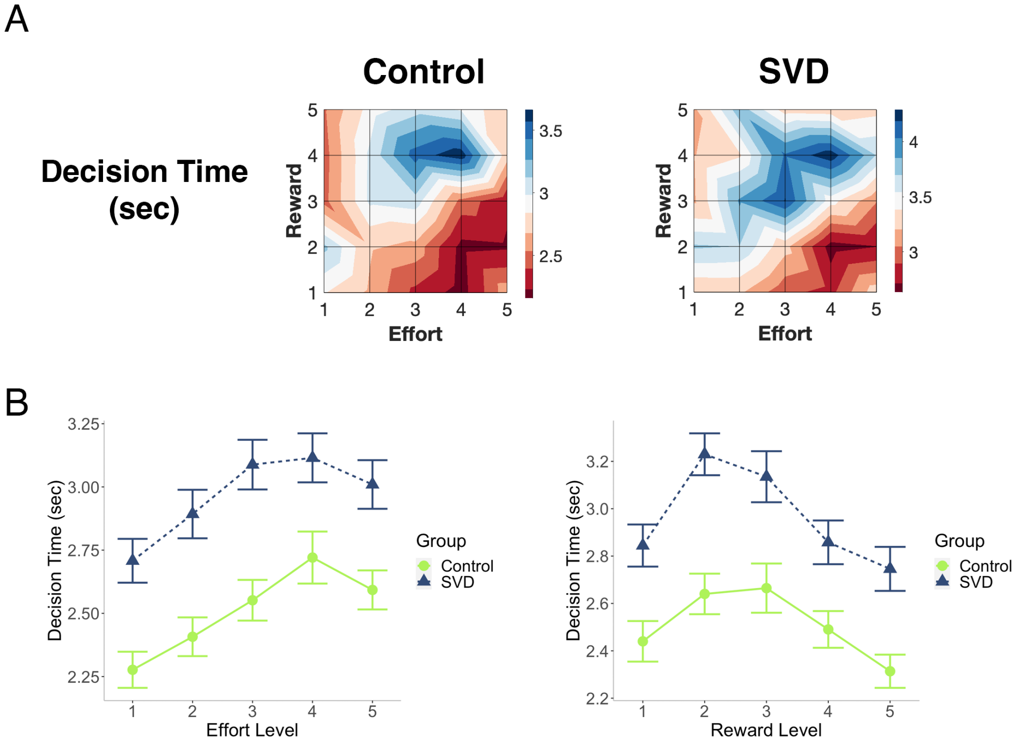


Figure 5.4: **Effect of reward and effort on reaction time.** **(A)** Participants from both groups were quicker to come to a decision (accept or reject) when reward increased. However, in high conflict situations i.e. high reward and high effort, participants took longer to process the offers before making their decisions (blue areas). **(B)** Across all effort and reward levels, SVD participants took longer to make their decisions than controls. Error bars show ± SEM.

Reaction Time				
Name	Estimate	SE	t_{12742}	p-value
(Intercept)	2.27	0.25	9.13	**<0.001**
Group	0.47	0.16	2.30	**<0.01**
Reward	-0.056	0.019	-2.95	**<0.01**
Effort	-0.55	0.38	-1.44	0.15
Group * Reward	0.0015	0.012	0.13	0.90
Group * Effort	0.074	0.24	0.31	0.76
Reward * Effort	0.17	0.044	3.89	**<0.001**
Group * Reward * Effort	-0.025	0.028	-0.91	0.36

Table 5.3: **Generalised linear mixed-effects models examining the effect of group, reward, and effort on reaction time.** Models were specified as follows: reaction time 1 + group * reward + group * effort + reward * effort + group * reward * effort + (1 + reward * effort | participant)

5.4.5 HDDM of EBDM data

To gain further insight into the mechanisms behind changes in EBDM in SVD, an HDDM was applied to the data using Bayesian statistical methods. HDDM is useful here because it takes advantage of both choice and reaction time data to obtain model parameters corresponding to latent psychological processes behind EBDM (Wiecki, Sofer, & Frank, 2013).

The results from HDDM showed that the influence of effort on drift rate was significantly weaker in SVD participants compared to healthy controls (ve; Controls: μ = -0.69, SD = 0.23, SVD: μ = -0.46, SD = 0.40, p(Control > SVD) > 99%; Figure 5.5A). The effect of reward on drift rate was similar between the two groups (vr; p(Control > SVD) = 78.9%), as was the effect of the interaction between reward and effort on drift rate (vr x e; p(Control > SVD) = 62.5%).

Consistent with the raw results reported in section 5.4.2 above, non-decision time was significantly longer in SVD participants compared to the control group (t; Controls: μ = 1.13, SD = 0.27, SVD: μ = 1.34, SD = 0.35, p(SVD > Control) > 99%; Figure 5.5B). The two groups did not differ in terms of their threshold for reaching a decision (a) or bias (z) (p(Control > SVD) = 89.9% and 75.5%, respectively) (Figure 5.5C & 5.5D).

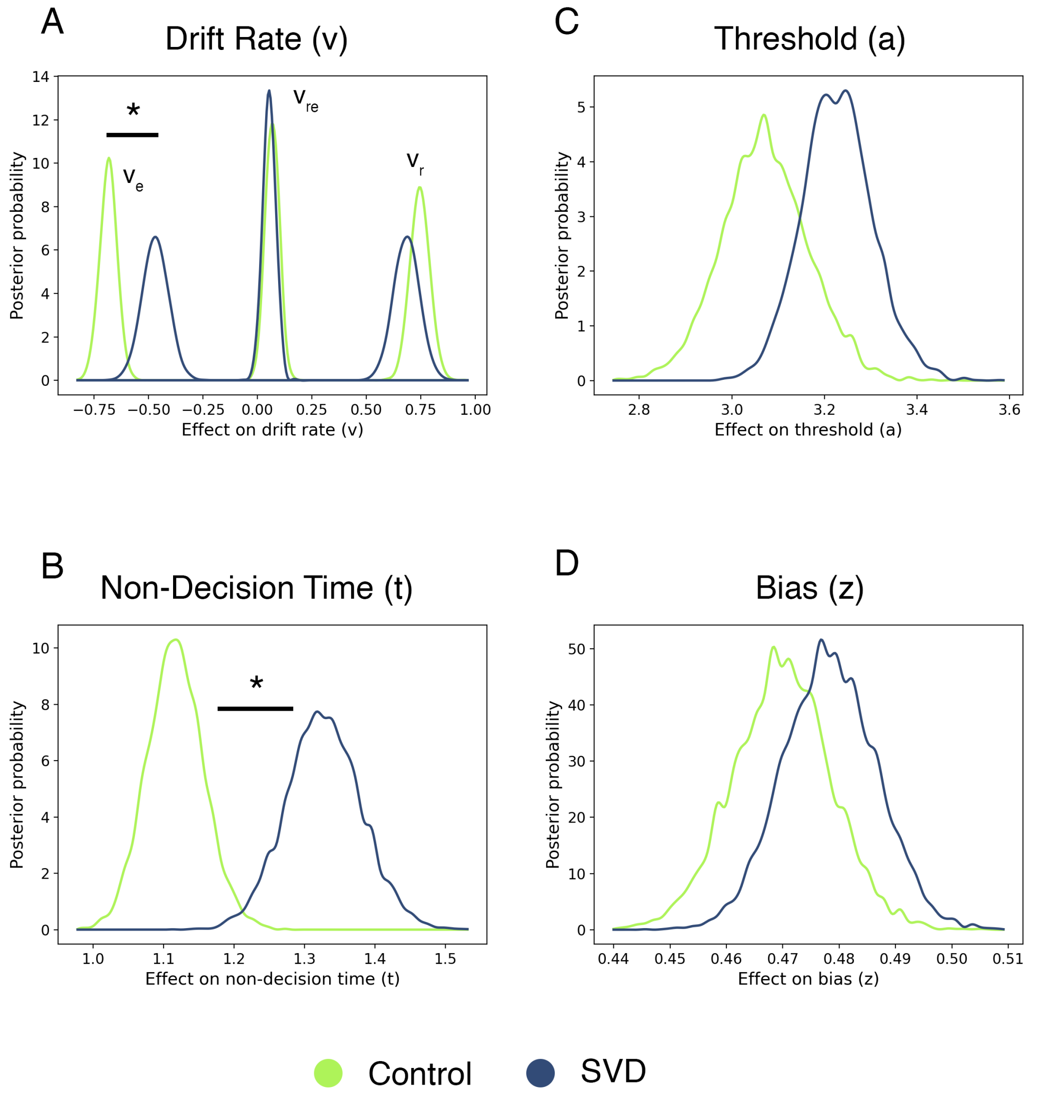


Figure 5.5: **Difference in HDDM parameters between Control and SVD. (A)** The drift rate for SVD participants was less sensitive to changes in effort compared to healthy controls. No differences were seen in how the drift rates for the two groups responded to changes in reward levels or the interaction between reward and effort. **(B)** People with SVD also had a longer non-decision time based on the HDDM. Other parameters from the model such as threshold (a) and bias (z) were not significantly different as demonstrated in **(C)** and **(D)** respectively.

5.4.6 Association between HDDM parameters with apathy and depression

To investigate the relationship between parameters obtained using HDDM and apathy (as measured by the AMI), linear regression models controlling for age, sex, and years of education were performed with HDDM metrics as predicted variables. The same analysis was repeated for depression by substituting the scores on the BDI-II in place of AMI. The results did not demonstrate any significant association between any of the HDDM metrics and total AMI or total BDI-II (Figure 5.6 & Figure 5.7, respectively).

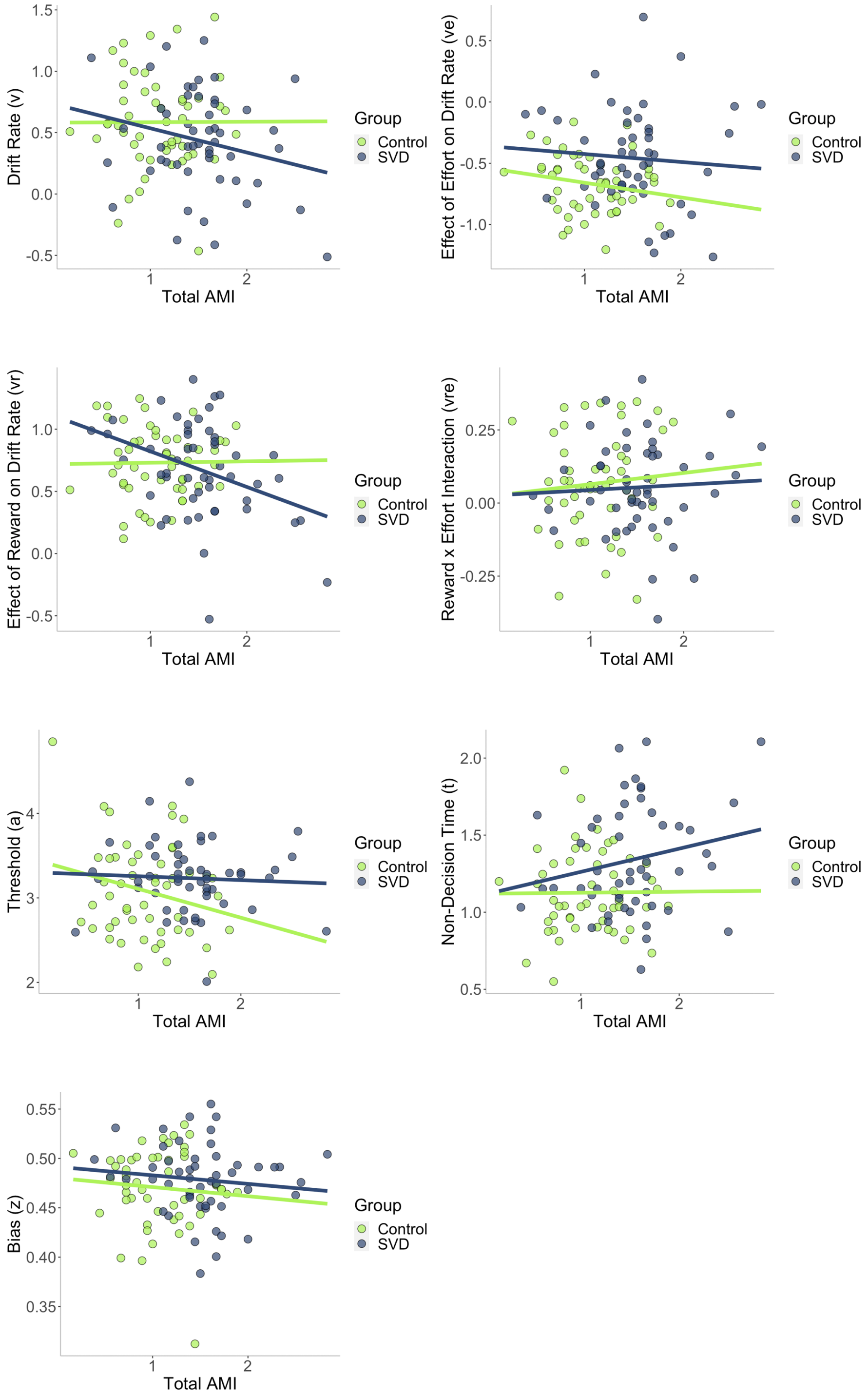


Figure 5.6: **Correlation between HDDM parameters and apathy as measured by the AMI.** No significant associations were found for all of the metrics examined.

