Risk and resilience in cognitive ageing



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A thesis submitted for the degree of

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Abstract

Whilst advancing age is, on average, associated with declining cognitive abilities, the course of cognitive ageing is highly variable at the individual level. The overall aim of this thesis was to improve understanding of risk and protective factors associated with variability in cognitive ageing. I first explored the effect of Alzheimer's risk gene 'APOE' on cognition in healthy adults, and by reviewing the extensive literature, I showed that APOE genotype can have diverse cognitive consequences via multiple neurobiological mechanisms, each with applications to distinct aspects of cognitive ageing and Alzheimer's disease (AD). I also investigated subjective memory impairment (SMI), which like APOE is associated with increased AD risk, but is also commonly reported by healthy older adults. By presenting a clinical case of persistent SMI, and reviewing evidence for the long-term relevance of brain characteristics in SMI, I reported that MRI can detect early differences in brain structure that herald subsequent cognitive impairment, valuable in clinical settings to identify the most at-risk SMI cases.

I also investigated protective factors that preserve cognitive ability in some older adults, particularly whether the brain supports this superior cognitive ageing in multiple ways, via some older adults maintaining more 'youthful' brains, and others harnessing additional functional resources to 'adapt' to the challenge of brain ageing. Using structural and functional brain metrics alone, I identified multiple patterns of brain ageing predicted to be associated with superior cognitive ageing, and compared cross-sectional and longitudinal cognitive performance, as well as multi-modal MRI metrics acquired at multiple time points between groups. Across these analyses, I found convergent evidence that maintenance of more 'youthful' brain structure and function is associated with prior and continued superior cognitive and brain outcomes, particularly in grey and white matter structure, so promotion of this brain profile should be a goal of interventions. High frontal resting-state connectivity in older adults with poorer brain structure was not associated with the predicted cognitive performance benefit, when compared to those with lower structural and functional brain characteristics. Overall, this thesis provides novel insights into risk and protective factors related to variability in cognitive ageing, upon which further use of sensitive cognitive and imaging measures, and unique populations such as the oldest-old, can expand to inform markers and interventions to maximise cognitive abilities in later life.

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List of Abbreviations

ACE-R	Addenbrooke's Cognitive Examination – Revised
AD	Alzheimer's disease
ADLs	Activities of daily living
ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
APOE	Apolipoprotein E gene
ApoE	Apolipoprotein E protein
B0	Static magnetic field
BBR	Boundary-based registration
BDNF	Brain-derived neurotrophic factor
BET	Brain Extraction Tool
BIANCA	Brain Intensity Abnormality Classification Algorithm
BL	Baseline
BNT	Boston Naming Test
BOLD	Blood Oxygenation Level Dependent
CHA	Cognitive Health in Ageing
CSF	Cerebrospinal fluid
CNS	Central nervous system
COMT	Catechol-O-methyltransferase
CT	Computerised Tomography
dlPFC	Dorsolateral prefrontal cortex
DNA	Deoxyribonucleic acid
DOF	Degrees of freedom
DPUK	Dementias Platform UK
DTI	Diffusion Tensor Imaging
DTIFit	Tool for fitting the diffusion tensor model in FSL
EPI	Echo Planar Imaging
FA	Fractional Anisotropy
FAST	FMRIB's Automated Segmentation Tool
FLAIR	Fluid-attenuated inversion recovery

FIX	FMRIB's ICA-based Xnoiseifier
fMRI	Functional magnetic resonance imaging
FMRIB	Oxford Centre for Functional MRI of the Brain
FLIRT	FMRIB's Linear Image Registration Tool
FNIRT	FMRIB's Non-linear Image Registration Tool
FSL	FMRIB's Software Library
FU	Follow-up
FWE	Family-wise error
FWHM	Full Width Half Maximum
GLM	General Linear Model
GM	Grey matter
HC	Healthy control
HPC	Hippocampus
HVLT-R	Hopkins Verbal Learning Test Revised
IC	Independent component
ICA	Independent component analysis
MB	Multi-band
MCFLIRT	Motion Correction FLIRT
MCI	Mild Cognitive Impairment
MD	Mean diffusivity
md	Mean differences
MELODIC	Multivariate Exploratory Linear Optimised Decomposition into Independent Components
MMSE	Mini-mental state examination
MNI	Montreal Neurological Institute
MoCA	Montreal Cognitive Assessment
MRC	Medical Research Council
MRI	Magnetic Resonance Imaging
MTL	Medial temporal lobe
n.s.	Non-significant
OCMR	Oxford Centre for Clinical Magnetic Resonance Research

OFC	Orbitofrontal cortex
OxDARE	Oxford Dementia and Ageing Research
PD	Proton density
PET	Positron emission tomography
PVE	Partial volume estimate
RCF	Rey-Osterreith Complex Figure test
RD	Radial diffusivity
ROI	Region of interest
RS	Resting-state
RSN	Resting-state network
SD	Standard deviation
SMI	Subjective Memory Impairment
SNP	Single Nucleotide Polymorphism
SPSS	Statistical Package for Social Sciences
STAC	Scaffolding Theory of Aging and Cognition
TBSS	Tensor-based spatial statistics
TE	Echo time
TFCE	Threshold-free cluster enhancement
TI	Inversion time
TOPF	Test of Premorbid Function
TR	Repetition time
TMT	Trail Making Test
VBM	Voxel-based morphometry
vlPFC	Ventrolateral pre-frontal cortex
vmPFC	Ventromedial pre-frontal cortex
WAIS-R	Wechsler Adult Intelligence Scale –Revised
WM	White matter
WMH	White matter hyperintensities

Publications during thesis

Publications resulting from this thesis

O'Donoghue, M.C., Murphy, S.E., Zamboni, G., Nobre, A.C. & Mackay, C.E. (2018) APOE genotype and cognition in healthy individuals at risk of Alzheimer's disease: a review. *Cortex, 104: 103-123.*

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Murphy, S.E., **O'Donoghue, M.C**., Blackwell, S.E., Nobre, A.C., Browning, M. & Homes, E.A. (2017) Increased rostral anterior cingulate activity following positive imagery training in healthy older adults. *Social Cognitive and Affective Neuroscience,* 12(12): 1950-1958.

Mok, R.M, **O'Donoghue, M.C.,** Myers, N.E. & Nobre, A.C. (*in prep*) Neural markers of category-based selective working memory in aging.

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O'Donoghue, M.C., Filippini, N., Zsoldos, E., Suri, S., Kivimaki, M., Singh-Manoux, A., Ebmeier, K. & Mackay, C.E. (2016) Individual differences in the neural mechanisms of superior cognitive aging: diffusion imaging and longitudinal cognitive findings. Annual Meeting of the Society for Neuroscience, San Diego, USA.

O'Donoghue, M.C., Filippini, N., Zsoldos, E., Suri, S., Kivimaki, M., Singh-Manoux, A., Ebmeier, K. & Mackay, C.E. (2017) Individual differences in the neural mechanisms of superior cognitive ageing: structure, function and cognition. Biannual Meeting of the British Neuroscience Association, Birmingham, UK.

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Chapter 1. Overview and objectives

1.1. Overview

On average, advancing age is associated with gradual cognitive decline, as well as changes in brain structure and function. Cognitive decline is an expected and accepted part of getting older (Salthouse, 2009), such that the level of ability considered 'normal-for-age' in an 80 year old is substantially lower than that considered normal for someone in their 50s (Rogalski et al., 2013). However, the course of cognitive ageing is affected by a myriad of risk and protective factors (Lindenberger, 2014). Consequently, at the individual level there is substantial heterogeneity in the trajectory of cognitive ageing. Some older adults organically show remarkably intact cognitive abilities, performing well above the expectations for their age (e.g. Harrison et al., 2012). In others, normal-for-age cognitive performance can mask early pathological changes in the brain that lead to rapid cognitive impairment (e.g. Sperling et al., 2011). Given that 'normal-for-age' cognition underestimates the cognitive abilities of some older adults, and over-estimates the cognitive health of others, it is crucial to go beyond 'averages' to increase our understanding of individual differences in ageing.

Maintenance of cognitive abilities in later life is essential for preservation of independence and quality of life in old age (Agüero-Torres et al., 2001; Fiocco & Yaffe, 2010). As the elderly population continues to grow globally (World Health Organization, 2015), the need for ways to maximise cognitive health in later life is

more vital than ever. Greater knowledge of risk and protective factors that contribute to individual differences in cognitive ageing will inform how best to preserve or enhance cognitive abilities in later life. My DPhil thesis uses cognition, genetics and neuroimaging to understand aspects of risk and resilience that influence or reflect heterogeneity in cognitive ageing.

The principal objective of this thesis is to investigate risk and protective factors associated with variability in cognitive ageing (see *Figure 1.1*). I do this by describing genetic and neuroimaging markers that indicate increased risk of cognitive decline in currently healthy older adults. I also investigate protective factors that allow some older adults to preserve a high level of cognitive ability in a series of chapters that address key gaps in current understanding of the neural mechanisms that support superior cognitive ageing. Deeper understanding of these factors that relate to variability in cognitive ageing will ultimately contribute to maximising cognitive abilities in old age, by informing interventions to boost or preserve cognitive abilities and improving biomarkers to identify as early as possible those most at risk of decline.

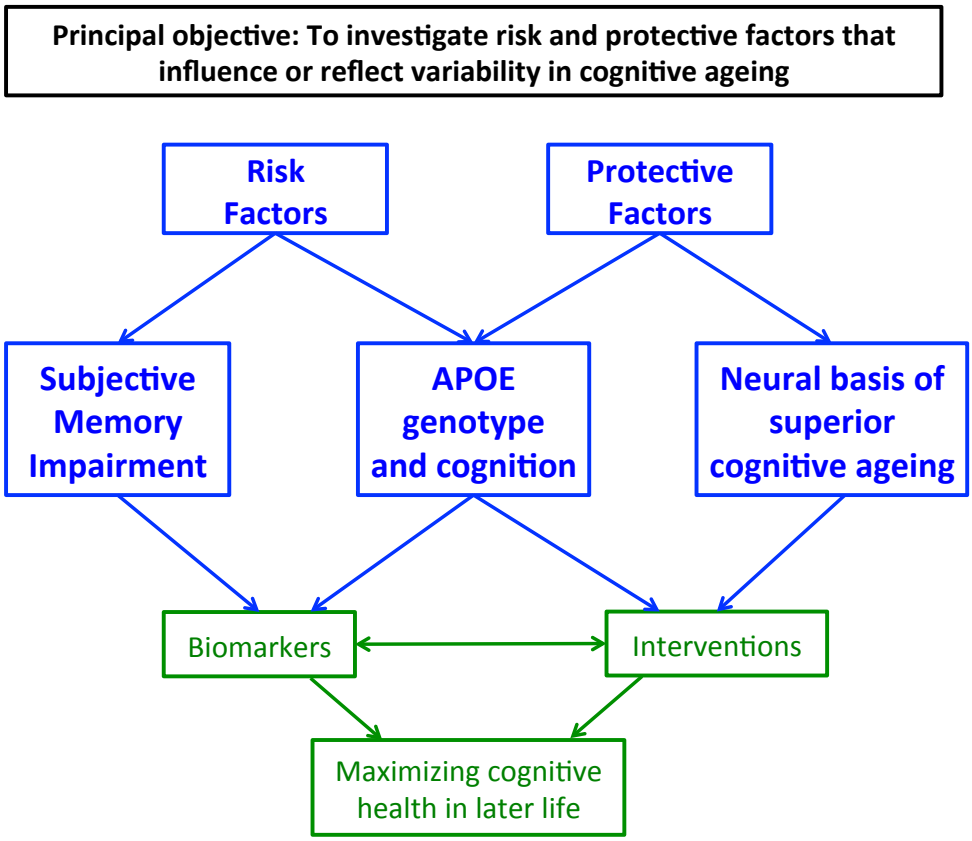


Figure 1.1. **Overview of the principal objective and key topics of this thesis (blue), and the ultimate intended impact of this research (green).**

1.2. Methods for investigating variability in cognitive ageing

In this thesis, I utilise two key methodological approaches that are vital for unmasking heterogeneity in cognitive ageing: MRI and longitudinal assessment.

Magnetic Resonance Imaging (MRI) offers a 'window' to the living brain. By exploiting the effect that magnetic fields exert on protons in water molecules, MRI provides a flexible, non-invasive tool that allows *in-vivo* imaging of tissue. Multi-modal MRI techniques can probe varied aspects of brain structure and function. MRI has revealed structural brain changes prior to the onset of cognitive impairment (e.g. Smith et al., 2007), and higher brain activation in healthy older adults that perform

particularly well on cognitive tests (e.g. Eyler et al., 2011). As such, MRI provides an invaluable link between the ageing brain and cognitive change, to go beyond average cognitive performance. A background to MRI acquisition and analysis is included in *Appendix 1.1*.

Longitudinal data have been instrumental in demonstrating the divergent trajectories of older adults' cognitive abilities, as shown in *Figure 1.2* (Wilson et al., 2002a). Longitudinal assessment is crucial to monitor stability or decline over time, associate long-term outcomes with baseline metrics, and provide more sensitive, within-person measures to detect change. In my thesis, I have utilised data from existing studies, in addition to collecting my own data, to permit longitudinal investigations, not usually feasible in the timescale of a DPhil. An overview of data collected and used in this thesis is included in *Appendix 1.2.*

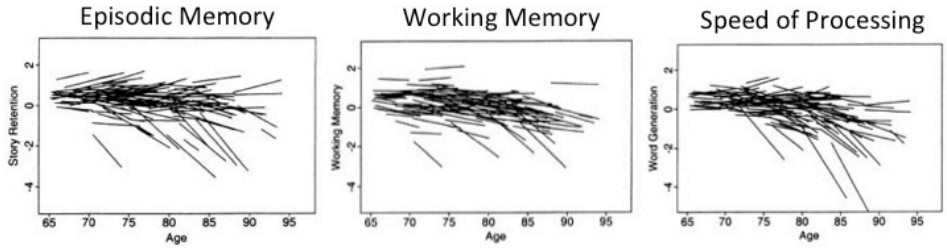


***Figure 1.2*. Individual longitudinal trajectories of cognitive performance in healthy older adults** in domains that show the most age-related change on average. Adapted from Wilson et al., 2002a.

1.3. APOE genotype and variability in cognitive ageing

Normal genetic variation is one known source of individual differences in cognitive ageing, via genetic factors that either accelerate or prevent cognitive decline. Given the strong association of the apolipoprotein (APOE) ε4 allele with increased risk of Alzheimer's disease (AD; Genin et al., 2011), there is considerable research interest in understanding whether APOE genotype influences cognition in healthy adults. Despite a substantial literature, findings are inconsistent and often difficult to interpret. There is ongoing controversy over separating the direct contribution of APOE genotype to individual differences in cognition from the influence of prodromal dementia pathology. Variable methodology across studies has further complicated the issue. These challenges have limited what can be learnt about processes underlying cognitive ageing and dementia by studying the influence of APOE genotype on cognition.

With a focus on two distinct, but compatible, neurobiological mechanisms by which APOE genotype may influence cognition, in Chapter 2 I present an introductory review of the extensive APOE and cognition literature, and explore key methodological challenges for disentangling the effects of APOE on cognition. I conclude with recommendations for future research to maximise the translational potential of this research for the development of cognitive markers that identify those most at risk of decline, and interventions to ameliorate the negative consequence of APOE genotype on individual difference in cognitive ageing. This chapter has been accepted for publication in *Cortex* (O'Donoghue et al., 2018).

1.4. Subjective memory impairment and variability in cognitive ageing

Subjective memory impairment (SMI) is defined as subjective concern of cognitive decline reported by individuals with normal-for-age cognitive scores (Jessen et al., 2014a). SMI is associated with increased risk of future mild cognitive impairment (MCI) or AD diagnosis (Mitchell et al., 2014). In some cases, SMI may represent the earliest sign of AD. However, SMI is common in older adults. Many cases are simply 'worried well', and it is difficult to distinguish these individuals from those in whom SMI indicates increased risk of AD. Consequently, SMI is often dismissed in clinical practice with gentle 'reassurance and discharge' (Jenkins et al., 2015), meaning important opportunities for earlier monitoring and diagnosis are missed. To facilitate identification of those in whom SMI is the first sign of AD, greater understanding of additional risk markers is required. MRI-based biomarkers may be particularly useful, as changes in brain structure precede onset of clinical symptoms in AD by several years (Tondelli et al., 2012).

In Chapter 3, I present an introductory review of the literature on the association MRI-based brain indices and long-term cognitive and clinical outcomes in SMI. I also present a clinical case of remarkably persistent SMI reported for almost 40 years before a clinical diagnosis of AD was reached, for whom I performed the most recent reported cognitive and MRI assessments as part of my direct involvement in the Deep and Frequent Phenotyping Feasibility Study in Oxford. I further present a 3D visualisation of *in-vivo* progressive hippocampal atrophy in early AD, which can be viewed via weblink. Work from this chapter has been submitted for publication

(O'Donoghue et al., submitted) and was awarded Best Poster Prize at the OxDARE Memory Research day 2015.

1.5. Characterising variability in healthy cognitive ageing

Although decline in mental faculties has been considered a ubiquitous feature of normal ageing, research shows that cognitive decline is not an inevitable part of ageing. Some older adults maintain the same level of cognitive performance over many years (e.g. Habib et al., 2007; Yaffe et al., 2009), even in cognitive domains that decline most with age (Wilson et al., 2002a). Other studies identify older adults with cognitive abilities typical of much younger adults (e.g. Gefen et al., 2015; Harrison et al., 2012). Understanding how some older adults organically preserve cognitive abilities in later life is a valuable way to find interventions to boost cognition in old age (Eyler et al., 2011; Rosano et al., 2012; Rowe & Kahn, 1998).

Whilst it is well established that changes in brain structure and function underpin age-related declines in cognition (Hedden & Gabrieli, 2004), the neural mechanisms that support superior cognitive abilities in later life are relatively less understood. Cognitively 'successful' adults have been shown to demonstrate higher brain function compared to younger adults, interpreted as adaption to age-related declines in the brain (Reuter-Lorenz & Park, 2014). Other evidence suggests cognitively superior older adults may maintain more 'youthful' brain structure and function (Nyberg et al., 2012). Individual differences may therefore exist in the neural basis of superior cognitive ageing, supported by youthful brain structure and function in some older adults, and by adaption to age-related declines in others.

However, methodology of existing studies has so far precluded direct identification of such individual differences. In Chapter 4, I addressed this by using a multi-modal MRI-based approach to identify multiple patterns of brain ageing predicted to be associated with superior cognitive ageing within a sample of healthy older adults. By identifying groups of 'maintainers', 'adapters' and 'decliners' based on brain metrics alone, and then comparing cognition between groups, I avoid *a priori* definition of superior cognition. This chapter has been prepared as a manuscript for publication (O'Donoghue et al., *in preparation*).

1.6. Cognitive trajectories of variability in cognitive ageing

Association of baseline brain metrics with subsequent cognitive performance can evaluate the potential of these brain metrics as markers of long-term cognitive outcomes. As longitudinally maintained cognition is the optimal cognitive trajectory for older adults, it is crucial to identify the brain characteristics that underpin long-term 'superior' cognitive abilities, rather than just cross-sectional high performance. In Chapter 5, I examined the longitudinal cognitive performance of the 'maintainer', 'adapter' and 'decliner' groups proposed in Chapter 4. I identified these groups based on baseline brain metrics, as in Chapter 4, and compared cognitive performance over the subsequent 4 years between groups. With this approach, I aimed to establish which baseline brain profiles are associated with a more optimal cognitive trajectory, i.e. the least cognitive decline, and which may indicate risk of subsequent cognitive decline.

1.7. Neural trajectories of variability in cognitive ageing

The cross-sectional MRI used in Chapters 4 and 5 to identify 'maintainers', 'adapters' and 'decliners' captures only a snapshot of what are assumed to be continuous changes in the brain with age. How the brain characteristics of the 'maintainer', 'adapter' and 'decliner' groups, proposed in Chapter 4, change over time is unclear, but can provide further evidence to support the association of these baseline brain metrics with divergent trajectories of ageing. Therefore, examining the brain characteristics of these groups after several years can provide some insight into the significance of baseline characteristics for subsequent brain health. In Chapter 6, I investigated the subsequent brain characteristics of baseline 'maintainer', 'adapter' and 'decliner' groups by comparing structural and functional brain metrics acquired after 4 years between groups defined on baseline brain characteristics. With this approach, I aimed to gain further insight into which baseline brain profiles have the most favourable long-term outcomes.

1.8. Summary of research questions

To investigate risk and protective factors that related to variability in cognitive ageing:

- *How does genetic variability affect cognitive ability in healthy older adults? (Chapter 2)*
- *Do MRI markers facilitate assessment of Alzheimer's risk in cases of persistent subjective memory impairment? (Chapter 3)*
- *Do individual differences exist in the neural mechanisms that support superior cognitive ageing? (Chapter 4)*
- *Do baseline brain metrics proposed to support superior cognitive ageing relate to trajectories of future cognitive ability? (Chapter 5)*
- *Do baseline brain metrics proposed to support superior cognitive ageing relate to brain characteristics several years later? (Chapter 6)*

Chapter 2. Genetic influence on variability in cognition in healthy adults: the APOE gene.

Genetics are an important determinant of cognitive ability (Plomin et al., 2001), and variability in cognitive ageing has been linked to multiple genes, e.g. COMT, BDNF (Greenwood & Parasuraman, 2003; Raz et al., 2010a). However, apolipoprotein-E (APOE), which has genetic variants associated with increased risk and protection against Alzheimer's disease development, has been the most extensively studied. The impact of APOE genotype on cognition in healthy adults remains controversial, and this has limited our ability to inform interventions and biomarkers by understanding the influence of APOE genotype on cognition. In this chapter, I review the extensive evidence for APOE genetic effects on cognition in currently healthy adults, and focus on two neurobiological mechanisms by which APOE genotype may influence individual differences in cognitive ageing. I explore methodological challenges for disentangling the cognitive effects of different neurobiological mechanisms of APOE, and conclude with methodological recommendations to maximise the translational potential of this research. *A modified version of this chapter has been accepted for publication in Cortex as a review article titled 'APOE genotype and cognition in healthy individuals at-risk of Alzheimer's disease'* (**O'Donoghue et al., 2018).**

2.1. Introduction

Since the discovery of APOE-ε4 as a genetic risk factor for AD (Corder et al., 1993; Saunders et al., 1993), researchers have investigated whether healthy ε4-carriers

show impaired cognition or more rapid cognitive decline compared to non-carriers, as a source of variability in healthy cognitive ageing (e.g. Deary et al., 2002, 2003a; Greenwood et al., 2005a; Helkala et al., 1996), or early sign of impending dementia (e.g. Bondi et al., 1995; Staehelin et al., 1999; Wetter et al., 2005). Understanding the association between APOE genotype and cognition in healthy adults can aid development of preclinical biomarkers for AD, and inform interventions to boost cognition in older adults. However, the reported effects of APOE on cognition are highly inconsistent, and interpretation of these mixed findings is complicated by conceptual and methodological challenges.

A major challenge in understanding the association between APOE and cognition is the difficulty disentangling direct influences of APOE genotype on a 'cognitive phenotype' (Greenwood et al., 2005a; Greenwood & Parasuraman, 2003) from the influence of greater prodromal AD pathology in the at-risk group (Smith et al., 1998). In part, this stems from a conceptual challenge where the two possibilities have been framed as competing 'hypotheses' to explain the effect of APOE on cognition (Bunce et al., 2014; Foster et al., 2013; Greenwood et al., 2005b; Greenwood & Parasuraman, 2003; Greenwood et al., 2014; Hofer et al., 2002; Negash et al., 2009; Parasuraman et al., 2002), with evidence supporting one 'hypothesis' interpreted as evidence against the other (e.g. Bondi et al.,1999; Foster et al., 2013; Small et al., 1998; Smith et al., 1998). However, the proposed direct vs. pathology-mediated cognitive effects of APOE genotype are underpinned by different neurobiological mechanisms, and these need not be mutually exclusive. Dissecting the relative

influence of each mechanism on cognitive performance will ultimately elucidate their roles in cognitive ageing and Alzheimer's disease.

2.2. Neural mechanisms of APOE genotype influence on cognition

The APOE gene has three major allelic variants - ε2, ε3 and ε4. Individuals possess two APOE alleles, one inherited for each parent, resulting in three homozygous genotypes – ε2ε2, ε3ε3, ε4ε4 - and 3 heterozygous genotypes – ε2ε3, ε2ε4, ε3ε4. APOE-ε3 is the most common allele, estimated to be present in 68-86% of the Caucasian population, compared to 10-23% and 4-14% for the ε4 and ε2 alleles, respectively (Davignon et al., 1988; Gerdes et al., 1992; Myers et al., 1996; Singh et al., 2006).

The APOE gene codes for the apolipoprotein-E lipid-transport protein (ApoE), responsible for movement of cholesterol between cells (Mahley, 1988), and provides essential lipids for central nervous system (CNS) functions such as neuronal growth, synaptic plasticity, and neuronal maintenance and repair (Liu et al., 2013). Structural differences in ApoE proteins that result from allelic variation in APOE genotype are associated with isoform-specific alterations of such CNS functions. For example, animal models report delayed neuronal development, lower dendritic spine density and reduced long-term potentiation in ε4-carriers (Nwabuisi-Heath et al., 2014; Dumanis et al., 2009; Trommer et al., 2004), whilst human ε4-carriers have shown reduced synaptic plasticity, altered myelin formation, and poorer outcomes following neuronal injury, such as traumatic brain injury (Arendt et al., 1997; Dean et al., 2014; Zhou et al., 2008).

The APOE-ε4 allele is the best known genetic risk factor for sporadic Alzheimer's disease (Corder et al., 1993; Rocchi et al., 2003). Carriers of the ε4 allele show increased risk and earlier age of onset of AD, compared to non-carriers (Borgaonkar et al., 1997; Corder et al., 1993; Sando et al., 2008). In contrast, possession of an ε2 allele may provide protection against AD diagnosis, possibly via maintenance of synaptic integrity (Suri et al., 2013). The mechanisms by which APOE-ε4 increases AD risk are not fully understood, but a role in greater deposition and/or reduced clearance of amyloid-β, a hallmark pathological feature of AD, has been proposed (Huang et al., 2004). Possession of an APOE-ε4 allele is neither necessary nor sufficient for development of AD (Henderson et al., 1995; Hyman et al., 1996); however, approximately half of ε4-homozygotes will develop AD by age 85, compared to only 10% of non-carriers (Genin et al., 2011).

2.2.1 'Prodrome'

APOE genotype may influence cognition in currently healthy adults indirectly via an increased presence of early AD pathology in APOE-ε4 carriers. Whilst AD is typically diagnosed after age 65 (McKhann et al., 1984), the accumulation of pathology begins years prior to the onset of clinical symptoms (Ohm et al., 1995; Tondelli et al., 2012), and progressive cognitive impairment, particularly in episodic memory (Bondi et al., 2008; Weintraub et al., 2012), is also detectable years before a diagnosis is made (Amieva et al., 2005; Wilson et al., 2011). A proportion of any sample of currently healthy older adults will be in the prodromal stage that precedes clinical diagnosis of AD (Sliwinski et al., 1996). The increased risk and earlier age of onset of AD in APOE-

ε4 carriers (Blacker et al., 1997; Corder et al., 1993; Sando et al., 2008) means the proportion of prodromal individuals will be greater in this at-risk group, compared to non-carriers.

According to the '*prodromal hypothesis*' (Foster et al., 2013; Smith et al., 1998), cognitive deficits in healthy APOE-ε4 carriers, particularly in samples aged over 60 years, reflect the indirect effect of prodromal AD pathology in a subset of ε4-carriers who will go on to be diagnosed with AD. Some researchers argue that APOE genotype itself has no direct influence on cognition, but rather observed ε4-related cognitive deficits result entirely as a consequence of prodromal AD. In support of this, a number of studies reported elimination of ε4-related deficits after exclusion of incident AD cases (Bondi et al., 1999; Hayden et al., 2009; Hofer et al., 2002; Knight et al., 2014; Praetorius et al., 2013; Winnock et al., 2002; Laukka et al., 2013; c.f. Jonker et al., 1998), and significantly faster cognitive decline in ε4-carriers in domains affected in early AD (Bretsky et al., 2003; Caselli et al., 2011; Haan et al., 1999; Helkala et al., 1996; Hofer et al., 2002; Hyman et al., 1996; Mayeux et al., 2001; Packard et al., 2007; Riley et al., 2000; Schiepers et al., 2012; Small et al., 1998; Yaffe et al., 1997), as well as mediation of cognitive deficits in ε4-carriers by the presence of MCI rather than APOE genotype itself (Foster et al., 2013).

2.2.2 'Phenotype'

In contrast, other researchers consider that APOE genotype may exert a direct effect on cognition, independent of future AD diagnosis, via genotype-specific influences on neurobiological processes that affect cognition (Greenwood & Parasuraman,

2003; Parasuraman & Greenwood, 2004). This *cognitive neurogenetic* approach (Greenwood & Parasuraman, 2003; Parasuraman & Greenwood, 2004) proposes a cascade of events linking genotype to cognitive phenotype. As the isoform structure of a protein depends on the specific genotype of the coding gene, this will result in isoform-specific alteration of *neurobiological endophenotypes*, ultimately producing variable *cognitive phenotypes.*

According to the '*phenotype hypothesis*' (Greenwood et al., 2005a; Greenwood & Parasuraman, 2003; Parasuraman et al., 2002), the putative roles of ApoE in CNS function provide an altered neural endophenotype by which APOE genotype may result in a 'cognitive phenotype'. According to this hypothesis, cognitive differences in ε4-carriers are not confined to older adults and are independent of subsequent AD diagnosis (Greenwood et al., 2005a). Corroborative findings from neuroimaging studies in younger adults (under 60 years) suggest APOE-ε4 is associated with differences in the brain prior to the onset of AD pathology, in a manner independent of future AD, with similar patterns observed in at-risk ε4-carriers and low-risk ε2-carriers, compared to ε3-carriers, in task and resting-state fMRI, as well as white matter integrity (e.g. Trachtenberg et al., 2012a; Trachtenberg et al., 2012b; Westlye et al., 2012).

A direct effect of APOE on a cognitive phenotype is likely to be subtle, as cognitive ability is influenced by multiple genes, environmental factors, and gene-environment interactions (Marian, 2012). However, the increasing influence of genetics on cognition with age (e.g. McGue & Christensen, 2002), possibly due to age-related

neuronal and neurochemical losses that highlight the genetic influences on cognition (Lindenberger et al., 2008), suggests normal allelic variation may particularly contribute to variability in cognitive abilities in older adults.

2.3. Literature Search

For this comprehensive review of APOE and cognition studies in healthy adults, online searches were performed in PubMed using combinations of the following search terms: 'APOE', 'apolipoprotein', 'cognition', 'cognitive', 'performance', 'cognitive ability', and 'cognitive abilities'. Only studies published from 1993, when APOE genotype was identified as a risk factor for AD (Corder et al., 1993), were considered. Studies that used neuropsychological measures, forming the majority of the literature, were considered for inclusion in *Table 2.1* and *Table 2.2*. Functional MRI studies were not included and are reviewed elsewhere (Trachtenberg et al., 2012c).

2.4. Summary of research findings

A large proportion of studies that investigated the influence of APOE genotype on cognition in the absence of diagnosed dementia compared the performance of older adults on neuropsychological tests between APOE-ε4 carriers and non-carriers, particularly on measures of episodic memory (Small et al., 2004; Wisdom et al., 2011). The effect of APOE on cognition has also been investigated across the lifespan, from children to the oldest-old, using cross-sectional and longitudinal cognitive measures spanning a range of cognitive domains, including semantic memory, working memory, executive function, processing speed, attention,

visuospatial processing, language, intelligence, and tests of global cognition, as well as a smaller selection of experimental cognitive tasks.

Despite this breadth of investigation, a consistent pattern of results has failed to emerge. Whilst many cross-sectional studies have reported significant cognitive deficits in APOE-ε4 carriers compared to non-carriers, across a range of cognitive domains (Bondi et al., 1995; Bondi et al., 1999; Caselli et al., 2001; Chey et al., 2000; Deary et al., 2002, 2004; Flory et al., 2000; Houston et al., 2005; Izaks et al., 2011; Jacobson et al., 2005a; Jacobson et al., 2005b; Laukka et al., 2013; Levy et al., 2004; Liu et al., 2010; Luciano et al., 2009a; Luck et al., 2015; Nao et al., 2017; O'Hara et al., 2008; Reed et al., 1994; Rosen et al., 2002; Rosen et al., 2005; Sager et al., 2005; Schmidt et al., 1996; Schultz et al., 2008; Striepens et al., 2011; Welsh-Bohmer et al., 2009; Wetter et al., 2005), other studies have found no significant effect of APOE genotype on cognition (Bathum et al., 2006; Berteau-Pavy et al., 2007; Bunce et al., 2011; Caselli et al., 1999; Caselli et al., 2002; Chen et al., 2002; Driscoll et al., 2005; Duchek et al., 2006; Foster et al., 2013; Greenwood et al., 2000; Jorm et al., 2007; Kim et al., 2002; Liu et al., 2010; Luciano et al., 2009b; Payton et al., 2006; Quintas et al., 2014; Reiman et al., 1996; Richter-Schmidinger et al., 2011; Salo et al., 2001; Small et al., 2000; Ward et al., 2014; Wetter et al., 2006; Ystad et al., 2009; Zhang et al., 2015a; Zhang et al., 2015b). *Table 2.1* summarises the reported effects of APOE on cross-sectional neuropsychological measures of cognition, including the cognitive domains tested in each case (definition of cognitive domains is detailed in *Appendix 2*). A small number of studies reported superior performance in ε4-carriers, although such findings are typically restricted to young (e.g. under 30; Mondadori et al., 2007;

Schultz et al., 2008) or very old (e.g. over 80 years; Carrión-Baralt et al., 2009; Smith et al., 1998) samples.

Table 2.2 summarises the reported APOE effects from longitudinal studies, including sample age at baseline, length of follow-up period, and screening at baseline and follow-up(s). Many such studies have reported more rapid cognitive decline in APOE-ε4 carriers (Andrews et al., 2016; Baxter et al., 2003; Bretsky et al., 2003; Carmelli et al., 2000; Caselli et al., 2004; Caselli et al., 2011; Caselli et al., 2009; Christensen et al., 2008; Donix et al., 2012; Greenwood et al., 2014; Helkala et al., 1996; Hofer et al., 2002; Jochemsen et al., 2012; Jonker et al., 1998; Mayeux et al., 2001; Praetorius et al., 2013; Riley et al., 2000; Schiepers et al., 2012; Shadlen et al., 2005; Small et al., 1998; Tupler et al., 2007; Wilson et al., 2002b), with some also reporting baseline ε4-related deficits (Barnes et al., 2013; Blair et al., 2005; Lavretsky et al., 2003; Packard et al., 2007; Sapkota et al., 2017; Yaffe et al., 1997; Zehnder et al., 2009). However, other longitudinal studies observed no difference in rate of cognitive decline between genotype groups (Batterham et al., 2013; Bunce et al., 2004; Bunce et al., 2014; Cohen et al.,. 2001; Deary et al., 2003a; Dik et al., 2000; Jarvik et al., 2005; Juva et al., 2000a; Knight et al., 2014; Mortensen & Høgh, 2001).