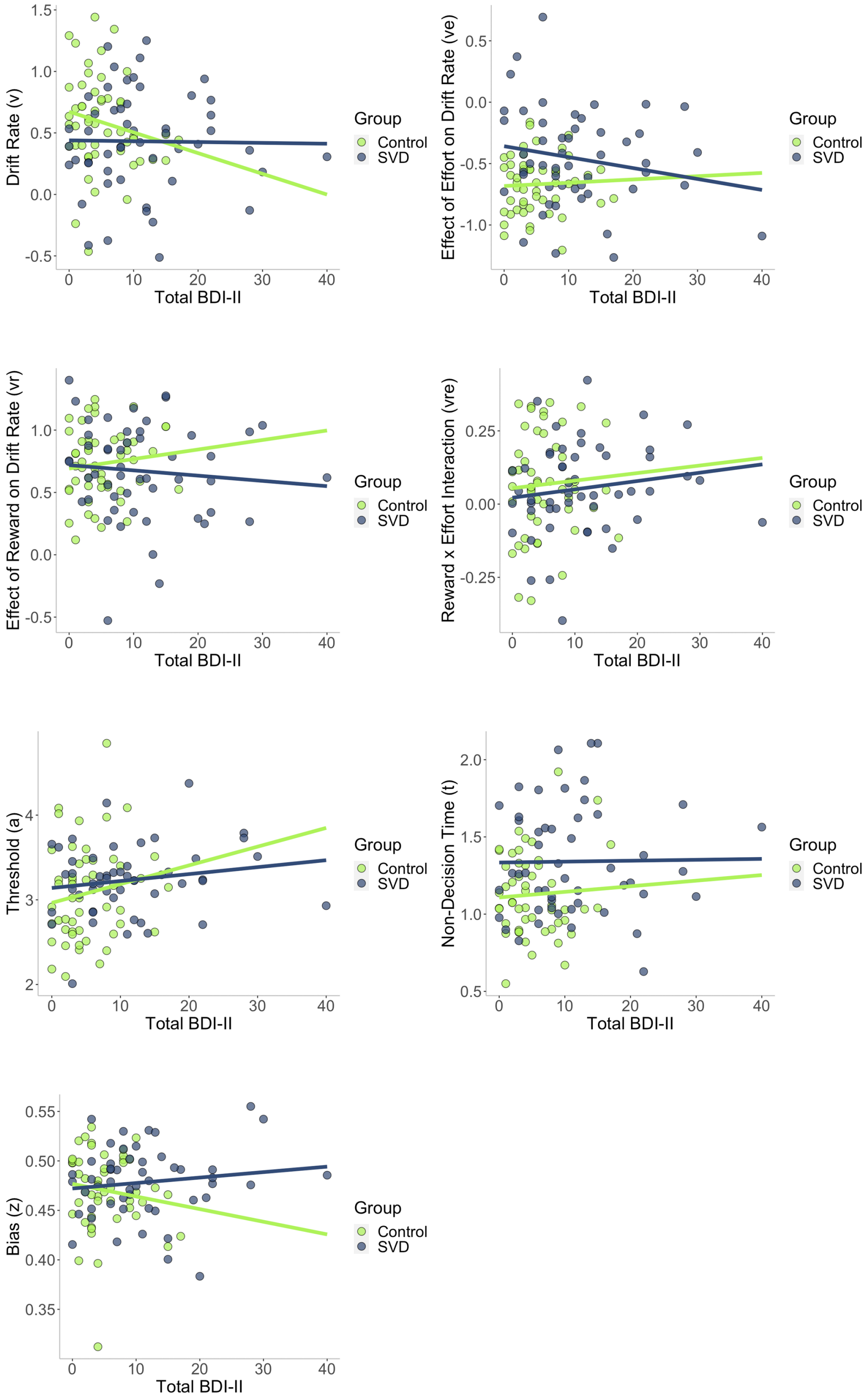


Figure 5.7: **Correlation between HDDM parameters and depression as measured by the BDI-II.** No significant associations were found for all of the metrics examined.

5.5 Discussion

This study provides evidence that SVD is associated with deficits in EBDM. Overall, although participants in this sample with SVD accepted a similar proportion of offers to healthy controls, the two groups diverged with respect to how effort levels affected offer acceptance. Specifically, SVD participants were more averse to accepting offers when effort levels were low (Figure 5.3B) but demonstrated the same response to offers as healthy controls at higher effort levels. A more straightforward picture emerges from data on reaction times, with the SVD group being slower on average to make a decision regardless of the reward or effort level.

Combining offer acceptance and reaction time into a single model using the HDDM revealed two key insights about how EBDM is affected in SVD. First, the effect of effort on drift rate (ve) was weaker in SVD. Second, non-decision time i.e., the amount of time spent on decision-independent processes like visual perception, motor planning and movement execution was longer in SVD.

How do these results fit in with those obtained using EBDM tasks in different patient populations? The most obvious comparison is with previous work conducted by Saleh et al. on a cohort of sporadic SVD patients of whom 33% had apathy as indicated by AES scores > 34 (Saleh, Le Heron, et al., 2021). In their investigation, apathetic SVD patients accepted fewer offers overall, were less responsive to low levels of reward, and were more averse to high levels of effort. Another study recruited CADASIL patients with or without apathy (indexed by the AES and LARS) and compared their performance to age- and gender-matched controls (Le Heron, Manohar, et al., 2018). Apathetic CADASIL patients (i.e., 11 out of the 19 patients) accepted fewer offers than non-apathetic CADASIL patients or healthy controls, but this effect was only seen at low reward levels. A more subtle change was observed in PD patients with apathy (measured by the LARS) who exhibited reduced offer acceptance particularly at the low-reward, low-effort end of the spectrum (Le Heron, Plant, et al., 2018). Thus, the common thread that runs across all these cohorts is that apathetic patients, regardless of the underlying neurological condition, appear to have reduced incentivisation by low amounts of reward.

The present study approached this issue from a slightly different perspective. Here, the question of interest was not so much whether apathy modulates EBDM metrics as described above. Instead, the emphasis was on how EBDM was altered in the presence of SVD. The picture that emerged was different from that obtained in previous studies of apathetic patients. First, both healthy controls and SVD patients demonstrated the expected overall response to increasing reward or effort, by accepting more offers when rewards increased, and accepting fewer offers as effort increased. However, the two groups differed significantly in terms of how they responded to changes in effort levels. Specifically, when effort required was low, the SVD group accepted fewer offers than healthy controls, indicating that they were more sensitive to low effort levels.

What explains the relative aversion to low effort in SVD? One possibility is apathy. However, in this study, only 8 out of the 51 SVD participants (i.e., 16%) (and none amongst healthy controls) met the cut-off score for apathy on the AMI. Moreover, when AMI scores were used in a continuous, as opposed to a dichotomised manner, no significant associations were found between AMI scores and any of the behavioural metrics in either group. One reason for this may be the lack of spread of AMI scores in both groups. In comparison, previous work using similar experimental setups have involved higher percentages of apathetic patients, for example, 58% of CADASIL patients in one report (Le Heron, Manohar, et al., 2018), and 33% of sporadic SVD patients in another study (Saleh, Le Heron, et al., 2021). Not surprisingly, if very few people were apathetic in this study, then it would make it more difficult to identify the impact of apathy on EBDM. Thus, one explanation for the lack of an effect may simply be the paucity of SVD patients with apathy in this study sample. Furthermore, a self-measure like AMI may not be the most sensitive measure for apathy particularly if people have lost some insight into their condition. Instead, a better tool for identifying apathy might be the caregiver version of the AMI (AMI-CG). In one study that examined correlations between measures of apathy, AMI-CG showed a strong correlation with the LARS-I (Lille Apathy Rating Scale Caregiver Version) but only moderate correlations with NPI-Q (Neuropsychiatric Inventory Apathy Score) as well as the AMI itself (Klar et al., 2022).

Another possibility is that the EBDM deficit observed in SVD may be dissociable from apathy. Although EBDM has proven itself to be a useful conceptual framework for studying apathy and anhedonia (Husain & Roiser, 2018), altered EBDM may not be restricted entirely to clinical apathy. Changes in how people evaluate the relative cost of effort against the value of reward may arise not only from a neuropsychiatric origin (e.g. apathy) but also as a consequence of cognitive deficits, for example due to alterations in attention, executive function, or working memory (Gaubert, Borg, & Chainay, 2022; Ouerchefani, Ouerchefani, Allain, Ben Rejeb, & Le Gall, 2019). In a recent study using the Iowa Gambling Task, for example, decision-making metrics like net score and strategy changes correlated with performance on tests of executive function and working memory (Ouerchefani et al., 2019). The impact of cognitive impairment on reward processing was highlighted in a recent review on motivational dysfunction in schizophrenia patients (Saleh, Jarratt-Barnham, Fernandez-Egea, & Husain, 2021). Indeed, previous work using a similar paradigm on genetic SVD (CADASIL) revealed significantly lower mean ACE scores in the CADASIL cohort (mean, SD: 92.3, 5.3) compared to healthy control participants (mean, SD: 96.6, 2.4) (Le Heron, Manohar, et al., 2018). Apart from reduced sensitivity to effort or reward, deficits in motivated behaviour may also arise from poor integration of affective with cognitive information, making it more challenging to use this information to guide behaviour (Heerey, Bell-Warren, & Gold, 2008).

Offer acceptance was not the only metric impacted by SVD. Participants with SVD also required longer to decide compared to healthy controls. This was not surprising given the commonly acknowledged deficit in processing speed that may be seen in SVD (Duering et al., 2014; Hotz et al., 2021; Prins et al., 2005). Conventional tests of processing speed such as the timed measure of the Trail Making Test part B used in the study by Duering et al. (Duering et al., 2014), provide one value that is used to represent 'decision time' or 'response time'. While this is useful to know, it can also oversimplify what was actually taking place when participants were making their decisions. An alternative way to understand processing speed is to deconstruct it into (i) the amount of time needed for decision-making as well as (ii) non-decision time i.e., time spent on decision-independent processes like visual perception, motor planning and movement execution. In this chapter, the finding that non-decision time was prolonged in SVD might suggest a possible mechanism for the increase in overall processing speed seen in this condition. To my knowledge, this is the first study to use HDDM to demonstrate an increase in non-decision time occurring in the context of reduced processing speed in SVD.

Processing speed is closely tied to perceptual speed because perception determines how information is acquired and processed (Baltes, Rudolph, & Zacher, 2019). According to one theory of processing speed, the degradation in cognitive performance that occurs when processing is slow results from two mechanisms: (i) the inability to execute relevant operations successfully due to limited time and

(ii) because the products of earlier processing stages may no longer be available after later processing stages are finished (Salthouse, 1996). Whether any of these deficits occur in SVD remains to be established, and future work is needed to specifically address this question.

This study was not without its limitations. One weakness is the lack of an actual cost to making effortful decisions. Although participants got to experience what the different effort levels represented at the start of the experiment, they were not required to expend any actual effort (apart from pressing the left or right arrow keys) during the decision-making phase. Instead, they were merely asked to think about how they would respond if told that to obtain a certain number of apples they would have to expend the amount of effort displayed on the screen in front of them. Therefore, it might be argued that participants may not have been able to accurately portray the true cost of effortful decision-making for rewards in this experiment. Another weakness is the low numbers of participants with apathy in both the cohorts tested in this experiment, thus limiting its ability to draw further conclusions about the relationship between EBDM and apathy in SVD.

5.6 Conclusion

In summary, the findings in this chapter provide a better characterisation of the nature of EBDM deficits in SVD. They suggest that dysfunctional EBDM may arise independently of the development of clinical diagnoses of apathy and depression, at least as measured by the AMI and BDI. This has important repercussions for how we approach and understand decision-making deficits in SVD as they may not occur solely in the context of mood disturbances but also due to impairments in attention, executive function, or working memory.

6 | Neural correlates of effort-based decision making in cerebral small vessel disease

6.1 Abstract

SVD is known to be associated with apathy. One way this manifests itself is in the form of deficits in EBDM. This chapter utilised the HDDM-derived behavioural parameters obtained from the EBDM experiment carried out in the previous chapter to first identify correlations between EBDM performance with WMH and subcortical volumes. Then, VBM and TBSS were employed to examine whether, respectively, grey matter atrophy or compromised white matter microstructural integrity demonstrated any relationships with EBDM measures. Neither WMH volume nor the volume of subcortical structures revealed any significant associations with EBDM metrics after correcting for multiple comparisons. However, atrophy of the nucleus accumbens in SVD participants predicted higher apathy scores. VBM identified a small cluster in the right occipital lobe where grey matter atrophy was correlated with higher threshold for decision making across all participants, as well as two clusters in the left medial frontal and right occipital lobes where grey matter atrophy was associated with more apathy. TBSS indicated that increased ISOVF in several white matter tracts was associated with reduced threshold for decision making as well as shorter non-decision time in healthy controls and SVD participants. These results provide some information regarding the neural basis of EBDM in health and how it is altered in some instances by the presence of SVD.

6.2 Introduction

Neuropsychiatric symptoms such as anxiety, emotional lability, and depression, are common manifestations in a broad range of neurological diseases including SVD (Clancy, Gilmartin, et al., 2021). Like the underlying disease itself, they often develop insidiously, making it difficult not just to pinpoint the existence of neuropsychiatric symptoms to begin with, but also to attribute them to SVD (Lind et al., 2006; Rensma, van Sloten, Launer, & Stehouwer, 2018; van der Mast et al., 2008). One example of a common neuropsychiatric symptom in SVD is apathy, which can be conceptualised as loss of motivation that results in reduced goal-directed behaviour (Marin, 1991). Apathy can be observed in up to 50% of people with SVD as well as 92% of vascular dementia patients (Hollocks et al., 2015; Kazui et al., 2016). The presence of apathy leads to poor functional outcome and reduced quality of life not just in patients themselves but also for their caregivers (Feast et al., 2016; Tierney, Woods, Weinborn, & Bucks, 2018). Unfortunately, many uncertainties remain about whether apathy exists before, develops together, or manifests only in established stages of SVD (Aubignat et al., 2023; Brodaty, Liu, Withall, & Sachdev, 2013). Furthermore, when apathy does occur, relatively little is known about the brain mechanisms responsible for its development, either in healthy populations or those with neurological diseases (Kos et al., 2016).

An early description of apathy viewed it as the consequence of lesions or dysfunctions involving the prefrontal cortex-basal ganglia axis (Levy & Dubois, 2006). This framework divided the underlying mechanisms responsible for apathy into three subtypes of disrupted processing: ‘emotional-affective’, ‘cognitive’, and ‘auto-activation’. These subtypes were thought to be useful because they were associated with dysfunction involving different brain regions. Impaired ‘emotional-affective’ processing referred to the inability to forge the necessary connection between emotional-affective signals and the ongoing or forthcoming behaviour. This first subtype was related to lesions in the orbital-medial prefrontal cortex or to subregions of the basal ganglia such as the ventral striatum or ventral pallidum. Dysfunctional ‘cognitive’ processing, the second subtype, reflected problems in coming up with the plan of actions needed for the desired behaviour. This defect appeared to be associated with lesions of the dorsolateral prefrontal cortex as well as the dorsal caudate nucleus. The third subtype i.e., disrupted ‘auto-activation’ processing, referred to the inability to self-activate thoughts or self-initiate actions, and was correlated with bilateral lesions of the internal portion of the globus pallidus. One issue with this viewpoint was the lack of clarity about how the different components map onto underlying normal neurobiological systems responsible for motivated behaviour in the first place (Le Heron, Apps, & Husain, 2018).

A more recent conceptualisation attempted to provide a framework that was more closely aligned to processes underlying normal motivated behaviour (Le Heron et al., 2019). According to this perspective, motivated behaviour can be explained in terms of three fundamental processes. First, a value system calculates the worth of an entity in terms of their hedonic or aversive potential. This value system appears to depend on the ventral striatum and the ventromedial prefrontal cortex (Haber & Behrens, 2014). Second, a mediating system translates this value information into appropriate behavioural responses. This mediating system, which depends on the ventral striatum and anterior cingulate cortex, functions as a ‘limbic/motor’ interface under the influence of the mesolimbic dopamine system (Mogenson, Jones, & Yim, 1980). Finally, a motor system made up of the posterior mid-cingulate cortex, supplementary motor area, and dorsal striatum, produces the desired behaviour (Le Heron et al., 2019). Disruption of any of the three processes outlined above can result in apathy.

In SVD, this disruption can occur due to several causes that are not necessarily mutually exclusive, including the presence of WMH, damage to subcortical structures, grey matter atrophy, as well as reductions in white matter microstructural integrity. A recent systematic review and meta-analysis found 28 studies analysing apathy in SVD and concluded that apathy was associated with increasing WMH severity (Clancy, Gilmartin, et al., 2021). The involvement of subcortical structures in the development of apathy has been shown before in PD (Morris et al., 2023). In this study, the researchers examined a group of people with PD with and without apathy, as measured using the informant-rated Neuropsychiatric Inventory apathy subscale, at baseline and after a 2-year follow-up. In particular, they were interested in discovering variables that correlated with the development of apathy in those who were non-apathetic at baseline. Rs-fMRI data revealed that non-apathetic PD patients who later went on to develop apathy had increased functional connectivity between the nucleus accumbens and dorsal anterior cingulate cortex. Moreover, those who already had apathy at baseline had reduced grey matter volume in bilateral mid/dorsal anterior cingulate cortex as well as the left caudate and nucleus accumbens. This raises the question whether the same regions are also implicated in the development of apathy in SVD.

The availability of diffusion MRI data has allowed researchers to investigate in more detail how white matter damage may be responsible for apathy in SVD. In one study involving 121 patients with SVD, voxel-based analysis found apathy to be associated with reduced FA especially in limbic association tracts like the anterior cingulum, fornix, and uncinate fasciculus (Hollocks et al., 2015). A meta-analysis of fMRI studies in healthy individuals revealed that effort demands correlated with activity in the pre-supplementary motor area (pre-SMA) and ventromedial prefrontal cortex (vmPFC) whereas signaling net value was associated with activity in the vmPFC and ventral striatum (Lopez-Gamundi et al., 2021).

This chapter seeks to explore the relationship between apathy (indexed using the AMI questionnaire as well as through EBDM behavioural metrics) and neuroimaging parameters obtained through structural and diffusion MRI. These associations will be examined across the whole cohort comprising of control and SVD participants, as well as in each cohort separately, to determine if they are a general phenomenon or represent dysfunction that is specific to SVD.

6.3 Methods

6.3.1 Participants and clinical measures

This study included 51 participants with a clinical diagnosis of SVD (age: μ = 68.92, SD = 9.03, 25 females) and 51 healthy elderly controls (age: μ = 66.71, SD = 6.25, 31 females) who completed the EBDM experiment detailed in Chapter 5. As part of the assessment, all participants also answered several questionnaires measuring general cognition (ACE), apathy (AMI), depression (BDI-II), and overall well-being (WHO Five Well-Being Index and Cantril Ladder) (summarised in Table 5.1 in the previous chapter).

Permission for the study was obtained from the Ethics Committee at the University of Oxford (RAS ID: 248379, Ethics Approval Reference: 18/SC/0448). All participants agreed to take part in the study and were offered monetary compensation in return.

6.3.2 Experimental paradigm and behavioural analysis

Participants first completed the EBDM task described in Chapter 5. In this experiment, they were offered certain numbers of apples (between 1 and 13) for several levels of effort (ranging from 1 to 5, corresponding to 16, 32, 48, 64, and 80% of maximal voluntary contraction measured at the start of the experiment). Different combinations of apples and reward levels were shown, and participants were required to decide if it was worth expending the amount of effort required in order to obtain the number of apples displayed on the screen. They did this by pressing the left or right arrow keys on a standard keyboard corresponding to the location of the word “Yes” or “No” on the screen in front of them.

Raw metrics derived from this experiment included the proportion of offers accepted as well as reaction times on a trial-by-trial basis. These were then used as input for HDDM (described in more detail in the previous chapter) resulting in several key parameters for each participant: threshold (a), non-decision time (t), drift rate (v), and bias (z).

6.3.3 MRI acquisition and pre-processing

The protocol for acquiring structural and diffusion MRI scans was described in Chapter 2. Briefly, structural and diffusion MRI scans were obtained using a 3T siemens Verio scanner at the John Radcliffe Hospital in Oxford. Structural images included: T1-weighted sequence (MPRAGE, field of view: 208 x 256 x 256 matrix, TR 2000 ms, TE 1.94 ms, TI 880 ms, flip angle 8°, voxel-size 1.0 mm isotropic) and T2-fluid attenuated inversion recovery, or T2-FLAIR, sequence (TR 5000 ms, TE 397 ms, TI 1800 ms, flip angle 120°, voxel-size 1.1 x 1.0 x 1.0 mm). Diffusion-weighted images were obtained using an echo planar sequence (TR 3600 ms, TE 92 ms, voxel size 2.0 x 2.0 x 2.0 mm) with opposite phase encoding directions (AP and PA) to allow for more robust distortion correction (AP: 104 directions, 8 b=0 s/mm2, 50 b=1000 s/mm2, 50 b=2000 s/mm2 and PA: 7 directions, 4 b=0 s/mm2).

MRI data were then pre-processed as follows:

Total WMH volume was obtained by segmenting and quantifying WMH lesions seen on FLAIR images using BIANCA (Griffanti et al., 2016). BIANCA is a fully automated, supervised method for the detection of WMH. It employs the k-nearest neighbour algorithm to determine the probability that a voxel represents WMH based on its intensity and spatial characteristics. The output of BIANCA was binarized such that voxels classified as WMH had a value of 1.0 and all other voxels had a value of 0. For each participant, the total WMH volume was then calculated using the command line tool *fslstats*.

Subcortical volumes were calculated using the script *run_first_all* in FSL. This script segments several subcortical structures using models constructed from manually segmented images, producing mesh and volumetric outputs. The command line tool *fslstats* was then used to determine the volume of the following subcortical structures: nucleus accumbens, amygdala, caudate, hippocampus, pallidum, putamen, and thalamus. For the purposes of this chapter, the volume of a named subcortical structure represents the mean volume of the left and right side.

To prepare for the VBM analysis, a study-specific grey matter template was first created using brain-extracted T1 images of all participants. This study template was then used as a target for non-linear registration of grey matter images from each participant. These images were then combined into a 4D image which was smoothed using a sigma 3mm Gaussian kernel.

TBSS was used to provide information regarding anatomical connectivity in the brain. Diffusion-weighted images were first corrected for susceptibility-induced distortions, eddy currents, and subject movement using the tools *topup* and *eddy* in FSL. Then, pre-processed diffusion data were fit with 2 models, DTI and NODDI using the command line tools *dtifit* and AMICO (Daducci et al., 2015), respectively. A total of 5 diffusion metrics were obtained for each voxel: FA and MD from the DTI model, as well as NDI, ODI, and ISOVF from NODDI. TBSS was then used to create 5 different white matter skeletons, one for each diffusion metric, prior to voxel-wise statistical analysis.

6.3.4 Statistical analysis

WMH and subcortical volumes

The relationship between WMH volume and EBDM parameters was analysed using linear regression, controlling for age, sex, and years of education. An interaction term was included to determine if the association between WMH volume and different EBDM metrics was modified by the presence of SVD. This analysis was repeated to test for a significant association between WMH volume and apathy indexed by total AMI score.

The same approach was also used to investigate potential correlations between subcortical volumes and EBDM measure as well as subcortical volumes and total AMI score.

VBM

The aim of the VBM analysis (Ashburner & Friston, 2000; Good et al., 2001) was to identify areas of grey matter atrophy demonstrating positive or negative associations with EBDM or apathy parameters across the whole cohort. To that end, a GLM was employed using age, sex, and years of education as covariates. A separate GLM was utilised to detect any differences in the slope of the linear relationship between grey matter atrophy and EBDM/apathy metrics between healthy control and SVD participants. This may occur, for example, due to a behavioural parameter exhibiting a positive association with grey matter atrophy in one cohort, but a negative association in the other group. All comparisons were conducted using the *randomise* function with 5000 permutations. TFCE was used to correct for multiple comparisons. Results were considered significant at $\alpha = 0.05$.

TBSS

TBSS-style analysis (S. M. Smith et al., 2006) employed the same GLMs used for VBM to first identify associations between diffusion parameters and EBDM or apathy metrics across the whole cohort. Then, separate GLMs were used to investigate if any group differences existed in the linear relationship between diffusion metric and EBDM measure or apathy i.e., total AMI score. As before, all comparisons were carried out using the *randomise* function with 5000 permutations. Results were corrected for multiple comparisons using Threshold Free Cluster Enhancement (TFCE) and were considered statistically significant at $\alpha = 0.05$.

6.4 Results

6.4.1 Relationship between WMH and EBDM or apathy metrics

Linear regression analysis, controlling for age, sex, and years of education, found no significant association between WMH volume and any of the metrics obtained from HDDM (drift rate, non-decision time, threshold, and bias) (Figure 6.1A-D). This was true for both Control and SVD participants as there was no interaction of group and WMH volume for any of the parameters tested. Similarly, no significant correlation was observed between WMH volume and total AMI score.

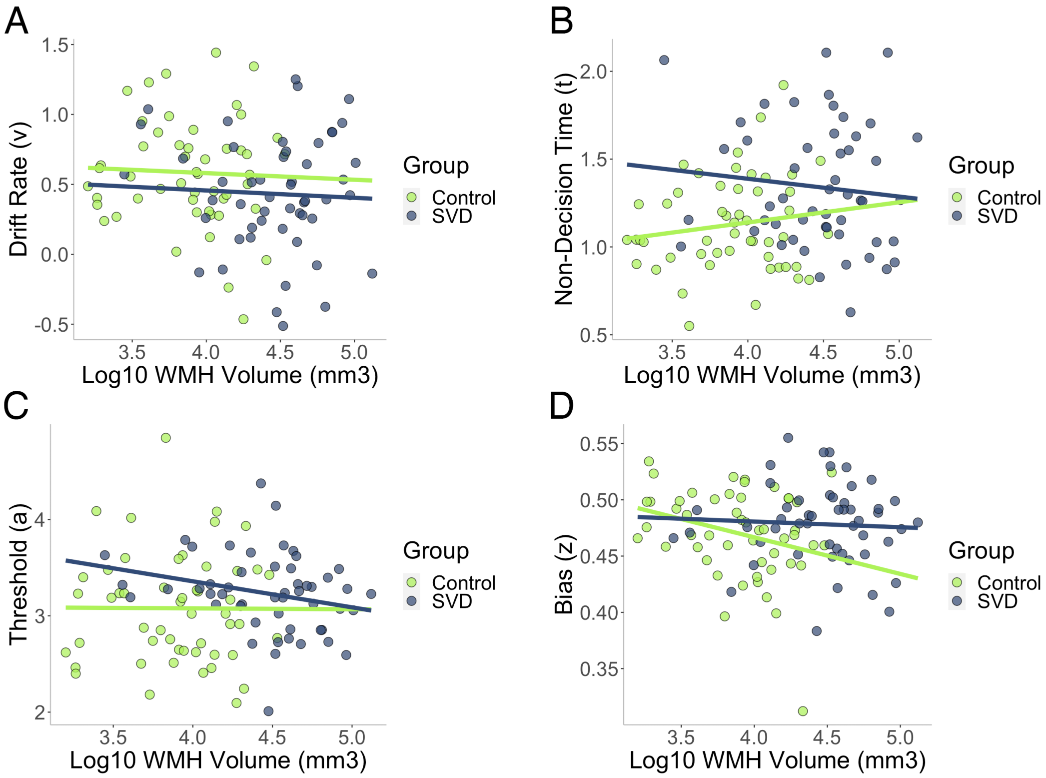


Figure 6.1: **WMH volume did not correlate with EBDM metrics obtained via HDDM.** Plots showing the relationship between $\log_{10}$ of WMH volume and HDDM-derived EBDM metrics representing drift rate, non-decision time, threshold, and bias (**A-D** respectively). No significant association was found between WMH volume and any of the behavioural parameters. Having a diagnosis of SVD did not alter this lack of a relationship.

6.4.2 Relationship between subcortical volumes and EBDM or apathy metrics

To investigate if performance on this EBDM task varied as a function of the volumes of subcortical structures, linear regression analyses were conducted, controlling for age, sex, and years of education. The subcortical structures included in these analyses were the nucleus accumbens, amygdala, caudate, hippocampus, globus pallidum, putamen, and thalamus. For each subcortical entity, the volume used represented the mean of the left and right side of the structure concerned.

Across all participants, the threshold (a) for decision-making exhibited significant positive correlations with the volumes of the hippocampus and thalamus (hippocampus: β = +0.00034, t_{95} = 2.62, p = 0.010; thalamus: β = +0.00026, t_{95} = 2.42, p = 0.018) (Figure 6.2). The slope of this relationship did not differ between Control and SVD participants for the hippocampus. A significant group x structure interaction was observed for the thalamus whereby SVD participants had a lower slope compared to healthy controls (β = -0.00025, t_{95} = -2.09, p = 0.039), indicating a weaker relationship between threshold and thalamic volume for people with SVD. Two other subcortical structures namely the nucleus accumbens and putamen demonstrated associations that approached statistical significance (p = 0.073 and p = 0.053, respectively). However, none of these correlations survived correction for multiple comparisons.

No significant associations were found between non-decision time (t), drift rate (v), and bias (z) with any of the seven subcortical structures (Figure 6.3, 6.4, and 6.5, respectively).