In studies that assessed APOE genotype effects on multiple cognitive domains in the same sample, ε4-related deficits have often been reported in some, but not all, domains, suggesting a domain-specific effect of APOE-ε4. Episodic memory appears to be particularly affected. However, the pattern of spared vs. impaired domains is inconsistent across studies, and whilst many studies have reported an ε4-related

deficit in at least one cognitive domain, the majority of comparisons have resulted in non-significant effects (see *Table 2.1* and *Table 2.2*). Meta-analyses addressing the domain specificity of APOE effects on cognition, primarily in older samples (60+ years), suggest specific ε4-related impairments in episodic memory, executive function, global cognition, and possibly perceptual speed, but no effect of genotype on verbal ability, attention, visuospatial function, and primary memory (Small et al., 2004; Wisdom et al., 2011).

Interpretation of these heterogeneous findings is challenging. Methodology varies substantially among studies, making cross-study comparisons difficult. Since most studies use older samples, it is often unclear whether observed ε4-deficits reflect a direct effect of APOE on cognition or the presence of prodromal AD. In many cases, it is also difficult to resolve whether the absence of significant APOE effects reflects a genuine lack of genetic effect, or rather a lack of statistical power or insensitive cognitive measures.

Disentangling the cognitive consequences of the neurobiological mechanisms by which APOE may influence cognition is essential, as they can provide insight into separate neurobiological processes, with applications to distinct aspects of cognitive ageing and Alzheimer's disease (see *Figure 2.1*). To address this, methodology that is targeted to addresses specific research questions is required. Consideration of 'prodromal' and 'phenotype' as distinct but compatible mechanisms, rather than competing hypotheses, will aid the separation of direct and prodromal effects of

APOE on cognition. In the next section, I highlight key methodological challenges for investigating the cognitive effects of different underlying neurobiology of APOE.

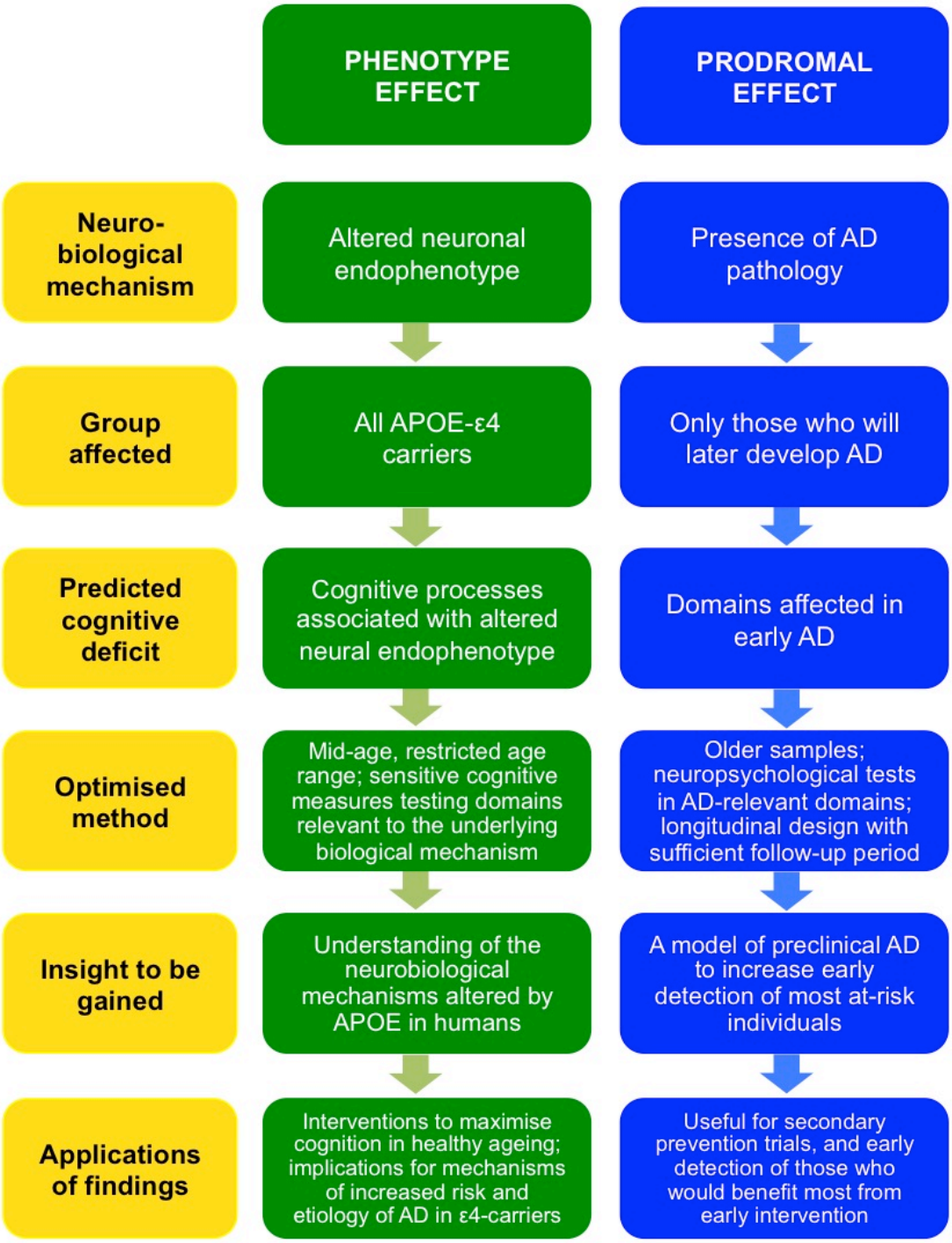


Figure 2.1. **An overview of the possible phenotype and prodrome effects of APOE on cognition, and potential insights to be gained from increased understanding of each mechanism**

***Table 2.1*. Cross-sectional neuropsychological performance by domain**

APOE effect in multiple tested domains | APOE effect in one tested domain | No APOE effect in any tested domains

Study	Age	Sample Size	Effect	*Episodic Memory*	*Verbal Episodic Memory*	*Non-Verbal Episodic Memory*	*Semantic Memory*	*Working Memory*	*Executive Function*	*Attention*	*Speed of Processing*	*Visuospatial Processing*	*Language*	*Intelligence*	*Global Cognition*	*Other*
Yu et al (2000)	19-21	126														
Schultz et al (2008)	19.9	626														
Bunce et al (2011)	20-24	1821														
Jorm et al (2007)	20-24	2097														
Mondadori et al (2007)	22.8	340														
Richter-Schmidinger et al (2011)	24.6	135														
Zhang et al (2015a)	27.5	282														
Nao et al (2017)	27.8	72														
Bunce et al (2011)	40-44	1830														
Jorm et al (2007)	40-44	2182														
Flory et al (2000)	46.0	220														
Liu et al (2010)	<50	1122														
Liu et al (2010)	>50	1021														
Zhang et al (2015a)	51.9	131														
Sager et al (2005)	53.0	452														
Izaks et al (2011)	55.0	4135														
Schultz et al (2008)	55.1	626														
Caselli et al (2001)	55.9	80														
Reiman et al (1996)	55.9	235														
Caselli et al (2002)	56.1	250														
Caselli et al (1999)	56.5	100														
Levy et al (2004)	59.0	176														
Greenwood et al (2000)	59.6	97														
Schmidt et al (1996)	60.5	214														
Bunce et al (2011)	60-64	1794														
Jorm et al (2007)	60-64	2281														
Small et al (2000)	60-73	202														
Ward et al (2014)	62.2	422														
Ystad et al (2009)	62.2	170														
Rosen et al (2002)	62.2	42														
Rosen et al (2005)	62.4	40														
Payton et al (2006)	62.9	766														
Reed et al (1994)	63.0	40														

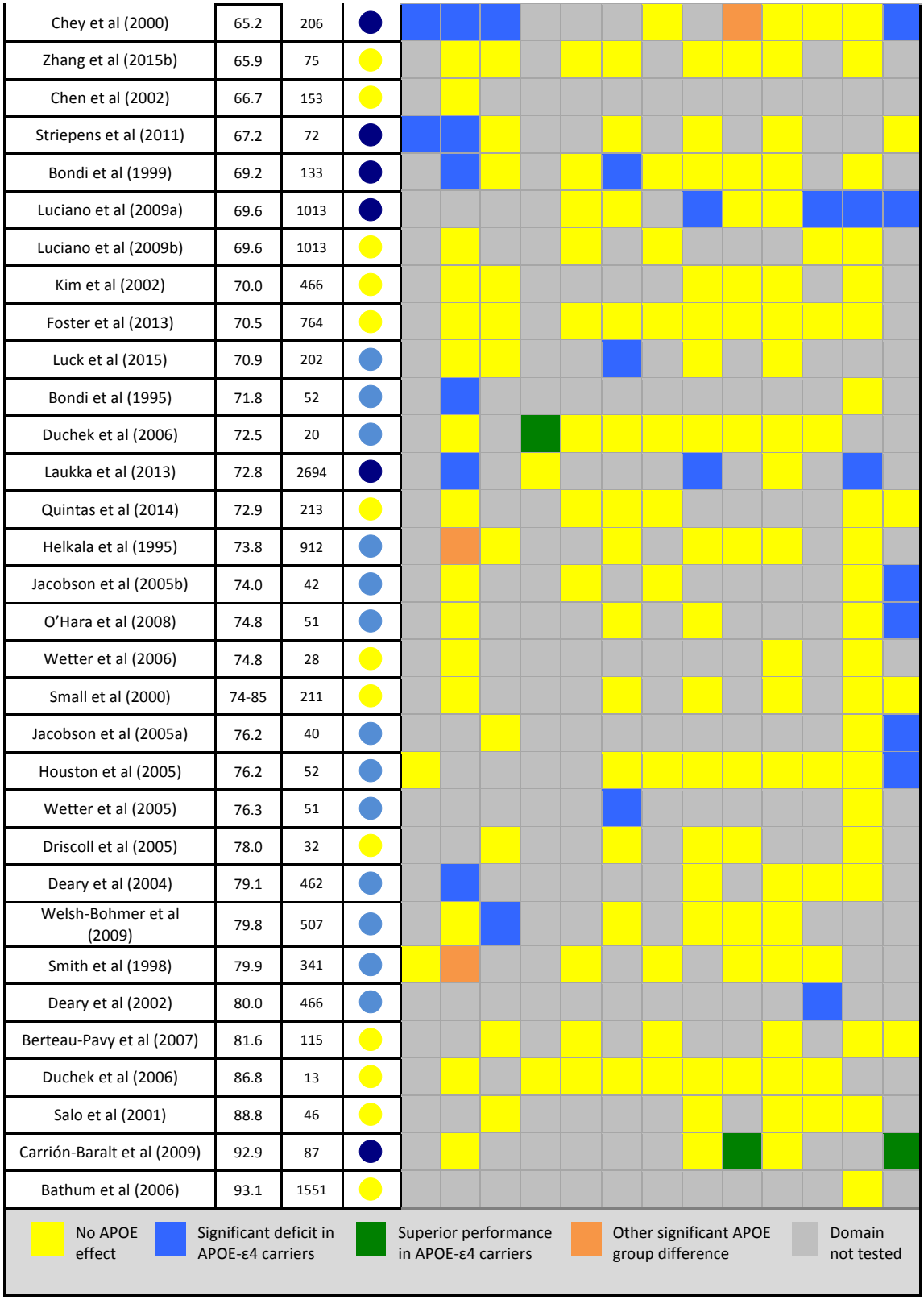
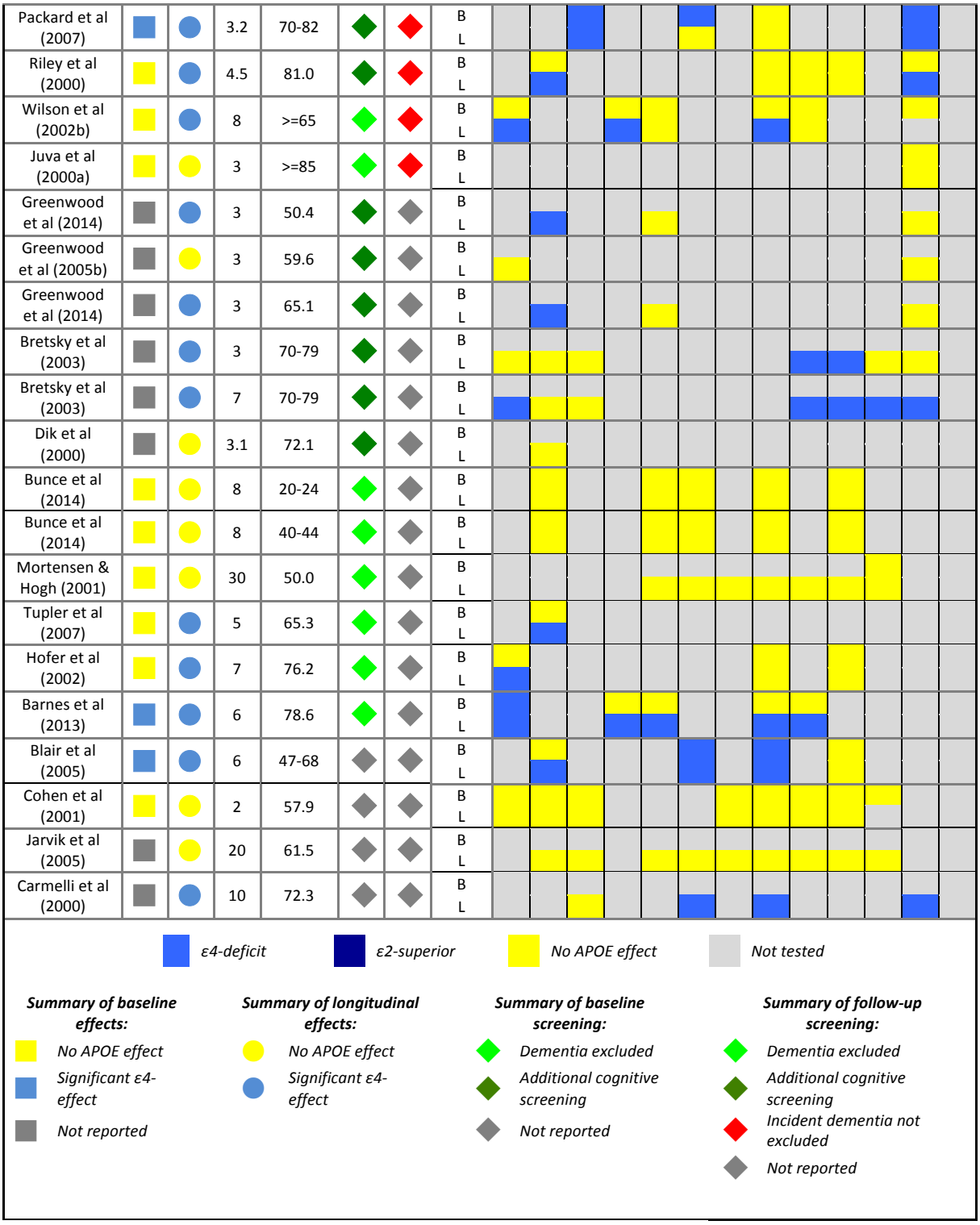

Chey et al (2000) 65.2 206
Zhang et al (2015b) 65.9 75
Chen et al (2002) 66.7 153
Striepens et al (2011) 67.2 72
Bondi et al (1999) 69.2 133
Luciano et al (2009a) 69.6 1013
Luciano et al (2009b) 69.6 1013
Kim et al (2002) 70.0 466
Foster et al (2013) 70.5 764
Luck et al (2015) 70.9 202
Bondi et al (1995) 71.8 52
Duchek et al (2006) 72.5 20
Laukka et al (2013) 72.8 2694
Quintas et al (2014) 72.9 213
Helkala et al (1995) 73.8 912
Jacobson et al (2005b) 74.0 42
O'Hara et al (2008) 74.8 51
Wetter et al (2006) 74.8 28
Small et al (2000) 74-85 211
Jacobson et al (2005a) 76.2 40
Houston et al (2005) 76.2 52
Wetter et al (2005) 76.3 51
Driscoll et al (2005) 78.0 32
Deary et al (2004) 79.1 462
Welsh-Bohmer et al (2009) 79.8 507
Smith et al (1998) 79.9 341
Deary et al (2002) 80.0 466
Berteau-Pavy et al (2007) 81.6 115
Duchek et al (2006) 86.8 13
Salo et al (2001) 88.8 46
Carrión-Baralt et al (2009) 92.9 87
Bathum et al (2006) 93.1 1551
No APOE effect
Significant deficit in APOE-ε4 carriers
Superior performance in APOE-ε4 carriers
Other significant APOE group difference
Domain not tested

Table 2.2. **Longitudinal neuropsychological performance by domain**

Study	Baseline effect	Longitudinal effect	Follow-up period, yrs	Baseline age, yrs	Baseline screening	Follow-up screening	Baseline/ Longitudinal effects	*Episodic Memory*	*Verbal Episodic Memory*	*Non- Verbal Episodic Memory*	*Semantic Memory*	*Working Memory*	*Executive Function*	*Attention*	*Speed of Processing*	*Visuospatial Processing*	*Language*	*Intelligence*	*Global Cognition*	*Other*
Baxter et al (2003)			2	<60			B													
							L													
Baxter et al (2003)			2	>=60			B													
							L													
Bunce et al (2014)			8	60-64			B													
							L													
Zehnder et al (2009)			2	68.3			B													
							L													
Sapkota et al (2017)			9	<70			B													
							L													
Sapkota et al (2017)			9	>=70			B													
							L													
Knight et al (2014)			10	71.7			B													
							L													
Mayeux et al (2001)			7	75.9			B													
							L													
Batterham et al (2013)			12	76.2			B													
							L													
Schiepers et al (2012)			8	79.0			B													
							L													
Caselli et al (2011a)			6.3	56.5			B													
							L													
Caselli et al (2009)			5.2	58.9			B													
							L													
Caselli et al (2004)			2.8	60.0			B													
							L													
Donix et al (2012)			2	62.0			B													
							L													
Jonker et al (1998)			3	74.8			B													
							L													
Small et al (1998)			3	81.8			B													
							L													
Jochemsen et al (2012)			3.8	57.0			B													
							L													
Christensen et al (2008)			4	60-64			B													
							L													
Andrews et al (2016)			8	62.5			B													
							L													
Lavretsky et al (2003)			2.2	66.5			B													
							L													
Helkala et al (1996)			3.5	72.5			B													
							L													
Shadlen et al (2005)			3.3	75.4			B													
							L													
Bunce et al (2004)			6	79.1			B													
							L													
Praetorius et al (2013)			10	>80			B													
							L													
Deary et al (2003)			66	11.0			B													
							L													
Yaffe et al (1997)			6	71.0			B													
							L													


Packard et al (2007) 3.2 70-82 B L
Riley et al (2000) 4.5 81.0 B L
Wilson et al (2002b) 8 >=65 B L
Juva et al (2000a) 3 >=85 B L
Greenwood et al (2014) 3 50.4 B L
Greenwood et al (2005b) 3 59.6 B L
Greenwood et al (2014) 3 65.1 B L
Bretsky et al (2003) 3 70-79 B L
Bretsky et al (2003) 7 70-79 B L
Dik et al (2000) 3.1 72.1 B L
Bunce et al (2014) 8 20-24 B L
Bunce et al (2014) 8 40-44 B L
Mortensen & Hogh (2001) 30 50.0 B L
Tupler et al (2007) 5 65.3 B L
Hofer et al (2002) 7 76.2 B L
Barnes et al (2013) 6 78.6 B L
Blair et al (2005) 6 47-68 B L
Cohen et al (2001) 2 57.9 B L
Jarvik et al (2005) 20 61.5 B L
Carmelli et al (2000) 10 72.3 B L
ε4-deficit
ε2-superior
No APOE effect
Not tested
Summary of baseline effects:
No APOE effect
Significant ε4-effect
Not reported
Summary of longitudinal effects:
No APOE effect
Significant ε4-effect
Summary of baseline screening:
Dementia excluded
Additional cognitive screening
Not reported
Summary of follow-up screening:
Dementia excluded
Additional cognitive screening
Incident dementia not excluded
Not reported

2.5. Methodological challenges

2.5.1 Age

Age is a major methodological challenge for separating direct cognitive effects of APOE from the cognitive consequence of early AD pathology. The long prodromal period of AD makes it difficult to rule out the influence of AD pathology in elderly samples, particularly given the earlier age of AD onset in APOE-ε4 carriers. To minimise inclusion of prodromal AD, most studies use cognitive screening in older samples. However, the method of cognitive screening used varies greatly between studies (see *Table 2.2*). More recently, studies have moved to investigate the effect of APOE on cognition in mid-adulthood (30-60 years) samples, before AD pathology is likely to accumulate.

Several observations indicate that the association between APOE genotype and cognition changes across the lifespan. Children and young adults (under 30 years) who possess an APOE-ε4 allele have demonstrated superior cognitive performance (e.g. Bloss et al., 2010; Mondadori et al., 2007; Schultz et al., 2008; Wright et al., 2003; although see Ihle et al., 2012). This effect is proposed to reflect 'antagonistic pleiotropy', where the influence of a gene changes across the lifespan, being evolutionarily advantageous in early life, but exerting a negative effect later in life (Han & Bondi, 2008; Tuminello & Han, 2011; Williams, 1957).

At the other end of the lifespan, superior cognitive performance has been reported in the oldest ε4-carriers (over 80 years) compared to non-carriers (Carrión-Baralt et

al., 2009; Duchek et al., 2006), as well as attenuation of ε4-deficits observed in young-old carriers (Negash et al., 2009; Riley et al., 2000; Smith et al., 1998). These cognitive effects correspond with reported attenuation in the oldest-old of the association between APOE-ε4 and AD risk (Blacker et al., 1997; Breitner et al., 1999; Corrada et al., 2013; Farrer et al., 1997; Juva et al., 2000a; Valerio et al., 2014). The oldest-old non-demented APOE-ε4 carriers have been proposed to represent 'selective survivors' (Duchek et al., 2006), resilient to the negative influences of APOE-ε4 on development of AD (Rebeck et al., 1994) or cardiovascular disease (Stengård et al., 1996) earlier in life. However, the attenuation of APOE-ε4 associations with cognition or AD risk in the oldest-old has not been consistently reported (Geßner et al., 1997; Nilsson et al., 2006; Rebeck et al., 1994), and some studies have found no APOE effects (Bathum et al., 2006; Juva et al., 2000b; Riley et al., 2000; Salo et al., 2001; Small et al., 1998; Welsh-Bohmer et al., 2009) or ε4-related cognitive deficits in the oldest-old (Berteau-Pavy et al., 2007; Praetorius et al., 2013; Riley et al., 2000; Small et al., 1998).

2.5.2 Cognitive measures

Cognitive measures are key to unpicking the prodromal and direct effects of APOE on cognition. Most studies have used neuropsychological measures of cognition, often utilising existing data from established ageing cohorts, which, whilst well validated and quick to administer, may lack the sensitivity and specificity to detect a subtle APOE cognitive phenotype, particularly in mid-adulthood samples. Consistent with this, a recent meta-analysis found no evidence for an APOE genotype effect on midlife neuropsychological performance (Lancaster et al., 2017a).

Sensitive 'cognitive assays' that target specific cognitive processes have also been used to investigate the subtle direct cognitive effects of APOE genotype. Several studies in older adults have reported selective ε4-related deficits on sensitive cognitive neuroscience-based measures of prospective memory, implicit learning, spatial navigation and working memory (Berteau-Pavy et al., 2007; Driscoll et al., 2005; Duchek et al., 2006; Negash et al., 2007; Reinvang et al., 2010; Rosen et al., 2002), but whether these reflect a direct effect of APOE or the influence of incipient AD is unclear.

Only a small number of studies with mid-adulthood samples have used sensitive cognitive measures, although this number is increasing. In a series of experiments, Greenwood and colleagues demonstrated cross-sectional and longitudinal selective deficits in attentional disengagement, scaling of attention during a visual search task (Espeseth et al., 2006; Greenwood et al., 2000, 2005a, 2005b; Negash et al., 2009), and retention of visuospatial information in working memory (Greenwood et al., 2005a; although see Greenwood et al., 2014) in mid-adulthood APOE-ε4 carriers. Other researchers have expanded the investigation of APOE effects in this age group to other cognitive domains. For example, in middle-aged adults performing a long-term memory-guided attention task, APOE genotype had no significant effect on explicit memory or memory-guided attention, but ε4-homozygotes showed an impaired correlation between memory and attention, indicating the memories guiding attentional orienting in ε4-homozygotes were not explicitly available (Salvato et al., 2016). Additionally, Zokaei et al. (2017) found a behavioural *advantage* in male APOE-ε4 carriers on a short-term memory paradigm, with less mislocalisation of a

remembered item to the location of another item held in memory, interpreted as a possible example of antagonistic pleiotropy in midlife.

The breadth of domains studied with sensitive cognitive assays remains relatively limited to those impaired in patients with AD or medial temporal lobe (MTL) damage, and investigation of further neurobiologically relevant domains with sensitive cognitive assays is warranted. To robustly investigate the direct effect of a gene on behaviour, the measured phenotype should reflect the likely altered neurobiological endophenotype, to provide a plausible and mechanistic association between genotype and phenotype (Goldberg & Weinberger, 2004). Additional cognitive processes that are biologically related to the proposed influence of APOE genotype on CNS function e.g. synaptic plasticity and neuronal repair (Liu et al., 2013), should therefore be explored. Tasks that assess long-term learning may be particularly sensitive to such effects of APOE genotype on CNS function. More neurobiologically-driven assessment of cognitive domains may also be advantageous for studies that aim to utilise prodrome-related APOE-ε4 cognitive deficits as a biomarker, for example, domains outlined in a recent consensus statement on recommended cognitive outcomes in preclinical AD, including verbal episodic memory, working memory, and navigation in egocentric space (Ritchie et al., 2017).

2.5.3 Sample size and longitudinal design

The lower frequency of APOE-ε4 in the population, compared to APOE-ε3, has resulted in consistently smaller APOE-ε4 samples in most studies, unless specifically matched between groups (e.g. Caselli et al., 1999, 2001; Salvato et al., 2016; Zokaei

et al., 2017). There are also relatively few investigations of the specific effect of APOE-ε2 on cognition, due to the low occurrence of the ε2 allele in the population (although see Bartrés-Faz et al., 1999; Batterham et al., 2013; Blair et al., 2005; Bloss et al., 2010; Bunce et al., 2014; Chey et al., 2000; Chiang et al., 2010; Greenwood et al., 2000; Helkala et al., 1995, 1996; Hofer et al., 2002; Marioni et al., 2016; Pendleton et al., 2002; Quintas et al., 2014; Salo et al., 2001; Staehelin et al., 1999; Ward et al., 2014; Wilson et al., 2002b; Lancaster et al., 2017b).

The required sample size may depend on the neurobiological mechanism of APOE under investigation. Longitudinal studies are required to investigate prodromal APOE-ε4 cognitive effects in relation to clinical outcomes, e.g. for biomarker development. Therefore, a large initial sample is required, as cognitive effects will be driven by only a subsample with early AD, and some participants may be lost to follow-up. Sufficient sample size is particularly important if incident AD cases will be retrospectively excluded from baseline analysis, as these cases are more likely to be excluded from the already smaller APOE-ε4 group (e.g. Batterham et al., 2013). Elimination of initially significant baseline APOE effects after exclusion of incident AD (e.g. Bondi et al., 1999; Hayden et al., 2009; Hofer et al., 2002; Knight et al., 2014; Praetorius et al., 2013) may have resulted from degraded statistical power in some cases. In contrast, a subtle APOE-related cognitive phenotype should be present in all ε4-carriers, therefore smaller samples may be sufficient, as long as the cognitive measures used test appropriate domains and are sufficiently sensitive.

2.6. Recommendations for future research

In the previous sections, I have outlined the mixed reported effects of APOE on cognition, and discussed how key methodological factors complicate the interpretation of these findings. Some studies have attempted to facilitate interpretation of equivocal APOE-cognition associations by addressing individual methodological challenges (e.g. larger sample size or under-studied cognitive domain). However, the interactive nature of these methodological factors requires multiple aspects of methodology to be optimised simultaneously to simplify the interpretation of APOE and cognition results. Future studies can improve our understanding of the prodromal and direct routes of APOE influence on cognition by employing methodology targeted at specific mechanisms and research questions.

2.6.1 Recommendations for prodromal effect of APOE on cognition

A growing body of work suggests that at least some cognitive deficits in currently healthy older APOE-ε4 carriers are due to prodromal AD. These findings do not rule out the possibility of additional mechanisms of direct APOE influence on cognition, and are important in demonstrating that cognitive deficits relating to future diagnosis of AD can be detected early, in adults currently considered to be healthy. Prodromal AD-related ε4 cognitive effects can be utilised in future studies to develop preclinical cognitive biomarkers to more precisely identify individuals most at-risk. Secondary prevention clinical trials enriched with those most at-risk of AD will reduce the sample size and longitudinal period required to assess treatment efficacy (Holland et al., 2012). Cognition can provide cheap, quick and non-invasive preclinical biomarkers to be used alone, or in combination with other biomarkers,

such as CSF, PET or MRI metrics, to identify those who will benefit most from treatment and track early treatment efficacy.

Future studies aimed at utilising APOE genotype to characterise the cognitive markers of prodromal AD pathology in ε4-carriers require participants in whom prodromal AD is likely to be present (i.e. over 60s), as well as longitudinal designs to measure clinical outcomes, with sufficient follow-up period to allow for conversion to AD. The cognitive domains tested should be focused on those affected in early AD to minimise multiple comparisons.

2.6.2 Recommendations for phenotype effect of APOE on cognition

As evidence for APOE-related alterations of CNS functions has primarily come from animal literature, evidence of an APOE cognitive phenotype would provide support for an altered neural endophenotype in humans. Not only will this knowledge provide greater understanding of the biological processes altered by APOE genotype, but crucially it can inform how genetic variability contributes to individual differences in cognition, providing targets for interventions to maximise cognition in non-pathological ageing.

Whilst future studies avoid the influence of prodromal AD when investigating an APOE cognitive phenotype by excluding volunteers positive for preclinical AD biomarkers, e.g. increased PET-amyloid or reduced CSF-amyloid (Sperling et al., 2011), limited resources and invasiveness of procedures means such screening is not always feasible or ethical. Instead, the use of mid-adulthood samples (30-50 years) is

recommended to investigate a cognitive phenotype prior to the development of AD pathology, whilst also avoiding possible antagonistic pleiotropic effects of APOE on cognition earlier in life. Future research should also examine cognitive domains relevant to the putative neurobiological mechanisms affected by APOE-ε4 using sensitive and specific cognitive measures. Effects on long-term learning, reflecting alterations in synaptic plasticity, provide an informative initial target.

Furthermore, if APOE-ε4 has a cognitive phenotype independent of future AD diagnosis, APOE-ε2 genotype may also be associated with its own cognitive phenotype, although the supporting neurobiological mechanism is not clear. Amyloid aggregation is an unlikely candidate, as the oldest-old ε2-carriers have a similar presence of amyloid pathology compared to ε4-carriers, despite reduced risk of dementia (Berlau et al., 2009). Instead, APOE-ε2 may promote synaptic integrity, suggested by greater dendritic arborisation observed in APOE-ε2 transgenic mice, vs. ε3 and ε4 (Dumanis et al., 2009), or facilitate anti-inflammatory processes, as ApoE2 appears to be more effective at protecting cells from oxidative stress-induced cell death compared to ApoE3 and ApoE4 (Miyata & Smith, 1996).

2.7. Conclusions

APOE genotype is the strongest genetic risk factor for AD, yet the influence of APOE on cognition in healthy adults remains controversial. Some evidence suggests that at least some APOE-ε4 cognitive deficits are due to early AD pathology, whilst sensitive measures of cognition are beginning to reveal subtle cognitive effects of APOE genotype in mid-adulthood, prior to the onset of the AD prodromal period. To

unpick the direct and prodromal cognitive consequences of APOE genotype, future studies need to address specific research questions with methodology that is appropriate to neurobiological mechanism being investigated. Furthermore, as MRI studies have identified subtle differences in brain structure and function related to APOE genotype in the absence of overt cognitive effects (Heise et al., 2011; Suri et al., 2015), combining an optimised cognitive approach with MRI will provide increasingly rich neurobiological evidence to understand the risk and protective effects of APOE genotype for cognition. In the next chapter, I will discuss subjective memory impairment, another aspect of cognitive ageing where MRI can be used to go beyond cognitive effects to provide greater information about risk of cognitive decline.

Chapter 3. Subjective memory impairment and use of MRI for identifying Alzheimer's disease risk: case report and review

APOE-related cognitive effects discussed in the previous chapter are just one of many markers that may indicate increased risk of cognitive decline in older adults. Subjective memory impairment (SMI) is also associated with increased risk of cognitive decline, as are changes in the brain detected with MRI, e.g. hippocampal atrophy. However, both SMI and structural atrophy are observed in healthy older adults, so individually are insufficient to precisely identify those at risk of subsequent cognitive impairment. Despite mounting evidence that SMI in some cases is a sign of preclinical AD, the limited ability to discriminate such cases from those who are 'worried-well' means SMIs are often disregarded in clinical practice, missing crucial opportunities for monitoring, and contributing to distress in patients. Use of MRI markers in cases of SMI may provide more detailed information to facilitate assessment of risk of cognitive impairment. In this chapter, I present a case report of unusually persistent SMI reported for almost four decades before a clinical diagnosis of AD was made to illustrate the clinical challenge of SMI and need for validated biomarkers. I also present a literature review of longitudinal studies that investigate the long-term significance of MRI-detected differences in the brain in individuals with SMI, and propose that MRI markers may be particularly useful in a clinical setting. *A modified version of this chapter has been submitted for publication.*

3.1. Introduction

3.1.1 Subjective memory impairment

Subjective memory impairment (SMI) is defined as subjective concerns of declining cognitive ability in older adults with normal-for-age objective cognitive scores (Jessen et al., 2014a). Reports of SMI are common in older adults, with a prevalence of 22-75% (e.g. Ginó et al., 2010; Holmen et al., 2013; Jonker et al., 1996), depending on the population sampled (e.g. Silva et al., 2014). Likelihood of reporting SMI is increased in adults who are older, female, have depressive symptoms, high neuroticism, low education, low physical activity or poor health (Mark & Sitskoorn, 2013).

3.1.2 Increased risk of Alzheimer's disease associated with SMI

Compared to healthy older adults, presence of SMI is associated with increased subsequent cognitive decline (e.g. Dik et al., 2001; Dufouil, Fuhrer, & Alpérovitch, 2005; Samieri et al., 2014), and greater progression to MCI and AD (e.g. Geerlings, Jonkers, Bouter, Ader, & Schmand, 1999; Gifford et al., 2014; Luck et al., 2010). A recent meta-analysis showed individuals with SMI are twice as likely to develop dementia compared to cognitively healthy individuals without SMI (Mitchell et al., 2014).

Several risk factors have been associated with increased conversion of SMI to a clinical diagnosis, including treatment-seeking (Rabin et al., 2017), worry about subjective concerns (Jessen et al., 2010), informant corroboration (Rabin et al., 2017; Mendonça et al., 2015), progression of subjective impairment (Kryscio et al., 2014),

family history of dementia (Mark & Sitskoorn, 2013), impact on everyday function (Sargent-Cox et al., 2011), lower objective cognitive performance (Fonseca et al., 2015), high socioeconomic status (Mark & Sitskoorn, 2013) and high level of education (e.g. Jonker et al., 2000; van Oijen et al., 2007).