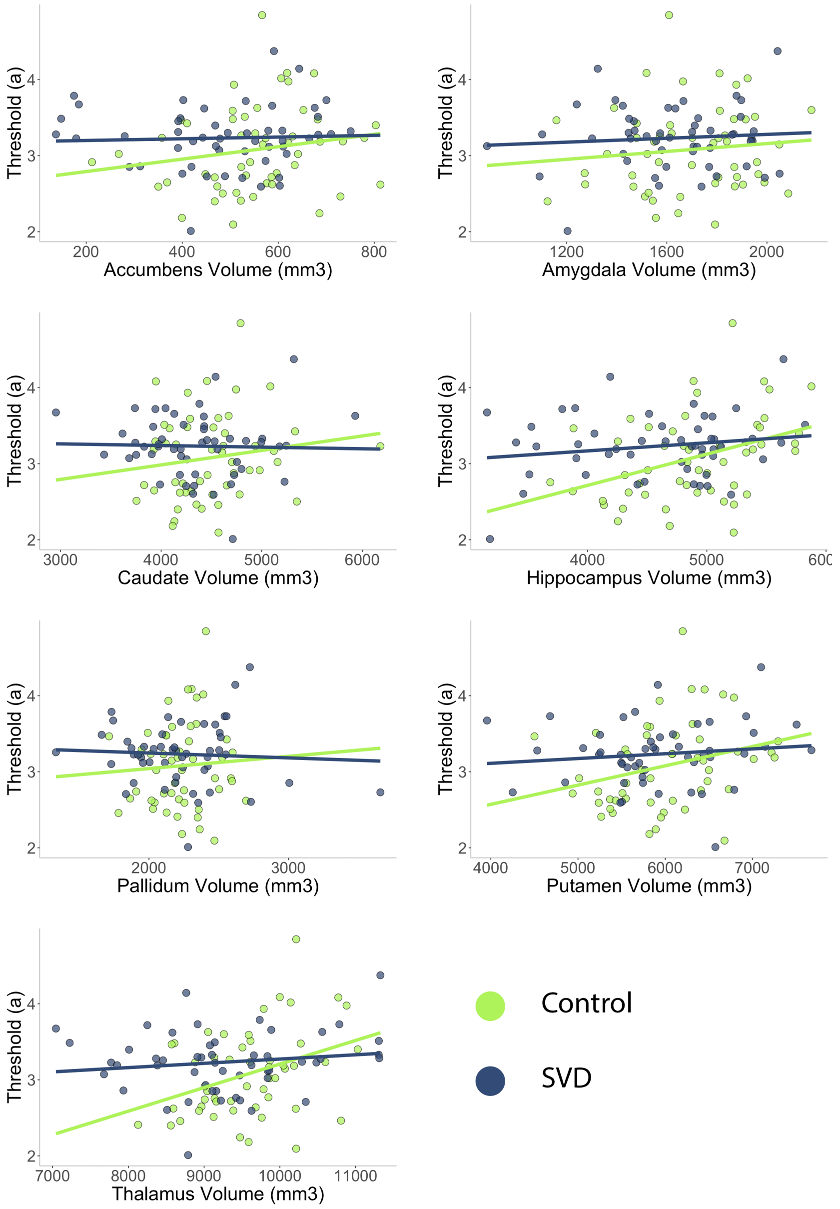


Figure 6.2: **The relationship between subcortical volumes and threshold (a).** Scatterplots showing how the volumes of several subcortical structures correlated with the threshold parameter obtained via HDDM. Significant associations were seen for the hippocampus and thalamus across all participants. In addition, SVD participants had a weaker relationship between threshold and thalamic volume compared to healthy controls.

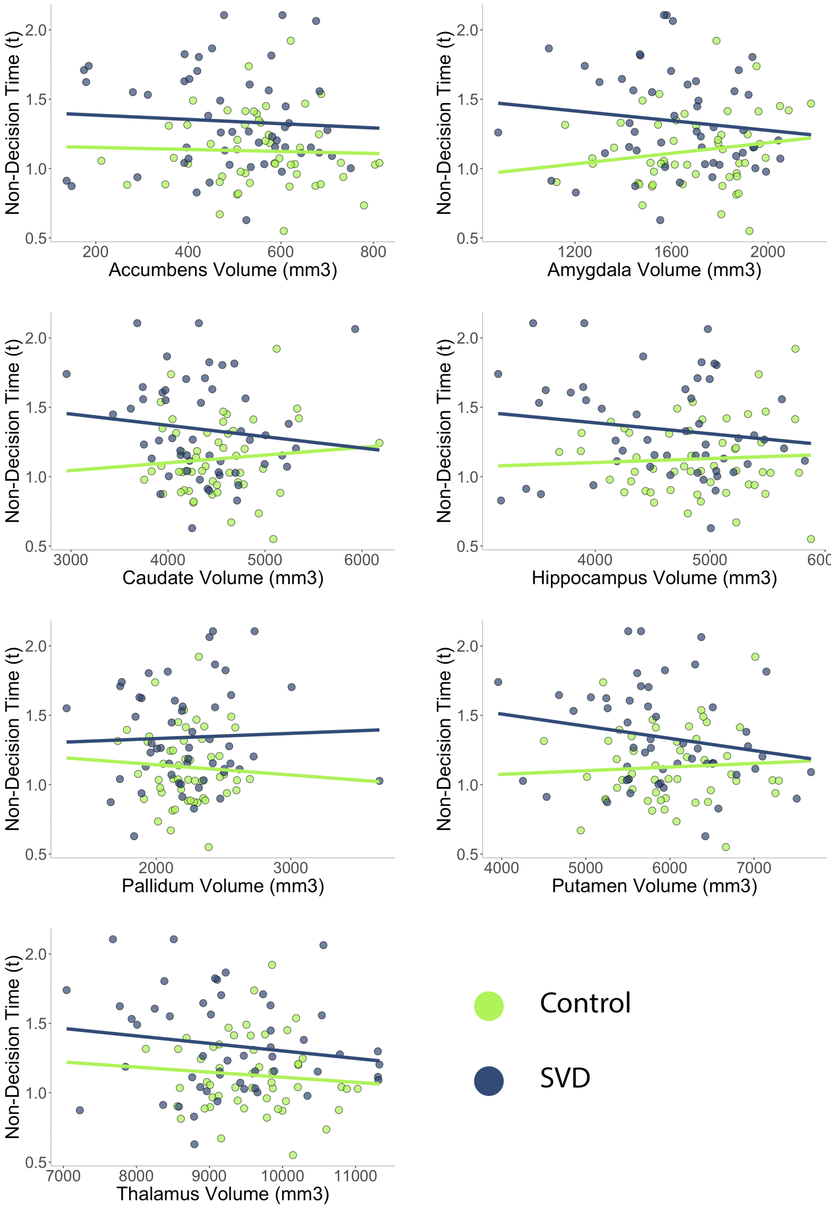


Figure 6.3: **The relationship between subcortical volumes and non-decision time (t).** No significant association was seen between all subcortical structures tested and non-decision time.

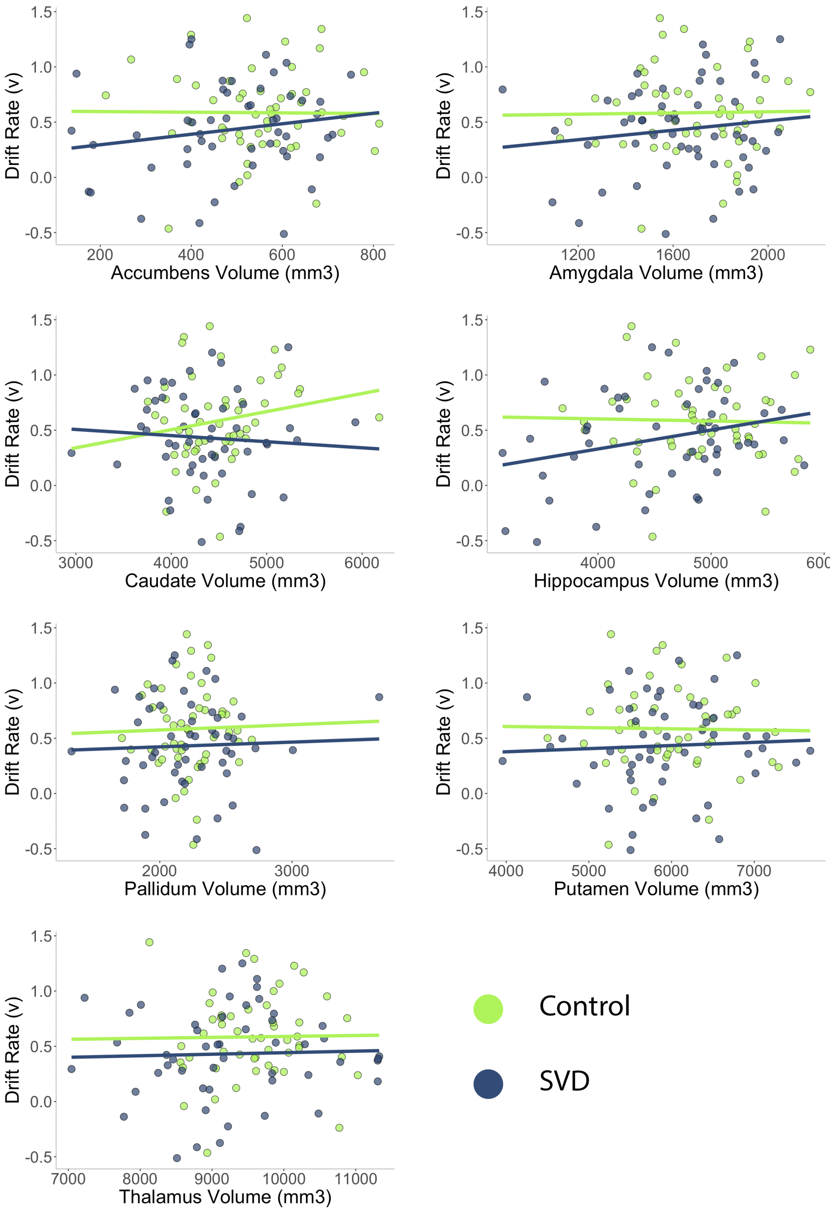


Figure 6.4: **The relationship between subcortical volumes and drift rate (v).** No significant association was seen between all subcortical structures tested and drift rate.

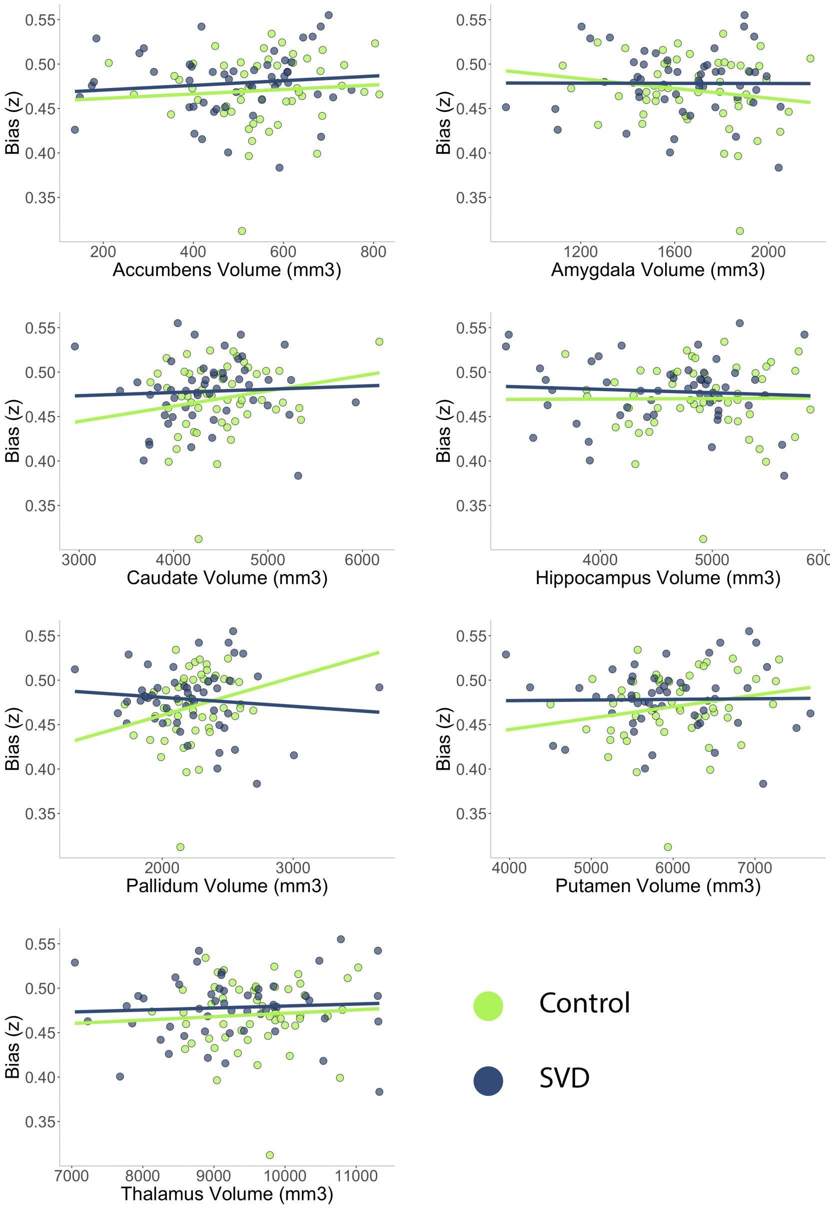


Figure 6.5: **The relationship between subcortical volumes and bias (z).** No significant association was seen between all subcortical structures tested and bias.

Linear regression was also used to investigate for correlations between subcortical volumes and total AMI score. For the nucleus accumbens, although there was no significant relationship with total AMI score across the whole cohort, a significant difference existed for the interaction between group and nucleus accumbens volume. Specifically, the volume of the nucleus accumbens was negatively correlated with total AMI score in SVD participants (β = -0.0016958, t_{46} = -3.376, p = 0.00150) but not in healthy elderly controls (p = 0.0828). No other subcortical structure demonstrated significant relationships with total AMI score either across the whole cohort or within each group individually.

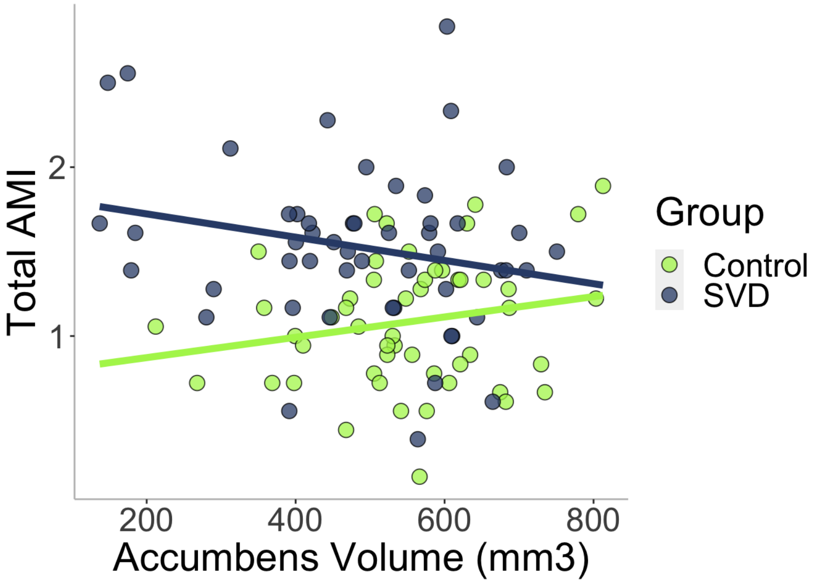


Figure 6.6: **The relationship between nucleus accumbens volume and total AMI score.** In SVD participants, atrophy of the nucleus accumbens was associated with higher total AMI score (a measure of apathy). This association was not present in healthy elderly controls.

6.4.3 VBM analysis with EBDM and apathy metrics

To test for correlations between local grey matter volume and EBDM metrics, VBM was conducted using structural MRI scans from the whole cohort. After correcting for multiple comparisons with TFCE, a small cluster was detected in the right occipital lobe (Figure 6.7) where lower grey matter volume was associated with lower threshold for decision making, and vice versa. Table 6.1 provides more information about the size and coordinate of this cluster, whereas Table 6.2 lists down percentages for its actual location based on the Harvard-Oxford Cortical Structural Atlas included with FSL.

VBM analysis was also performed to determine if local grey matter volume was associated with apathy scores. Here, two clusters were discovered—in the left medial frontal lobe and right occipital lobe—where grey matter atrophy was associated with higher total AMI scores (Figure 6.8). Table 6.3 provides information regarding cluster sizes and coordinates, while Table 6.4 details the extent to which each cluster can be found in the labelled atlas regions.

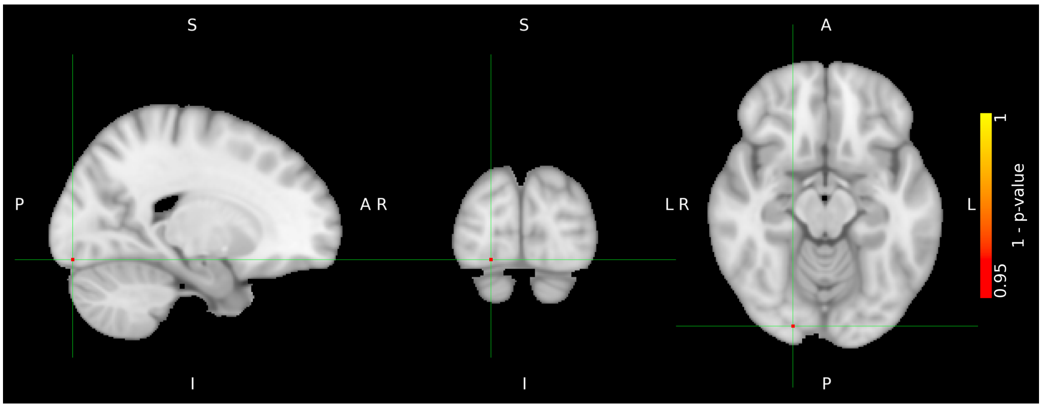


Figure 6.7: **VBM analysis using EBDM metrics.** Across both healthy elderly controls and people with SVD, lower grey matter volume in a small region in the right occipital cortex (shown in crosshairs) was associated with lower decision-making threshold as calculated using HDDM.

-	No. of voxels	1 - p max	MAX X (vox)	MAX Y (vox)	MAX Z (vox)	COG X (vox)	COG Y (vox)	COG Z (vox)
Cluster 1 (Right occipital)	4	0.95	35	18	29	34.5	17.8	28.8

Table 6.1: **Size and coordinate of significant cluster obtained with VBM.** Cluster information includes the number of voxels in the significant cluster, its significance value, X/Y/Z coordinates of the maximum intensity voxel, as well as X/Y/Z coordinates of the Centre of Gravity (COG) representing the weighted average of the coordinates by intensities within each cluster. A small cluster comprising of 4 voxels was detected in the right occipital lobe. This was the only region that survived correction for multiple comparisons using TFCE.

Cluster 1 (Right occipital)	
Atlas region	Percentage (%)
Right occipital fusiform gyrus	29.5
Right occipital pole	21.0
Right lateral occipital cortex, inferior division	8.0
Right lingual gyrus	3.5

Table 6.2: **Location of significant cluster based on the probabilistic Harvard-Oxford Cortical Structural Atlas.** The numbers shown represent the extent (in percentages) that voxels in the cluster are members of certain labelled regions within the atlas.

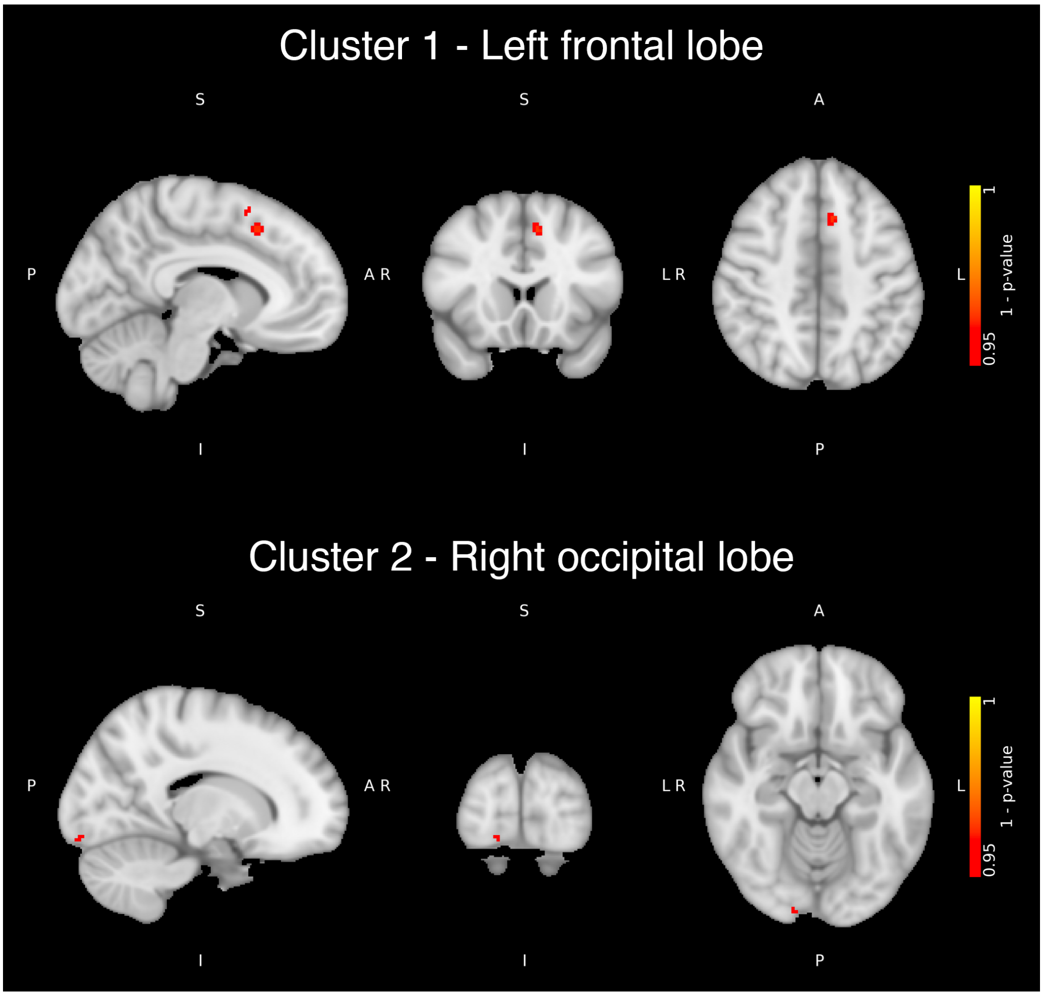


Figure 6.8: **VBM analysis using total AMI score.** Across the whole cohort, grey matter atrophy of the left medial frontal lobe and right occipital lobe correlated with higher apathy as measured using total AMI scores.

-	No. of voxels	1 - p max	MAX X (vox)	MAX Y (vox)	MAX Z (vox)	COG X (vox)	COG Y (vox)	COG Z (vox)
Cluster 1 (Left medial frontal)	68	0.964	49	72	59	48.3	70	62.6
Cluster 2 (Right occipital)	7	0.952	37	17	29	36.9	17	29.6

Table 6.3: **Size and coordinate of significant cluster obtained with VBM.** Cluster information includes the number of voxels in the significant cluster, its significance value, X/Y/Z coordinates of the maximum intensity voxel, as well as X/Y/Z coordinates of the Centre of Gravity (COG) representing the weighted average of the coordinates by intensities within each cluster. Two clusters were discovered where grey matter atrophy correlated with more apathy as measured using total AMI scores.

Cluster 1 (Left medial frontal)	
Atlas region	Percentage (%)
Left superior frontal gyrus	24.3
Left paracingulate gyrus	20.6
Left supplementary motor cortex	6.7
Left cingulate gyrus (anterior division)	0.3
Cluster 2 (Right occipital)	
Atlas region	Percentage (%)
Right occipital pole	30.3
Right occipital fusiform gyrus	13.6
Right lingual gyrus	8.0
Right lateral occipital cortex, inferior division	3.9

Table 6.4: **Location of significant clusters based on the probabilistic Harvard-Oxford Cortical Structural Atlas.** The numbers shown represent the extent (in percentages) that voxels in the cluster are members of certain labelled regions within the atlas.

6.4.4 TBSS analysis with EBDM and apathy metrics

The relationship between white matter microstructural integrity and HDDM-derived behavioural metrics was examined using TBSS. This was performed across the entire cohort to begin with, and where significant associations were found, further analyses were conducted to determine if there were any group differences in the correlations seen.

The XTRACT Human Connectome Project (HCP) probabilistic atlas was used to identify relevant white matter tracts (Figure 6.9, top row). Briefly, this atlas was created using an automated region-of-interest (ROI) based tractography approach resulting in the extraction of 42 white matter tracts in the human brain (Warrington et al., 2020). White matter tracts in this atlas include association fibres, commissural fibres, limbic fibres, and projection fibres. TBSS analysis was performed using a mask derived from skeletonised FA data that was averaged across all participants (Figure 6.9, bottom row, in green).

Two significant relationships emerged as a result of this analysis:

First, higher ISOVF in several white matter tracts was associated with lower decision-making threshold across all participants i.e., for both healthy elderly controls and people with SVD. Using the *atlasquery* command in FSL revealed that 14 white matter tracts demonstrated more than 1% involvement in the region where this relationship was identified (Table 6.5). The extent of inclusion of individual tracts can be expressed as the percentage of the whole tract in which the abovementioned negative relationship (with decision-making threshold) was detected. As can be seen in Table 6.5 and Figure 6.10, the four tracts with the largest involvements were the left arcuate fasciculus, left superior longitudinal fasciculus, left middle longitudinal fasciculus, and left optic radiation.

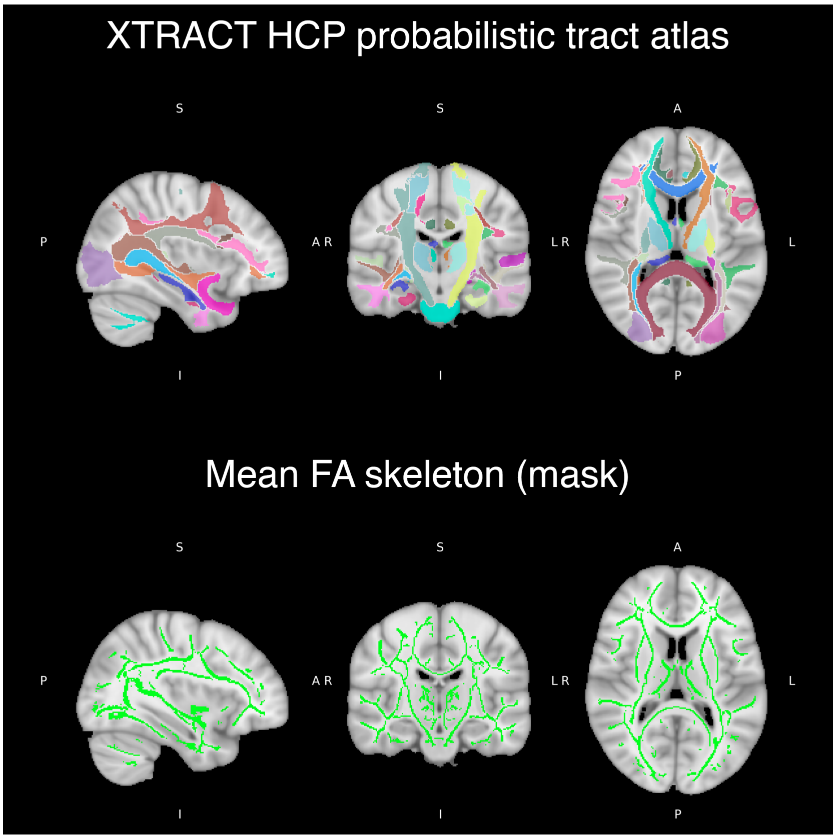


Figure 6.9: **Atlas and mean FA skeleton mask used for the TBSS analysis.** The XTRACT HCP probabilistic tract atlas (**top row**) provides topographical information on 42 white matter tracts in the human brain. TBSS analysis was conducted using a mask derived from FA values across the whole cohort (**bottom row**, shown in green).

Second, higher ISOVF in several white matter tracts was associated with lower non-decision time in the whole cohort. In total, 17 white matter tracts exhibited this negative association (Table 6.6). Tracts with the most involvement included the left inferior fronto-occipital fasciculus (IFOF), left middle longitudinal fasciculus, left optic radiation, and left corticospinal tract (Figure 6.11).