In some individuals, SMI is considered to be the earliest manifestation of preclinical AD, before MCI on the continuum to AD (Fonseca et al., 2015; Jessen et al., 2014b). The preclinical phase of AD is increasingly important in research and clinical settings as a critical period for intervention to prevent the insidious accumulation of AD pathology in the years before symptom onset. As SMI may precede a clinical diagnosis by approximately 15 years (Reisberg et al., 2008), SMI affords an opportunity to identify preclinical individuals, most advantageously, before any objective cognitive impairment has occurred.

3.1.3 Challenges identifying increased AD risk in SMI

Despite mounting research interest in SMI as a preclinical AD marker (Jessen et al., 2014b; Molinuevo et al., 2017), in clinical practice SMI is often dismissed with 'reassurance and discharge' (Jenkins et al., 2015). Those reporting SMI represent a heterogeneous group, and multiple alternative etiologies may contribute to reported SMI, including poor sleep, medication, and non-AD dementias (Rabin et al., 2017). Furthermore, SMI may remain stable or disappear over time (de Groot et al., 2001; Wehling et al., 2007), and many reporting SMI are 'worried-well', whose objective cognition does not decline more rapidly than usual (Mendonça et al., 2015; Mitchell et al., 2014). Depressive symptoms may also account for some SMI (e.g. Buckley et

al., 2013), although the association of SMI and depression is complex. For example, complaints of cognitive dysfunction may be a feature of late-life depression (Naismith et al., 2012), but depressive symptoms may also represent a psychological reaction to SMI or concurrent symptom of underlying brain changes responsible for SMI.

The prognostic value of SMI is also unclear. Several studies found no association between baseline SMI and subsequent cognitive decline (e.g. Hollands et al., 2015; Mol et al., 2006) or clinical diagnosis (Silva et al., 2014). Heterogeneity in methodology, including the type of complaint measured (specific domain vs. general cognition), the sample studied (clinic vs. community), and method of measuring of SMI (single question vs. multi-item questionnaire) may also influence the clinical significance of reported SMIs.

The limited ability to discriminate in whom SMI heralds future AD from normal ageing (Mendonça et al., 2015), as well as controversial clinical significance of SMI have contributed to SMI being of little concern in clinical settings (Jenkins et al., 2015). However, disregard for SMI in clinic can result in distress for patients and delayed monitoring and diagnosis. The current challenge in this field is therefore to identify and validate additional markers that increase the prognostic value of SMI. Next, I present a clinical case of unusually persistent SMI, reported for almost four decades before a clinical diagnosis of AD was made, to illustrate need for validated markers to improve the utility of SMI in clinic.

3.2. Case Report

3.2.1 Case description

A 52-year old headmistress with family history of dementia attended a general neurology clinic in 1993 with subjective concerns of slowly progressing memory impairment, first apparent in her 30s. Detailed neuropsychological assessment revealed moderate verbal memory impairment (e.g. delayed paragraph recall = 67%) and mild non-verbal memory impairment (e.g. visual retention errors = 7), but above-average performance in other cognitive domains (e.g. WAIS-R IQ = 125; graded naming = >99th percentile; full neuropsychological scores are reported in *Appendix 3*). Her spouse corroborated that she was forgetful around the house. A CT scan appeared normal. No further action was taken.

Ten years later, the patient re-presented to medical attention, and again 9 times over the following 6 years (GP and memory clinic), with persistent concerns of increasingly poor memory. Repeated cognitive assessment revealed gradual decline in memory scores, but maintained performance in other cognitive domains, well within or above the range expected for her age. Activities of Daily Living (ADLs) were reported to be well-preserved, although she had taken early retirement because of her memory concerns.

Due to preserved performance in non-memory domains, her poor memory was considered inconsistent with dementia, and the patient was reassured that there was no dementing illness. Her concerns instead were attributed to anxiety and

hypervigilance for memory failures. However, no formal diagnosis of any psychiatric condition was given. She expressly felt that clinicians thought she “might be inventing her symptoms”.

A diagnosis of MCI was given in 2009 at age 68, 16 years after initial presentation, when an MRI brain scan showed hippocampal atrophy (see *Figure 3.1*). A diagnosis of probable AD was given 9 months later when her spouse reported decline in everyday function, and Donepezil treatment commenced. Since diagnosis, the patient has actively volunteered in several research studies, producing an unusually rich longitudinal data set. After diagnosis, the participant was found to be APOE-ε4 homozygous, and amyloid- and tau-positive using PET imaging.

3.2.2 Methods

Briefly, longitudinal neuropsychological scores acquired over 15 years were compared to age- and education-matched normative data. Longitudinal MRI data acquired over 6 years were compared to healthy elderly female controls (N=27) to illustrate characteristic AD-related progressive grey matter (GM) atrophy over time in the patient. Detailed methods and supplementary results are shown in *Appendix 3*.

3.2.3 Results

Longitudinal cognitive performance on the Mini-Mental State Examination (MMSE; Folstein et al., 1975) and Hopkins Verbal Learning Test (HVLT-R; Brandt & Benedict, 2001) was normal-for-age or above-average preceding AD diagnosis (*Figure 3.2a*). Clock drawing performance remained above-average even after AD diagnosis. Other neuropsychological data spanning up to 20 years are reported in *Appendix Table 3.A.*

Serial T1-weighted MRI scans illustrate clear hippocampal atrophy (*Figure 3.1*). Compared to healthy controls, the patient showed steady decline in structural markers, despite highly variable cognitive scores. GM atrophy was most rapid in hippocampal, temporal and frontal region (*Figure 3.3*). Slower decline in GM volume was observed in parietal and occipital regions. Occipital volume was well within the range of healthy controls across time points. *In-vivo* atrophy is shown in a 3D movie (see *Appendix Figure 3.A*) and unmistakably illustrates progressive hippocampal atrophy over 6 years.

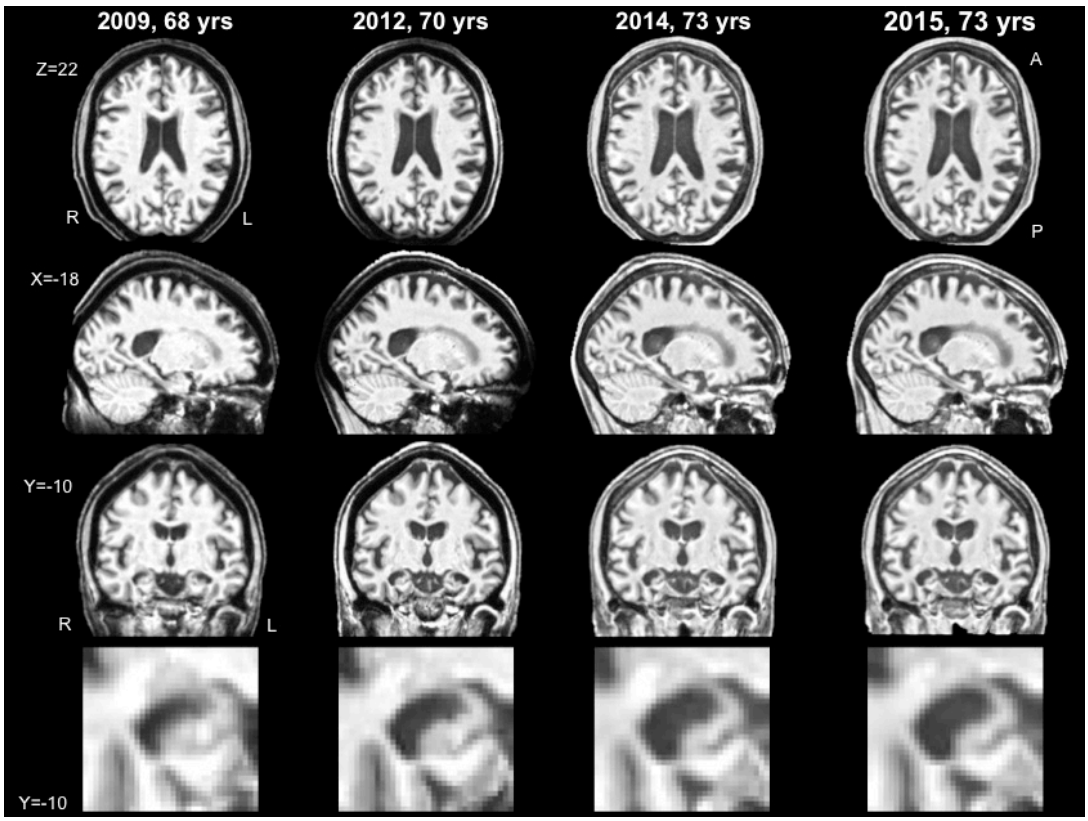


Figure 3.1. **Longitudinal structural MRI over 6 years. Patient's T1 structural MRI scans at four time points between 2009 and 2015 (first scan at diagnosis). Axial (first row), sagittal (second row), and coronal (third row) cross-sectional are shown, with an enlarged view of the right hippocampus (fourth row). Coordinates are in MNI space.**

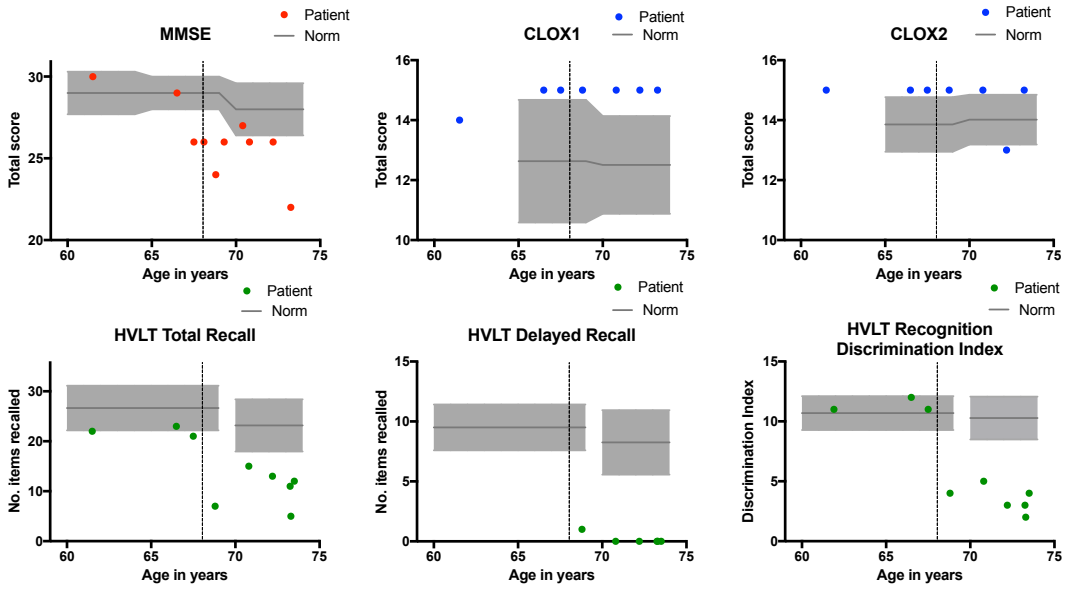


Figure 3.2. **Longitudinal neuropsychological scores over 15 years. Longitudinal patient cognitive scores plotted against age- and education-matched norms. Vertical line represents age at diagnosis. Horizontal line and shaded area represents the normative mean and standard deviation, respectively.**

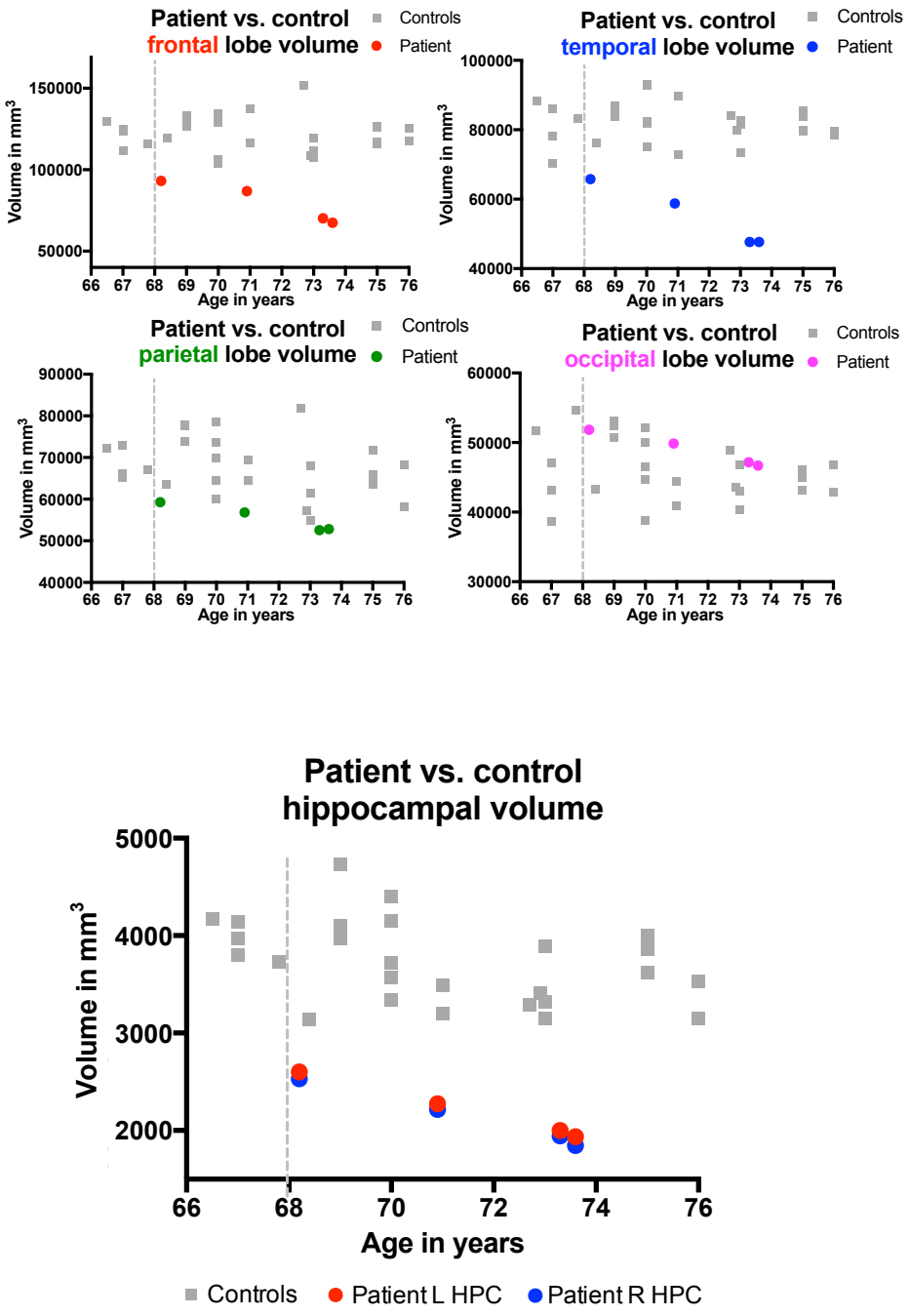


Figure 3.3. **Longitudinal GM volumes in frontal, temporal, parietal, occipital and hippocampal regions over 6 years. GM volume in frontal, temporal, parietal and occipital lobes averaged for both hemispheres. Hippocampal volume plotted for patient as right and left hippocampus separately and averaged bilateral hippocampal volume plotted for controls. *Abbreviations:* GM – grey matter; R – right; L – left; HPC – hippocampus.**

3.3. Literature review

3.3.1 Why MRI?

As this case shows, clinical history and neuropsychological scores alone can present a complex picture on which it is difficult to assess the prognosis of SMI. However, MRI-derived biomarkers may facilitate the assessment of risk in cases of SMI. Structural MRI is an established marker of AD-related neurodegeneration that occurs downstream from earlier protein aggregation (Jack et al., 2013). Structural atrophy correlates with Braak staging, tangle density and cognitive decline (ten Kate et al., 2017), and topographically, GM loss in AD overlaps with the distribution of tau pathology (e.g. Braak & Braak, 1991). Crucially, differences in the brain can be detected with MRI at least 10 years prior to AD diagnosis (Tondelli et al., 2012). The non-invasive nature and wide availability of MRI make it particularly advantageous for clinical use.

3.3.2 Cross-sectional studies of SMI using MRI

Use of MRI in cross-sectional studies has revealed a range of structural and functional differences in those with SMI, including *reduced GM structure and cortical thickness* (e.g. Amariglio et al., 2015; Cantero et al., 2016; Hafkemeijer et al., 2013; Hong et al., 2015; Jessen et al., 2006; Kim et al., 2013; Meiberth et al., 2015; Perrotin et al., 2015, 2017; Ryu et al., 2017; Schultz et al., 2015; Teipel et al., 2017; Tepest et al., 2008; van der Flier et al., 2005), *reduced WM integrity and volume* (e.g. Hong et al., 2015; Ryu et al., 2017; Selnes et al., 2012; Yasuno et al., 2015), *increased WMH load* (de Groot et al., 2001; Stewart et al., 2008)*, altered resting-state functional connectivity* across a number of RSNs (Contreras et al., 2017; Hafkemeijer et al.,

2013; Vega et al., 2016; Wang et al., 2013; Yasuno et al., 2015) and *altered task-related brain function* across a number of paradigms (Dumas et al., 2013; Erk, 2011; Hu et al., 2017; Rodda et al., 2011; Rodda et al., 2009). Differences in brain structure and function observed in those with SMI are often spatiotemporally consistent with preclinical AD, with topographically similar brain regions affected in SMI and AD, and the extent of differences in SMI is often intermediate between healthy controls and those with MCI/AD (Hong et al., 2015; Jessen et al., 2006; Perrotin et al., 2015; Selnes et al., 2012; Tepest et al., 2008; Wang et al., 2016; Wang et al., 2012). In addition, the majority of studies that controlled for depressive symptoms found results were not substantially altered, suggesting the association of SMI and MRI metrics is independent of depressive symptoms. A selection of studies, however, did not observe any alteration in brain structure and function in those with SMI (e.g. Bartley et al., 2012; Kiuchi et al., 2014; Lauriola et al., 2017; López-Sanz et al., 2016; Miranda et al., 2008; Rowe et al., 2010).

3.3.3 Longitudinal studies of SMI using MRI

Whilst cross-sectional MRI findings overall support SMI as a stage of preclinical AD, longitudinal studies are essential to validate the prognostic value of cross-sectional SMI-related differences in brain structure and function. Furthermore, as findings from cross-sectional studies are diluted by averaging across different possible etiologies, longitudinal studies are important for unmasking heterogeneity in SMI. Serial MRI scans are also required to assess the use of MRI markers to monitor disease progression, e.g. to establish sensitivity of MRI to detect changes over time.

In the next section, I review existing longitudinal studies of SMI that utilised MRI, to illustrate the current status of the field.

3.3.3.1 Inclusion criteria

For inclusion in this mini-review, studies must have: 1) assessed subjective cognitive complaints in objectively unimpaired adults, and 2) included baseline MRI and longitudinal cognitive/clinical outcomes *or* included longitudinal MRI assessments. This resulted in 10 studies, summarised in *Table 3.1*. Studies that used baseline CSF (Eckerström et al., 2017; Van Harten et al., 2013a; Van Harten et al., 2013b) or EEG (Prichep et al., 2006) were not included.

3.3.3.2 Baseline MRI and longitudinal cognitive decline

Peter et al. (2014) used a support vector machine, trained on an independent sample of AD and healthy controls (HC), to classify SMI and HC participants as more or less similar to an AD GM pattern at baseline. The SMI group showed greater similarity than HCs to the AD-like GM pattern, with hippocampal and parahippocampal regions contributing most to the classification. Increasing similarity to the AD-like GM pattern at baseline in the SMI group was associated with greater decline in memory over the subsequent 2.5-3 years. However, another study found only a trend association between longitudinal memory decline and baseline hippocampal volume in an SMI group, although the association between memory decline and baseline glucose metabolism in the right precuneus was significant (Scheef et al., 2012). Baseline imaging variables were not associated with longitudinal memory performance in the HC group. In a third study, whilst baseline cognitive complaints were associated with greater objective cognitive change over

the following two years, those with severe WMHs in addition to higher cognitive complaints experienced the greatest subsequent cognitive decline (Dufouil et al., 2005). More recently, cortical thickness in frontal, temporal and parietal regions in a sample with SMI was associated with decline in memory, but not attention or executive functions, over the subsequent four years (Verfaillie et al., 2018a). In the same cohort, more randomly organised GM network, indexed by lower path length values and lower clustering coefficients, were associated with subsequent decline in language and global cognition (Verfaillie et al., 2018b).

3.3.3.3 Baseline MRI and longitudinal clinical progression

Ferreira et al. (2017) investigated whether AD-like GM atrophy at baseline predicted clinical progression of SMI. Using multivariate analysis, a 'disease severity index' was calculated, capturing whether each individual of an SMI group had an 'AD-like' (13%, n=11) or 'HC-like' (87%, n=75) GM pattern at baseline. Cross-sectionally, AD-like SMI had lower cognitive scores, higher clinical scores and higher PET amyloid burden, the latter comparable to an MCI control group. After 7.5 years, 72.7% of the AD-like SMI progressed to MCI, AD or died, compared to only 17.6% (n=13) and 11.7% (n=8) of HC-like SMI and HC, respectively. Rates of cognitive change in AD-like SMI were also significantly faster than HC and HC-like SMI, and were comparable to MCI. Therefore, this disease severity index identified asymptomatic individuals at high risk of clinical progression.

In another study, comparison of baseline MRI metrics between those with SMI that progressed to a clinical diagnosis and those with stable SMI over 3-4 years revealed

thinner cortex in a range of regions including precuneus, right parahippocampal, middle frontal, medial temporal lobe (MTL) and lower HPC volume in those showing clinical progression (n=49, 16% of original sample) compared to those that remained stable (n=253) (Verfaillie et al., 2016). Progression was also associated with lower CSF amyloid and higher CSF tau at baseline, compared to those that remained stable. Another study comparing progressing vs. stable groups found baseline reductions in entorhinal, but not hippocampal volume, although this sample combined MCI and SMI (Dickerson et al., 2001).

3.3.3.4 Longitudinal MRI

Two studies have investigated longitudinal changes in brain metrics associated with SMI. Both studies suggest that SMI follows, rather than precedes, changes in brain structure. Cherbuin et al. (2015) found SMI reported at follow-up was associated with hippocampal atrophy over the preceding four years, whilst baseline SMI was not associated with hippocampal atrophy over time. In a separate study, baseline SMI in a large cohort of healthy older adults (n=1334) was only associated with subsequent change in hippocampal volume, whilst SMI reported at follow-up was associated with increasing subcortical white matter hyperintensities (WMH) and CSF volume, and reduction in total GM and hippocampal volume, over the preceding four years (Stewart et al., 2011). Interestingly, there was a quadratic relationship between brain atrophy and both baseline and follow-up SMI, where those with SMI demonstrated most and least structural loss, possibly reflecting lower baseline volumes in some SMI, thus less decline over the follow-up period (Stewart et al., 2011). Whether this reflects later-life loss or developmental differences is unclear.

Table 3.1. **Summary of longitudinal studies using MRI to investigate subjective memory impairment**											
Study	**No. subjects**	**Recruitment**	**Follow-up period**	**Baseline measures**	**Follow-up measures**	**Field strength**	**Image**	**Imaging analysis**	**Statistical methods**	**Aim**	**Result**
Baseline MRI and longitudinal cognitive decline											
Dufouil et al., 2005	332 HC	Community	-4, 0, 2 years	MRI Cognitive	Cognitive	1.0T	T2, PD	Classed as severe/non-severe WMH	Odds ratio	To investigate whether SMI & WMH predict cognitive decline over 2 years	Greatest 2 year cognitive change was observed in those with SMI & WMH.
Scheef et al., 2012	27 SMI 48 HC	Clinic	35 months	MRI Cognitive FDG-PET	Cognitive	3.0T	T1	ROI-based	Mixed model ANOVA	To establish a link between MRI biomarker evidence and cognitive decline in SMI	Longitudinal memory performance was marginally associated with BL glucose metabolism and HPC volume in regions significantly reduced compared to HC at BL.
Peter et al., 2014	24 SMI 53 HC	Clinic	40-45 months	MRI Cognitive	Cognitive	3.0T	T1	Support vector machine	SEM; growth curve modeling	To evaluate association of baseline GM patterns with longitudinal cognitive performance in SMI & HC	SMI showed more AD-like GM at BL compared to HC. Similarity to AD-GM at baseline was significantly associated with longitudinal decline in memory, but not speed or executive functions.
Verfaillie et al., 2018a	233 SMI	Clinic	3 years	MRI Cognitive	Cognitive	1.0T, 3.0T	T1, T2, FLAIR	ROI-based	Linear mixed model	To investigate the association of regional cortical thickness and cognitive decline in 4 domains in those with SMI	No association of baseline cognition and cortical thickness was found, but subsequent decline in memory was associated with thinner frontal, temporal and occipital GM at baseline.
Verfaillie et al., 2018b	231 SMI	Clinic	3 years	MRI Cognitive CSF	Cognitive	1.0T, 3.0T	T1	Grey matter network	Linear mixed model	To investigate whether indicators of random network organisation are associated with longitudinal cognitive decline in SMI	More random organisation of baseline GM networks, e.g. lower network size and path length, was associated with steeper subsequent decline in language and global cognition in individuals with SMI.

Baseline MRI and longitudinal clinical progression											
Dickerson et al., 2001	23 SMI	Clinic	39 months	MRI Cognitive Clinical	Clinical	1.5T	T1	Manual tracing	ANOVA; logistic regression	To determine the earliest sites of pathological involvement in AD disease processes	Reduced entorhinal, but not HPC, volume observed in SMI-AD converters compared to SMI non-converters. Only entorhinal volume significantly predicted conversion to AD.
Verfaillie et al., 2016	302 SMI	Clinic	3-4 years	MRI Cognitive Clinical CSF	Clinical Cognitive	1.0T, 3.0T	T1	Freesurfer ROI based; vertex analysis	Cox hazard ratio	To investigate whether BL cortical thickness is related to incident clinical progression in individuals with SMI	Those with SMI who converted to AD had thinner MTL and lower HPC volume compared to stable SMI.
Ferreria et al., 2017	86 SMI 69 HC 45 MCI 38 AD	Community	7.5 years	MRI Cognitive Clinical PiB-PET	Clinical Cognitive	3.0T	T1	Freesurfer; multivariate analysis	Survival analysis, mixed effect models	To investigate whether SMI with AD-like and HC-like GM patterns differed according to disease progression over 7.5 years	SMI with AD-like GM pattern at BL showed increased likelihood of clinical progression and greater cognitive decline over the subsequent 7.5 years.
Longitudinal MRI											
Stewart et al., 2011	1337 HC	Community	4 years	MRI Cognitive Clinical	MRI Cognitive Clinical	1.5T	T1, T2	Automated GM/WMH segmentation	(Logistic) regression	To investigate the relationship of SMI to previous and subsequent changes in WMH and brain volume	SMI at FU was associated with change in total GM, HPC volume and WMH load over 4 years preceding MRI; BL SMI was associated with HPC atrophy only over subsequent 4 years.
Cherbuin et al., 2015	305 HC	Community	4 years	MRI Clinical	MRI Clinical	1.5T	T1	Manual tracing	Multiple regression	To investigate whether SMI in healthy individuals is associated with hippocampal atrophy	SMI at FU was associated with HPC atrophy over the preceding 4 years; BL SMI not associated with subsequent HPC atrophy.

Abbreviations: No. - number; MRI – magnetic resonance imaging; HC – healthy control; SMI – subjective memory impairment; MCI – Mild Cognitive Impairment; AD – Alzheimer's disease; FDG-PET – fludeoxyglucose positron emission tomography; PiB-PET – Pittsburg B compound positron emission tomography; CSF – cerebrospinal fluid; T1- T1-weighted; T2 – T2-weighted; PD – proton density; FLAIR – fluid attenuated inversion recovery; WMH – white matter hyperintensity; ROI – region of interest; GM – grey matter; ANOVA – analysis of variance; SEM – structural equation modeling; BL – baseline; FU- follow-up; HPC – hippocampus; MTL – medial temporal lobe.

3.4. Discussion

SMI has potential as a marker for early identification of AD risk, and may provide enriched samples for preclinical AD trials. However, the clinical case reported here clearly illustrates the challenges that SMI presents in clinical practice. By definition, objective cognition is unimpaired in SMI, meaning neuropsychological assessment alone is insufficient to assess future AD risk. Biomarker evidence should be used in cases of persistent SMI to orientate appropriate reassurances and clinical follow-up, although the particular markers to use and in which individuals are yet to be fully established. MRI-based markers provide an ideal candidate, due to sensitivity to cross-sectional differences in brain structure and function in SMI, as well as initial longitudinal support for the relevance of baseline MRI characteristics for long-term clinical outcomes. Further validation of these MRI markers is required.

3.4.1 MRI in longitudinal studies of SMI

The relatively small number of studies that have assessed the long-term significance of SMI-related differences in the brain provide preliminary support for use of MRI to indicate increased risk of subsequent cognitive decline and clinical progression in individuals with SMI. GM patterns at baseline differ depending on long-term clinical outcome (Verfaillie et al., 2016) and AD-like baseline GM metrics are associated with greater risk of subsequent cognitive and clinical decline (Ferreira et al., 2017). The GM regions that are most informative are also consistent with well-establish regions that change in the course of AD. However, further studies are required to establish the metrics and analysis methods that best indicate future prognosis. Studies that include serial MRI scans suggest SMI follows, rather than precedes, structural

changes in the brain (Cherbuin et al., 2015; Stewart et al., 2011). Therefore, cross-sectional MRI may be sufficient to indicate future prognosis, by identifying differences in the brain that have already occurred by presentation of SMI. Further studies using serial MRI are required to establish the dynamics of brain changes associated with SMI to use MRI for monitoring clinical progression. Future studies can also investigate whether multiple imaging modalities, including functional measures, contribute unique information to risk assessment and monitoring.

3.4.2 Case summary

The need for increased understanding of SMI and validated markers is clearly illustrated in the case presented here. Despite repeated clinical assessments, above-average performance in this case of unusually persistent SMI led to unsupported reassurance of the absence of dementing disease. Overstating the absence of dementia risk was a source of significant distress for this patient, who had clearly expressed her wish to know her risk of developing dementia. Unsupported reassurances resulted in missed opportunities for earlier monitoring and diagnosis, delayed access to services, and deprived the patient of opportunities to make informed lifestyle changes and autonomous decisions about her future.

Use of MRI prior to diagnosis may have added to the clinical history and neuropsychological profile to indicate that increased monitoring was required in this case. Although MRI scans were acquired from diagnosis onwards in this case, AD-related changes in the brain occur gradually, and lower GM compared to peers at initial scan is likely to have been detectable earlier. Use of biomarkers is particularly

warranted in this case due to the presence of numerous factors associated with increased progression of SMI to AD, e.g. informant corroboration, repeated medical attention seeking, and family history of dementia.

3.4.3 The future for SMI in the clinic – who and how to assess?

SMI represents a significant proportion of memory clinic attendances (Garcia-Ptacek et al., 2014), and it is not feasible or ethical to extensively assess everyone. The 'reassurance and discharge' of SMI in clinic (Jenkins et al., 2015) may result in part from limited personnel and resources. Therefore, a clearer idea of *who* to target with biomarker investigations is required. Validation of risk factors associated with increased risk of AD in SMI, e.g. progression of SMI and high education, will be beneficial. Additionally, careful interpretation of clinical history, neuropsychological scores and changes in everyday function, as well as consideration of the patient's wishes, is also important. Premorbid function should also be taken into account, as high functioning individuals may remain 'normal-for-age', despite the presence of AD pathology.

Not only do we need to identify *who* to follow up, but also *how* to most usefully assess these individuals. MRI cannot replace clinical history or neuropsychological assessment, but can add positive or negative predictive value to facilitate clinical decision-making (Scheltens et al., 2002). Longitudinal studies have demonstrated the association of baseline MRI metrics with cognitive and clinical progression in objectively unimpaired individuals with SMI. The case illustrates, albeit after diagnosis, that relatively simple structural markers can track change, and may

provide more stable metrics to monitor decline, compared to variable cognitive scores over time.

3.5. Conclusion

As disease-modifying treatments for AD are not currently available, early disclosure of risk is not always considered a priority in clinics (Dubois et al., 2016). However, the focus on preclinical intervention in drug development means that intervention in asymptomatic individuals will be required once such drugs are available. This necessitates a substantial change in the mentality towards identification and management of preclinical AD in clinical settings. Whilst SMI alone lacks the sensitivity and specificity to predict subsequent cognitive decline and dementia (Jessen et al., 2014a), other biomarkers may add to the assessment of risk. Standardisation of quantitative MRI markers, normative data, and automated processing will be valuable for clinical use. Further longitudinal studies are required to determine the best metrics to track change and validate the significance of MRI-detected brain characteristics in SMI for long-term cognitive decline. In the next chapter, I aimed to use MRI in older adults to demonstrate that MRI characteristics in older adults may not only be associated with future cognitive decline, but also preservation of cognitive functions.

Chapter 4. Individual differences in neural mechanisms of superior cognitive ageing

As demonstrated in the previous chapter, MRI is able to unmask variability in a heterogeneous group that is otherwise missed by examining the group on 'average'. Whilst used in relation to SMI to uncover *risk* of cognitive impairment, MRI may also be able to reveal variability in *resilience* to cognitive decline. In ageing research, healthy older adults have traditionally been treated as a homogeneous group, compared on average to younger adults or older adults diagnosed with dementia. However, examining older adults 'on average' will incorporate currently healthy older adults experiencing cognitive decline related to prodromal AD pathology (as in Chapter 2), and underestimate the ability of some older adults with 'above-average' abilities who may be protected from cognitive decline. Moreover, older adults may preserve cognitive abilities in more than one way. In this chapter, I use MRI to detect individual differences in how the brain supports relatively superior cognitive ageing.

A modified version of this chapter has been prepared for submission for publication.

4.1. Introduction

Growing evidence demonstrates that cognitive decline is not an inevitable part of ageing. Whilst advancing age is, on average, associated with declining cognition (Hedden & Gabrieli, 2004), at the individual level there is remarkable heterogeneity in the pattern of cognitive ageing (e.g. Christensen et al., 1999; Habib et al., 2007; Wilson et al., 2002a). Many older adults maintain their cognitive abilities over a number of years (e.g. Barnes et al., 2007; Josefsson et al., 2012; Wilson et al., 2011),

or show remarkably intact cognitive functions, performing well above what is 'normal' for their age (e.g. Dixon & de Frias, 2014; Rogalski et al., 2013). Understanding how some older adults organically maintain a high level of cognitive ability may be one of the best ways to find interventions to enhance cognitive ability or prevent cognitive decline with age (Rowe & Kahn, 1998).

The neural mechanisms that support superior cognition in later life are not fully understood. According to the 'Scaffolding Theory of Aging and Cognition' (STAC) (Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Park, 2014), some older adults engage supplementary neural circuitry to 'adapt' to the challenge of brain ageing, supported by reported greater task-related brain activation in cognitively successful older adults compared to performance-matched younger adults (e.g. Cabeza et al., 2002; Morcom et al., 2003; Morcom et al., 2007; Spreng et al., 2010). Other evidence, however, suggests that more 'youthful' brain structure and function in older adults is associated with superior cognition (Burzynska et al., 2012; Düzel et al., 2011; Fandakova et al., 2015; Pudas et al., 2013). This is captured in the concept of 'brain maintenance' (Nyberg et al., 2012), where the lack or postponement of, rather than the ability to cope with, age-related brain changes is the key determinant of cognition. Therefore, individual differences may exist in the neural basis of superior cognitive ageing, supported by brain maintenance in some older adults, and by adaption to age-related declines in others. However, direct evidence for such individual differences is currently lacking (c.f. Düzel et al., 2011), as most studies compare brain measures between older groups defined *a priori* as high and low

cognitive performers, precluding the opportunity to identify multiple mechanisms within cognitively superior older adults.