Higher ISOVF associated with lower decision-making threshold		
White matter tract	Left/Right	Percentage (%)
Arcuate Fasciculus	Left	5.1432
Superior Longitudinal Fasciculus 1	Left	4.7864
Middle Longitudinal Fasciculus	Left	4.6495
Optic Radiation	Left	4.3102
hline Frontal Aslant Tract	Left	3.8964
Inferior Fronto-Occipital Fasciculus	Left	3.5789
Superior Thalamic Radiation	Left	3.5262
Superior Longitudinal Fasciculus 3	Left	3.4853
Corticospinal Tract	Left	3.2518
Anterior Thalamic Radiation	Left	2.9643
Superior Longitudinal Fasciculus 2	Left	2.6619
Forceps Minor	Not applicable	2.2576
Forceps Major	Not applicable	1.8268
Acoustic Radiation	Left	1.3899

Table 6.5: **White matter tracts demonstrating significant negative associations between ISOVF and decision-making threshold.** Higher ISOVF values in these tracts predicted lower thresholds for decision making across the whole cohort. The numbers in the rightmost column reflect the percentage of each individual tract in which this negative relationship was demonstrated.

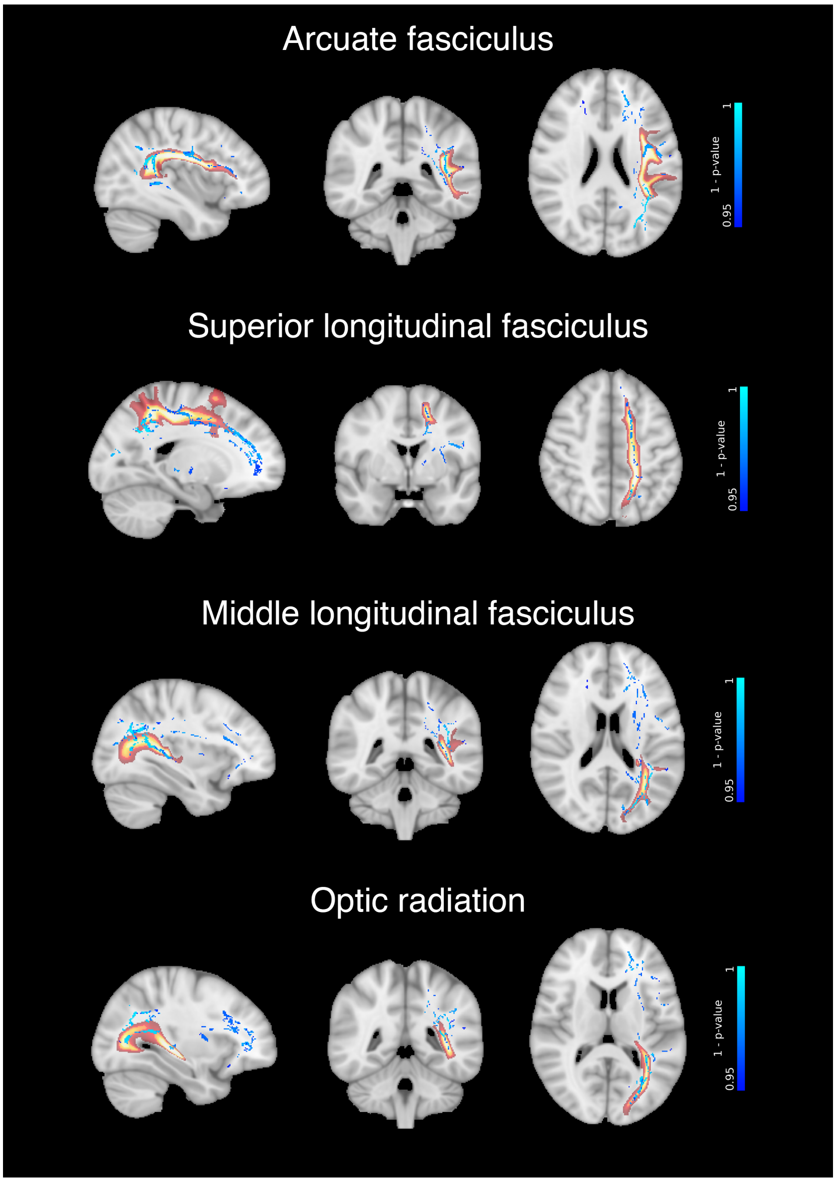


Figure 6.10: **White matter tracts exhibited a negative relationship between ISOVF and decision-making threshold.** Higher ISOVF in 14 white matter tracts including the arcuate fasciculus, superior. longitudinal fasciculus, middle longitudinal fasciculus, and optic radiation (all in the left hemisphere) was associated with lower decision-making threshold across all participants.

Higher ISOVF associated with lower decision-making threshold		
White matter tract	Left/Right	Percentage (%)
Inferior Fronto-Occipital Fasciculus	Left	8.6242
Middle Longitudinal Fasciculus	Left	6.9527
Optic Radiation	Left	5.6829
Corticospinal Tract	Left	4.4215
Superior Thalamic Radiation	Left	3.4923
Acoustic Radiation	Left	3.2938
Arcuate Fasciculus	Left	3.0138
Frontal Aslant Tract	Right	2.7936
Anterior Thalamic Radiation	Left	2.6617
Inferior Longitudinal Fasciculus	Left	2.4538
Inferior Fronto-Occipital Fasciculus	Right	2.4177
Uncinate Fasciculus	Left	2.3743
Superior Longitudinal Fasciculus 2	Left	1.9076
Superior Longitudinal Fasciculus 3	Left	1.6238
Superior Longitudinal Fasciculus 3	Right	1.5098
Anterior Thalamic Radiation	Right	1.3149
Uncinate Fasciculus	Right	1.1947

Table 6.6: **White matter tracts demonstrating significant negative correlations between ISOVF and non-decision time.** Higher ISOVF values in these tracts predicted shorter non-decision times across the whole cohort. The numbers in the rightmost column reflect the percentage of each individual tract in which this negative relationship was detected.

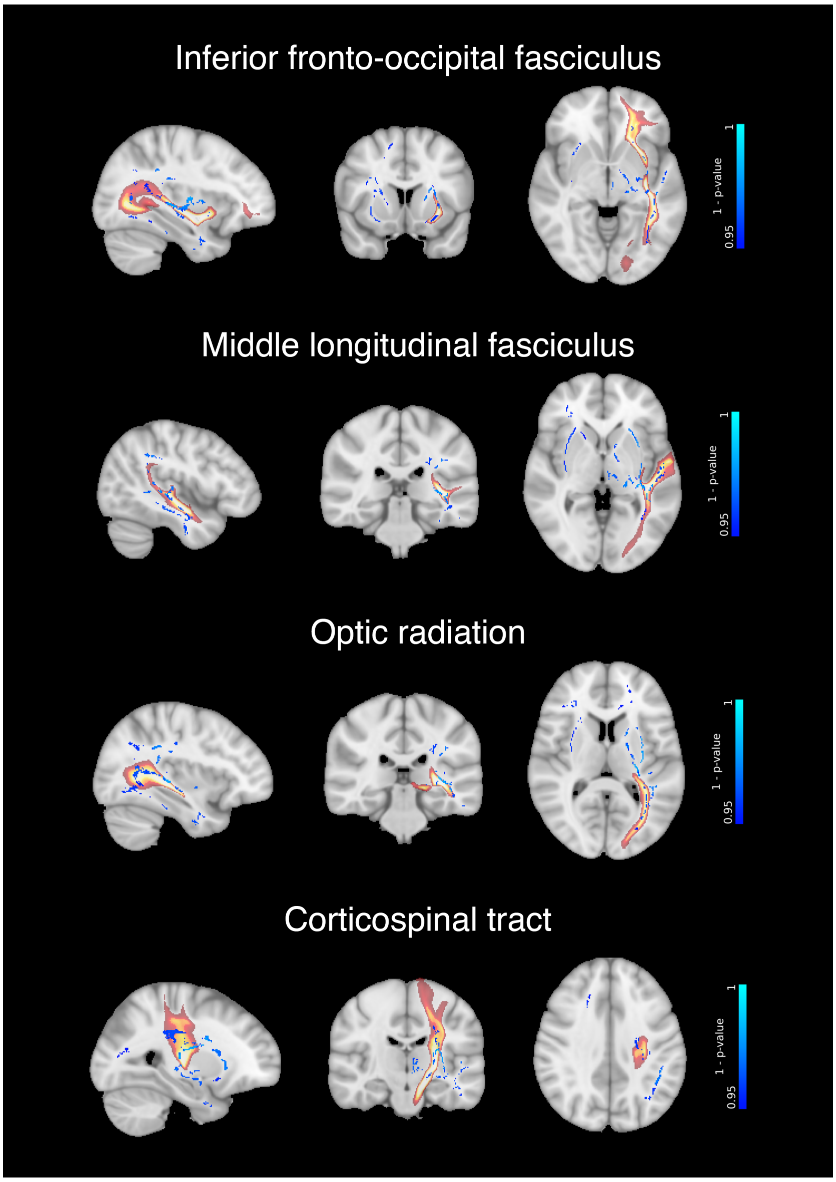


Figure 6.11: **White matter tracts exhibited a negative relationship between ISOVF and non-decision time.** Higher ISOVF in 17 white matter tracts including the inferior fronto-occipital fasciculus, middle longitudinal fasciculus, optic radiation, and corticospinal tract (again, all in the left hemisphere) was associated with reduced non-decision time across all participants.

6.5 Discussion

This chapter sought to identify the neural correlates of EBDM in a cohort of healthy elderly and SVD participants using several MRI modalities. EBDM was chosen due to its conceptual link with the clinical syndrome of apathy. Similar to Chapter 4 which examined the link between structural and diffusion MRI with VSTM, the analyses conducted in this chapter investigated whether any neural correlates of EBDM and apathy were applicable across the whole cohort or were specific to people with SVD. The findings in this chapter can be summarised as follows:

First, WMH volume did not demonstrate any significant association with behavioural measures of EBDM or with total AMI scores. Second, thalamic and hippocampal volumes exhibited a positive correlation with decision-making threshold in uncorrected analysis. In addition, SVD participants had a weaker association between thalamic volume and threshold compared to healthy elderly controls, although none of these results survived correction for multiple comparisons. However, the two groups differed in how the volume of the nucleus accumbens was related to apathy, such that atrophy of the nucleus accumbens was associated with more apathy in people with SVD but not in control participants. Third, VBM revealed that lower grey matter volume in the right occipital lobe was related to lower threshold for decision making. This was accompanied by the finding that grey matter atrophy in the right occipital lobe and left medial frontal lobe were correlated with more apathy. Finally, analysis of white matter microstructural integrity using TBSS showed that higher ISOVF in several white matter tracts was associated with both lower decision-making threshold and reduced non-decision time.

WMH remains a poor predictor of EBDM deficits and apathy

This study failed to demonstrate any significant relationship between WMH volume and EBDM metrics or apathy score. This suggests that WMH volume may not be a good marker for identifying people who are at risk of developing deficits in EBDM or who may go on to experience apathy. One possible reason for this is that WMH volume measurement itself is still an experimental procedure, with no automated approach yet available that can identify WMH accurately without visual assessment and manual correction from human operators (Wardlaw, Valdes Hernandez, & Munoz-Maniega, 2015). Another explanation may be the absence of more fine-tuned data on the location of WMH in the brain. One example of a study that included location data for WMH was the AGES-Reykjavik Study (Grool et al., 2014). This involved 4,354 persons without dementia in whom apathy symptoms were assessed using 3 items from the 15-item GDS. Regression analysis revealed that participants with 2 or more apathy symptoms were more likely to have WMH in the frontal lobe.

In addition to the reasons outlined above, there is some evidence to indicate that WMH may only represent the “tip of the iceberg”, with tissue structural changes actually spreading into normal-appearing white matter (Maniega et al., 2015; O’Sullivan et al., 2001). Thus, despite appearances that are superficially similar, the presence of WMH may affect individuals differently depending on how severe or widespread the damage is in normal-appearing white matter. Failure to account for this may mean that the full scope of damage to the brain is ignored as well. This underlines the importance of looking beyond WMH—whether qualitatively or quantitatively—towards other, more advanced neuroimaging modalities when trying to establish a relationship between SVD and impairments in EBDM or neuropsychiatric symptoms like apathy.

Association between nucleus accumbens atrophy and apathy

At the level of subcortical structures, initial analyses suggested associations between hippocampal and thalamic volumes with the threshold parameter for EBDM although these no longer met the criteria for statistical significance after correcting for multiple comparisons. Nevertheless, it is possible to speculate on the significance these findings. With regards to the hippocampus, Biderman et al. have argued that this structure, known for its role in long-term memory, can also act as a bridge between past experience and future decisions (Biderman, Bakkour, & Shohamy, 2020). In this experiment, it is possible that participants may have kept a memory of how they have responded to different combinations of effort and reward offered to them in previous trials. This may then have influenced, to a certain extent, how they responded to the next offer, allowing them to achieve some degree of internal consistency in decision-making. The possibility that hippocampal atrophy might be associated with decreased threshold for decision-making is intriguing, not least because threshold reductions may not necessarily improve the decision-making process. Instead, it may reflect a reduced desire or capability to consider all aspects of the effort-reward combination in a comprehensive manner, leading to less thoughtful decision-making as if people "can't be bothered" to weigh the pros and cons of the offer.

As for the thalamus, previous reports have shown how interactions between the thalamus and prefrontal cortex are crucial for resolving uncertainty in decision making (Kosciessa, Lindenberger, & Garrett, 2021; Mukherjee, Lam, Wimmer, & Halassa, 2021). One study in which young adults were asked to attend to varying numbers of task-relevant features while undergoing EEG and fMRI testing found that in response to greater uncertainty, upregulation of thalamic activity produced a shift in the cortex from a rhythmic to an asynchronous/excited state that enhanced sensitivity to all stimulus features (Kosciessa et al., 2021). Whether the EBDM paradigm used in this experiment contained enough elements of uncertainty to engage the thalamus in this manner is uncertain. However, given the myriad of roles that the thalamus plays particularly in terms of sensory processing, it is possible that dealing with uncertainty is only one mechanism of decision making that can be disrupted with atrophy of the thalamus (Mitchell et al., 2014). The link with reduced threshold for decision making suggests that there is less capacity for engaging with uncertainty. In other words, people may not be willing to expend cognitive resources to properly evaluate different combinations of effort and reward, and therefore may simply reduce the threshold needed for a yes/no decision to simplify the whole process.