Here, we aimed to provide direct evidence for individual differences in the neural mechanisms supporting superior cognitive ageing using a multi-modal MRI-based approach to avoid an *a priori* definition of superior cognition. Based on the compensatory scaffolding and brain maintenance models, expected brain profiles of cognitively superior older adults can be predicted. Those who functionally adapt for age-related brain changes to preserve cognitive abilities would show reduced brain structure, but greater brain function, compared to young adults, whereas those who 'maintain' a youthful brain would be relatively similar to younger adults in brain structure and function (see *Figure 4.1*). Older adults with lower brain structure *and* function compared to younger adults would be expected to show declines in cognition.

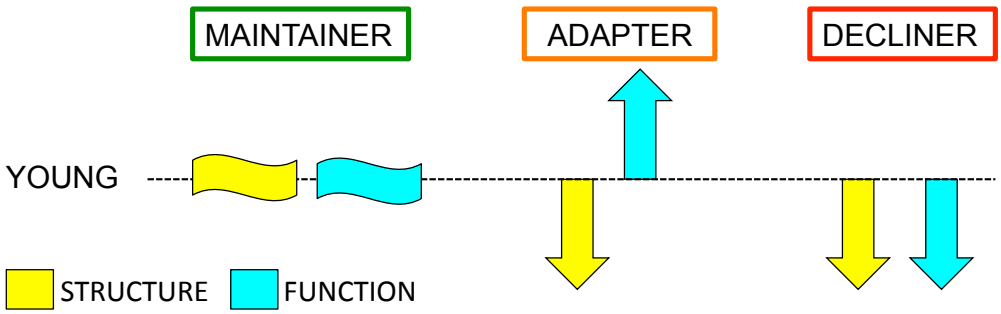


***Figure 4.1*. Predictions of the brain status of maintainers, adapters and decliners, based on Nyberg et al. (2012) outline of brain maintenance and Reuter-Lorenz & Park (2014)'s Scaffolding Theory of Ageing and Cognition**

The primary objective of this study was to identify multiple patterns of brain ageing associated with superior cognitive ageing within a sample of healthy older adults. We predicted that maintainers, adapters and decliners could be identified solely using brain metrics proposed to support superior cognitive ageing (Reuter-Lorenz & Park, 2014; Nyberg et al., 2012; Filippini et al., 2012). To test this, structural and resting-state MRI measures from a large sample (N=343) of high-functioning older adults were combined to categorise individuals as *maintainers* ('youthful' brain structure and function), *adapters* (lower structure and higher function) or *decliners* (lower structure and function) relative to averages in younger adults. Structural and functional brain metrics were extracted from brain regions affected by age, namely lower grey matter (GM) volume and higher frontal network resting-state (RS) coherence in older vs. younger adults (Filippini et al., 2012). After identifying the groups, cross-sectional cognition measured at MRI scan, and longitudinal cognition measured over the 15 years preceding MRI, was compared between groups. We predicted that maintainers and adapters would perform better at scan, and show less cognitive decline over time, compared to decliners. Cross-sectional measures of white matter hyperintensities (WMHs) and white matter (WM) integrity, derived from FLAIR and diffusion-weighted MRI respectively, were also compared to investigate group differences in brain health. We predicted that the more 'youthful' maintainers would show fewer WMHs compared to adapters and decliners, whilst maintainers and adapters would show more intact WM integrity compared to decliners, as preserved WM connectivity may allow adapters to engage additional functional resources.

4.2. Methods

4.2.1 Participants

4.2.1.1 Classification sample

The sample consisted of 343 older adults (age range 60-82) from the Whitehall-II imaging sub-study (Filippini et al., 2014). Established at University College London in 1985, Whitehall-II is a longitudinal cohort of 10,308 British civil servants, of whom 800 participants have completed MRI and cognitive testing at the Oxford Centre for Functional MRI of the Brain (FMRIB). This sample is derived from 563 participants on whom data were available. Inclusion criteria for this analysis was absence of any neurological condition, no current psychiatric diagnosis, availability of both resting-state and structural MRI scans, no structural abnormality noted on structural MRI and a score of at least 26 on the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005). All participants provided written informed consent and ethical approval for the study was obtained from the University of Oxford Central University/Medical Sciences Division Interdisciplinary Research Ethics Committee (MSD/IDREC/2010/P17.2).

4.2.1.2 ROI sample

An independent sample of 27 healthy community-dwelling older adults aged 50 to 78 and 27 healthy young adults aged 20 to 35 was used to create the structural and functional ROIs used to extract MRI metrics for group definition. Data were originally collected for a study investigating the effect of APOE on the brain (Filippini et al.,

2009; Filippini et al., 2011). All older adults scored over 95 on the Addenbrooke's Cognitive Examination – Revised (ACE-R; Mioshi et al., 2006).

4.2.2 Data acquisition

4.2.2.1 Imaging

Participants were scanned on the 3T Siemens Magnetom Verio (Siemens, Erlangen, Germany) at the FMRIB centre, using a 32-channel head coil. The neuroimaging protocol included the following acquisitions (detailed description in Filippini et al., 2014):

Structural MRI: A high-resolution T1-weighted image was acquired using a Multi-Echo (MEMPR) sequence. Repetition time (TR) = 2530ms, echo time (TE) = 1.79/3.65/5.51/7.37ms, voxel dimensions = 1.0x1.0x1.0mm.

Resting-state fMRI (rs-fMRI): A multi-band resting-state scan was acquired whilst participants were asked to lie in dimmed light with their eyes open, blink normally and not fall asleep. TR = 1300ms, TE = 40ms, voxel dimensions = 2.0x2.0x2.0mm, multi-band factor = 6, number of volumes = 460. A high-contrast single-band image was also acquired to improve registration of low-contrast MB images (TR = 7430ms, TE = 40ms, voxel dimensions = 2.0 x 2.0 x 2.0mm, MB factor = 1, number of volumes = 1), and as well as magnitude and phase fieldmap images for correction of distortions related to B0 field inhomogeneities (TR = 400ms, TE = 5.19/7.65ms, voxel dimensions = 3.0 x 3.0 x 3.0mm).

Diffusion-weighted MRI (dwMRI): A diffusion-weighed sequence with 60 directions and b-value=1500s/mm^2 was acquired, along with 5 b=0s/mm^2 volumes. TR = 8900ms, TE = 91.2ms, voxel dimensions = 2.0x2.0x2.0mm. GRAPPA parallel imaging was used. A single non-diffusion weighted (b=0 s/mm^2) was acquired with the reversed phase encoding direction for use in correction of susceptibility-induced distortions (Andersson et al., 2003).

Fluid Attenuated Inversion Recovery (FLAIR) MRI: A FLAIR image was acquired for identification and quantification of WMHs. TR = 9000ms, TE = 73ms, voxel dimensions = 0.9x0.9x3.0mm.

4.2.2.2 Cognition

4.2.2.2.1 Cross-sectional cognitive assessment

Participants completed a comprehensive neuropsychological battery at the time of scan, assessing a range of cognitive domains including *global cognition* (Montreal Cognitive Assessment, MoCA; Nasreddine et al., 2005), *visual copying and recall* (Rey Complex Figure Test, RCF; Meyers & Meyers, 1995), *verbal learning and recall* (Hopkins Verbal Learning Test, HVLT-R; Brandt & Benedict, 2001), *short-term memory* (Digit Span forward, Wechsler, 2008), *working memory* (Digit Span backwards, Digit Span sequential; Wechsler, 2008), *executive function* (Digit Coding; Wechsler, 2008), *fluency* (Letter fluency, Nasreddine et al., 2005; Category fluency; Hsieh et al., 2013), *semantic memory* (Boston Naming Test, BNT; Kaplan et al., 2001), *visual attention and task switching* (Trail Making Test, TMT; Lezak et al., 2004), and *premorbid IQ* (Test of Premorbid Function, TOPF; Wechsler, 2009).

4.2.2.2.2 Longitudinal cognitive assessment

Participants also completed a shorter battery of neuropsychological measures administered at three testing waves prior to the MRI scan. Measures of *immediate free recall* (20 word free recall; see Singh-Manoux et al., 2003), *fluency* (Letter fluency, Nasreddine et al., 2005; Category fluency; Hsieh et al., 2013), *vocabulary* (Mill Hill vocabulary test; Raven, 1958), and *verbal/non-verbal reasoning* (Alice Heim 4-I, AH4-I; Heim, 1970) were completed at phases 5, 7, 9 over a period of 10 years, with the most recent assessment approximately 5 years before MRI scanning and cross-sectional neuropsychological assessment. The Mini-Mental State Examination (MMSE; Folstein et al., 1975) was also completed 3 times prior to the MRI scan at phases 7, 9 and 11, most recently approximately 1 year before the scan.

4.2.2.3 Additional measures

DNA was extracted from blood samples drawn using Vacutainer CPT tubes (Becton Dickinson) and genotyped for the APOE gene. The full assessment protocol is reported in Filippini et al. (2014).

4.2.3 Image analysis

Imaging data were analysed using FSL tools (FMRIB's Software Library, http://fsl.fmrib.ox.ac.uk/; Smith et al., 2004).

4.2.3.1 Resting-state fMRI

Resting-state data were analysed using FSL's MELODIC tool (Multivariate Exploratory Linear Optimised Decomposition into Individual Components; http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/MELODIC). Single-subject data were pre-

processed using motion correction, brain extraction, and high pass temporal filtering with a cut-off of 100s. Pre-processed data were denoised using FIX (FMRIB's ICA-based Xclassifier; Salimi-Khorshidi et al., 2014; Griffanti et al., 2014), an automatic classification tool that classifies components from the single-subject ICA as signal or noise, and removes noise components from the data. Spatial smoothing was applied after FIX using a Gaussian kernel of full-width at half maximum (FWHM) of 6mm. Data were then registered to the individual structural scan and standard space images using boundary-based registration (Greve & Fischl, 2009) and FMRIB's non-linear registration tool (FNIRT; http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FNIRT).

Pre-processed images were fed into a group-level ICA, where individual scans were temporally concatenated into a single 4D file and decomposed into 25 components. Artefactual components were identified (N=4), and combined with the frontal component derived from the old and young sample (see 4.2.3.3 ROI-definition), to use as input for dual regression analysis (similar to Griffanti et al., 2016a), where first, the group components are entered in a linear regression to estimate the associated time course in each individual subject, and second, this time course is used to estimate subject-specific spatial maps.

4.2.3.2 Structural MRI

T1 structural images were skull-stripped using FSL's Brain Extraction Tool (BET; Smith, 2002). Brain tissues were segmented using FMRIB's Automated Segmentation Tool (FAST; Zhang et al., 2001) to create partial volume estimates (PVEs) for GM, WM and cerebrospinal fluid (CSF).

4.2.3.3 ROI definition

Regions of brain structure and resting connectivity significantly affected by age were used as ROIs to extract structural and functional metrics for identification of groups. Structural VBM and resting-state dual regression analyses in Filippini et al. (2012) were repeated, using updated FSL tools and approaches where relevant (see *Appendix 4* for supplementary method and results). Regions of significantly reduced GM density and significantly increased resting-state coherence in older adults were identified, as in Filippini et al. (2012). These significant regions were binarised to create structural and functional ROIs (*Figure 4.2*) used for classification.

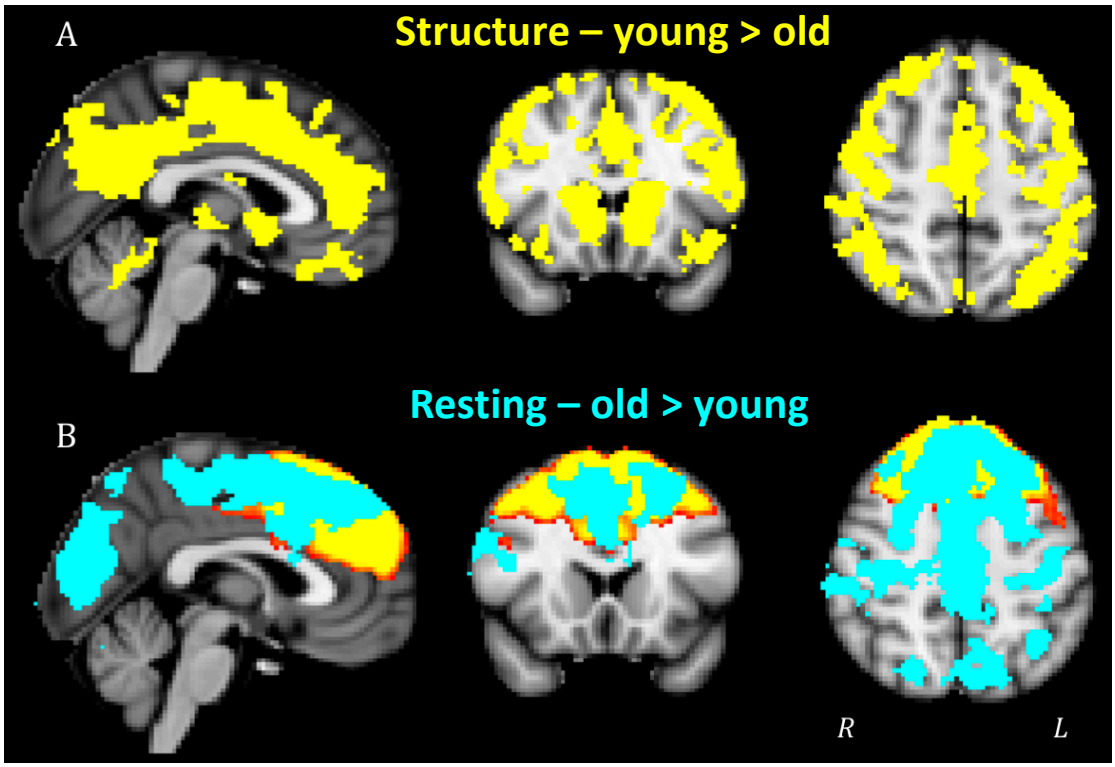


***Figure 4.2*. Age-related differences in brain structure and resting-state function.**

(A) Regions of reduced GM density in older, relative to younger adults, cluster-corrected (Z>2.3) and FWE-corrected at p<0.05. (B) Regions of increased coherence (blue) in older, relative to younger adults, in the frontal RSN (red/yellow), cluster-corrected (Z>2.3) and FWE-corrected at p<0.05. Image coordinates: x=2, y=18, z=52, MNI space.

4.2.3.4 Classification

GM volume and mean frontal network coherence were extracted from the structural and functional ROIs, respectively, for each Whitehall subject. For GM volume, the structural ROI mask was registered to the individual's structural scan initially using linear registration (FLIRT) with 12 DOF, then using non-linear registration (FNIRT). GM volume within the registered ROI was extracted from the GM PVE resulting from FAST, and normalised by whole brain volume (sum of GM, WM, CSF PVEs). For resting-state coherence, the mean connectivity within the functional ROI was extracted from the spatial maps resulting from dual regression, representing the coherence of each voxel's time-course with the frontal RSN. GM and RS metrics were extracted for each young participant in the same manner, and the average and standard deviation (SD) GM and RS were calculated for the young sample.

Older participants were defined as maintainers, adapters or decliners relative to the average and SD GM and RS for young adults (see *Figure 4.3*). Maintainers were classified as GM structure greater than one SD below the mean GM in young, and RS within one SD of the average young function. Adapters were classified as GM less than one SD below the mean GM in young, and RS above the mean young RS. Decliners were classified as GM less than one SD below the mean GM in young, and RS less than one SD below the mean function in young.

4.2.3.5 White matter integrity

Raw diffusion-weighted images were pre-processed using TOPUP (Andersson et al., 2003), to correct for susceptibility-induced distortions, and EDDY (Andersson &

Sotiropoulos, 2016), to correct for participant motion and eddy currents. DTIFIT, part of FMRIB's Diffusion Toolbox, was used to fit the diffusion tensor model at each voxel and derive fractional anisotropy (FA), mean diffusivity (MD) and radial diffusivity (RD) spatial maps. Whole-brain voxel-wise comparison of FA was conducted using tract-based spatial-statistics (TBSS; Smith et al., 2004). Individual FA maps were non-linearly registered to the FMRIB58 FA template, and then to the MNI152 standard space. The mean of all FA images was skeletonised and thresholded at 0.2. Individual FA maps were then projected to the thesholded skeleton and passed into voxel-wise statistical analysis using Randomise (Winkler et al., 2014), a non-parametric permutation inference program. MD and RD images were also compared with TBSS using the same approach. Results are shown at $p<0.05$ FWE corrected for multiple comparisons across space. Two participants were not included due to poor quality diffusion-weighted data.

4.2.3.6 White matter hyperintensities

White matter hyperintensities were quantified using BIANCA (Griffanti et al., 2016b), a fully automated, supervised method for WMH detection. BIANCA produces a probability per voxel of being WMH, using a k-nearest neighbour algorithm utilising intensity and spatial features. The BIANCA algorithm was trained using a set of FLAIR images hand-labeled by a trained operator, and WMHs were then automatically segmented on FLAIR images using features extracted from FLAIR and FA images. The output probability map of lesions was thresholded and binarised, and used to extract the total volume of WMHs for each subject. One participant was not included due to poor quality of the FLAIR image.

4.2.4 Statistical analysis

Non-imaging data were analysed using SPSS (SPSS Inc., Chicago, IL.). Demographics were compared between the ROI-sample young and old, and between the ROI-sample old and classification sample using independent t-tests for continuous data and chi-square tests for categorical data. Cross-sectional neuropsychological scores and WMH volumes were compared between classified groups using one-way ANOVA. Significant main effects were investigated using post-hoc pairwise comparisons with a Bonferroni procedure to control for family-wise error. Brown-Forsythe's F and *p* statistics are reported where Levene's test of homogeneity of variance was significant.

Longitudinal neuropsychological scores were compared between identified groups using repeated measures ANOVA, with 'time' (time 1, time 2, time 3) as a within-subject factor and 'group' (maintainer, adapter, decliner) as a between-subject factor. The 'time*group' interaction was the primary outcome of interest, to indicate between-groups differences in cognitive change over time.

Due to the unusual gender distribution of the Whitehall-II cohort (>70% males, Singh-Manoux et al., 2012), cross-sectional and longitudinal analyses were also conducted using ANCOVA with gender as a covariate and using ANOVA including male participants only to probe the influence of the gender distribution on results. Demographics for the three groups with females excluded are reported in *Appendix Table 4.A*.

4.3. Results

4.3.1 Demographics and sample characteristics

In the classification sample of 343 older adults, mean age at time of scan was 68.9 years (SD=5.0) and mean years of education was 14.8 (SD=3.2). The classification sample had a greater proportion of males, fewer years of education and was significantly older than the older adults in the independent ROI sample (see *Table 4.1*).

Table 4.1. **Demographics of ROI and Classification samples**

	Young vs. Old ROI sample			Classification sample	
	Young N=27	Old N=27	*p*	Old N=343	*p*
Age, in years	28.0 (4.3)	64.6 (7.4)	**<0.001**	68.9 (5.0)	**0.02**
Education, in years	18.9 (1.9)	17.7 (2.9)	0.08	14.8 (3.2)	**<0.001**
ACE-R score	-	99.3 (1.2)	-	-	-
MoCA score	-	-	-	28.2 (1.3)	-
Sex, N female	10 (37.0%)	16 (59.3%)	0.10	69 (20.1%)	**<0.001**
APOE, % ε4-carriers	13 (50.0%)	10 (40.0%)	0.70	71 (20.7%)	**<0.03**

Values represent mean (SD) unless otherwise stated. *Abbreviations*: ACE-R – Addenbrooke's Cognitive Examination-revised version; MoCA – Montreal Cognitive Assessment; APOE – apolipoprotein E gene*;* – indicates data were not collected.

4.3.2 Group identification and characteristics

The classification procedure resulted in 51 adapters, 98 maintainers and 59 decliners (see *Figure 4.3*). 39.4% of participants did not fit into these three groups (middle left N=63; top right N=20; bottom left N=52). There was no difference in age, years of education or APOE genotype between the three groups (see *Table 4.2*). Gender was

significantly different between groups [χ^2[2, 208]=30.95, p<0.001], with more females in the maintainer group compared to both adapters [χ^2[1, 149]=17.34, p<0.001] and decliners [χ^2[1, 157]=17.92 p<0.001]. Adapters and decliners did not differ significantly on gender (p=0.77). All significant differences remained after Bonferroni correction for multiple comparisons.

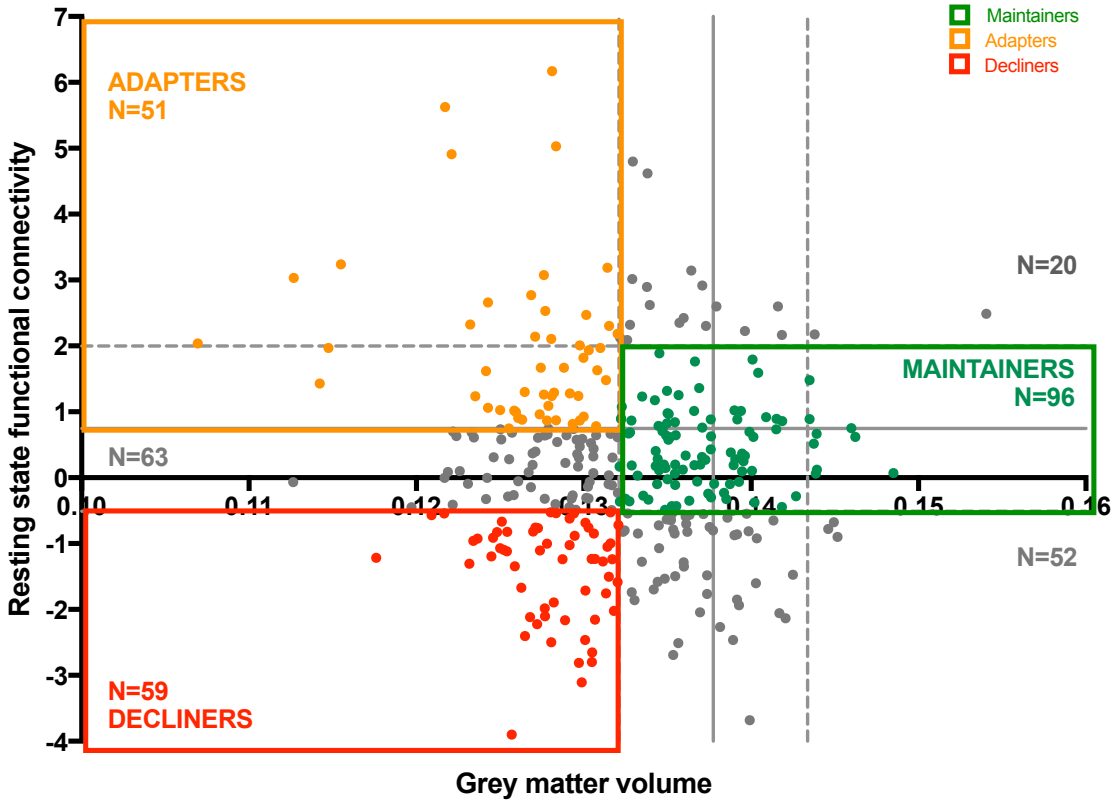


Figure 4.3. **Brain volume plotted against frontal resting-state function in healthy older adults.** Brain volume represents grey matter volume within the age-affected ROI normalised by whole brain volume and brain function is functional connectivity from frontal component connectivity map within the age-affected ROI. Solid and dashed grey lines represent the average and +/- 1 standard deviation in young adults, respectively. Green – maintainers, orange – adapters, red – decliners.

Table 4.2. **Demographics of maintainers, adapters and decliners**				
	Maintainers (N=98)	Adapters (N=51)	Decliners (N=59)	*p*
Age, years	68.6 (4.7)	70.3 (5.0)	69.0 (5.7)	0.17
Education, years	14.4 (3.2)	14.9 (3.2)	15.3 (3.2)	0.24
Sex, % female	34.7%	3.9%	7.7%	**<0.001**
APOE, % ε4-carriers	18.4%	17.6%	30.5%	0.14
TOPF-estimated IQ	115.5 (7.6)	116.2 (7.6)	115.5 (6.2)	0.84

Values represent mean (SD) unless otherwise stated. *Abbreviations*: APOE – apolipoprotein E; TOPF – Test of Premorbid Function; IQ – intelligent quotient.

4.3.3 Cognition

4.3.3.1 Cross-sectional cognition

Cognitive scores from time of scan are plotted in *Figure 4.4*. One-way ANOVA revealed a significant effect of group on *MoCA* [$F(2,205)=3.99$, $p=0.02$, $r^2=0.04$], *HVLT total recall* [$F(2,205)=3.29$, $p=0.04$, $r^2=0.03$], *HVLT delayed recall* [$F(2,136.3)=3.36$, $p=0.04$, $r^2=0.03$], *HVLT retention* [$F(2, 121.9)=3.28$, $p=0.04$, $r^2=0.03$], and *digit coding* [$F(2, 205)=3.19$, $p=0.04$, $r^2=0.03$]. Post-hoc comparisons using Bonferroni correction revealed a trend for worse performance by decliners on *MoCA* [$p=0.06$, d=0.38] and *HVLT total recall* [$p=0.09$, d=0.38] compared to maintainers. Adapters performed significantly worse than maintainers on *HVLT delayed recall* [$p=0.03$, d=0.42] and *digit coding* [$p=0.04$, d=0.43], with a trend for lower performance on *HVLT retention* [$p=0.07$, d=0.37] and *MoCA* [$p=0.06$, d=0.40]. Adapters also demonstrated significantly lower *HVLT retention* scores than decliners [$p=0.04$, d=0.44]. Other post-hoc comparisons were non-significant. Detailed statistical results are reported in *Appendix Table 4.B*. To account for the multiple ANOVAs conducted, we performed

additional Bonferroni correction on the main group effects, producing a significance threshold of $p<0.003$. Accordingly, none of the main group effects survived.

After performing ANCOVA with gender as a covariate, the main effect of 'group' remained significant for *MoCA* [F(2,204)=3.34, p=0.04, η_p^2=0.03], *HVLT delayed recall* [F(2,204)=3.38, p=0.04, η_p^2=0.03] and *HVLT retention* score [F(2,204)=3.67, p=0.03, η_p^2=0.04], whilst *HVLT total recall* [F(2,204)=2.35, p=0.10, η_p^2=0.02] and *digit coding* [F(2,204)=2.91, p=0.06, η_p^2=0.03] were at trend. Post-hoc comparisons were similar to those resulting from the ANOVA (see *Appendix Table 4.B*). Inclusion of only males in the one-way ANOVA resulted in a significant difference between groups for *MoCA score* only [F(2,166)=4.17, p=0.02, η_p^2=0.05], whilst *HVLT delayed recall* [F(2, 134.2)=2.47*,* p=0.09, η_p^2=0.03], and *HVLT retention* scores [F(2,123.7)=2.51, p=0.09, η_p^2=0.03] were at trend. Post-hoc comparisons for *MoCA* score revealed, relative to maintainers, decliners performed significantly worse [p=0.03, d=0.48], whilst adapters remained at trend for worse performance [p=0.07, d=0.43]. Again, none of the main group effects survived Bonferroni correction.

4.3.3.2 Longitudinal cognition

Longitudinal cognitive results are illustrated in *Figure 4.5* and detailed in *Table 4.3*. Across the whole sample, cognitive performance declined over time, shown by the significant main effect of 'time' for all cognitive measures ($p<0.002$), except vocabulary (p=0.70). However, the 'time-by-group' interaction did not reach statistical significance for any cognitive measure (ps >0.2). The main effect of 'group' was significant for *immediate verbal recall* [F(2, 168)=4.87, p=0.009, η_p^2=0.06],

where compared to maintainers, decliners performed significantly worse on average across time points [*p*=0.02, mean difference (*md*)=-0.77], and adapters trended to worse performance [*p*=0.06, *md* =-0.71]. There was also a trend for 'group' effect on MMSE [F(2, 182)=2.68, *p*=0.07, η_p^2=0.03], with maintainers performing better than adapters. All other group effects were non-significant (*p*s >0.5). After Bonferroni correction, all significant effects of 'time' remained significant, whilst the 'group' effect on *immediate verbal recall* no longer reached statistical significance.

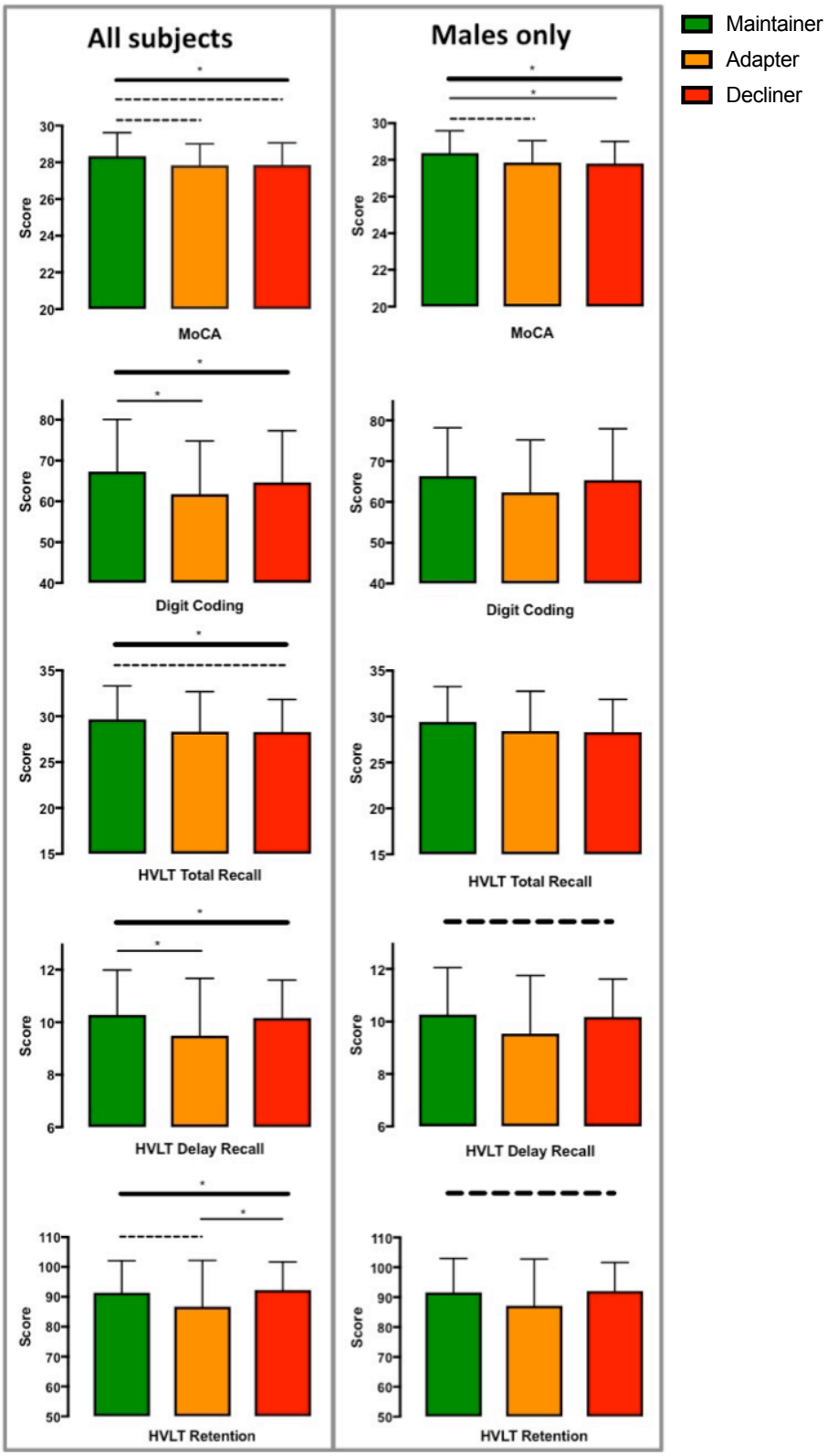


Figure 4.4. **Cross-sectional neuropsychological performance by group**

Figure shows mean, SD and significance testing results for the full sample (left column) and male-only sample (right column). * indicates significant effect at $p<0.05$. Heavy solid line with star indicates a significant main effect of group at $p<0.05$; heavy dashed line indicates a trend to main effect; light solid line with star indicates a significant pairwise comparison; light dashed line indicates a trend for pairwise comparison.

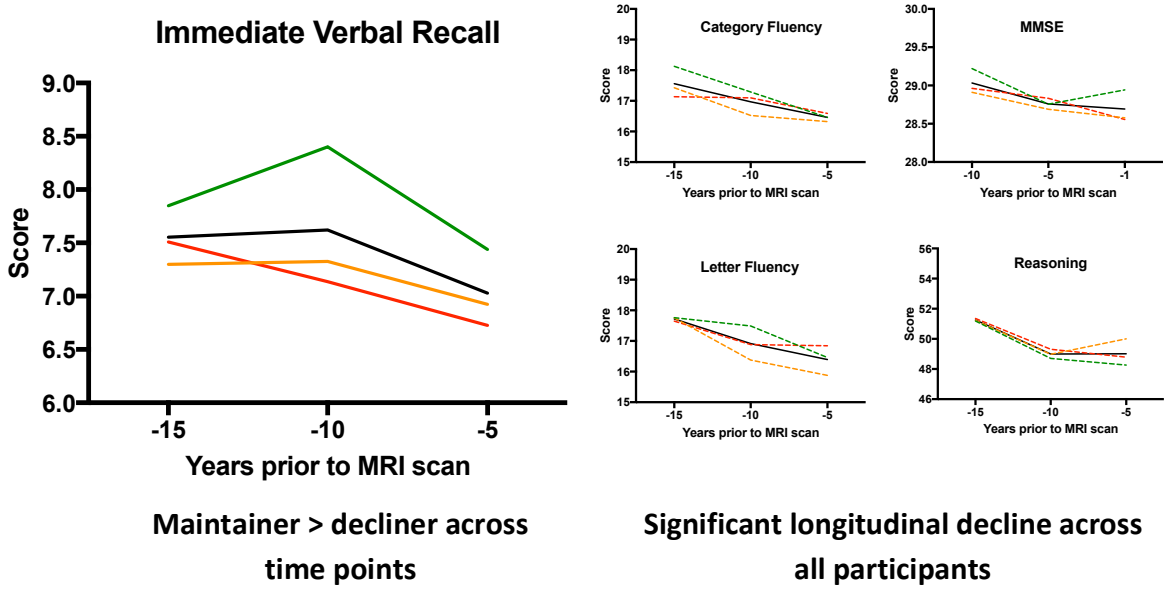


***Figure 4.5*. Longitudinal neuropsychological performance over the years prior to MRI scanning.** Shown for the full sample only**.** Green – maintainers, orange – adapters, red – decliners, black – average of three groups. The x-axis indicates number of years prior to MRI scan.

Both the ANCOVA and ANOVA with males only produced non-significant group-by-time interactions for all cognitive measures, whilst the effect of 'time' remained significant for all measures, except vocabulary. The group difference in *immediate verbal learning* across time points also remained significant across analyses, although the significantly poorer performance by decliners compared to maintainers in both ANOVAs with all participants (above) and male participants only [p=0.03, *md* = -0.80] was only at trend for the ANCOVA [p=0.08, *md* =-0.67]. A further significant main effect of group on longitudinal MMSE score was revealed only in the ANOVA with males only [$F(2, 149)=3.73$, p=0.03, η_p^2=0.05]. Adapters performed significantly worse than maintainers across time points [p=0.04, *md*=-0.31], whilst decliners did not differ significantly from either maintainers or adapters. Detailed statistical results are reported in *Table 4.3.* Longitudinal cognitive scores for all participants vs. males only are illustrated in *Appendix Figure 4.B.*

Table 4.3. **Longitudinal cognition prior to MRI scan compared between maintainers, adapters and decliners**

Cognitive measure	Analysis	N			Time			Time-by-Group			Group			Pairwise (*p*)		
		M	A	D	F	*p*	η_p^2	F	*p*	η_p^2	F	*p*	η_p^2	M vs. A	M vs. D	A vs. D
Category fluency	*ANOVA*	80	40	51	10.08	<0.001	0.06	1.29	0.27	0.02	0.41	0.66	0.01	*ns*	*ns*	*ns*
	ANCOVA	80	40	51	10.25	<0.001	0.06	1.51	0.20	0.02	0.67	0.52	0.01	*ns*	*ns*	*ns*
	ANOVA-m	52	38	48	10.03	<0.001	0.07	0.94	0.44	0.01	0.40	0.67	0.01	*ns*	*ns*	*ns*
Letter fluency	*ANOVA*	80	40	51	12.30	<0.001	0.07	1.30	0.27	0.02	0.38	0.69	<0.01	*ns*	*ns*	*ns*
	ANCOVA	80	40	51	10.86	<0.001	0.06	0.91	0.46	0.01	0.62	0.54	0.01	*ns*	*ns*	*ns*
	ANOVA-m	52	38	48	11.52	<0.001	0.08	1.40	0.23	0.02	0.32	0.73	0.01	*ns*	*ns*	*ns*
Reasoning	*ANOVA*	80	40	51	23.01	<0.001	0.12	1.11	0.35	0.01	0.10	0.90	<0.01	*ns*	*ns*	*ns*
	ANCOVA	80	40	51	15.61	<0.001	0.09	0.77	0.55	0.01	0.64	0.53	0.01	*ns*	*ns*	*ns*
	ANOVA-m	52	38	48	16.32	<0.001	0.11	0.62	0.65	0.01	0.31	0.73	0.01	*ns*	*ns*	*ns*
Immediate Free Recall	*ANOVA*	80	40	51	6.58	0.002	0.04	1.52	0.20	0.02	4.87	0.01	0.06	0.06	0.02	*ns*
	ANCOVA	80	40	51	7.01	0.001	0.04	1.37	0.24	0.02	3.11	0.05	0.04	*ns*	0.08	*ns*
	ANOVA-m	52	38	48	6.99	0.001	0.05	1.46	0.21	0.02	4.14	0.02	0.06	0.08	0.03	*ns*
Vocabulary	*ANOVA*	80	40	51	0.35	0.70	<0.01	0.45	0.77	0.01	0.66	0.52	0.01	*ns*	*ns*	*ns*
	ANCOVA	80	40	51	0.43	0.65	<0.01	0.43	0.78	0.01	0.29	0.75	<0.01	*ns*	*ns*	*ns*
	ANOVA-m	52	38	48	0.46	0.64	<0.01	0.35	0.85	0.01	0.32	0.73	0.01	*ns*	*ns*	*ns*
MMSE	*ANOVA*	86	45	54	7.83	<0.001	0.04	1.45	0.22	0.02	2.68	0.07	0.03	*ns*	*ns*	*ns*
	ANCOVA	86	45	54	8.31	<0.001	0.04	1.77	0.14	0.02	2.63	0.08	0.03	*ns*	*ns*	*ns*
	ANOVA-m	57	44	51	8.04	<0.001	0.05	1.22	0.30	0.02	3.73	0.03	0.05	0.04	*ns*	*ns*

Abbreviations: N – number of participants; M - maintainer, A – adapter, D – decliner; F – F statistic; p – p statistic; η_p^2 - partial eta squared; ns – non-significant >0.1; ANOVA – analysis of variance with all participants; ANCOVA – controlling for gender; ANOVA-m – ANOVA with males only.

4.3.4 Cross-sectional MRI metrics

4.3.4.1 White matter hyperintensities

Total WMH volume was significantly different between groups [F(2, 204)=3.17, p=0.04, η_p^2=0.03], illustrated in *Figure 4.6*. Post-hoc comparisons showed decliners had significantly greater WMH volume compared to maintainers [p=0.048, d=0.37] whilst adapters WMH load was not significantly different to either maintainers [p=0.42] or decliners [p=1.00]. However, after adjusting WMH volume by whole brain volume to correct for differences in head size, the main effect of 'group' no longer reached statistical significance [F(2, 204)=1.56, p=0.21, η_p^2=0.02].

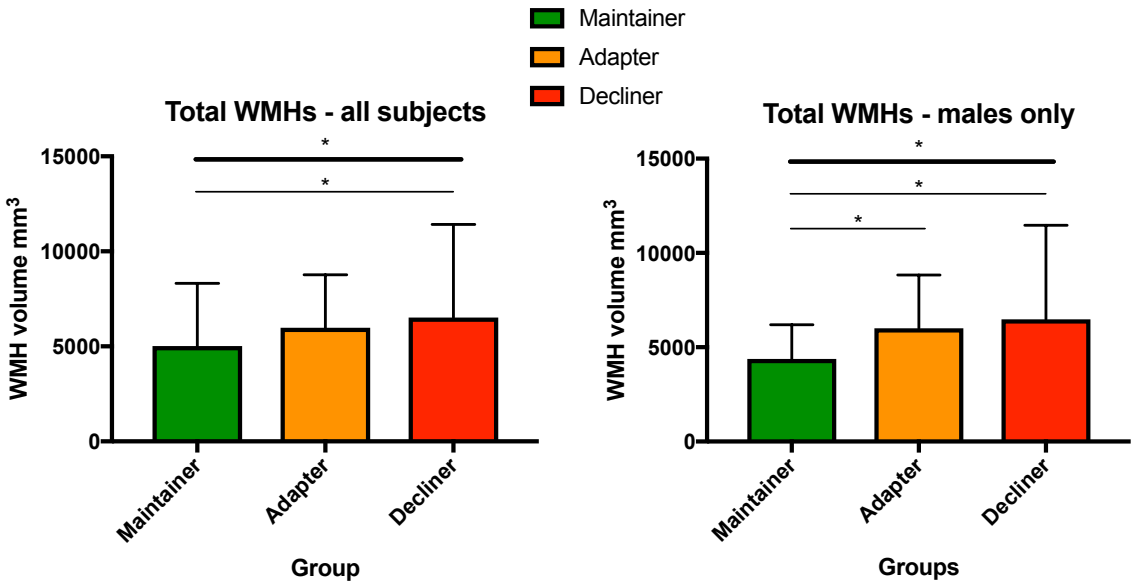


Figure 4.6. **White matter hyperintensity load by maintainer, adapter and decliner group.**
Shown for all participants and males only. Heavy solid line indicates signfiicant main effect of group. Light solid line indicates significant post-hoc pairwise comparison. * indicates p<0.05

Using unadjusted WMH volumes, the effect of group on WMH volume was significant in both the ANCOVA [F(2, 203)=5.03, p=0.007, η_p^2=0.05] and ANOVA with males only [F(2, 102.5) = 5.95, p=0.004, η_p^2=0.07]. In both cases, decliners had

significantly greater WMH load than maintainers [ANCOVA: *p*=0.008, d=0.37; ANOVA-males: *p*=0.003, d=0.57]. In the males only ANOVA, adapters also had significantly greater WMH load than maintainers [*p*=0.04, d=0.70], but not decliners [*p*=1.00] (*see Figure 4.6*). Using whole-brain adjusted WMH volumes in the ANCOVA and ANOVA-males only did not alter these results. Statistical comparisons are detailed in *Table 4.4* and *Appendix Figure 4.C*.

***Table 4.4*. Results of between groups comparison of white matter hyperintensity load**

Test	Details	WMH	F	*p*	η_p^2	Pairwise (*p*)		
						M vs. A	M vs. D	A vs. D
ANOVA	All participants	Raw	3.17	0.044	0.03	ns	0.048	ns
ANOVA	All participants	Norm	1.56	0.213	0.02	ns	ns	ns
ANCOVA	All participants, gender covariate	Raw	5.03	0.007	0.05	ns	0.008	ns
ANOVA	Males only	Raw	5.95	0.004	0.07	0.002	0.011	ns

Abbreviation: WMHs – white matter hyperintensities, M - maintainer, A – adapter, D – decliner; F – F statistic; p – p statistic; η_p^2- partial eta squared; ns – non-significant >0.1; norm – normalised for whole-brain volume.

4.3.4.2 White matter integrity

Whole-brain WM analysis with TBSS revealed a widespread effect of group membership on FA values (*Figure 4.7a*). Post-hoc t-tests revealed higher FA in adapters relative to decliners, localised to the right corona radiata and posterior internal capsule (*Figure 4.7b*). There were no other significant differences in FA between groups, and no group difference in whole-brain voxel-wise analyses of MD or RD. *Figure 4.7c* shows boxplots for the mean FA for each group (including both males and females), extracted from the region of significant adapter vs. decliner group difference. Mean FA within this region correlated significantly with RS

extracted within the functional ROI across the three groups [r=0.26, 95% CI [0.13, 0.39], p<0.001], illustrated in *Figure 4.8*.

Statistical analyses were also run with male participants only, and all participants with gender modeled as a covariate of no interest, with a widespread effect of group membership again in both analyses (*Appendix Figure 4.D*). The significantly greater FA in adapters compared to decliners was replicated in both analyses, as was the correlation between FA and RS [ANCOVA: r=0.27, 95% CI [0.14, 0.40], p<0.001; ANOVA with males only: r=0.30, 95% CI [0.16, 0.44], p<0.001]. A further significant effect was revealed, representing higher FA in maintainers than adapters, localised in the splenium and body of the corpus callosum and corticospinal tract in the male only ANOVA, extending to include bilateral inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, forceps major and forceps minor when covarying for gender. For males only, a third significant contrast revealed significantly higher FA in decliners compared to adapters in the splenium, body and genu of the corpus callosum. RS within the functional ROI was negatively correlated with FA in regions of maintainers > adapters [r=-0.19, 95% CI [-0.35, -0.03], *p*=0.007] across participants and decliners > adapters [r=-0.28, 95% CI [-0.44, -0.11], *p*<0.001] across males only. There were no significant effects on MD or RD either when females were removed or gender included as a covariate.

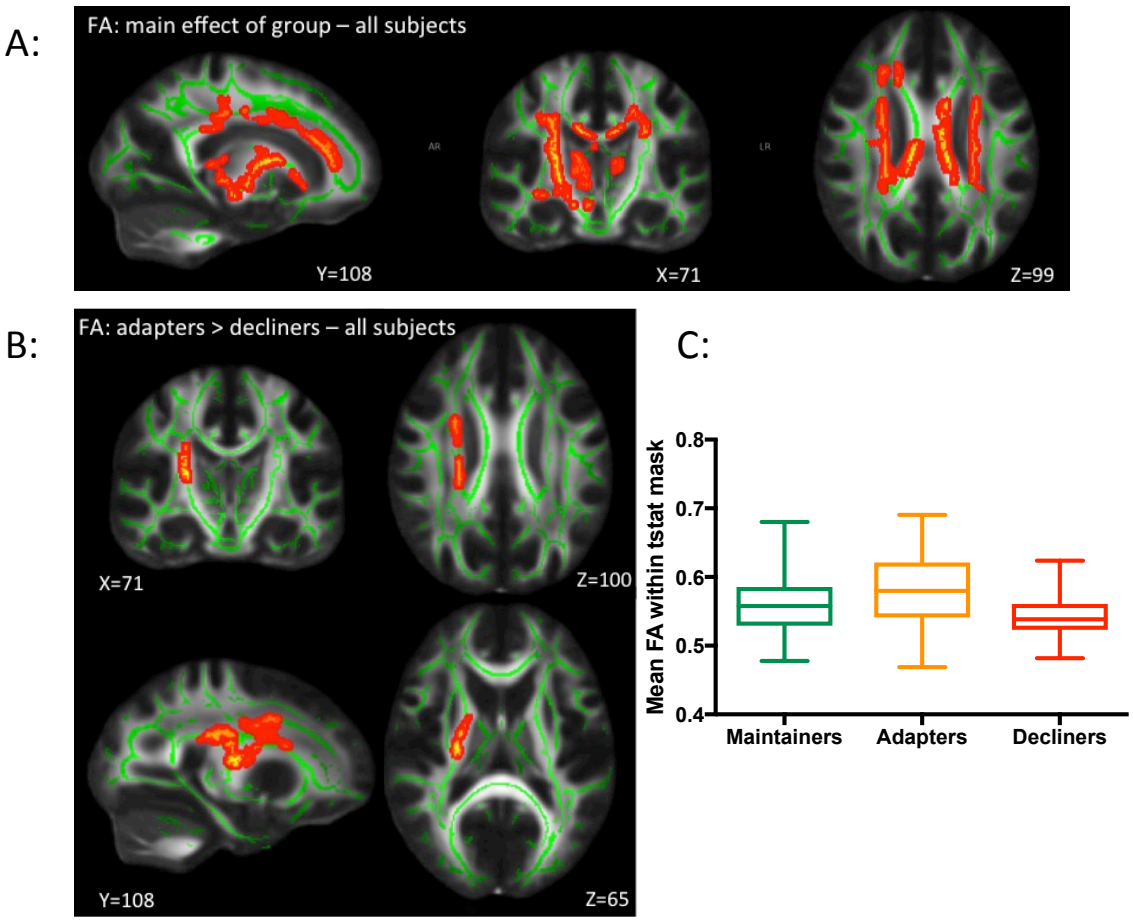


Figure 4.7. **Results of TBSS analysis comparing FA between groups.**

A) Regions where FA is significantly affected by 'group', $p<0.05$ FWE-corrected. B) Regions of significantly lower FA in decliners compared to adapters, $p<0.05$ FWE-corrected. Significant regions have been dilated for illustrative purposes. Coordinates are in anatomical space. C) Box plot of the mean FA extracted within the region of significant difference between adapters and decliners, shown by group.

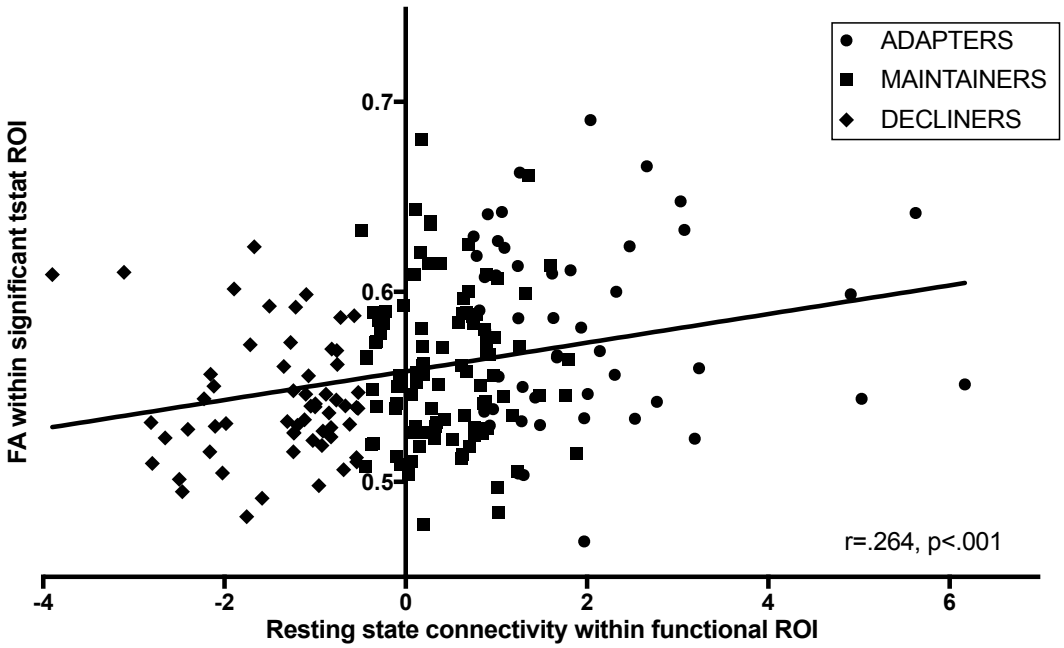


Figure 4.8. **Correlation of mean FA with frontal resting-state coherence.**

Mean FA was extracted within the region of significantly reduced FA in decliners compared to adapters (*Figure 4.7*). Frontal RS connectivity was extracted within the functional ROI (*Figure 4.2*).

4.4. Discussion

This study aimed to use a novel multi-modal MRI-based approach to identify multiple patterns of brain ageing associated with superior cognitive ageing, to provide direct evidence for individual differences in the neural basis of superior cognition in later life. Using structural and functional brain metrics alone, we were able to identify groups of maintainers, adapters and decliners resembling our predictions; however, only maintainers demonstrated superior cognition, suggesting higher resting-state coherence in adapters is not beneficial to cognition. Nonetheless, significant differences in white matter hyperintensity burden and white matter integrity between groups indicate that use of GM and RS metrics to define groups captures more widespread differences in brain health. Further positive

association of WM integrity and resting-state coherence suggests that preserved WM integrity may underlie the higher RS observed in adapters.

4.4.1 Identification of groups

We found that over 60% of our large sample of high-functioning older adults were identified as maintainers, adapters or decliners, consistent with our prediction that these groups could be identified solely using brain metrics proposed to support superior cognitive ageing. These brain metrics aimed to capture age-related changes in brain structure and function undergone in adapters and decliners, and preservation of brain health in maintainers. Our observation of significantly more females in the maintainer group was not anticipated, but may relate to risk factors more common in males, e.g. Framingham stroke risk, that have been shown in this cohort to be associated with reduced grey matter volume (Zsoldos et al., 2018).

4.4.2 Cognitive differences between groups

Consistent with our predictions, compared to maintainers, decliners demonstrated poorer cross-sectional MoCA score and immediate verbal recall, as well as poorer immediate verbal memory over the 15 years prior to MRI scanning. These findings may point to a specific difference in immediate verbal memory between maintainers and decliners. The presence of longitudinal as well as cross-sectional differences indicates memory performance in decliners was already lower prior to the MRI scan. However, the absence of group difference in cognitive score over time means it is unclear whether this reflects our assumptions of different trajectories of cognitive and brain ageing in maintainers and decliners, or rather stable differences between groups across the lifespan.

In contrast, the predicted superior cognitive performance in adapters relative to decliners was not observed on any cross-sectional or longitudinal measure. Instead, adapters performed *worse* than maintainers at time of scan on delayed verbal recall and working memory, as well as poorer verbal retention compared to decliners. Taken together, these cognitive results suggest that the greater resting-state coherence observed in adapters is not beneficial to cognition.

Several key considerations impact the interpretation of these cognitive results. All participants in the study, including decliners, have a good level of cognitive ability, with MoCA scores >25 at time of scan required for inclusion to minimise the influence of early AD pathology. The neuropsychological measures available in this cohort also have limited sensitivity and specificity to detect subtle individual differences between healthy older adults, thus ceiling/floor effects may have influenced outcomes. Furthermore, Bonferroni correction applied to the main group effects rendered all three-way cognitive comparisons non-significant. However, the effect sizes for main effects were small-to-medium (0.02-0.05) and post-hoc pairwise comparisons produced moderate effect sizes (~0.4) (Cohen, 1988). Finally, whilst the lack of observable group-by-time interaction for longitudinal cognition is inconsistent with the prediction of greater cognitive decline in decliners than other groups, the degree of decline on neuropsychological measures in the years preceding the MRI scan may be insufficient to detect changes over time. As the longitudinal cognitive measures were not administered at the time of MRI scanning, the most recent wave of longitudinal cognitive assessment was several years before the MRI scan, therefore divergence of cognitive trajectories between groups in the

years immediately preceding the MRI cannot be evaluated, and may have contributed to the lack of group-time interaction.

4.4.3 White matter differences between groups

As WMHs are a commonly observed age-related pathology (Deary et al., 2003b), our finding of greater WMH load in decliners than maintainers corroborates our prediction of lower WMH burden in the more 'youthful' maintainers. WMHs in older adults have also previously been associated with cognitive decline (e.g. Brickman et al., 2011), consistent with predictions that decliners demonstrate poorer cognition due to poorer brain health. In older adults grouped on WMH load, those with the most WMHs also showed the greatest age-related brain atrophy (Habes et al., 2016), reflecting our findings of greater WMH burden in those with the lowest GM. Habes et al. additionally only found an association of WMH with cognition for immediate verbal recall, the same domain on which maintainers and decliners differ in our data.

We also observed significantly greater FA in adapters compared to decliners in the corona radiata and posterior internal capsule. As evidence shows that functional connectivity reflects the brain's underlying structural connectivity (Van Den Heuvel et al., 2009), the association of regional FA with frontal RS across groups suggests preserved WM integrity may underlie opposing patterns of functional connectivity in adapter and decliner groups. Whilst engagement of additional functional resources may involve cortico-cortico association fibres or commissural fibres connecting cerebral hemispheres, our differences are observed in projection fibres, connecting

cerebral cortex to lower brain regions, and the functional significance of FA differences in these regions is unclear.

4.4.4 Impact of gender on findings

Adjustment for gender, due to the gender difference observed between groups, did not substantially alter the cognitive or white matter results. Controlling for gender in cognitive analyses reduced some significant cross-sectional group differences to trend levels, likely due to loss of statistical power. However, despite the loss of power, the male only sample revealed significant post-hoc comparisons for cross-sectional MoCA score for maintainer vs. adapters, and as well as a significant difference in longitudinal MMSE score, with better performance in maintainers than adapters across time points. Similarly, in male only samples, greater WMH load of adapters vs. maintainers became significantly different. However, the differences in WMH load and longitudinal immediate verbal recall between decliners and maintainers was unaffected by gender adjustments.

Several subthreshold group effects on WM integrity were revealed after controlling for gender in the TBSS analyses. Greater FA found in maintainers compared to adapters is consistent with adapters having experienced a greater extent brain ageing. The negative correlation of FA in the corpus callosum with prefrontal brain function is also consistent with previous findings (Hakun et al., 2015; Persson et al., 2006), and may reflect a possible compensatory response to compromised structure, or a loss of specificity of functional networks in response to anatomical breakdown (e.g. Hawellek et al., 2011).

4.4.5 Advantages and limitations of this approach

This study offers a novel approach to investigate individual differences in how the brain supports superior cognitive ageing in a large sample of healthy older adults with many years of longitudinal cognitive data. In particular, the novel MRI-based approach for identifying maintainers, adapters and decliners avoids the need for *a priori* definition of superior cognition, which is challenging and often arbitrary. Variability in the cognitive domain, measure and method for defining high vs. low performers (e.g. median split, top % vs. bottom %) is likely to have contributed to variable results in previous studies. Comparison of brain metrics between older adult groups defined on *a priori* cognitive performance also suffers a circularity problem, and will produce differences in the brain regions that underpin that cognitive function.

However, we must consider some potential limitations in the interpretation of our results. As previously mentioned, the high level of cognitive performance and the small cross-sectional and longitudinal cognitive differences observed limited our ability to detect subtle differences between groups. The use of cross-sectional imaging data to define maintainers, adapters and decliners also required assumptions to be made that lower GM and higher RS reflect changes with age. Use of age-affected ROIs to extract the brain metrics used for classification, within which we expected to find variable GM volume and RS coherence across older adults, reduces these assumptions to some extent, but further longitudinal neuroimaging will help address this limitation in future studies.

The use of only a single structural and functional ROI, respectively, to extract brain metrics, as well as the use of only resting-state and GM volume to define groups, is a simplification of the manifold changes known to occur in the brain with age. Many types of age-related decline may lead to functional adaption including accumulation of pathology, microbleeds, reduced neurochemicals or reductions in brain activity elsewhere in the brain. We focused on frontal RSN in this study as the prefrontal cortex is the primary locus of scaffolding according to the STAC (Park & Reuter-Lorenz, 2009), and is also the most reported site of purported compensatory over-activation (Eyler et al., 2011), across a range of cognitive tasks. Age-related increases in frontal RS coherence has also been associated with analogous increases in task-based activation (Filippini et al., 2012), and superior cognitive performance in healthy older adults (Jockwitz et al., 2017). However, age may affect multiple RSNs (Ferreira & Busatto, 2013) and any compensatory function may involve changes within and between more than one of these networks. The focus on resting-state fMRI in this study may also have contributed to the unexpected patterns findings in the adapter group. Whilst RS-fMRI advantageously avoids task-related influences on brain function and reflects the intrinsic functional architecture of the brain, adaptive increases in brain function that benefit cognitive performance may only occur in response to task demands.

4.5. Conclusions

The concepts of 'adaption' and 'maintenance' as underpinning superior cognitive ageing are not mutually exclusive. According to the STAC approach, older adults with greater 'brain maintenance' require less compensatory scaffolding (Grady, 2007;

Reuter-Lorenz & Park, 2014). Here, we proposed that multiple patterns of brain ageing associated with superior cognition could be identified within a sample of healthy older adults. By combining GM volume and frontal RS-coherence extracted from age-affected ROIs, groups defined as maintainers, adapters and decliners were indeed identified purely using brain metrics. Decliners demonstrated significantly poorer cognition compared to maintainers, but not adapters. In fact, adapters performed the worse on several measures of cognition, suggesting higher frontal RS observed in 'adapters' is not associated with superior cognitive performance. Further use of longitudinal cognition and MRI acquired *after* baseline definition of groups will be important to determine the future cognitive trajectory of these brain profiles at baseline. In the next chapter, I will identify these same maintainer, adapter and decliner groups in a separate cohort with longitudinal performance measured after baseline scanning to investigate whether the subsequent cognitive trajectory differs as expected between the proposed brain profiles.

Chapter 5. The baseline brain profile of subsequent cognitive success

In the field of preclinical AD, the association of disease-relevant baseline brain characteristics with subsequent longitudinal cognitive performance has been investigated to evaluate these brain metrics as markers of impending cognitive decline, as with SMI in Chapter 3. A similar approach applied to superior cognitive ageing can establish the baseline brain characteristics that are associated with the best (e.g. stable) and worst (e.g. declining) subsequent cognitive trajectories. In the previous chapter, I proposed 'maintainer' and 'adapter' groups as two different brain profiles that would support concurrent superior cognition. However, these brain profiles may have different implications for long-term cognitive abilities. To build on our understanding of the multi-modal brain profiles proposed in Chapter 4, in this chapter I investigated the subsequent longitudinal cognitive performance of the 'maintainer', 'adapter' and 'decliner' groups to establish the future cognitive trajectory associated with these baseline brain profiles.

5.1. Introduction

Serial cognitive assessment of older adults has shown that a stable level of cognitive performance over several years is not unusual, representing 30-60% of samples in some studies (e.g. Mayeux et al., 2001; Rubin et al., 1998; Wilson et al., 2011). Whilst lifestyle and health factors such as physical activity and lack of diabetes have been associated with longitudinally maintained cognition in later life (e.g. Barnes et al., 2007; Habib et al., 2007), the neural phenotype(s) that support such a stable cognitive trajectory in old age are not well understood. Older adults defined as

'superior' based on cross-sectional cognitive performance may later become cognitively impaired (e.g. Chodosh et al., 2007). Therefore, brain characteristics associated with cross-sectional 'superior' cognition in older adults are not necessarily those that support continued stability of cognitive functions. Longitudinal cognitive assessment is therefore essential to identify the long-term cognitive outcomes of baseline brain metrics.

Older adults with stable cognitive performance for 5-20 years *before* MRI scanning have better structural brain characteristics, e.g. larger hippocampal and MTL volumes, greater cingulate microstructural integrity and higher FA in the anterior corpus callosum, compared to those with declining performance (Fleischman et al., 2013; Persson et al., 2006; Rosano et al., 2012). The functional brain characteristics of such individuals is less clear, as greater PFC activation during memory encoding has been associated with both previous stability (Pudas et al., 2013) and prior decline in memory performance (Persson et al., 2006). Cognitive stability prior to MRI scanning also does not ensure subsequent continued stability, so brain characteristics must be associated with longitudinal cognition assessed after baseline MRI acquisition to evaluate these brain metrics as markers of future cognitive stability.

Here, we aimed to establish the subsequent cognitive trajectories of groups defined on multi-modal baseline brain profiles predicted to be associated with superior cognition. The three groups proposed in the previous chapter reflect a snapshot of cognitive and brain characteristics at time of scan, intended to capture divergent

trajectories of cognitive ageing that have started before baseline assessment. The 'maintainer' and 'adapter' brain profiles are proposed to reflect the relative avoidance or adaption to age-related brain changes respectively, predicted to be associated with better cognitive performance than the 'decliner' profile, thought to capture previous neural and cognitive declines. These different trajectories of cognitive and brain ageing are expected to continue after baseline assessment, with 'maintainers' continuing to maintain cognitive performance, and 'decliners' continuing to decline, whilst 'adapters' may retain a level of cognitive performance, but subsequently experience cognitive decline when adaptive processes become overwhelmed (Park & Reuter-Lorenz, 2009). Investigating the subsequent longitudinal cognitive performance of these groups will not only help to validate these predictions, but may also provide markers to identify and stratify older adults based on their risk of subsequent cognitive decline.

The primary objective of this chapter was to establish the longitudinal cognitive trajectories associated with baseline brain profiles predicted to support superior cognitive ageing. To achieve this, we utilised data from a cohort of healthy older adults who underwent repeat neuropsychological testing and MRI scanning approximately four years after initial baseline assessment. Longitudinal cognitive performance was compared between 'maintainer', 'adapter' and 'decliner' groups identified using baseline brain structure and function, proposed in Chapter 4. As the longitudinal cohort in this chapter had a smaller sample than used in the previous chapter, we modified the group identification procedure to maximise the sample size for each identified groups. We predicted that 'maintainers' would demonstrate

the least subsequent cognitive decline, and 'decliners' would exhibit the greatest cognitive decline. 'Adapters' were predicted to show cognitive change intermediate to 'maintainers' and 'decliners', reflecting temporary preservation of cognitive abilities, but subsequent cognitive decline when compensatory processes are overwhelmed. However, the results of the previous chapter suggested higher RS might not benefit cognition, in which case 'adapters' would show a declining cognitive trajectory, similar or worse than 'decliners'. We also compared cross-sectional cognitive performance between groups to compare results to those from the previous chapter.

5.2. Methods

5.2.1 Participants

Participants for this study were recruited from a total of 138 participants who took part in one of two studies conducted in 2012-2013 (details of the original studies are included in *Appendix 1.2*). Inclusion criteria at baseline included: 60+ years of age, fluent English speaking, no psychoactive medication, ≥26 MMSE score, and no previous diagnosis of cognitive impairment.

After an average of 4.0 years (33-59 months), 79 participants were recruited to the follow-up study. The only inclusion criterion for the follow-up study was participation in either of the baseline studies. Of the 59 not enrolled in the follow-up study, 44 did not respond to the invitation to take part, 2 were deceased, and 13 declined to take part due to ongoing health problems, having moved away from the area, or no longer being interested in participating in research. Of the 79 older adults

enrolled, 53 had participated in the Cognitive Health in Ageing (CHA) study and 26 had participated in the Exercise study. All participants provided written informed consent, and ethical approval for the study was obtained from the University of Oxford Central University/Medical Sciences Division Interdisciplinary Research Ethics Committee (R47658/RE001).

5.2.2 Data acquisition

5.2.2.1 Baseline MRI acquisition

At baseline, participants from both cohorts completed a multi-modal 3T MRI scanning session.

CHA study: Participants were scanned on the 3T Siemens Magnetom Trio (Siemens, Erlangen, Germany) at the OCMR centre, using a 32-channel head coil. A high-resolution T1-weighted image was acquired using a MPRAGE sequence (parameters detailed in *Appendix 1.2*). An EPI resting-state scan was acquired whilst participants were asked to lie in dimmed light with their eyes open, blink normally and not fall asleep (parameters detailed in *Appendix 1.2*). CHA participants only completed MRI scanning once, on completion of a computer training intervention that was not found to have any effect on brain structure or resting-state function (*unpublished*).

Exercise study: Participants were scanned on the 3T Siemens Magnetom Verio (Siemens, Erlangen, Germany) at the FMRIB centre, using a 32-channel head coil. A high-resolution T1-weighted image was acquired using a multi-echo sequence (parameters detailed in *Appendix 1.2*). A multi-band resting-state scan was acquired

whilst participants were asked to lie in dimmed light with their eyes open, blink normally and not fall asleep (parameters detailed in *Appendix 1.2*). Exercise participants completed MRI scanning before and after an exercise intervention. As exercise interventions have been shown to have short-term effects on brain structure (e.g. Thomas et al., 2012), the pre-intervention MRI scans have been used for this analysis.

5.2.2.2 Longitudinal cognitive assessment

At baseline, participants from both cohorts completed the same neuropsychological battery that assessed a range of cognitive domains, including *global cognition* (Montreal Cognitive Assessment, MoCA; Nasreddine et al., 2005), *visual copying and recall* (Rey Complex Figure Test, RCF; Meyers & Meyers, 1995), *verbal learning and recall* (Hopkins Verbal Learning Test, HVLT-R; Brandt & Benedict, 2001), *short-term memory* (Digit Span forward, Wechsler, 2008), *working memory* (Digit Span backwards, Digit Span sequential; Wechsler, 2008), *executive functions* (Digit Coding; Wechsler, 2008), *fluency* (Verbal fluency, Nasreddine et al., 2005; Category fluency; Hsieh et al., 2013), *visual attention and task switching* (Trail Making Test, TMT; Lezak et al., 2004), and *premorbid IQ* (Test of Premorbid Function, TOPF; Wechsler, 2009). Participants from both studies completed the cognitive assessment pre- and post-training. Data from the post-training cognitive assessment are used here to minimise learning effects. Change scores for pre-to-post training cognitive assessments from the baseline studies are illustrated in *Appendix Figure 5.A*, and demonstrate similar change across participants and cohorts.

In the follow-up study, participants repeated the same neuropsychological assessment battery. Alternative versions of tests were used, where available.

5.2.2.3 Additional measures

APOE genotype was determined using saliva samples collected using Oragene DNA Genotek system (DNA Genotek, Ottawa, Canada). DNA extraction and genotyping was performed by LGC Genomics using a TaqMan SNP genotyping assay.

5.2.3 Definition of groups

Participants were divided into 'maintainer', 'adapter' and 'decliner' groups based on their baseline T1-derived GM volume and RS functional connectivity. Baseline MRI data were incomplete for four participants (all from the CHA study) due to claustrophobia (N=2), missed scan due to illness (N=1), and technical problems (N=1). Therefore the final sample consisted of 75 participants. There was no significant difference in baseline age, years of education, baseline MoCA or follow-up period between those with complete imaging data (N=75) and those with missing data (N=4).

5.2.3.1 MRI pre-processing

Imaging data were analysed using FSL tools (FMRIB's Software Library, http://fsl.fmrib.ox.ac.uk/; Smith et al., 2004). As the two baseline cohorts were scanned using different scanners and sequences, data for the two cohorts were pre-processed separately, but following the same general process described below. Details of the cohort-specific pre-processing are included in *Appendix 5.*

Structural images: Brain-extracted T1 images were segmented using FAST (Zhang et al., 2001) to create PVEs for GM, WM and CSF. GM volume was extracted within the structural ROI defined from an external old vs. young VBM analysis (described in Chapter 4.2.3.3 ROI definition; see *Figure 4.2*). A binary mask of the structural ROI was registered to each individual's T1 structural scan using non-linear registration (FNIRT) itialised with linear registration (FLIRT) with 12 DOF. GM volume within the registered ROI was extracted from the GM PVE resulting from FAST, and normalised by whole brain volume (sum of GM, WM, CSF PVEs).