One finding that did survive correction for multiple comparisons was the differential association between volume of the nucleus accumbens and apathy. Specifically, atrophy of the nucleus accumbens predicted total AMI scores in people with SVD but not in healthy elderly controls. The role of the nucleus accumbens in motivated behaviour has been studied extensively (Kelley & Berridge, 2002; Schultz, 2000; Wise, 2002). It is commonly included as part of an area called the ventral striatum, comprising the nucleus accumbens itself as well as adjacent areas in the rostral caudate nucleus and the ventral-rostral putamen (Haber & Behrens, 2014). In the Introduction to this chapter, the ventral striatum was postulated to subserve the value system that calculates the worth of an offer in terms of its potential reward or effort cost. Thus, one might hypothesize that dysfunction of this system may be a possible mechanism for apathy in SVD.

Link between grey matter atrophy with apathy

In the VBM analysis, atrophy of a tiny region in the right occipital lobe was found to be correlated with lower decision-making threshold (Figure 6.7). Due to the size of this cluster which comprised of only 4 voxels, the biological significance of this area for decision making needs to be interpreted with caution. Traditionally, the occipital lobes have been understood to play fundamental roles in visual perception and processing. Dysfunction of this region, therefore, would not be expected to directly affect a task such as EBDM. As part of the protocol for the experiment, participants would have been excluded if they had trouble seeing the information presented on the screen. Nevertheless, it is still possible to speculate on the importance of this finding, particularly in terms of the relationship between deficits in visual processing and decision-making using information presented visually. Although the amount of information presented to the participants during the experiment should not be overwhelming (Figure 5.1, previous chapter), the addition of a time limit (i.e., 10 seconds in total) for making a response may cause a shift in decision-making strategy. That is, participants with some degree of visual processing deficit may be willing to make the trade-off of requiring less evidence to support their decision to accept or reject an offer.

More salient to the topic is the relationship between local grey matter atrophy and apathy. Here, a larger cluster was found in a region of the left medial frontal lobe made up of the superior frontal gyrus, paracingulate gyrus, supplementary motor cortex, and anterior division of the cingulate gyrus (Table 6.4) where lower grey matter volumes correlated with higher total AMI scores i.e., more apathy (Figure 6.8). This finding is compatible with the conceptual framework proposed by Le Heron et al. (Le Heron et al., 2019) whereby similar areas, especially the anterior division of the cingulate gyrus and the supplementary motor cortex, play a crucial role in motivated behaviour. It is not surprising, therefore, to detect the association between atrophy of these regions with apathy. One important aim of this chapter was to investigate if these brain-behaviour relationships were applicable across the whole cohort or was specific to those with SVD. Here, no significant group differences were demonstrated in the linear relationship between local grey matter volume and apathy, suggesting that it did not arise as a function of having SVD.

Impact of reduced white matter microstructural integrity on EBDM metrics

Neurological conditions like SVD are increasingly being viewed from the perspective of large-scale brain networks (Seeley et al., 2007; ter Telgte et al., 2018), where clinical deficits are explained in terms of disruptions to structural and/or functional connectivity. The TBSS results in this chapter provide evidence to support this notion. Out of all the DTI and NODDI metrics tested, only ISOVF showed significant correlations with some of the EBDM parameters. Thus, to comprehend the nature of these alterations, it is important to first delve into the meaning behind changes in ISOVF. Conventionally, higher ISOVF has been interpreted to mean increased extracellular water volume, such as that found in neuroinflammatory states (Andica et al., 2021; Sykova & Nicholson, 2008). Support for this notion comes from previous reports demonstrating higher ISOVF in conditions like multiple sclerosis (Hagiwara et al., 2019; T. Schneider et al., 2017), hypertension (Suzuki et al., 2017), and PD (Kamagata et al., 2017) where some element of neuroinflammation is thought to be relevant to the disease process. As for sporadic SVD, a recent paper revealed that ISOVF had a negative association with processing speed (Konieczny et al., 2021). The common thread that runs across all these studies is that higher ISOVF represents a more pathological state regardless of the disease being studied.

In this chapter, increased ISOVF was related to reduced threshold for EBDM in several white matter tracts in the left hemisphere such as the arcuate fasciculus, superior longitudinal fasciculus, and middle longitudinal fasciculus. The arcuate fasciculus in the left hemisphere, which connects Broca's area in the frontal lobe with Wernicke's area in the posterior temporal lobe, is thought to be critical for language and speech functions (Becker, Loh, Coulon, & Meguerditchian, 2022; Catani & Mesulam, 2008; Catani & Thiebaut de Schotten, 2012; Dick & Tremblay, 2012). Why it appears to be involved in EBDM, especially in terms of determining the threshold for accepting or rejecting offers, remains to be elucidated. Although the task itself lacked any obvious verbal or auditory component, it is not entirely inconceivable that participants may have relied on some sort of auditory memory to track what the threshold should be given their past choices, consistent with the use of a phonological loop in working memory (Baddeley & Hitch, 1974).

The superior longitudinal fasciculus consists of three distinct branches (Catani, 2016): the first branch (SLF I) connects the superior parietal lobule and precuneus to the superior frontal and possibly to some areas in the anterior cingulum. The second branch (SLF II) links the anterior intraparietal sulcus and angular gyrus to posterior regions of the superior and middle frontal gyrus, while the third branch (SLF III) connects the intraparietal sulcus and inferior parietal lobule to the inferior frontal gyrus. Across the whole cohort used in this study, the negative association between ISOVF and decision-making threshold was seen in all three branches of the SLF (Table 6.5). Together, these three branches play important roles in language, attention, memory, and emotions (Kamali, Flanders, Brody, Hunter, & Hasan, 2014; Ramos-Fresnedo, Segura-Duran, Chaichana, & Pillai, 2019). Here, changes in EBDM threshold may be the result of alterations in one or more of these domains. For example, fluctuating attention or impaired working memory may cause decisions to be made at lower thresholds because of the failure to process the breadth of information available. Alternatively, emotional lability may push people into making more impulsive decisions without considering the pros and cons of their deliberations.

Evidence for the existence of the middle longitudinal fasciculus was controversial until its delineation by diffusion MRI segmentation and tractography (Makris et al., 2009; Maldonado et al., 2013). Based on its anatomical connections, there have been speculations that this tract is involved in auditory, language, and attention processes (Latini et al., 2021). Using focused cadaveric dissections augmented by diffusion MRI data in healthy individuals from the Human Connectome Project, Kalyvas et al. demonstrated a close relationship between the middle longitudinal fasciculus and the auditory cortex, suggesting its role in auditory function (Kalyvas et al., 2020). Others, however, point to its connectivity with the parietal lobe to support the argument that it is crucial for focusing attention (Steffens, Wang, Manning, & Pearlson, 2017; Tremblay et al., 2019). As with the superior longitudinal fasciculus above, changes in attentional processing may be one mechanism by which damage to the middle longitudinal fasciculus may produce reductions in the threshold for decision making.

Another EBDM metric that appeared to be associated with diffusion parameters was non-decision time. Non-decision time encompasses time needed for decision-independent processes such as stimulus perception as well as planning and subsequent execution of movement. In this experiment, higher ISOVF was associated with lower non-decision times in several white matter tracts predominantly in the left hemisphere (Table 6.6) including the inferior fronto-occipital fasciculus (IFOF), middle longitudinal fasciculus, optic radiation, and corticospinal tract.

The IFOF originates from the inferior and medial surface of the occipital lobe and mainly terminates in the ventrolateral frontal cortex and frontal pole, with smaller segments terminating in the rostral portion of the superior frontal gyrus (Catani, 2016). It is thought to play a crucial role in the reading, attention, and visual processing (Catani & Thiebaut de Schotten, 2012). In addition, the IFOF may also serve to coordinate goal-oriented behaviours by acting as a connection between the cingulo-opercular salience network and the frontoparietal executive network (Conner et al., 2018). Given the possible functions outlined above, it would be reasonable to assume that reduced integrity of the IFOF might lead to prolonged non-decision times. Instead, the opposite was discovered in this study whereby damage to the IFOF was associated with reduced non-decision times. It is important to note, however, that non-decision time in this study was not measured directly, but instead was inferred using HDDM which may affect its accuracy. Furthermore, a decrease in non-decision time does not automatically mean the outcome is better for participants. It could, in theory, mean that less mental processing was allocated for stimulus perception, or that motor planning was carried out in a less precise manner. Dysfunction of other white matter pathways like the optic radiation and corticospinal tract may also lead to sub-optimal EBDM outcomes through similar mechanisms.

6.6 Conclusion

The aim of this chapter was to investigate the association between structural and diffusion MRI on the one hand, and apathy on the other, as measured not just with questionnaire data (total AMI score) but also using an EBDM behavioural paradigm. The results highlighted here illustrate the value of using multiple MRI modalities to gain a deeper understanding of the neural basis of apathy and EBDM deficits in health and how these can be disrupted in SVD.

7 | General discussion

In this thesis, I applied advanced neuroimaging techniques as well as behavioural paradigms to investigate the impact of SVD on brain and behaviour. Through extensive testing of a cohort of participants with SVD who were compared with a cohort of healthy elderly controls, I was able to identify a range of alterations involving memory and motivation, as well as provide insights into the neural correlates underpinning these changes. In this chapter, I provide a summary of these findings before proceeding to discuss the implications and future directions originating from this research.

7.1 Summary of experimental findings

7.1.1 Neuroimaging biomarkers of SVD

In Chapter 2, neuroimaging data from all participants were analysed to determine how structural and diffusional parameters differed between healthy elderly controls and people with SVD. As expected, total WMH volume was higher on average in the SVD group, although many in the healthy elderly cohort also demonstrated some amount of WMH (Figure 2.1). Comparison of the volumes of subcortical structures revealed smaller hippocampi and nucleus accumbens bilaterally in SVD, although none of these differences survived correction for multiple comparisons (Table 2.2). Nevertheless, this raises interesting questions about how SVD may lead to deficiencies in memory and motivation, two entities that are known to rely on these aforementioned structures. Both topics were subsequently explored further in Chapters 3 and 4 (for memory) as well as Chapters 5 and 6 (for motivation).

VBM was conducted to investigate whether were differences in local grey matter volume between the two cohorts. Here, I showed that SVD in the sample I studied was associated with atrophy of the right middle temporal gyrus, crus I of the left cerebellum, left precentral gyrus, and bilateral nucleus accumbens (Figure 2.2). In addition, TBSS analysis using two different modelling approaches towards the diffusion data i.e., DTI and NODDI, indicated widespread reduction of white matter microstructural integrity involving multiple tracts including the arcuate fasciculus, acoustic radiation, anterior thalamic radiation, cingulum, corticospinal tract, forceps major, forceps minor, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, middle longitudinal fasciculus, optic radiation, and superior longitudinal fasciculus (Figure 2.3). Finally, using resting state fMRI data, I demonstrated that apparent changes in functional connectivity seen in SVD were primarily driven by motion (Figure 2.7).

Together, these results reinforce the idea that SVD is associated with wide-ranging disruptions in brain structure (and potentially, function) that go beyond what are commonly seen and reported on routine clinical neuroimaging. These changes need to be accounted for in order to fully comprehend how SVD exerts its detrimental effects clinically and to explore useful avenues for treatment.

7.1.2 Impact of SVD on VSTM

Cognitive deficits in SVD were hitherto thought to primarily involve executive function and processing speed. One reason for the apparent lack of impairment in other domains may be the relative insensitivity of conventional tests of, for example, memory. In Chapter 3, I set out to show that SVD also affects VSTM. Using the OMT, a more recent behavioural paradigm with a continuous response measure, I first demonstrated that participants with SVD had lower accuracy and required more time to identify and localise items during the experiment (Figure

3.2-3.4). Then, I applied mixture modelling to dissect the sources of error during the task, revealing that SVD was associated with increased imprecision, guessing, and misbinding (Figure 3.53.7).

To facilitate subsequent analyses of the behavioural data, I conducted a factor analysis which distilled all the OMT metrics into two separate factors representing (i) error and (ii) response time. The error factor was significantly higher in SVD participants compared to healthy elderly controls, whereas response time was similar between the two cohorts (Figure 3.10). This suggests that some of the impairment in identification and localisation times that were part of the raw metrics obtained in the OMT was due to difficulties with memory rather than processing speed *per se*.

7.1.3 Neural correlates of VSTM in SVD

Chapter 4 extends the findings from the previous chapter by combining them with neuroimaging data to identify the neural correlates of VSTM in health and SVD. I started by demonstrating that the two OMT factors (error and response time) did not correlate with total WMH volume or the volumes of seven subcortical structures: amygdala, caudate, hippocampus, nucleus accumbens, globus pallidum, putamen, and thalamus (Figure 4.1 - 4.3). To investigate the relationship between VSTM performance and local grey matter volume, I applied VBM to structural T1-weighted images from all participants. This highlighted the potential involvement of a cluster in the right occipital cortex and right cerebellum, whereby atrophy of this region correlated with making more VSTM errors. More specifically, in SVD participants, atrophy of the right lingual gyrus (part of the right occipital cortex) as well as lobules V and VI of the right cerebellum were associated with more VSTM errors, whereas no such relationship was seen in healthy elderly participants (Figure 4.4).

In addition to the grey matter analysis, I also performed TBSS to determine how changes in diffusion parameters related to VSTM performance. Diffusion parameters were obtained using two different modelling approaches described in Chapter 2 i.e., DTI and NODDI. For the DTI model, lower FA and higher MD values across large parts of the white matter skeleton were associated with increased VSTM errors (Figure 4.5). In general, this was true for all participants, but in certain segments of the white matter skeleton e.g. the anterior thalamic radiation, cingulum bundle, forceps major, superior longitudinal fasciculus, SVD participants showed a stronger positive correlation between VSTM error and MD. This hints at the potential for using changes in MD to act as a more sensitive marker of cognitive dysfunction in SVD (Figure 4.6).

Application of the NODDI model revealed that lower NDI, higher ODI, and higher ISOVF, were all correlated with more VSTM errors (Figure 4.7). However, no between-group differences were seen for any of these parameters.

Finally, no significant associations were identified between diffusion metrics and the second OMT factor i.e., response time.

7.1.4 Impact of SVD on EBDM

Another focal area of research in SVD is how the condition may lead to neuropsychiatric symptoms like apathy, anxiety, and depression. In Chapter 5, I sought to illustrate the link between SVD and apathy using an EBDM paradigm in which participants were given the task of accepting or rejecting offers based on different combinations of reward and effort levels. Here, healthy elderly control and SVD participants did not differ in terms of the proportion of offers they were willing to accept (Figure 5.2A). However, those in the SVD group took longer to make their decisions (Figure 5.2B).