Resting-state fMRI: Single-subject data were pre-processed using motion correction, brain extraction, high pass temporal filtering with a cut-off of 100s and B0 unwarping with fieldmaps, and decomposed into a set of spatially independent components using FSL's MELODIC tool (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/MELODIC). Pre-processed data were denoised using FIX (Salimi-Khorshidi et al., 2014; Griffanti et al., 2014). 'Cleaned' data were registered to the MNI standard space using BBR (Greve & Fischl, 2009) and FNIRT (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FNIRT), and then spatially smoothed. Group-ICA components were identified separately for each baseline cohort, by temporal concatenation of pre-processed images into a single 4D file then decomposition into 25 components using group-ICA. Artefactual group-level components were identified and merged with the frontal RSN used to defined groups in the Chapter 4 (see *4.2.3.1 Resting-state fMRI*) to create a 4D file entered into dual regression to derive time courses and subject-specific spatial maps for each input component. For each subject, the mean connectivity within the functional ROI

(described in Chapter 4.2.3.3 ROI definition; see *Figure 4.2*) was extracted from the subject-specific spatial maps derived from dual regression.

5.2.3.2 Classification of groups

'Maintainer', 'adapter' and 'decliner' groups were identified in each of the two baseline cohorts separately to avoid the different baseline acquisition parameters biasing group definition. For each cohort, the median GM volume within the structural ROI and median RS coherence within the functional ROI were calculated. 'Maintainers' were identified based on GM greater than the median, 'adapters' were identified as GM less than the median and RS greater than the median, whilst 'decliners' were identified as GM and RS less than the median (see *Figure 5.1*).

5.2.4 Statistical analysis

Demographical information was compared between the baseline cohorts and identified groups using independent t-tests and one-way ANOVA for continuous data and chi-square tests for categorical data. Cross-sectional neuropsychological scores were compared between identified groups using one-way ANOVA. Significant main effects were investigated using post-hoc pairwise comparisons with a Bonferroni procedure to control for family-wise error. Where Levene's test of homogeneity of variance was significant, Brown-Forsythe's F and *p* statistics are reported and Games-Howell post-hoc comparison correction was used. Kruskal-Wallis tests were used for non-normally distributed continuous data.

Longitudinal neuropsychological scores were compared between groups using repeated measures ANOVA, with 'time' (baseline, follow-up) as a within-subject

factor and 'group' ('maintainer', 'adapter' and 'decliner') as a between-subject factor. The 'group-by-time' interaction was the primary outcome of interest, to indicate between-group differences in cognitive change over time. Cognitive change scores between baseline and follow-up were also calculated (time 2 minus time 1 scores) and compared between groups using one-way ANOVA. One participant (decliner) with missing baseline cognitive data was not included in these analyses.

Baseline, follow-up and change scores were inspection for normality via visual inspection of plots and relevant statistics. All statistical analyses were conducted in SPSS (SPSS Inc., Chicago, IL.).

5.3. Results

5.3.1 Sample characteristics

In the sample of 75, the mean age at baseline was 67.5 years (SD=6.2) and the mean follow-up period was 4.0 years (SD=0.4). Between CHA and Exercise cohorts, there were no differences in age or MoCA score, either at baseline or follow-up, and no difference in gender or presence of APOE-ε4 allele. However, the CHA sample had significantly more years of education [$t(73)=2.44$, $p=0.017$, $d=0.61$] and higher estimated IQ [$t(73)=2.03$, $p=0.046$, $d=0.49$], whilst the exercise sample had significantly longer follow-up period [$t(72)=-5.36$, $p<0.001$, $d=1.33$] (see *Table 5.1*).

5.3.2 Group identification and characteristics

As shown in *Figure 5.1*, the group identification procedure resulted in 37 'maintainers' (24 CHA, 13 exercise), 18 'adapters' (13 CHA, 5 exercise), and 18

'decliners' (10 CHA, 8 exercise). Two participants (both CHA) fell at the median so were not included in any group. The demographics for the 73 categorised participants were largely unchanged (see *Appendix Table 5.A*), as were the comparisons between baseline cohorts, although the difference in estimated IQ between CHA and exercise groups at baseline was no longer significant (p=0.06).

Table 5.1. **Demographics of total sample, and shown by baseline cohort**

	Total sample (N=75)	CHA baseline (N=49)	Exercise baseline (N=26)	*p*
Follow-up period, yrs	4.0 (0.4)	3.9 (0.3)	4.3 (0.3)	**<0.001**
Age at baseline	67.5 (6.2)	67.2 (6.4)	67.8 (5.9)	0.70
Age at follow-up	71.9 (6.2)	71.7 (6.4)	72.4 (6.2)	0.21
MoCA at baseline	27.6 (2.1)	27.3 (2.2)	28.0 (1.8)	0.60
MoCA at follow-up	26.3 (2.1)	26.4 (2.2)	26.2 (2.0)	0.74
Years of education	15.8 (3.6)	16.5 (3.6)	14.4 (3.2)	**0.02**
Females, N (%)	43 (57.3%)	28 (57.1%)	15 (57.7%)	1.00
APOE*, ε4-carriers (%)	21 (28.8%)	14 (29.2%)	7 (28.0%)	0.89
TOPF-estimated IQ	113.6 (7.3)	114.8 (6.4)	111.3 (8.4)	**0.046**

Values represent mean(SD) unless otherwise stated. *Abbreviations*: CHA – cognitive health in Ageing; MoCA – Montreal Cognitive Assessment; APOE - apolipoprotein E; TOPF – Test of Premorbid Function; IQ – intelligence quotient. *APOE genotype unavailable for 2 participants (1 CHA, 1 exercise).

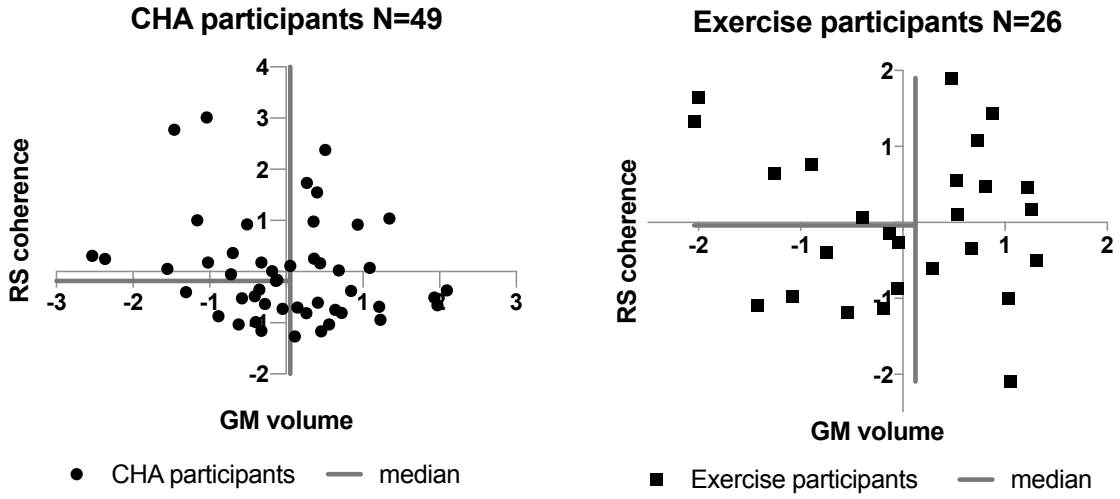


Figure 5.1. **Brain volume plotted against frontal resting-state function in healthy older adults, shown by baseline cohort. Brain volume represents grey matter volume within the age-affected ROI normalised by whole brain volume and brain function is functional connectivity from frontal component within the age-affected ROI. Dots/squares represent each individual participant, and the grey lines represent the median GM and RS. GM and RS values were z-scored for illustrative purposes.**

Between the three groups, there was no difference in years of education, APOE status, estimated IQ or MoCA score either at baseline or follow-up (see *Table 5.2*). However, there was a significant difference in age between groups, both at baseline [$F(2, 72)=9.27$, $p<0.001$, $\eta^2=0.21$] and follow-up [$F(2, 72)=8.53$, $p<0.001$, $\eta^2=0.20$], with 'adapters' significantly older than both 'maintainers' and 'decliners' at both time points. There was also a significant difference in gender distribution between groups [χ^2 $(2, 73)=18.11$, $p<0.001$], with a greater number of female 'maintainers' compared to both 'adapters' [$\chi^2(1, 55)=17.77$, $p<0.001$] and 'decliners' [$\chi^2(1,$

55)=5.67, p=0.02]. There was no significant difference in gender distribution between 'adapters' and 'decliners' (p=0.08).

Table 5.2. **Demographical information between maintainer, adapter and decliner groups**

	Maintainer (N=37)	**Adapter (N=18)**	**Decliner (N=18)**	***p***
Follow-up period, yrs	4.0 (0.4)	4.0 (0.3)	4.0 (0.4)	0.71
Age at baseline	65.6 (5.1)	72.5 (6.4)	66.4 (5.9)	**<0.001**
Age at follow-up	70.2 (5.2)	76.8 (6.4)	70.7 (6.1)	**<0.001**
MoCA at baseline	28.0 (2.1)	27.5 (1.9)	27.0 (2.2)	0.27
MoCA at follow-up	26.9 (2.2)	26.2 (2.2)	25.7 (1.6)	0.10
Years of education	15.8 (3.2)	14.9 (4.0)	16.6 (4.1)	0.41
Females, N (%)	30 (81.1%)	4 (22.2%)	9 (50.0%)	**<0.001**
APOE*, ε4-carriers (%)	9 (24.3%)	7 (38.9%)	4 (22.2%)	0.41
TOPF-estimated IQ	113.1 (7.0)	114.1 (8.3)	113.6 (7.6)	0.90

Values represent mean (SD) unless otherwise stated. *Abbreviations*: CHA – cognitive health in Ageing; MoCA – Montreal Cognitive Assessment; APOE - apolipoprotein E; TOPF – Test of Premorbid Function; IQ – intelligence quotient. *APOE genotype unavailable for 2 participants (1x adapter, 1x decliner).

5.3.3 Cognition

5.3.3.1 Cross-sectional cognitive performance

Cross-sectional baseline cognitive scores at time of scan were compared between groups to replicate the cross-sectional cognitive comparison at time of scan in the previous chapter. One-way ANOVA produced no significant between-group differences for any of the cognitive measures tested (see *Table 5.3*). Controlling for baseline cohort and gender did not alter results. For those with non-normal

distributions, non-parametric Kruskall-Wallis tests did not produce any significant group differences.

Cross-sectional comparisons of cognitive scores at follow-up with one-way ANOVA were also non-significant, although there was a trend for an effect of group on HVLT recognition [$F(2, 38.8)=2.67$, $p=0.08$, $\eta^2=0.09$], verbal fluency [$F(2, 70)=2.45$, $p=0.09$, $\eta^2=0.07$], TMT A [$F(2, 70)=2.99$, $p=0.06$, $\eta^2=0.08$] and TMT B time [$F(2, 56.0)=2.80$, $p=0.07$, $\eta^2=0.07$]. Post-hoc comparisons were non-significant, except for HVLT recognition where 'adapters' performed significantly worse than 'maintainers' only [$p=0.04$, $d=0.82$], and TMT B where 'decliners' performed significantly better than 'adapters' [$p=0.04$, $d=0.84$]. Non-significant post-hoc comparisons indicated 'adapters' performed worse on verbal fluency than 'maintainers', whilst 'decliners' had better for TMT A performance than 'maintainers' and 'adapters'. It should be noted that TMT performance is measured in 'time to complete the task', so a lower value represents better performance.

For measures with a non-normal distribution, non-parametric Kruskall-Wallis tests produced a marginally significant main effect of group on *HVLT recognition* [$H(2, 73)=6.20$, $p=0.045$] and *TMT A score* [$H(2,73)=6.36$, $p=0.042$], and trend results for *MoCA* [$H(2, 73)=4.95$, $p=0.08$], *TMT B* [$H(2, 73)=4.96$, $p=0.08$], and *HVLT delayed* [$H(2, 73)=4.93$, $p=0.09$]. Post-hoc comparisons paralleled those above, with poorer HVLT recognition performance in 'adapters' compared to 'maintainers' ($p=0.04$), and a trend for better TMT A performance in 'decliners' compared to both 'maintainers' and 'adapters'.

Table 5.3. **Neuropsychological scores between identified groups at baseline and follow-up**

	Time 1 - Baseline						
	Mean (SD)				**ANOVA**		
Measure	**Total**	**M**	**A**	**D**	**F**	***p***	**η^2**
MoCA	27.6 (2.1)	28.0 (2.1)	27.5 (1.9)	27.0 (2.2)	1.34	0.27	0.04
Category fluency	24.4 (5.5)	24.9 (5.9)	22.7 (4.4)	25.1 (5.3)	1.23	0.30	0.03
Verbal fluency	17.7 (4.9)	18.6 (4.6)	16.3 (4.9)	17.0 (5.2)	1.64	0.20	0.05
TMT A	26.2 (6.1)	25.7 (7.2)	27.2 (4.1)	26.0 (5.5)	0.36	0.70	0.01
TMT B	56.4 (21.1)	53.4 (21.3)	62.7 (24.6)	56.1 (16.0)	1.19	0.31	0.03
TMT B-A	30.4 (19.0)	28.0 (17.6)	35.5 (24.0)	30.0 (15.4)	0.95	0.39	0.03
RCF recognition	9.2 (1.7)	9.5 (1.8)	8.9 (1.1)	9.0 (2.1)	1.00	0.37	0.03
HVLT total	24.2 (5.3)	25.2 (5.2)	23.2 (5.8)	22.9 (5.2)	1.46	0.24	0.04
HVLT learning	3.6 (1.7)	3.5 (1.5)	3.4 (1.9)	3.9 (2.1)	0.44	0.65	0.01
HVLT delay	8.3 (3.0)	8.8 (2.8)	7.9 (3.2)	7.8 (3.4)	0.85	0.43	0.02
HVLT retention	84.3 (22.8)	87.2 (19.5)	83.3 (24.5)	79.0 (27.8)	0.76	0.47	0.02
HVLT recognition*	10.8 (1.4)	11.1 (1.1)	10.4 (1.7)	10.4 (1.7)	1.83	0.17	0.06
Digit forward	11.3 (2.3)	11.2 (2.1)	11.6 (2.5)	11.1 (2.6)	0.17	0.84	0.01
Digit backward*	9.7 (2.1)	9.5 (2.1)	10.4 (2.6)	9.5 (1.5)	1.13	0.33	0.03
Digit sequential*	9.1 (1.7)	9.1 (1.6)	8.7 (2.4)	9.4 (1.1)	0.68	0.51	0.02
Digit coding	69.0 (12.7)	68.7 (13.8)	67.0 (10.7)	71.6 (12.5)	0.59	0.56	0.02
	Time 2 - Follow-up						
	Mean (SD)				**ANOVA**		
Measure	**Total**	**M**	**A**	**D**	**F**	***p***	**η^2**
MoCA	26.4 (2.1)	26.9 (2.2)	26.2 (2.2)	25.7 (1.6)	2.38	0.10	0.06
Category fluency	23.4 (6.0)	24.2 (6.5)	21.2 (4.2)	23.9 (6.2)	1.70	0.19	0.05
Verbal fluency	19.1 (5.1)	19.8 (5.5)	16.8 (5.0)	19.9 (3.9)	2.45	0.09	0.07
TMT A	25.9 (8.1)	26.9 (8.2)	27.7 (9.2)	22.0 (5.3)	2.99	0.06	0.08
TMT B*	55.1 (22.1)	56.0 (24.5)	61.9 (22.1)	46.4 (13.6)	2.80	0.07	0.07
TMT B-A*	29.2 (19.0)	29.0 (19.8)	34.3 (23.2)	24.4 (10.4)	1.29	0.29	0.03
RCF recognition	8.2 (1.8)	8.2 (1.7)	8.0 (2.1)	8.4 (2.1)	0.20	0.82	0.01
HVLT total	25.9 (5.2)	26.9 (4.9)	23.9 (5.6)	25.7 (5.0)	2.00	0.14	0.05
HVLT learning	3.6 (1.6)	3.7 (1.7)	3.4 (1.5)	3.6 (1.8)	0.22	0.81	0.01
HVLT delay	8.4 (3.8)	9.3 (3.4)	7.2 (3.9)	7.9 (4.1)	2.20	0.12	0.06
HVLT retention	79.2 (30.6)	85.8 (26.4)	72.0 (33.6)	72.9 (34.1)	1.77	0.18	0.05
HVLT recognition*	10.7 (1.5)	11.1 (1.0)	10.1 (1.6)	10.6 (2.0)	2.67	0.08	0.09
Digit forward	11.5 (2.0)	11.4 (2.0)	11.6 (2.1)	11.8 (1.9)	0.21	0.81	s
Digit backward*	9.5 (2.3)	9.7 (2.7)	9.6 (2.1)	8.9 (1.2)	0.85	0.43	0.02
Digit sequential	9.2 (1.9)	9.5 (2.0)	8.7 (2.1)	9.3 (1.5)	0.90	0.41	0.03
Digit coding	63.3 (12.0)	63.2 (12.1)	61.7 (11.3)	65.1 (13.0)	0.36	0.70	0.01

Abbreviations: M – maintainer; A – adapter; D – decliner; F – F statistic; p – p statistic; MoCA – Montreal Cognitive Assessment; TMT – Trail Making Test; RCF – Rey Osterreith Complex Figure Test; HVLT – Hopkins Verbal Learning Test; *indicates F and p values from Brown-Forsythe test.

5.3.3.2 Longitudinal cognitive analysis

Spaghetti plots illustrate the trajectory of cognitive performance for each individual (*Figure 5.2*) and are also shown by baseline 'maintainer', 'adapter' and 'decliner' groups in *Appendix Figure 5.B.* These figures demonstrate substantial variability in longitudinal performance at the individual level, with some individuals declining, some improving and others remaining stable on each measure.

Repeated measures ANOVA revealed a significant main effect of 'time' for MoCA, category fluency, RCF recognition, digit coding, verbal fluency and HVLT immediate recall (see *Table 5.4* for details). This reflected a significant decline over time across the whole sample on MoCA, category fluency, RCF recognition, digit coding but a significant improvement on verbal fluency and HVLT immediate recall. There was also a trend for significant decline over time with HVLT retention (p=0.08). There was no significant main effect of time for TMT A, B or B-A, for forward, backward or sequential digit span, or for HVLT learning, delayed recall or recognition (*p*s >0.1). The average longitudinal cognitive trajectory for the entire sample is shown by neuropsychological measure in *Figure 5.3,* and by MRI-based groups in *Figure 5.4.*

The main outcome of interest was the group-by-time interaction, which was significant for only TMT A performance [$F(2,69)=3.63$, $p=0.03$, $\eta^2=0.10$]. As can be seen in *Figure 5.4*, this interaction reflects relatively stable TMT A performance in 'maintainers' and 'adapters', but longitudinal decrease in TMT A completion time in the 'decliner' group, representing a significant improvement in 'decliners'

performance over time. Group-by-time interaction effects for all other cognitive measures were non-significant.

There was a significant main effect of group for HVLT recognition [$F(1,69)=3.87$, $p=0.03$, $\eta^2=0.10$], reflecting poorer performance by 'adapters' compared to 'maintainers' across all time points [$p=0.046$, mean difference (*md*)=0.87]. There were no other significant main effects of group. Detailed statistical results for the longitudinal analysis are included in *Table 5.4.*

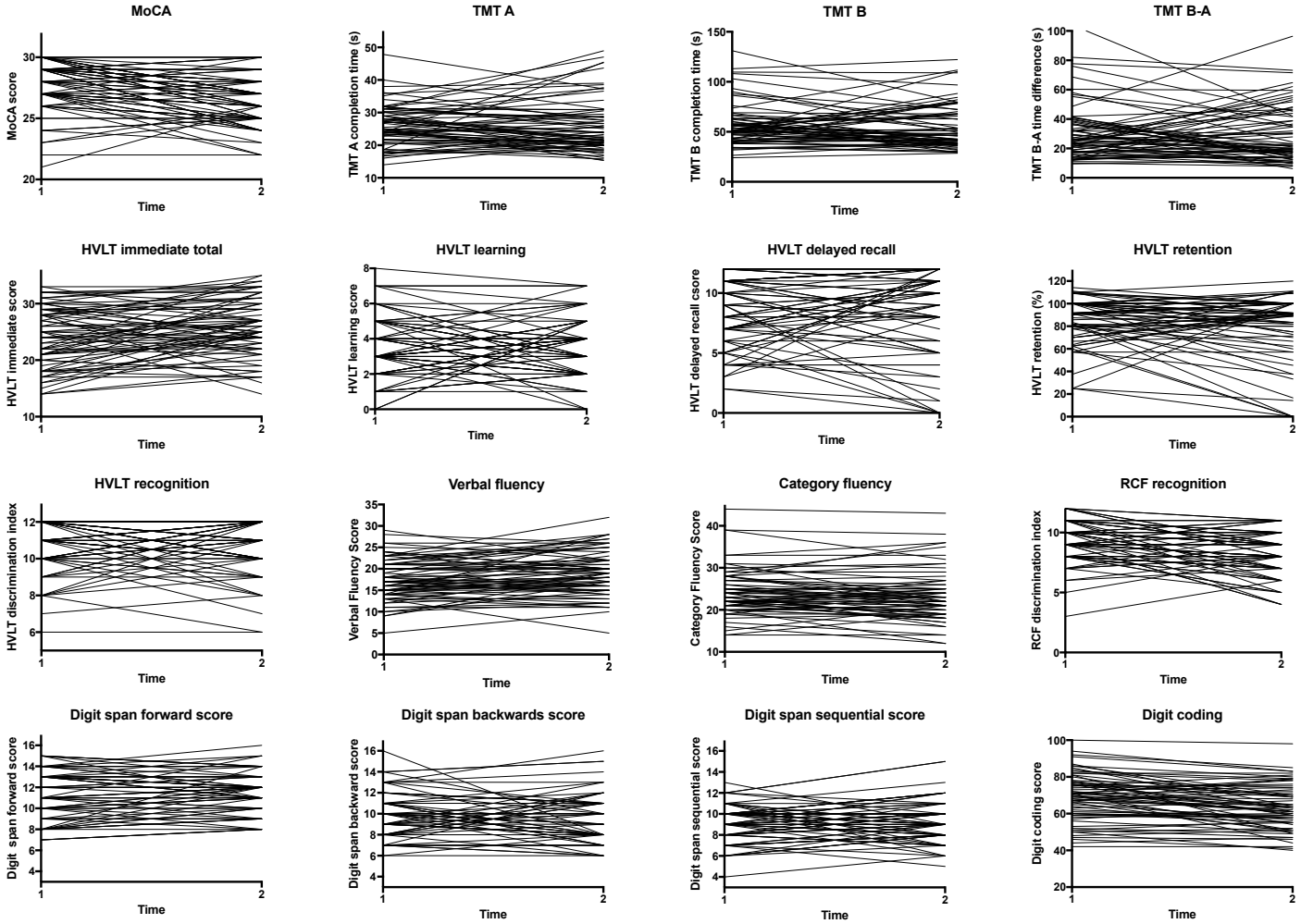


Figure 5.2. **Spaghetti plots showing the trajectory of longitudinal cognitive performance for each participant.**

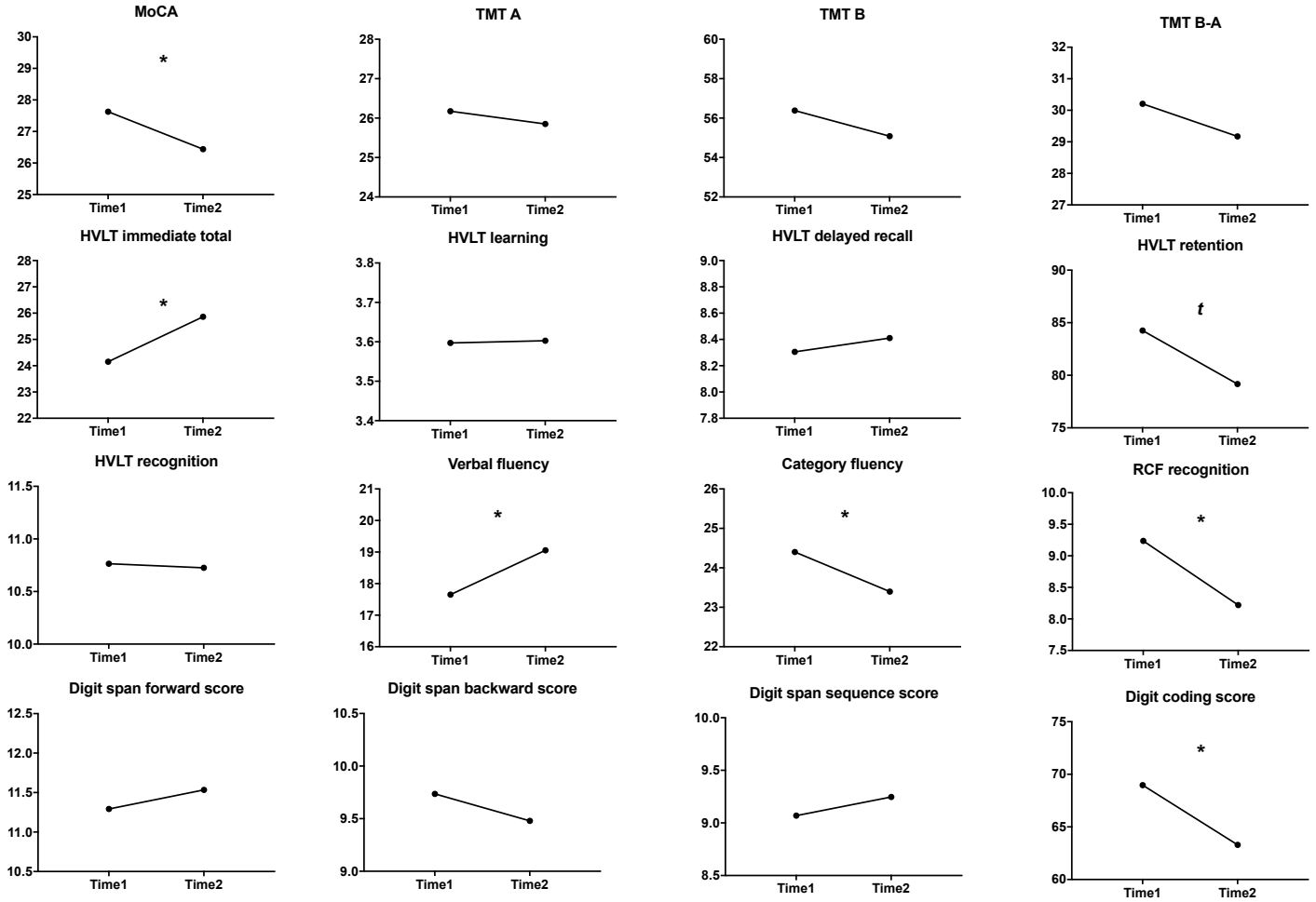


Figure 5.3. **Average longitudinal trajectory of neuropsychological performance by cognitive measure across the entire sample.**

* indicates significant main effect of time ($p<0.05$) in repeated measures ANOVA; *t* indicates a trend for effect of time.

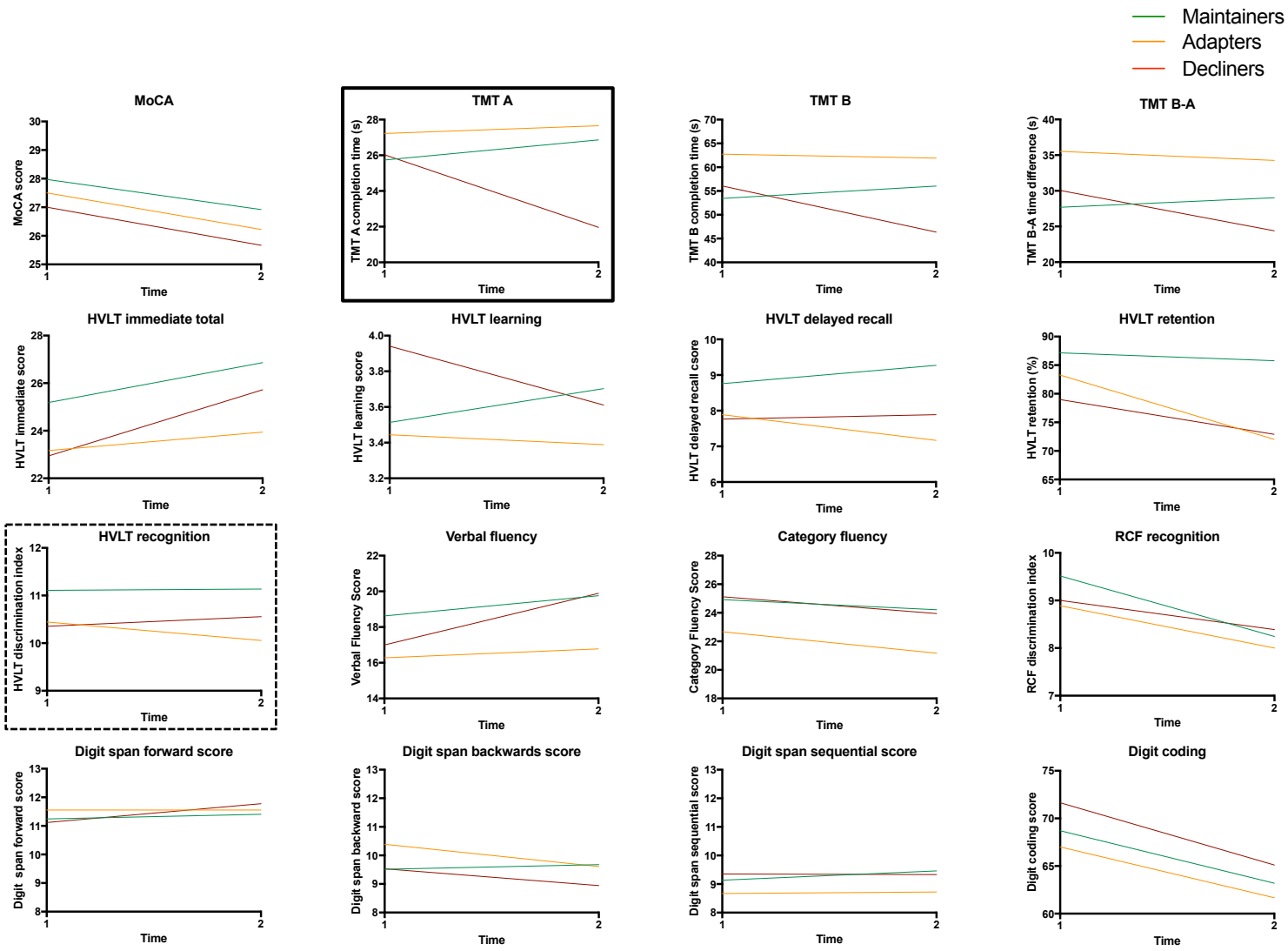


***Figure 5.4*. Mean trajectory of longitudinal cognitive performance for each group.**

The solid black box indicates the significant group-by-time interaction for TMT A performance. The dashed black box indicates the significant main effect of group on HVLT recognition performance. TMT A and B are measured in seconds to complete task, therefore lower represents better performance.

Table 5.4. **Longitudinal cognitive analysis statistical results.**

Cognitive measure	N			Time			Group-by-time			Group			Pairwise - group (*p*)		
	M	A	D	F	*p*	η_p^2	F	*p*	η_p^2	F	*p*	η_p^2	M vs. A	M vs. D	A vs. D
MoCA	37	18	17	19.25	<0.001	0.22	0.08	0.92	<0.01	2.28	0.11	0.06	*ns*	*ns*	*ns*
Category fluency	37	18	17	5.25	0.03	0.07	0.30	0.74	0.01	1.66	0.20	0.05	*ns*	*ns*	*ns*
Verbal fluency	37	18	17	7.79	0.007	0.10	1.43	0.25	0.04	2.16	0.12	0.06	*ns*	*ns*	*ns*
TMT A	37	18	17	1.10	0.30	0.02	3.63	0.03	0.10	1.59	0.21	0.04	*ns*	*ns*	*ns*
TMT B	36	18	17	1.17	0.28	0.02	1.82	0.17	0.05	1.65	0.20	0.05	*ns*	*ns*	*ns*
TMT B-A	35	18	17	0.59	0.45	0.01	0.49	0.62	0.01	1.17	0.32	0.03	*ns*	*ns*	*ns*
RCF recognition	37	18	17	12.68	0.001	0.16	0.57	0.57	0.02	0.54	0.58	0.02	*ns*	*ns*	*ns*
HVLT immediate	37	18	17	5.85	0.02	0.08	0.43	0.65	0.01	2.23	0.12	0.06	*ns*	*ns*	*ns*
HVLT learning	37	18	17	0.09	0.77	<0.01	0.44	0.64	0.01	0.27	0.76	0.01	*ns*	*ns*	*ns*
HVLT delayed	37	18	17	0.02	0.90	<0.01	0.90	0.41	0.03	1.89	0.16	0.05	*ns*	*ns*	*ns*
HVLT retention	37	18	17	3.23	0.08	0.05	0.78	0.46	0.02	1.61	0.21	0.04	*ns*	*ns*	*ns*
HVLT recognition	37	18	17	0.18	0.67	<0.01	0.59	0.56	0.02	3.87	0.03	0.10	*	*ns*	*ns*
Digit forward	37	18	17	1.27	0.26	0.02	0.49	0.61	0.01	0.08	0.92	<0.01	*ns*	*ns*	*ns*
Digit backwards	37	18	17	2.32	0.13	0.03	1.43	0.25	0.04	0.74	0.48	0.02	*ns*	*ns*	*ns*
Digit sequential	37	18	17	0.28	0.60	<0.01	0.22	0.80	0.01	1.04	0.36	0.03	*ns*	*ns*	*ns*
Digit coding	36	18	17	26.31	<0.001	0.28	0.04	0.96	<0.01	0.58	0.57	0.02	*ns*	*ns*	*ns*

Abbreviations: N – number of participants; M - maintainer, A – adapter, D – decliner; F – F statistic; p – p statistic; η_p^2 - partial eta squared; MoCA – Montreal Cognitive Assessment; TMT – Trail Making Test; RCF – Rey Osterreith Complex Figure Test; HVLT – Hopkins Verbal Learning Test; ns – non-significant >0.1; * denotes p<0.05

5.3.3.3 Cognitive change

Change in cognitive performance between baseline and follow-up was computed (see *Table 5.5*) and change scores are displayed by cognitive measure in *Figure 5.5*. Comparison of change scores between groups using one-way ANOVA revealed only one significant main effect of group for change in TMT A [F(2, 69)=3.63, p=0.03, η^2=0.10], reflecting significantly greater change in decliners compared to 'maintainers' [p=0.03, d=0.83], replicating the group-by-time effect from the repeated measure ANOVA. There was no difference in TMT A change scores between 'adapters' and either 'maintainers' [p=1.00] or 'decliners' [p=0.15]. However, the main effect was no longer significant after correcting for multiple comparisons.