Using generalised linear mixed-effects models, I showed that modulating reward and effort levels appeared to have the expected outcomes on offer acceptance. Participants accepted more offers as reward levels increased and effort required decreased. However, people with SVD accepted fewer offers than healthy elderly control participants at low effort levels (Figure 5.3). Another behavioural metric, decision time, decreased as a function of higher reward levels but did not change in response to variations in effort. Regardless of reward or effort level, SVD participants were slower to decide compared to healthy elderly controls (Figure 5.4).

To further explore the mechanism behind these EBDM changes, I employed hierarchical drift diffusion modelling (HDDM) on the choice and decision time data. This produced four main parameters: drift rate, non-decision time, threshold, and bias. In SVD, the influence of effort on drift rate was weaker, while non-decision time was longer (Figure 5.5). No group-differences were observed for the other two metrics.

The last part of this chapter revealed that none of the HDDM metrics demonstrated any significant associations with apathy (indexed by the AMI) or depression (measured using the BDI-II) (Figure 5.6 & 5.7).

7.1.5 Neural correlates of EBDM in SVD

In Chapter 6 of this thesis, I used a similar approach to the one described in Chapter 4 to gain some understanding of the mechanisms behind EBDM deficits in SVD. Briefly, correlations were sought between several neuroimaging parameters and EBDM behavioural metrics derived from HDDM.

Total WMH volume proved least useful for this purpose as it did not show any significant associations with EBDM measures (Figure 6.1). As for subcortical volumes, the threshold for decision making did appear to correlate positively with volumes of the hippocampus and thalamus. Furthermore, the association between thalamic volume and the threshold metric was weaker in SVD (Figure 6.2). However, none of these correlations survived correction for multiple comparisons. Interestingly, the two cohorts differed in how nucleus accumbens volume correlated with apathy. Lower nucleus accumbens volume was associated with more apathy in SVD participants but not in healthy elderly controls (Figure 6.6).

VBM analysis revealed that lower grey matter volume in a small cluster in the right occipital lobe was associated with lower decision-making threshold (Figure 6.7 & Tables 6.1-6.2). Furthermore, atrophy of the left frontal lobe and right occipital lobe also correlated with higher apathy scores (Figure 6.8 & Tables 6.3-6.4).

Finally, the relationship between HDDM metrics and white matter microstructural integrity was explored using TBSS. Two significant findings emerged from this analysis: First, higher ISOVF in several white matter tracts correlated with lower decision-making threshold across all participants (Figure 6.10 & Tables 6.5). Second, higher ISOVF also was significantly associated with reduced non-decision time in the whole cohort (Figure 6.11 & Tables 6.6).

7.2 The boundary between normal ageing and disease

One of the most important questions to answer when discussing SVD is how to distinguish the pathological state from normal, i.e., healthy ageing. Some would argue that the concept is an oxymoron: there is no such thing as healthy ageing because ageing itself is pathological. There is some logic behind this argument. As some authors have put it, ageing is ‘the predominant risk factor for most diseases and conditions that limit healthspan' (Kennedy et al., 2014). However, in many cases it is difficult to reconcile this notion of ageing being always problematic with the experience of many elderly people who are, for all intents and purposes, living healthy lives with no significant signs of disease.

WMH are a case in point. On the one hand, they have been linked with cognitive impairment, stroke, and neuropsychiatric symptoms (Clancy, Gilmartin, et al., 2021; O. K. L. Hamilton et al., 2021). On the other hand, they are also observed on neuroimaging of healthy elderly populations. To give these asymptomatic individuals a diagnosis like cerebral small vessel disease may come as a shock to them, posing more questions than answers about the best way to manage their newly diagnosed medical condition. Perhaps what is needed is some form of reference interval for clinical and research settings, akin to hippocampal normograms obtained from the scans of 19,793 people in the UK Biobank cohort (Nobis et al., 2019). Ideally, this would be quantitative rather than qualitative. However, this is challenging in view of the high technical variability in assessment of WMH across studies (Melazzini et al., 2021), in addition to the lack of a mechanistic understanding behind why the volumes vary considerably in healthy populations (Debette et al., 2019).

Due to increased recognition of the inadequacy of just relying on one neuroimaging feature for the diagnosis of SVD, attempts have been made to come up with a summary SVD score to ameliorate this (Duering et al., 2023; Staals, Makin, Doubal, Dennis, & Wardlaw, 2014). At present, these scores have mostly relied on qualitative neuroimaging parameters for the sake of simplicity, however, incorporating more quantitative neuroimaging measures as well as clinical and functional metrics may produce a more reliable tool for accurately identifying people with SVD.

As for neuropsychological or behavioural approaches in diagnosing SVD, both the VSTM and EBDM paradigms used in this thesis are not yet ready for routine clinical practice. Translating them from the experimental to the clinical domain requires overcoming two major challenges. First, there needs to be evidence that they are superior diagnostically compared to existing tools, and second, they must be feasible in terms of the time taken to administer as well as the costs involved in utilising these tests.

More broadly, attempts have been made to provide guidelines for better trial methodology in SVD. One example of this is FINESSE (Framework for Clinical Trials in Cerebral Small Vessel Disease) which puts forth recommendations on optimal choice of study populations, selection of clinical end points, use of brain imaging as surrogate outcome measures, new trial designs, prioritization of therapeutic targets through Mendelian randomisation genetic methods, as well as the utility of circulating biomarkers for selection of trial participants and as surrogate markers (Markus et al., 2022).

7.3 Advanced neuroimaging methods

As knowledge about SVD continues to develop, the limitation of adopting a purely lesion-based approach is becoming increasingly apparent. Lesion-based approaches dichotomise brain tissue into normal or abnormal, which is not particularly useful for a slowly progressive condition like SVD (van den Brink, Doubal, & Duering, 2023). To better reflect this reality, quantitative approaches have been adopted, providing a continuous measure of the changes in the brain thus enabling a more granular assessment to be made regarding possible pathology.

Diffusion MRI quantifies the movement of water which can be used to examine tissue microstructural integrity. Although most of the research on diffusion MRI changes in SVD have hitherto used the DTI model, more sophisticated approaches such as NODDI (used in this thesis) or DKI offer an alternative way of characterising subtle changes in the white matter of the brain that may occur in early-stage SVD. However, as shown in Chapters 2, 4, and 6 of this thesis, these complex models may not necessarily be better at differentiating between SVD and healthy ageing. One drawback of these techniques is the need to modify acquisition parameters, for example by sampling more directions or using multiple diffusion weightings, which increases scanning time and may not be feasible in clinical practice. Indeed, most of the neuroimaging work in this thesis employs research MRI methodology and thus may not yet be applicable to standard (i.e., clinical) MRI scans, let alone CT.

The most sophisticated method for analysing diffusion MRI data at present is to reconstruct brain networks using tractography and atlas-based parcellation schemes. Measures obtained using graph theory can then be used to identify disruptions to large-scale brain networks (Bassett & Sporns, 2017; Bullmore & Sporns, 2009), producing symptoms like cognitive impairment and apathy that may be seen in those with SVD. Briefly, this approach reimagines the brain in terms of nodes and their connecting edges. Nodes can be classified based on sulci and gyri anatomy, or cyto- and myeloarchitecture, while edges can be defined as the probability that two nodes are connected by a white matter tract. Once the network topology has been constructed, quantitative analysis can be carried out using, for example, network measures like degree and efficiency. Furthermore, there is evidence to show that the results from structural network analysis are highly reproducible, in contrast to using functional networks that are less reliable (Lawrence et al., 2018). In terms of quantifying disease burden and progression, however, the added value of network analysis compared to more straightforward approaches seems limited (Dewenter et al., 2022).

Apart from studying parenchymal changes in SVD, advanced MRI techniques can also be used to demonstrate dynamic abnormalities of the blood vessels themselves. This is important because parenchymal changes are only an indirect reflection of the health of small vessels in the brain, being downstream consequences of vessel pathology. To mitigate this, recent advances like dynamic contrast-enhanced MRI allow assessment of blood-brain barrier permeability (Thrippleton et al., 2019). Disruption to the blood-brain barrier is hypothesized to cause vessel stiffness, something that can be measured using cerebrovascular reactivity imaging (Thrippleton et al., 2018).

Perhaps the most exciting method for neuroimaging in SVD has been the use of ultrahigh field imaging at 7 Tesla (7 T) in humans. This is possibly a game-changer because it allows the imaging of small vessels themselves in vivo. Indeed, in one study using 7 T MRI, SVD patients were found to have fewer branches of the lenticulostriate arteries compared to normal controls (Seo et al., 2012). In addition, the number of branches correlated with delayed recall scores on the Rey's Complex Figure Test of visuospatial memory. Being able to visualise pathological changes at the earliest stages of disease may also allow more accurate evaluation of the impact of novel early-stage treatments on vascular function.

7.4 Interplay between SVD and neurodegenerative conditions

Although not explored specifically in this thesis, a complete understanding of the ramifications of having SVD cannot be achieved without also accounting for the effect of neurodegenerative conditions like AD or PD. While it is possible for SVD to be the only pathology, for example in CADASIL, the monogenic form of the disease, many people who develop cognitive impairment have both AD and SVD-related brain pathology to varying degrees (J. A. Schneider, Arvanitakis, Bang, & Bennett, 2007). The co-existence of these diseases can have additive or synergistic effects on cognitive impairment and, eventually, dementia, but each of them can also produce morbidity via distinct pathways. Therefore, it is crucial to be able to identify both the unique as well as the shared impact of these diseases on brain and behaviour (Koops & Jacobs, 2023).

The work in this thesis represents one possible way in which these goals may be achieved. By employing more sensitive behavioural and neuroimaging techniques in the same group of participants, it is possible to gain some understanding of the specific impact of SVD on various domains like memory and motivation. In addition, by administering the exact same tests in other cohorts like AD and PD, it becomes possible to appreciate both the unique impact of individual diseases as well as their shared properties. This better reflects what is happening in real life, where patients present with symptoms rather than with conveniently attached disease labels.

The trick, seemingly, is to know which level to look at. SVD and neurodegenerative diseases may have radically different molecular underpinnings, but it is possible that they affect common brain networks which thus leads to similar symptomatology (Husain, 2017).

7.5 Implications for treatment

For the vast majority of people, the aim of clinical research on diseases should be to help us come up with better ways to slow down or halt their progress, maybe even cure the underlying pathology. Unfortunately, for many neurological or neuropsychiatric issues that afflict patients at present, the treatments on offer are merely symptomatic, void of true understanding of the mechanisms behind their appearance. While this may be acceptable for some relatively harmless conditions, neurological diseases are responsible for 16.5% of global deaths, making them the second leading cause of death after heart disease (Vos et al., 2017). More worryingly, they account for 11.6% of disability-adjusted life-years (DALYs) globally, making them the leading cause of disability (Carroll, 2019).

What, then, can be done about these grim numbers? To start with, better preventive measures need to be instituted to help ease the burden of disease. Moreover, early detection becomes crucial to stop these conditions from progressing to a stage where disabilities no longer become amenable to treatment.

In terms of specific treatment strategies, the most important modifiable risk factor for SVD is hypertension, and results from the SPRINT-MIND trial indicate that treating blood pressure to a level below 120 mmHg was associated with reduced WMH progression as well as a decrease in the combined endpoint of mild cognitive impairment and probable dementia (Nasrallah et al., 2019; SPRINT MIND Investigators for the SPRINT Research Group et al., 2019). As for the use of antiplatelet therapy, current expert consensus recommends against prescribing this in covert SVD when no other indication for their use exists (Wardlaw et al., 2021). In those who have had a lacunar stroke, however, results from the SPS3 trial (Secondary Prevention of Small Subcortical Strokes) demonstrated that giving dual antiplatelet therapy i.e., aspirin and clopidogrel, did not significantly reduce the risk of recurrent stroke but did increase the risk of major haemorrhage and death significantly (SPS3 Investigators et al., 2012). Statin therapy, another commonly used treatment for cerebrovascular disease, was shown to reduce WMH progression and decline in executive function (Xiong et al., 2014), although some caution needs to be exercised in those with higher bleeding tendencies due to the slight increase in risk of haemorrhagic stroke (Amarenco et al., 2006). In the future, new treatment approaches for SVD may include mechanisms targeting endothelial dysfunction as well as systemic or central nervous system inflammation (Wardlaw, Smith, & Dichgans, 2019; Low, Mak, Rowe, Markus, & O'Brien, 2019; Walsh et al., 2021).

In this thesis, I have provided some insight into specific behavioural components and neuroimaging changes that could: i) help classify people as having SVD, and ii) act as markers for monitoring the efficacy of future treatments. However, several challenges need to be addressed before this knowledge can lead to breakthroughs in clinical care. First, translating the paradigms used in this research into tasks that can be used in real-life, more naturalistic settings, is key for their adoption. The OMT used in Chapter 3, while valuable in terms of providing data on VSTM, needs to be refined further prior to deployment in a busy, time-restricted, clinic setting. Second, ease-of-use and access need to be a priority. If proper diagnosis is dependent on the interpretation of advanced neuroimaging techniques such as the ones used in Chapter 2, few people are likely to benefit due to problems with availability of scanners or experts to analyse the scans. Third, these findings need to be validated in a larger cohort of patients who are better representatives of the at-risk population. Despite the stream of new studies claiming to offer novel ways of diagnosing or treating cognitive or neuropsychiatric deficits, very few of these actually make it into clinical practice. These are some of the barriers preventing the conversion of theoretical knowledge of SVD into practice-changing measures.

7.6 Concluding remarks

The aim of this thesis was to provide a better understanding of the impact of SVD on the brain and how these changes affect memory and motivation. In summary, the work presented here provided evidence for the:

1. Utility of different structural and diffusion modalities for differentiating SVD from healthy ageing
2. Existence and characteristics of VSTM deficits in SVD
3. Relationship between VSTM impairment and disruption of specific grey and white matter regions
4. Existence and characteristics of EBDM deficits in SVD
5. Relationship between EBDM impairment and disruption of specific grey and white matter regions

Combining questionnaires, behavioural paradigms, and neuroimaging in the same cohort allows more detailed conclusions to be made regarding the mechanism behind normal cognitive and psychological function as well as how these are affected by disease. In the future, it is hoped that better clinical trial design, in conjunction with commitment from policy makers to support methodologically-sound research projects, will lead to the development of evidence-based solutions to many of the current problems we face in clinical neuroscience.

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