Table 5.5. **Change in neuropsychological scores between identified groups at baseline and follow-up**

	Mean (SD)				ANOVA		
Measure	**Total**	**M**	**A**	**D**	**F**	***p***	**η_p^2**
MoCA	-1.15 (2.1)	-1.05 (2.2)	-1.28 (1.7)	-1.24 (2.5)	0.08	0.92	<0.01
Category fluency	-0.94 (3.5)	-0.70 (3.2)	-1.50 (4.4)	-0.88 (3.3)	0.30	0.74	0.01
Verbal fluency	1.38 (4.3)	1.14 (4.1)	0.50 (3.9)	2.82 (4.9)	1.43	0.25	0.04
TMT A	-0.34 (7.3)	1.13 (7.6)	0.43 (8.3)	-4.36 (3.7)	3.63	0.03	0.10
TMT B*	-1.53 (21.4)	2.02 (18.6)	-0.83 (28.0)	-9.80 (17.6)	1.64	0.21	0.05
TMT B-A*	-1.22 (20.6)	0.79 (17.1)	-1.26 (29.1)	-5.44 (16.8)	0.45	0.64	0.02
RCF recognition	-1.03 (2.1)	-1.27 (2.2)	-0.89 (1.9)	-0.65 (2.0)	0.57	0.57	0.02
HVLT total	1.64 (5.4)	1.68 (5.1)	0.78 (5.5)	2.47 (5.9)	0.43	0.65	0.01
HVLT learning	0.00 (2.0)	0.19 (1.9)	-0.06 (2.0)	-0.35 (2.2)	0.44	0.64	0.01
HVLT delay	0.10 (3.2)	0.51 (3.4)	-0.72 (3.0)	0.06 (2.9)	0.90	0.41	0.03
HVLT retention	-4.93 (27.9)	-1.17 (28.3)	-11.24 (28.2)	-6.2 (27.1)	0.80	0.46	0.02
HVLT recognition	-0.06 (1.5)	0.03 (1.3)	-0.39 (1.5)	0.12 (2.0)	0.59	0.56	0.02
Digit forward	0.21 (1.6)	0.16 (1.7)	0.00 (1.7)	0.53 (1.3)	0.49	0.61	0.01
Digit backwards	-0.26 (2.2)	0.16 (2.3)	-0.78 (2.7)	-0.65 (1.2)	1.43	0.25	0.04
Digit sequential*	0.18 (1.9)	0.32 (2.0)	0.06 (2.2)	0.00 (1.3)	0.24	0.79	0.01
Digit coding	-5.77 (8.8)	-5.81 (8.8)	-5.33 (9.2)	-6.18 (8.9)	0.04	0.96	<0.01

Abbreviations: M – maintainer; A – adapter; D – decliner; F – F statistic; p – p statistic; η_p^2 - partial eta squared; MoCA – Montreal Cognitive Assessment; TMT – Trail Making Test; RCF – Rey Osterreith Complex Figure Test; HVLT – Hopkins Verbal Learning Test; * indicates F and p values from Brown-Forsythe test.

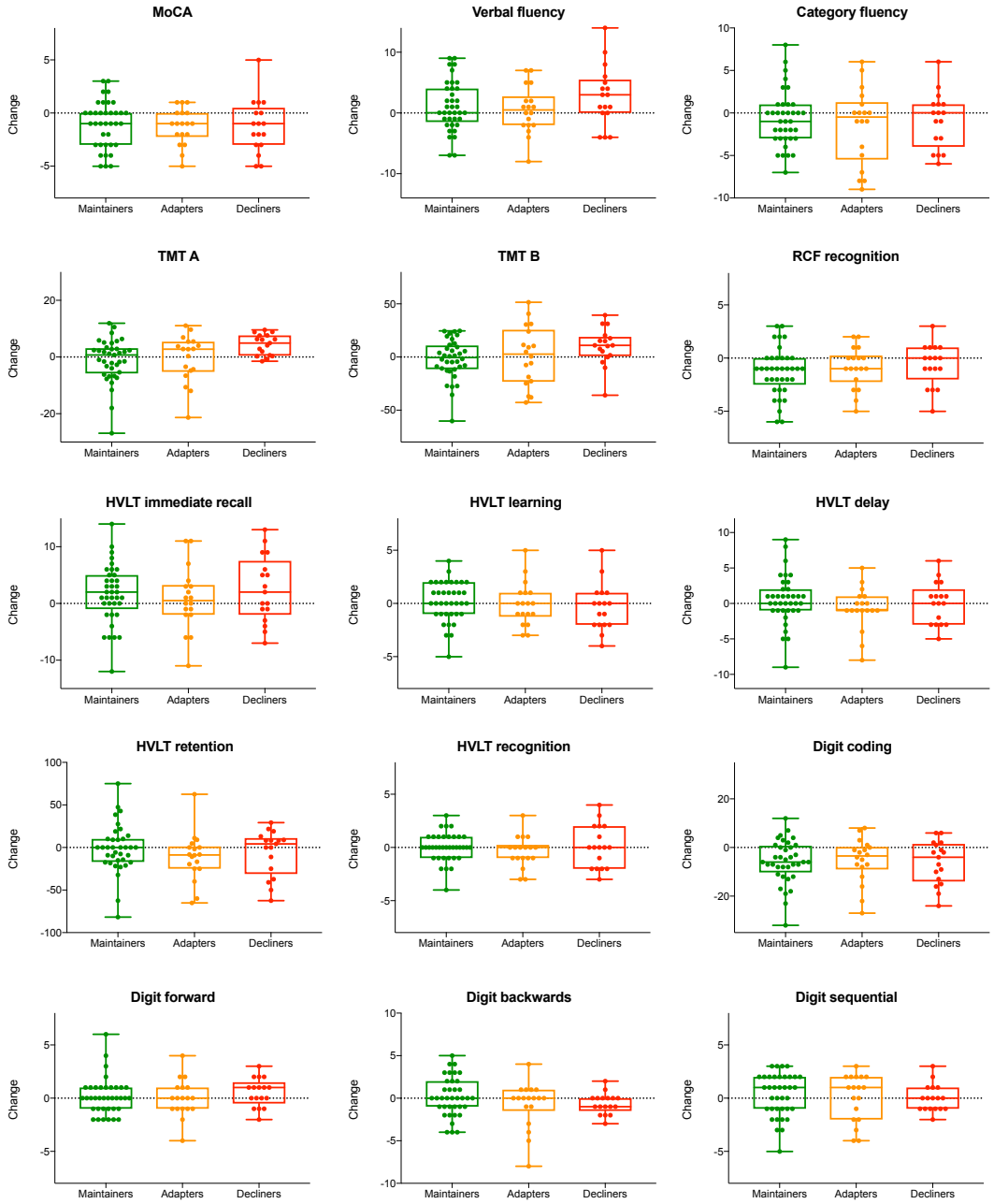


Figure 5.5. **Cognitive change scores shown for each individual participant by group** for each cognitive measure tested. Change scores for TMT A and B were recoded so that negative values represent a decline in performance over time and positive values represent an improvement in performance across all cognitive measures.

5.4. Discussion

The main objective of this chapter was to compare subsequent longitudinal cognitive performance between group defined on baseline brain profiles. We predicted that 'maintainers' would show the least cognitive change, 'decliners' would decline the most, and change in 'adapters' would be intermediate to the other groups. Using a procedure adapted from the previous chapter, we identified groups based on baseline brain structure and function, but did not observe the predicted differences in trajectories of cognitive performance. Nonetheless, 'adapters' demonstrated worse verbal memory across time points, adding to the suggestion that higher RS in 'adapters' is not associated with 'superior' cognitive performance, based on the results of the previous chapter. At the individual level, the variability in performance over time is striking, which may have implications for group-level results. Limitations in sample size and the availability of only two waves of cognitive assessment must be addressed in future work to build on these findings.

5.4.1 Longitudinal cognitive performance between groups

Contrary to predictions, 'decliners' did not have a particularly negative cognitive trajectory. 'Decliners' even showed significant improvement over time on trail making A performance, e.g. faster connection of numbered circles in ascending order. The additional trend at follow-up for faster trail making B performance (alternating between letters and numbers) suggests a more general improvement in speeded performance. Group-level cognitive trajectories shown in *Figure 5.5* do not indicate a particular improvement by decliners on other cognitive measures, and the significance of the improvement of trail making performance is unclear.

The superior verbal recognition performance by 'maintainers' observed across longitudinal time points parallels the superior longitudinal verbal memory performance by maintainers in Chapter 4. However, the absence of group-by-time interactions does not support the benign cognitive trajectory predicted for 'maintainers'. Nonetheless, the trend for poorer verbal fluency performance by 'adapters' at follow-up is consistent with poorer performance by adapters in Chapter 4. The absence of cross-sectional cognitive differences between groups at time of scan, as observed in the previous chapter, may reflect the smaller sample size in this chapter.

A particularly striking observation is the variability at the individual level in cognitive performance across the two time points. The spaghetti plots in *Figure 5.2* illustrates that improvement, decline and stability in cognitive scores over time is observed across all measures and across baseline levels of performance. On some measures in particular, e.g. HVLT recognition, individuals at each level of baseline performance transition to each possible score at follow-up. Such variability may limit how meaningful the 'average' is for each group, particularly when the sample is small, where individual participants can exert a greater impact on the group-level average.

5.4.2 Identification of groups

We adapted the group identification procedure from the previous chapter due to the smaller sample in this chapter. To maximise the sample in each group, the median GM and RS values were used as thresholds, and were derived from the older adults

themselves rather than a younger reference group. Whilst a median-split is a simple approach, this is the traditional method used to define superior agers based on cognitive performance (e.g. Espeseth et al., 2006; Mok et al., 2016; Persson et al., 2012) and has also been widely used in the ageing literature to subdivide older samples based on structural and functional brain metrics (e.g. Carmelli et al., 2000; Düzel et al., 2011; Hedden et al., 2012; Salami et al., 2012).

This adapted approach affects the assumptions that must be made about the identified groups. For example, those with GM volume above the median GM volume in older adults may still fall below the GM volume that is 'normal' for younger adults. By using within-sample medians to adjust for the different MRI scanners used for the two baseline cohorts, we must also assume that the median in the two groups is roughly equivalent, and there are equal proportions of each of the three brain profile groups in the two cohorts. The small sample sizes here may challenge this assumption. Using the adapted thresholds, the 'maintainer' group will always be larger than the other groups. Furthermore, *Figure 5.5* reveals variability in cognitive change scores within groups, particularly for 'maintainers', which may reflect the inclusion of individuals with extreme higher and lower RS metrics in the modified approach.

Nonetheless, the identified groups resemble those identified using the original procedure in the previous chapter. For example, a greater number of participants were identified as 'maintainers', and a larger proportion of 'maintainers' were female than compared to other groups. The poorer cognitive performance of

'adapters' identified with the modified procedure resembles cognitive performance of adapters in Chapter 4. Additionally in only this chapter, 'adapters' were significantly older than other groups, consistent with evidence of increasing frontal activation with age (e.g. Beason-Held et al., 2008; Davis et al., 2008; Gutchess et al., 2005; Nielson et al., 2002; Spreng et al., 2010).

5.4.3 Strengths and limitations

This retrospective longitudinal study provided an opportunity to investigate the longitudinal trajectories of different brain profiles. The range of domains assessed in the neuropsychological battery provides a number of measures on which to assess cognitive change, whereas many previous studies have only used a single measure of global cognition, which can obscure individual differences (Wilson et al., 2002a). Furthermore, use of cognition measured after rather than before MRI scanning, as in Chapter 4, may have increased sensitivity to detect effects due to increased between-subject variability relating to continued divergence of cognitive ageing processes.

However, there are several limitations that must be taken into account. In relation to the definition of groups, the modified method limits our ability to directly compare findings to the previous chapter. Within-sample definition of groups also may not have eliminated all possible sources of bias related to the different MRI acquisition at baseline. The small sample size may have limited statistical power to detect subtle effects between groups, suggested by the moderate-to-large effect sizes observed for marginally significant group differences (Cohen, 1988). Cognitive measures have

also been shown to have varying sensitivity to cognitive change at different levels of performance (Proust-Lima et al., 2007), which may have affected estimates of cognitive change here. Furthermore, the participants who returned for repeated testing may not be representative of the general population, and individuals who experienced a more precipitous cognitive decline may have been more likely to dropout.

Cognition was only assessed at two time points, which can yield unreliable estimates of cognitive change at the individual level (Wilson et al., 2002a). Change scores may also be affected by regression-to-the-mean, where extreme high or low scores at first assessment due to measurement error tend to be less extreme at second assessment (Salthouse, 2012). Having only two time points also means only linear changes in cognition over time can be examined, whilst some age-related cognitive changes have been shown to be non-linear, e.g. more rapid declines in older age (e.g. Rönnlund et al., 2005). Further repeated assessments are required to investigate differences in the rate of cognitive decline between groups. Finally, whilst we tried to minimise practice effects on cognitive scores, the significant improvement across all participants on verbal fluency and immediate verbal recall suggests practice effects may still have influenced results.

5.5. Conclusions

Investigating the cognitive consequences of baseline brain metrics in healthy older adults is key to validate the association of these brain profiles with superior cognitive ageing and enable identification of older adults who at baseline are not cognitively

different to their peers but are at risk of subsequent poorer cognition. The aim of this chapter was to compare longitudinal cognitive performance between groups based on baseline brain profiles to establish the association of these brain profiles with stable or declining trajectories of cognitive performance. Variability at the individual level in cognitive performance over time was striking, but the predicted group differences in longitudinal cognitive performance were not observed. Findings may have been influenced by the small sample size, the adapted procedure to identify groups, and psychometric artifacts, such as regression-to-the-mean. As comparison of multi-modal MRI metrics revealed neural differences between groups in Chapter 4, in the next chapter I compared brain metrics acquired several years after baseline assessment between the groups identified in this chapter to further probe the long-term consequences of these baseline brain profiles.

Chapter 6. Neural trajectories of variability in cognitive ageing

In the previous chapters, I examined cognitive performance before (Chapter 4) and after (Chapter 5) group definition, as well as at time of scan (Chapters 4 and 5), to probe whether cognition differs between groups and changes over time in the expected manner. In addition to anticipated cognitive changes, the brain characteristics of these groups are also expected to change over time. The baseline brain information used to define 'maintainer', 'adapter' and 'decliner' groups captures only a single snapshot of characteristics that are assumed to reflect continuous changes with age. Examining these brain characteristics several years after baseline definition of groups can provide additional evidence for the significance of baseline group membership for upcoming trajectory of ageing. In this chapter, I compared structural and functional brain metrics acquired several years after baseline scanning to establish the long-term consequences for the brain of baseline group membership.

6.1. Introduction

Over time, maintainers, who are proposed to have avoided age-related change in the brain at baseline scan, may subsequently experience some age-related changes but still relatively maintain the integrity of the brain and remain 'youthful' compared to other older adults (Nyberg et al., 2012). In contrast, continuation of the age-related change proposed to have occurred prior to baseline definition of adapters, based on lower GM and higher RS, may eventually overwhelm the adaptive capacity to cope with such deterioration, leading to decline in compensatory brain function

(Park & Reuter-Lorenz, 2009), and resulting in the 'decliner' profile originally proposed in Chapter 4. Therefore, it is possible that adapters and decliners form a continuum, where adapters become decliners after a threshold of age-related decline is passed. In this case, several years after group definition, decliners would show the poorest brain health, and adapters would show a reduction in RS activity.

However, in the previous chapters, whilst 'maintainers' have consistently shown the predicted more favourable cognitive and brain outcomes compared to the other groups, it is not yet clear that an 'adapter' profile is associated with a more optimal trajectory of ageing than a 'decliner' profile. In the previous chapters, 'adapters' have demonstrated poorer outcomes than predicted, e.g. worse cognitive performance compared to 'maintainers' in two separate cohorts (Whitehall-II in Chapter 4 and Cognitive Health/Exercise in Chapter 5). In contrast, the 'decliner' group has not clearly demonstrated the predicted worse outcomes, e.g. no evidence of poorer cognitive performance than adapters in either the Whitehall or the Cognitive Health cohort, and indeed some evidence of better cognitive performance than adapters in both cohorts, despite the highest WMH load in Chapter 4. On this evidence, the lower frontal activation in 'decliners' could be more favourable than the higher activation observed in 'adapters'. Consistent with a more benign interpretation of lower frontal activation, longitudinal imaging studies have associated increases in frontal brain activity over time with declining cognitive performance (Goh et al., 2013; Hakun et al., 2015; Pudas et al., 2018), and stable memory with longitudinal decreases in some regions of frontal activation (Beason-Held et al., 2008).

In this chapter, we aimed to establish the long-term brain characteristics of 'maintainer', 'adapter' and 'decliner' groups by comparing between these groups structural and functional MRI data acquired several years after group definition. We investigated this using the cohort described in Chapter 5, who underwent an MRI scan, in addition to cognitive testing, approximately 4 years after initial baseline assessment. Different MRI scanners were used at baseline and follow-up for logistical reasons, which precluded straightforward longitudinal comparison of time points. However, cross-sectional comparison of brain metrics several years after baseline definition of groups provides information about the relative differences between these groups after several years, and insight into the nature and organization of these brain profile groups. 'Maintainers', 'adapters' and 'decliners' were defined on baseline structural and functional brain metrics, as in the previous chapter, and grey matter volume, white matter integrity and resting-state connectivity at follow-up were compared between these groups. Based on the original predictions of the beneficial nature of the 'adapter' brain profile, we predicted that decliners would show the lowest GM and WM integrity at follow-up, to support the 'decliner' profile as a poorer outcome on a continuum after the 'adapter' profile. In this case, adapters may no longer demonstrate increased RS at follow-up, representing a decline in use of compensatory processes with continued age-related deterioration of the brain (Park & Reuter-Lorenz, 2009). However, if the 'decliner' profile is at least as favourable as 'adapter', as indicated by the results of the previous chapters, then adapters would show the lowest GM and WM integrity

at follow-up, and decliners may show higher RS, representing an increased use of adaptive processes with continued age-related decline.

6.2. Methods

6.2.1 Participants

A sample of 79 participants was recruited as described in the previous chapter (see *5.2.1 Participants*). For inclusion in this chapter, participants must have completed the MRI scan at the follow-up assessment. Fifteen participants (12 CHA baseline, 3 exercise baseline) did not complete the follow-up MRI scan due to illness during the scan (n=1), previous claustrophobia (n=3), and changes in MRI compatibility (n=11). Four of the 15 not scanned at follow-up were also those who did not complete the baseline MRI, and were not included in the previous chapter. Therefore, the sample for these analyses consisted of 64 participants (41 CHA baseline, 23 Exercise baseline). Demographics are reported in *Table 6.1* and are largely unchanged from the previous chapter. Again, the baseline CHA sample had significantly more years of education whilst the exercise sample had a significantly longer follow-up period (see *Table 6.1*). There was no difference in demographics between those scanned (n=64) and not scanned at follow-up (n=15; see *Appendix Table 6.A* for details).

Table 6.1. **Demographics for the total sample, also reported by baseline cohort**				
	Total sample (N=64)	CHA baseline (N=41)	Exercise baseline (N=23)	*p*
Follow-up period, yrs	3.9 (0.3)	3.8 (0.3)	4.2 (0.2)	**<0.001**
Age at baseline	67.4 (6.3)	67.3 (6.6)	67.7 (5.6)	0.81
Age at follow-up	71.8 (6.3)	71.6 (6.6)	72.2 (5.8)	0.72
MoCA at baseline	27.7 (2.1)	27.6 (2.2)	28.0 (1.9)	0.43
MoCA at follow-up	26.5 (2.2)	26.6 (2.2)	26.3 (2.1)	0.65
Years of education	15.7 (3.6)	16.5 (3.6)	14.2 (3.0)	**0.01**
Females, N (%)	36 (56.3%)	24 (58.5%)	12 (52.2%)	0.62
APOE*, ε4-carriers (%)	17 (26.6%)	11 (26.8%)	6 (26.1%)	0.99
TOPF-estimated IQ	113.7 (7.1)	114.9 (5.7)	111.4 (8.9)	0.10

Values represent mean (SD) unless otherwise stated. *Abbreviations*: CHA – Cognitive Health in Ageing; MoCA – Montreal Cognitive Assessment; APOE - apolipoprotein E; TOPF – Test of Premorbid Function; IQ – intelligent quotient. *APOE genotype unavailable for 2 participants (1 CHA, 1 exercise).

6.2.2 Data acquisition

6.2.2.1 MRI

Participants were scanned on the 3T Siemens Prisma (Siemens, Erlangen, Germany) at the Oxford Centre for Human Brain Activity (OHBA), using a 32-channel head coil. The neuroimaging protocol included the following:

Structural MRI: A high-resolution T1-weighted image was acquired using a MPRAGE sequence (TR = 1900ms, TE = 3.97ms, voxel dimensions = 1.0 x 1.0 x 1.0mm).

Resting-state fMRI: A multi-band resting-state scan was acquired whilst participants were asked to lie in dimmed light with their eyes open, blink normally and not fall asleep (TR = 730ms, TE = 34.6ms, voxel dimensions = 2.0 x 2.0 x 2.0mm, multi-band (MB) factor = 8, number of volumes = 825). A high-contrast single-band image was also acquired to improve registration of low-contrast MB images (TR = 730ms, TE =

34.6ms, voxel dimensions = 2.0 x 2.0 x 2.0mm, MB factor = 1, number of volumes = 1), and as well as magnitude and phase fieldmap images for correction of distortions related to B0 field inhomogeneities (TR = 482ms, TE = 4.92/7.38ms, voxel dimensions = 2.0 x 2.0 x 2.0mm).

Diffusion MRI: A diffusion weighted scan with 64 directions and b-value=1500s/mm^2 volumes, along with 5 b-value=0s/mm^2 volumes (TR = 3000ms, TE = 80ms, voxel dimensions = 1.5 x 1.5 x 1.5mm, MB factor = 4). The full sequence was also acquired with the reversed phase encoding direction for use in correction of susceptibility-induced distortions (Andersson et al., 2003).

6.2.3 Definition of groups

The method for group definition is described in the previous chapter (see *5.2.3 Definition of groups*). Those not scanned at follow-up (n=11) were removed from the groups identified in Chapter 5 based on the N=75 sample. Of the 11 participants removed, 7 were removed from the 'maintainer' group (5 CHA, 2 exercise), 2 from the 'adapters' (2 CHA) and 2 from the 'decliner' group (1 CHA, 1 exercise). As in Chapter 5, two participants (both CHA) fell at the median so were not included in any group, resulting in 62 participants categorised as 'maintainers', 'adapters' and 'decliners' (demographics for the N=62 sample are reported in *Appendix Table 6.B*).

6.2.4 Image analysis

6.2.4.1 Structural MRI

Whole-brain T1 images were analysed using FSL-VBM (Douaud et al., 2007). Briefly, structural images were brain-extracted using FSLanat

(https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/fsl_anat) and segmented by tissue type, using FAST (Zhang et al., 2001). A study-specific GM template was created by aligning the GM PVEs to a standard space using FNIRT, with aligned images then averaged, flipped along the x-axis and re-averaged. The template was based on an equal number of participants (N=16) from each of the three groups. Each subject's GM PVE was non-linearly registered to the study-specific template, and modulated by the Jacobian to correct for local expansion and contraction related to the non-linear spatial transformation. Modulated GM images were spatially smoothed using an isotropic Gaussian kernel of 2mm. A voxel-wise GLM was applied to compare GM density between groups, using Randomise permutation-based non-parametric testing (Winkler et al., 2014), with TFCE thresholding and a FWE-corrected significance threshold of $p<0.05$.

6.2.4.2 Diffusion MRI

Raw diffusion-weighted images were first pre-processed with TOPUP to correct for susceptibility-induced distortions, by estimating the susceptibility-induced field using the b=0 images from the two phase encoding directions (Andersson et al., 2003), producing a single corrected brain-extracted b=0 image. EDDY (e.g. Andersson et al., 2016; Andersson & Sotiropoulos, 2016) was used to apply TOPUP correction, to correct for eddy currents and participant movement, and replace outlier slices. The diffusion tensor model was then fit at each voxel of the pre-processed data to derive FA, MD, and RD spatial maps. Whole-brain voxel-wise comparison of FA was conducted using TBSS (Smith et al., 2004), involving non-linear registration of each individual FA map to the FMRIB58 FA template, and then MNI standard space, and

skeletonisation of the mean FA image. Individual FA maps were projected to the thresholded FA skeleton, thresholded at 0.3, and passed into voxel-wise statistical analysis using Randomise (Winkler et al., 2014). MD and RD images were also compared using TBSS using the same approach. Results are thresholded with TFCE and shown at $p<0.05$, FWE-corrected for multiple comparisons across space. Diffusion images were missing for one participant (maintainer) due to technical issues.

6.2.4.3 Resting-state MRI

Single-subject resting-state fMRI 4D images were pre-processed using MCFLIRT motion correction, brain extraction, high pass temporal filtering with a 100s cut off, and B0 unwarping using fieldmaps (Greve & Fischl, 2009). A high contrast pre-saturation image was supplied as an alternative reference image for registration and motion correction. Pre-processed images were decomposed into a set of spatially independent components (ICs) using MELODIC (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/MELODIC), and these ICs were used in FIX (Salimi-Khorshidi et al., 2014) to identify and remove noise components from the data. 'Cleaned' images were registered to the MNI standard space, and spatial smoothing was applied using an isotropic Gaussian kernel of 3mm.

To identify group-level RSNs, subject-specific pre-processed images were temporally concatenated in a group-level ICA and decomposed into 25 components. These components formed the input template for dual regression, where for each subject, the time course associated with each IC was identified, and then the associated

subject-specific spatial map. Resting-state connectivity was compared between groups for each RSN using a GLM applied in Randomise. Results are thresholded using TFCE and FWE-corrected at the $p<0.05$ level.

6.2.5 Statistical analysis

Non-imaging data were analysed using SPSS (SPSS Inc., Chicago, IL.). Demographics were compared between groups using independent t-tests and one-way ANOVA for continuous data and chi-square tests for categorical data.

6.3. Results

6.3.1 Group identification and characteristics

After removing the participants not scanned at follow-up from the groups identified in the previous chapter, there were 30 'maintainers' (19 CHA, 11 Exercise), 16 'adapters' (11 CHA, 5 Exercise) and 16 'decliners' (9 CHA, 7 Exercise), as shown in *Figure 6.1.* Between-group comparisons of demographical information (detailed in *Table 6.2*) were largely the same as in the previous chapter. Between the three groups, there was a significant group difference in age, both at baseline (BL) [$F(2,59)=8.52$, $p=0.001$, $\eta^2=0.22$] and follow-up (FU) [$F(2,59)=7.83$, $p=0.001$, $\eta^2=0.21$], with adapters significantly older than both 'maintainer' [BL: $p=0.001$; FU: $p=0.001$] and 'decliner' groups [BL: $p=0.006$; FU: $p=0.006$]. There was also a significant difference in gender between groups [$\chi^2(2,N=62)=13.54$, $p=0.001$], with significantly more female 'maintainers' compared to both 'adapter' [$\chi^2(1, N=48)=15.45$, $p<0.001$] and 'decliner' groups [$\chi^2(1,N=48)=4.71$, $p=0.03$]. There was no difference in gender distribution between 'adapters' and 'decliners' [$p=0.13$]. There was also no

significant difference between groups in follow-up period, years of education, APOE status, or MoCA score at baseline and follow-up.

***Table 6.2*. Demographics information between groups**

	Maintainer (N=30)	Adapter (N=16)	Decliner (N=16)	*p*
Follow-up period, yrs	4.0 (0.3)	3.9 (0.2)	4.0 (0.4)	0.86
Age at baseline	65.6 (5.3)	72.5 (6.7)	66.0 (5.3)	**0.001**
Age at follow-up	70.1 (5.3)	76.8 (6.8)	70.2 (5.5)	**0.001**
MoCA at baseline	28.2 (1.9)	27.8 (1.9)	27.0 (2.3)	0.18
MoCA at follow-up	27.2 (2.1)	26.4 (2.3)	25.6 (1.5)	0.05
Years of education	15.8 (3.1)	14.8 (4.2)	16.3 (4.1)	0.50
Females, N (%)	24 (80.0%)	4 (25.0%)	8 (50.0%)	**0.001**
APOE*, ε4-carriers (%)	7 (23.3%)	6 (37.5%)	3 (18.8%)	0.39
TOPF-estimated IQ	113.2 (6.7)	114.1 (7.9)	113.6 (7.8)	0.94

Values represent mean (SD) unless otherwise stated. *Abbreviations*: CHA – cognitive health in Ageing; MoCA – Montreal Cognitive Assessment; APOE - apolipoprotein E; TOPF – test of premorbid function; IQ – intelligent quotient. *APOE genotype unavailable for 2 participants (1x adapter, 1x decliner).

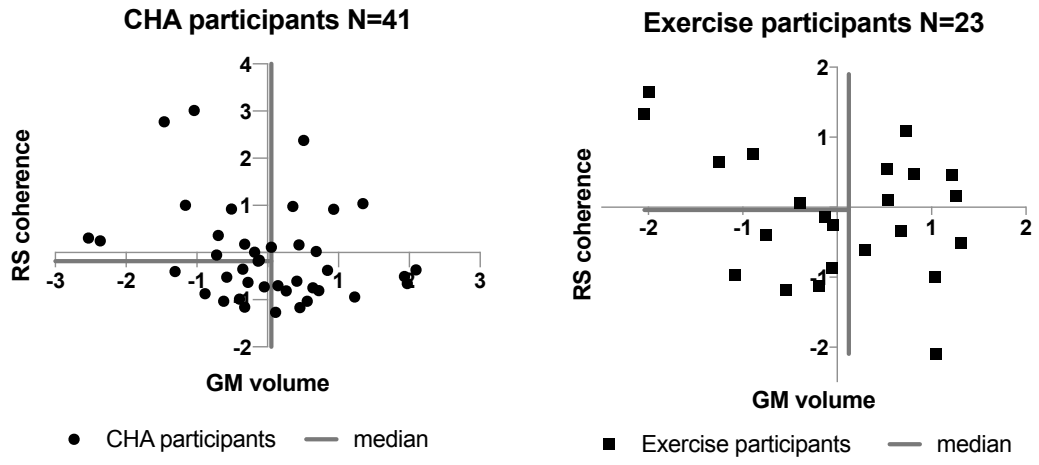


***Figure 6.1*. Grey matter volume plotted against frontal resting-state connectivity in healthy older adults, plotted by baseline study. Grey matter volume was extracted within the age-affected ROI and normalised by whole brain volume. Frontal resting-state connectivity was extracted from the frontal RSN within the age-affected functional ROI. Dots/squares represent each individual participant, and the grey lines represent the median GM and RS.**

6.3.2 Between-groups MRI

6.3.2.1 Structural MRI

Whole-brain GM analysis with VBM revealed a widespread effect of baseline group membership on GM density four years later (see *Appendix Figure 6.A*). In pairwise group comparisons, 'adapters' showed lower GM density compared to 'maintainers' in widespread regions including superior frontal gyrus, ventromedial PFC (vmPFC), ventrolateral PFC (vlPFC), orbitofrontal cortex (OFC), middle and inferior temporal gyrus, parahippocampal gyrus, temporal pole, insular cortex, precuneus, posterior cingulate, anterior cingulate, lateral occipital cortex, lingual gyrus, angular gyrus, cerebellum, hippocampus, amygdala, caudate and accumbens (*Figure 6.2a*). To a lesser extent, 'decliners' also showed lower GM density compared to 'maintainers', in bilateral vmPFC and OFC, left vlPFC and dorsolateral PFC (dlPFC), left insular, left temporal pole, bilateral Heschl's gyrus, bilateral hippocampus, right precentral gyrus (and left precentral gyrus to a lesser extent), left supramarginal gyrus, right angular gyrus, cerebellum, bilateral caudate, accumbens and amygdala (*Figure 6.2b*). There were no significant regions of lower GM density in 'maintainers' compared to either 'decliners' or 'adapters'.

'Decliners' did not demonstrate any regions of significantly lower GM compared to 'adapters'. However, 'adapters' showed significantly lower GM density compared to 'decliners' in right postcentral gyrus, bilateral precentral gyrus, occipital pole, lingual gyrus, parahippocampal gyrus and left hippocampus (see *Figure 6.2c*). Bilateral effects were generally more notable in the right hemisphere.

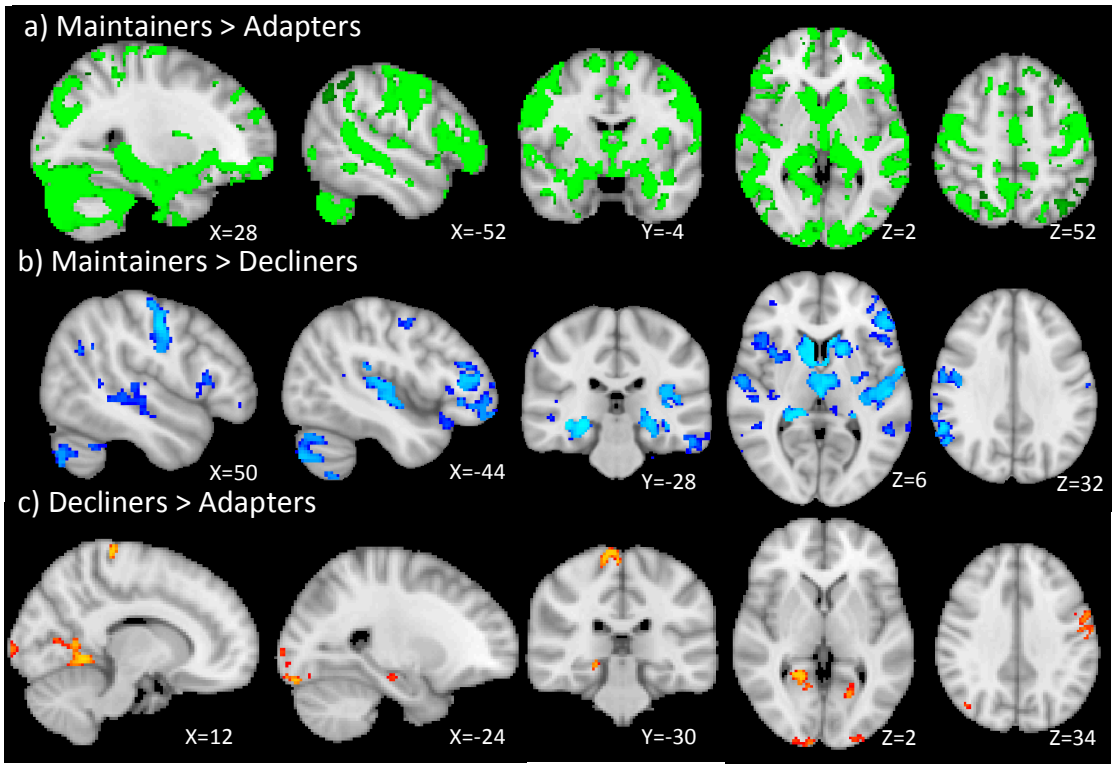


Figure 6.2. **Regions of lower grey matter density in a) adapters and b) decliners relative to maintainers, and lower GM density in c) adapters relative to decliners. Results are FWE-corrected at p<0.05. Coordinates are in MNI space.**

Compared to 'maintainers', the regions of lower GM in 'decliners' largely overlapped with regions of lower GM in 'adapters', shown in *Figure 6.3.* There were few regions of reduced GM in 'decliners' that were not also reduced in 'adapters' compared to 'maintainers', except in left inferior temporal gyrus. Furthermore, regions of higher GM density in 'decliners' compared to 'adapters' were almost entirely contained within regions of reduced GM density in 'adapters' compared to 'maintainers'.

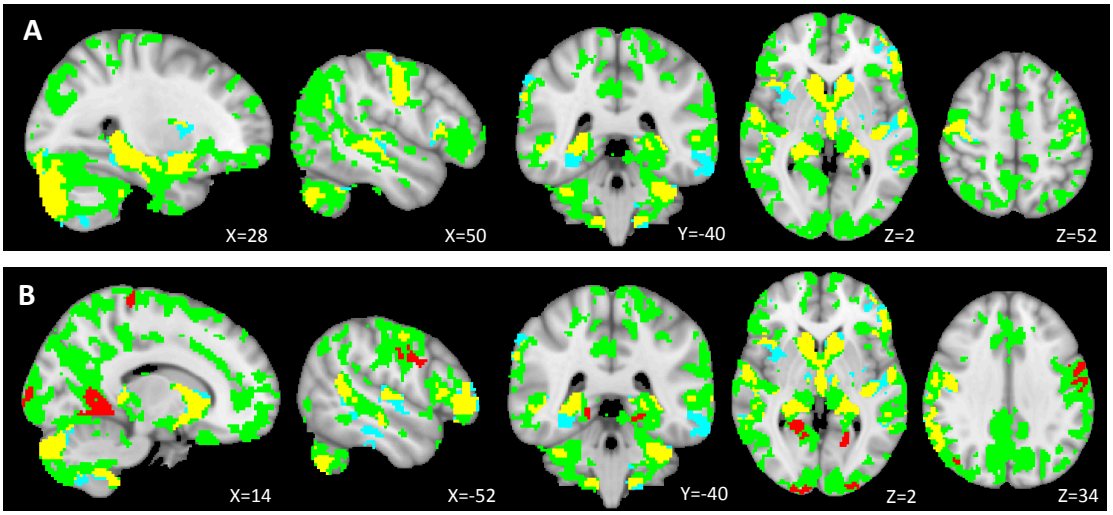


Figure 6.3. **Overlap of group differences in grey matter density.**

(A) Reduced GM density in adapters only and decliners only compared to maintainers shown in green and blue, respectively. Common areas of GM reduction in adapters and decliners is shown in yellow. (B) Shows the same results as in (A), but with regions of reduced GM in adapters compared to decliners added in red. Coordinates are in MNI space.

6.3.2.2 Diffusion MRI

Whole-brain WM analysis with TBSS revealed a widespread effect of baseline group membership on FA four years later (see *Appendix Figure 6.B*). Pairwise group comparisons revealed significantly lower FA in 'adapters' compared to 'maintainers' in bilateral inferior longitudinal fasciculus, corticospinal tract, forceps minor, forceps major, inferior fronto-occipital fasciculus, superior longitudinal fasciculus, posterior corona radiata, sagittal stratum, fornix, retrolenticular internal capsule, anterior thalamic radiation, right cingulum and the genu, body and splenium of the corpus callosum (*Figure 6.4a*). There were no regions of significantly lower FA in 'maintainers' compared 'adapters'. Neither were there any significant differences in FA between 'maintainers' and 'decliners'.

Compared to ‘decliners’, ‘adapters’ had significantly lower FA in widespread regions including bilateral superior corona radiata and posterior corona radiata, right anterior corona radiata, bilateral superior longitudinal fasciculus, left cingulum, body and splenium of the corpus callosum, bilateral external capsule, right posterior thalamic radiation, bilateral retrolenticular internal capsule, bilateral inferior longitudinal fasciculus, bilateral inferior fronto-occitipal fasciculus, right forceps major, and right forceps minor (*Figure 6.4b*). There were no regions of significantly lower FA in ‘decliners’ compared to ‘adapters’. The regions of lower FA in ‘adapters’ compared to ‘decliners’ overlapped with regions of lower FA in ‘adapters’ compared to ‘maintainers’, particularly in bilateral superior corona radiata, superior longitudinal fasciculus, the body and splenium of the corpus callosum, and right anterior corona radiata, forceps major, external capsule, posterior thalamic radiation and forceps minor (*Figure 6.5)*.

Comparison of MD and RD spatial maps between groups using TBSS revealed a widespread effect of group membership on both measures after four years (see *Appendix Figure 6.B*). Pairwise comparisons revealed group effects were driven by increased MD and RD in ‘adapters’ compared to both ‘maintainers’ (*Figure 6.4a*) and ‘decliners’ (*Figure 6.4b*), consistent with FA results demonstrating lower WM integrity in ‘adapters’. Alterations in MD and RD were topographically similar but more extensive than differences in FA.

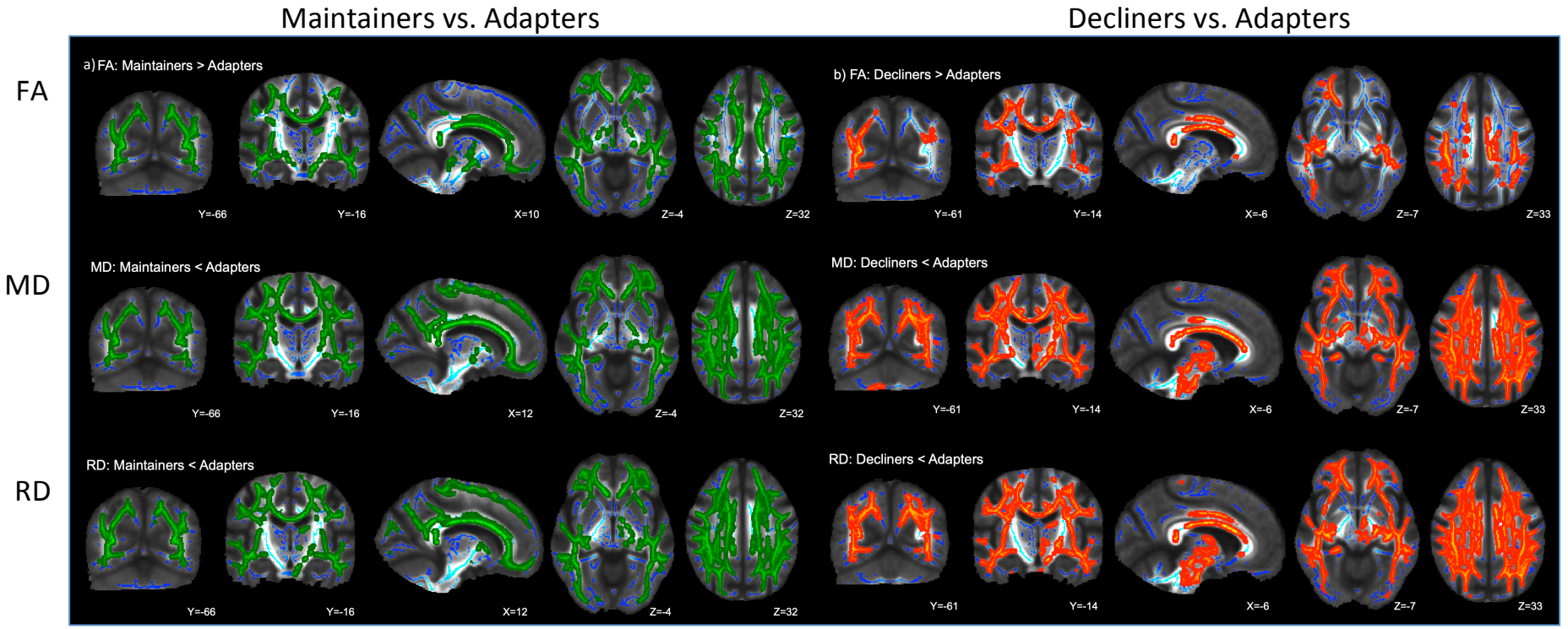


Figure 6.4. **Results of TBSS analysis comparing FA, MD and RD between baseline groups.**

Regions of significantly lower FA in adapters compared to a) maintainers and b) decliners. Regions of significantly higher MD in adapters compared to a) maintainers and b) decliners. Regions of significantly higher RD in adapters compared to a) maintainers and b) decliners. Results are $p<0.05$ FWE-corrected and dilated for illustrative purposes. Coordinates in MNI space.

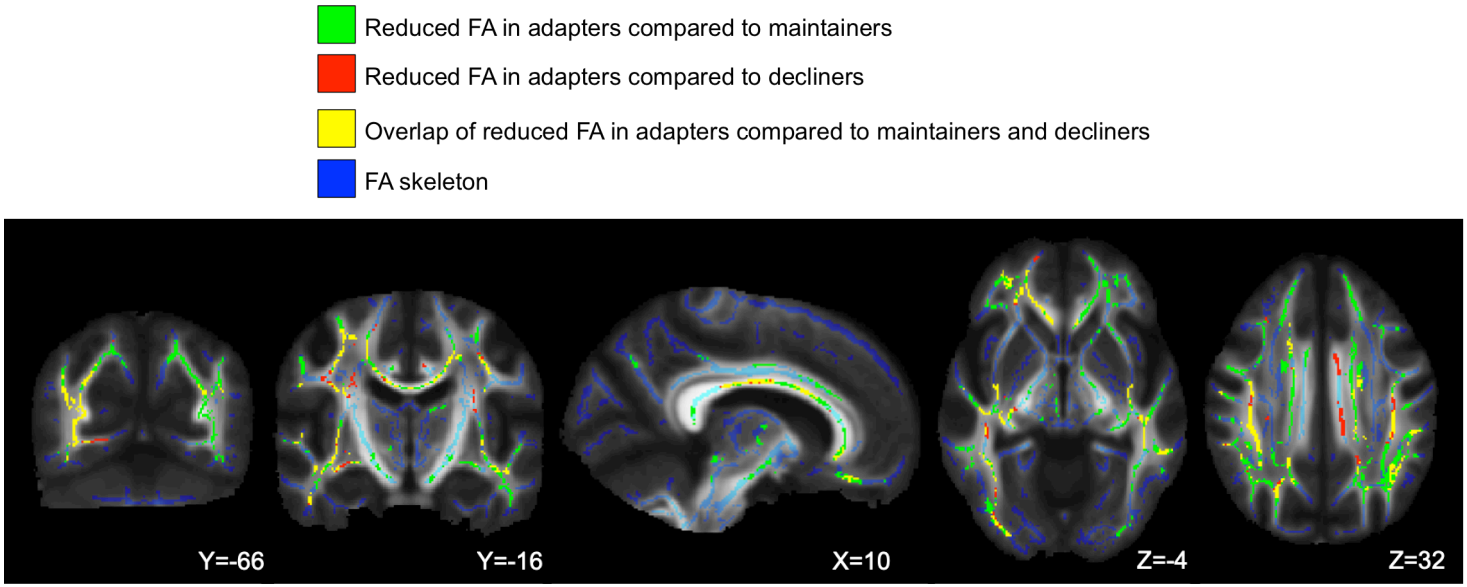


Figure 6.5. **Overlap of group differences in fractional anisotropy.**

Reduced FA in adapters compared to maintainers only (green), and in adapters compared to decliners only (red), as well as common areas of lower FA in adapters compared to maintainers and decliners (yellow), are shown over the mean FA skeleton (blue). Coordinates are in MNI space.

6.3.2.3 Resting-state MRI

Of the 25 group-level spatial maps, 18 were identified as biologically relevant RSNs (*Figure 6.6;* each briefly described in *Appendix 6*). The prefrontal RSN (8) derived from this sample represents the same network as the external template RSN used to define groups at baseline (see *4.2.3.3 ROI definition*).

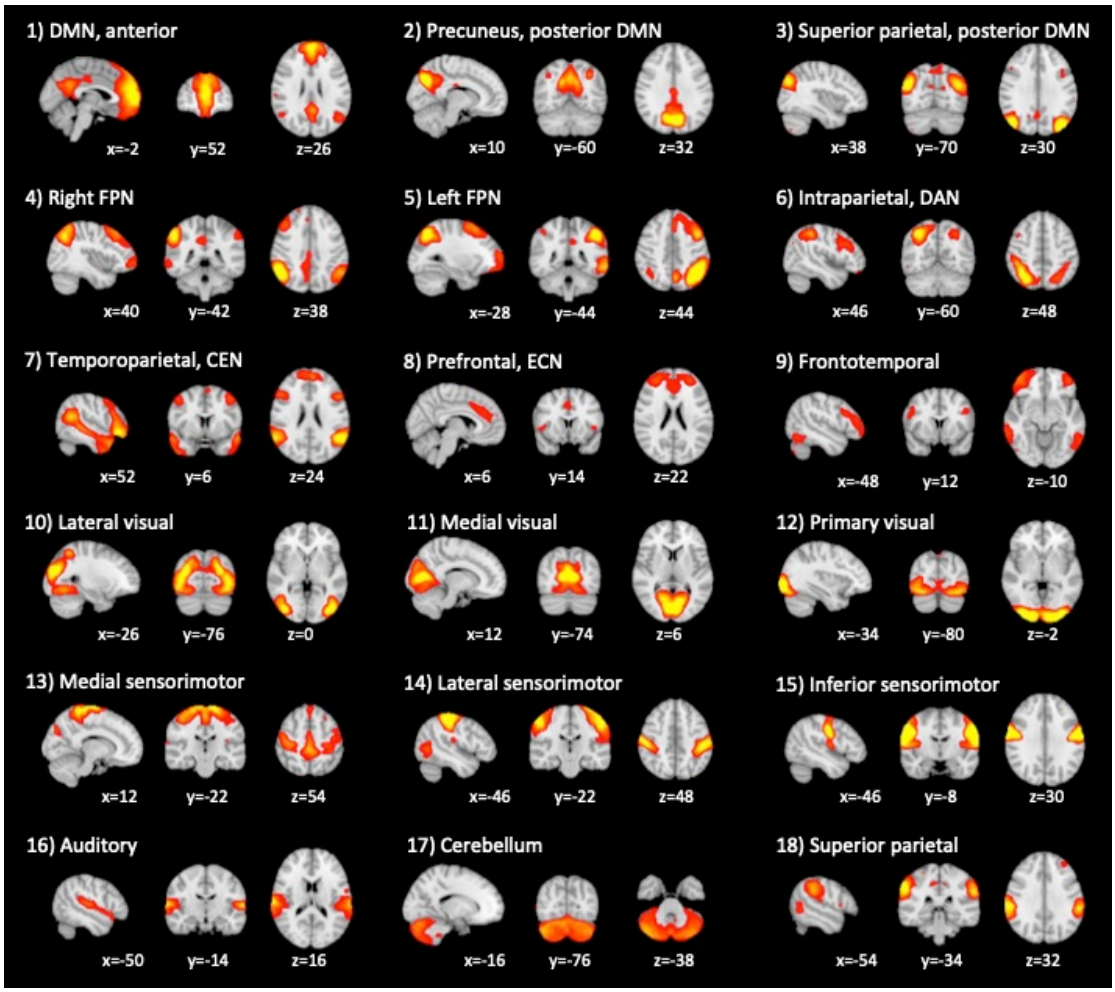


Figure 6.5. **Resting-state networks identified by group-ICA.**

Identified RSNs are 1) Default Mode Network (DMN), particularly the anterior portion, 2) Precuneus relating to posterior DMN, 3) superior parietal relating to posterior DMN, 4) right fronto-parietal network, 5) left fronto-parietal network, 6) intraparietal sulcus, resembling the Dorsal Attentional Network (DAN), 7) temporo-parietal regions, resembling the Central Executive Network (CEN), 8) prefrontal regions, resembling the Executive Control Network (ECN), 9) fronto-temporal regions, 10) lateral visual, 11) medial visual, 12) primary visual, 13) medial sensorimotor, 14) lateral sensorimotor, 15) inferior sensorimotor, 16) auditory cortex, 17) cerebellum, and 18) superior parietal regions. Coordinates are in MNI space.

Between-group analyses focused on the 6 RSNs with frontal components (4-9), the 3 DMN-related RSNs (1-3), due to the reported effect of age on DMN connectivity (Ferreira & Busatto, 2013), and a visual network (10) selected as a 'control' network. However, the main effect of group was not significant for any of the investigated networks. There was a trend for an effect of group for the prefrontal RSN (8) used to define groups at baseline (see above). Exploratory pairwise comparisons for this prefrontal network (8) were significantly only for greater connectivity in 'adapters' compared to 'maintainers', but this difference only survived thresholding in a small region in right posterior cingulate (*Figure 6.7a*). Inspection of uncorrected statistical maps revealed a bilateral effect in posterior cingulate, as well as in a small region in left vmPFC and right inferior frontal gyrus (*Figure 6.7b*). The posterior cingulate region overlapped with the functional ROI used to extract baseline RS metrics (see *Figure 4.2*), but the uncorrected differences in frontal regions did not overlap with either the functional ROI or the prefrontal RSN (8).

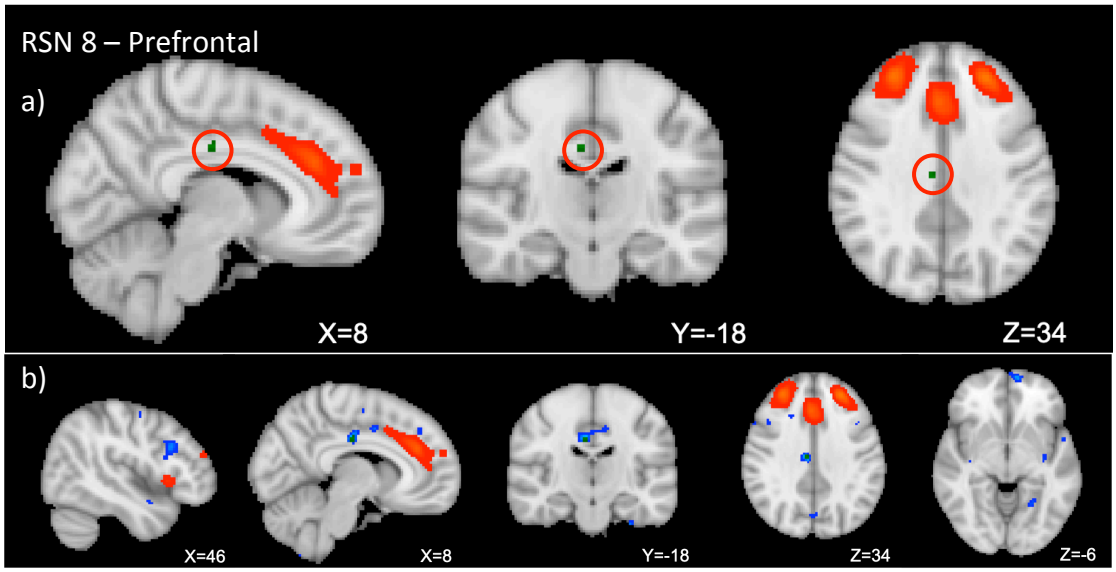


Figure 6.6. **Results of between-group comparisons of resting-state connectivity.**
Prefrontal RSN (8) shown in red; a) shows the region of significant higher connectivity of the prefrontal RSN in adapters compared to maintainers (green), FWE-corrected at $p<0.05$; b) also shows the uncorrected result for this contrast (blue). Coordinates are in MNI space.

6.4. Discussion

The primary objective of this chapter was to identify the structural and functional brain characteristics of 'maintainers', 'adapters' and 'decliners' several years after group definition. Between groups identified based on baseline GM and RS metrics, we compared measures of GM density, WM integrity and RS functional connectivity acquired four years after baseline scan. 'Adapters' showed the lowest GM and WM integrity compared to both 'maintainers' and 'decliners' after four years. However, there were no significant differences in RS connectivity across a range of DMN and frontal networks. The structural findings, at least, therefore suggest that lower GM and higher RS at baseline, as displayed by 'adapters', is associated with poorer future brain health than lower GM and lower RS at baseline, as displayed by 'decliners'.

6.4.1 Grey matter differences between groups after four years

More intact GM density in 'maintainers' relative to 'adapters' and 'decliners' after four years is consistent with 'maintainers' having preserved the relatively higher GM structure observed at baseline. However, this is not to say that 'maintainers' have not experienced GM atrophy over time. Indeed, longitudinal imaging studies of older adults with superior cognition have shown significant GM atrophy over time in these individuals, but the rate of decline is slower (Cook et al., 2017) or a greater baseline volume is preserved over time (Persson et al., 2012; Pudas et al., 2018), compared to more 'average' agers.

When compared to 'maintainers', we found that adapters had more extensive GM differences than 'decliners'. The topographical consistency of lower GM density in

'decliners' and 'adapters', and the intermediate extent of GM differences in 'decliners', could be interpreted as a continuum of GM atrophy between these groups. Consistent with this interpretation, regions of lower GM density in 'adapters' when compared to 'decliners' fell within the regions lower in 'adapters' vs. 'maintainers'. These findings are reminiscent of cross-sectional structural differences discussed in Chapter 3 in individuals with SMI, with topographically similar regions affected and intermediate extent of alterations between healthy control and MCI/AD groups, supporting SMI as a pre-MCI stage on the continuum to AD. Therefore, these GM results suggest that the 'adapter' brain profile may follow rather than precede a 'decliner' profile on a continuum of GM atrophy. It should also be considered that the 'adapter' group is significantly older at baseline, and *Figure 6.1* shows several 'adapters' with the lowest GM volumes at baseline, importantly observed for 'adapters' in both the CHA and exercise baseline cohorts. These factors may drive the relative group differences observed after four years, but both the older age and lower baseline GM have been determined by the baseline structural and functional brain characteristics of 'adapters'.

6.4.2 White matter differences between groups after four years

Consistent with the GM results, 'adapters' showed the poorest WM integrity after four years, demonstrated by lower FA and higher MD and RD compared to both 'maintainers' and 'decliners'. The greater extent of regions of lower FA in 'adapters' when compared to 'maintainers' than compared to 'decliners', and the overlap of regions of lower FA in 'adapters' compared to other groups, again can be interpreted as 'decliners' being intermediate to 'maintainers' and 'adapters' on a continuum of

declining WM structure. Common areas of lower FA in 'adapters' when compared to both other groups (*Figure 6.6)* were more prominent in superior tracts, which speculatively could reflect the superior-to-inferior gradient of greater-to-lesser vulnerability of WM tracts to age-related decline (Sexton et al., 2014).

We found no significant differences in WM integrity between 'maintainers' and 'decliners' after four years, in contrast to significantly lower GM density observed in 'decliners' compared to 'maintainers'. Whether this reflects preserved WM despite lower GM in 'decliners', or deterioration in WM despite relatively intact GM in 'maintainers', cannot be discriminated by these cross-sectional comparisons.

In contrast to the WM results of Chapter 4, there were no regions of greater WM integrity in 'adapters' compared to 'decliners' (or 'maintainers') after four years. Similarly, extensive differences in MD and RD were observed between groups in this sample only. The spatial overlap of the FA, MD and RD group differences found here is consistent with longitudinal evidence for spatially consistent annual decreases in FA and increases in MD and RD in older adults (Sexton et al., 2014). As WM measures compared between groups in Chapter 4 were acquired at the time of baseline group definition, whether the inconsistent findings between this and the prior chapter relate to the passage of time since baseline scanning, or specific cohort effects, is unclear.

6.4.3 Resting-state differences between groups after four years

The absence of significant differences in resting-state between groups after four years is somewhat surprising given the robust differences found for structural measures. A small effect was observed for the prefrontal RSN, a version of the same network used for extraction of baseline RS metrics for group definition, but otherwise there was little effect of group on other RSNs. As multiple RSNs have frontal components, differences in the specific frontal network used to define groups may also be observed in other frontal RSNs (e.g. Zamboni et al., 2013), but there is no evidence for this here. Therefore, the higher RS used to define groups here may be relatively specific to the prefrontal RSN, rather than a more general effect across networks, and use of a different RSN to define groups may distribute participants in a different way. It is also possible that differences in RS between groups at baseline are relatively subtle, despite the potential implications for cognition and brain structure. The analysis approach used here identifies regions that have different functional correlation with each large-scale RSN. In future, methods that look at the connectivity between smaller sub-regions of larger RSNs may identify differences in connectivity of regions within and between different RSNs.

6.4.4 Summary

In summary, ‘adapters’ showed the poorest structural brain health after four years, with lower GM density and WM integrity compared to other groups. The topography and extent of GM and WM group differences suggested differences in ‘decliners’ were intermediate to those observed between ‘maintainers’ and ‘adapters’. These structural results are consistent with an ‘adapter’ brain profile at baseline signalling

poor brain outcomes four years later. Direct longitudinal comparison of structural and functional brain metrics and correlation with longitudinal change in cognition can probe these results further.

6.4.5 Strengths and limitations

In this chapter, the availability of follow-up MRI scans allowed for characterisation of 'maintainer', 'adapter' and 'decliner' brain profiles several years after baseline scanning, to provide some insight into the long-term outcomes of these groups. Use of serial MRIs will be less influenced by factors that may affect cognitive performance and contribute to variability seen in the previous chapter, e.g. fatigue or practice effects, at least for structural metrics. In this chapter, we have also incorporated voxel-wise comparisons of GM and RS metrics, to go beyond the structural and functional ROIs used to define groups, and have extended the investigation of differences in RS between groups to other RSNs, revealing limited effects on networks other than that used for group definition.

However, there are several limitations that must be considered. A major limitation is the use of different MRI scanners at baseline and follow-up assessments, which was logistically necessary but precluded direct longitudinal comparison of structural and functional brain metrics over time. This limits what can be said about 'change' in brain metrics over time between groups, and limits us to relative, cross-sectional comparisons between groups, which may lead to different interpretations than longitudinal comparisons (e.g. Nyberg et al., 2010). Whilst this chapter includes multi-modal imaging, allowing for observation of similarities and divergence of group

differences across modalities, other imaging modalities could add further insight. For example, between-groups comparison of FLAIR-derived WMH load could probe whether the highest WMH load observed in decliners in Chapter 4 is replicated here. Finally, the sample size in each group is small, although group sizes are comparable to similar studies in this field (e.g. Hakun et al., 2015; Persson et al., 2012).

6.5. Conclusions

Establishing the structural and functional characteristics of maintainers, adapters and decliners several years after group definition can provide information to validate the predicted association of these groups with different trajectories of cognitive ageing. Between groups defined as 'maintainers', 'adapters' and 'decliners' at baseline, in this chapter I compared structural and functional brain metrics acquired several years after baseline, and found the lowest GM and WM integrity in 'adapters' after four years. Structural differences in 'decliners' were intermediate to 'maintainers' and 'adapters'. Rather than 'adapters' utilising compensatory function before proceeding to a 'decliner' profile after a threshold of age-related decline has been surpassed, these results suggest that higher RS and lower GM at baseline is associated with the poorest future brain health, whilst decliners may be intermediate on a continuum of structural decline. However, no significant differences were observed in RS connectivity between groups. Further direct longitudinal comparison of brain metrics between groups and association with longitudinal cognitive performance will expand on these findings. In the next chapter, I will provide a general discussion of the results and potential implications of the work reported in my DPhil thesis.

Chapter 7. General Discussion

7.1. Summary of objectives and main results

Decades of research have demonstrated the remarkable variability that occurs in the course of cognitive ageing. However, we still do not clearly understand the factors that underpin this heterogeneity or have prospective markers to indicate a person's impending cognitive trajectory. The overall aim of this thesis was to improve our understanding of risk and protective factors associated with variability in cognitive ageing, using neuroimaging and cognition to ultimately provide markers as well as mechanistic insight that will inform interventions.

Specifically, in Chapters 2-6 of this thesis I aimed to answer the following questions:

- *How does genetic variability affect cognitive ability in healthy older adults?*
- *Do MRI markers facilitate assessment of Alzheimer's risk in cases of persistent subjective memory impairment?*
- *Do individual differences exist in the neural mechanisms that support superior cognitive ageing?*
- *Do baseline brain metrics proposed to support superior cognitive ageing relate to trajectories of future cognitive ability?*
- *Do baseline brain metrics proposed to support superior cognitive ageing relate to brain characteristics several years later?*

In the next section, I summarise the main results of each chapter, and provide a brief answer to each question in the section subheadings.

7.1.1 APOE genotype has diverse cognitive consequences resulting from multiple neurobiological mechanisms.

In Chapter 2, I aimed to understand the effect APOE genotype has on cognitive performance in healthy adults, which is not clear despite substantial investigation, and has not previously been comprehensively reviewed. By synthesising and critically appraising the extensive literature in this field, I reported several novel observations in this chapter. The 'prodromal' and 'phenotype' explanations for APOE-related cognitive effects, repeatedly posed as competing alternative explanations, are not mutually exclusive but distinct mechanisms by which APOE genotype may influence cognition. Disentangling the cognitive consequences of these mechanisms is crucial, as the multiple ways in which APOE affects cognition can provide insight into distinct aspects of cognitive ageing and Alzheimer's disease. The neurobiology of APOE effects on cognition has key implications for study design and interpretation of findings, therefore greater consideration of the neurobiology of APOE and cognition is required. I identified gaps in the current literature and opportunities for future research to increase the translational potential of APOE and cognition research to provide cognitive markers and inform interventions. Therefore, I conclude that APOE genotype affects cognition in healthy adults in multiple ways via different neurobiological mechanisms.

7.1.2 Structural MRI detects differences in SMI associated with subsequent clinical and cognitive decline that will facilitate assessment of AD risk

In Chapter 3, I presented a clinical case of SMI persisting for decades before AD diagnosis, and showed robust structural decline in AD-related regions in this patient

despite highly variable cognitive performance. To evaluate the evidence for MRI-based markers of increased AD risk in those with SMI, I also reviewed longitudinal studies of SMI that used MRI, which has not previously been reviewed. Published evidence supports the relevance of MRI-detected structural characteristics for cognitive and clinical outcomes (e.g. Peter et al., 2014; Dufouil et al., 2005; Verfaillie et al., 2018a, 2018b, 2016) and the ability of MRI to detect clinically meaningful subgroups within individuals categorised as SMI (e.g. Ferreira et al., 2017). Therefore, this chapter shows that MRI can go beyond objective cognitive performance to detect early structural differences in the brain that herald oncoming cognitive and clinical impairment. MRI will be useful in cases of persistent SMI to avoid simple reassurance and discharge in clinic, and eventually identify SMI cases most at risk of subsequent cognitive decline for early monitoring and intervention. Thus far, few studies have used serial MRI scanning to investigate dynamic changes in the brains of individuals with SMI, and none have studied functional or diffusion MRI measures in relation to long-term outcomes, providing a direction of future research.

7.1.3 Individual differences in brain characteristics of healthy older adults exist, but are not associated with superior cognitive ageing in the expected manner

In Chapter 4, I investigated whether multiple patterns of brain ageing predicted to be associated with superior cognitive ageing, based on the 'brain maintenance' (Nyberg et al., 2012) and 'Scaffolding Theory of Aging and Cognition' (STAC; Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Park, 2014) models of neurocognitive ageing, could be identified using a simple multi-modal MRI-based approach. Using structural

and functional brain metrics alone, the predicted ‘maintainer’, ‘adapter’ and ‘decliner' groups were identified. Decliners and maintainers were found to have the highest and lowest WMH burden, respectively, whilst adapters showed regions of more intact WM integrity than decliners, in line with predictions. Compared to maintainers, decliners demonstrated poorer cognitive performance at time of scan, as well as poorer memory performance across the 15 years before MRI scanning, consistent with predictions. In contrast, adapters did not demonstrate the predicted superior cognitive performance compared to decliners, and had poorer cross-sectional cognitive scores compared to both maintainers and decliners.

Based on the results of this chapter, older adults with ‘more youthful’ brains (maintainers) but not those with low GM and high RS (adapters) have better cognition and brain health than older adults with low GM and low RS (decliners). These results support ‘brain maintenance’ as a neural basis of superior cognitive ageing, but do not support STAC as a model for preservation of a high level of cognition in later life.

7.1.4 Cognitive trajectories are highly variable over time, but are not clearly related to baseline brain characteristics proposed to support superior cognitive ageing

In Chapter 5, I reported the longitudinal cognitive performance of ‘maintainer’, ‘adapter’ and ‘decliner’ groups over the four years following baseline assessment. There were no observed differences in baseline cognitive performance between groups, and no evidence of significant group differences in decline over time. Crucially, there was no support for the predicted intermediate extent of cognitive change in ‘adapters’, who actually demonstrated worse cognitive performance at

follow-up compared to both ‘maintainers’ and ‘decliners’, as well as poorer word recognition across baseline and follow-up assessments compared to ‘maintainers’. Contrary to predictions that ‘decliners’ would experience the greatest cognitive decline, this group instead showed a significant improvement over time on a measure of processing speed. On average, there was significant change over time on most cognitive measures, representing decline on some measures but improvement on others. Overall, longitudinal cognitive trajectories were highly variable at the individual level. Whilst the results of this chapter do not illustrate a clear relationship between baseline brain profiles and subsequent *change* in cognitive performance, these findings again support the association of ‘brain maintenance’ with the best cognitive outcomes in older adults, but do not support STAC-based functional adaption as a basis of superior cognitive ageing.

7.1.5 Structural differences between groups after several years indicate poorest outcomes for baseline ‘adapters’

In Chapter 6, I investigated the structural and functional brain characteristics of ‘maintainer’, ‘adapter’ and ‘decliner’ groups four years after groups definition based on baseline brain metrics. When compared to ‘maintainers’, ‘adapters’ and ‘decliners’ had overlapping regions of significantly lower GM density, but GM differences in ‘adapters’ were more extensive than those observed in ‘decliners’. ‘Adapters’ also showed several regions of reduced GM density compared to ‘decliners’. WM integrity was significantly poorer in ‘adapters’ compared to both ‘maintainers’ and ‘decliners’, who did not differ in WM integrity. WM differences in ‘adapters’ were less extensive when compared to ‘decliners’ than when compared to

'maintainers', although the regions affected were topographically similar. There were no significant differences in resting-state connectivity between groups in several resting-state networks relating to frontal regions or the DMN, suggesting that if present, differences in resting-state connectivity between groups after four years are subtle. The results of this chapter are inconsistent with the STAC-based prediction of poorest brain outcomes in 'decliners', where 'adapters' become 'decliners' when the extent of neural decline overwhelms the capacity to functionally adapt, and instead show 'adapters' have the poorest structural brain outcomes four years after baseline group definition.

7.1.6 Summary

The research presented in this thesis on APOE genotype and SMI demonstrates the importance of considering the multiple mechanisms that may contribute to cognitive ageing, and the challenge and necessity of identifying subgroups within a heterogeneous population. These insights are applicable across the spectrum of cognitive ageing, particularly to the relatively understudied area of superior cognitive ageing, as I have done in this thesis.

The aim to identify multiple brain mechanisms for superior cognitive ageing based on the 'brain maintenance' and 'STAC' models provided an opportunity to empirically test the predictions of these models. Whilst these models provide a useful framework for thinking about neurocognitive ageing, the predictions of the models have not previously been directly tested. In Chapters 4-6, I tested these predictions in a hypothesis-driven way by operationalising the models using

thresholds of brain structure and function to define groups of maintainers, adapters and decliners. The combination of brain structure and function is key to testing the STAC model, which explicitly integrates these aspects of brain health, and the focus on frontal brain function also relates to the STAC assumption that the frontal lobe is the primary locus of 'scaffolding'. Whilst the association of 'brain maintenance' with superior cognitive ageing is somewhat obvious (Nyberg et al., 2012), STAC is a theoretical model, of which several aspects are rather speculative (Park & Reuter-Lorenz, 2009) and the compensatory role of increased brain function in older adults is not without controversy. As the STAC model potentially provides guidelines for successful ageing and directions for interventions (Park & Reuter-Lorenz, 2009), it is necessary to clearly establish that the STAC mechanisms are associated with superior cognitive abilities in old age. Therefore, a test of the STAC model is particularly important.

In testing these models in Chapters 4-6, I found a consistent pattern of results across datasets that suggest genuine findings with implications for both 'brain maintenance' and 'STAC' models. The results of Chapters 4-6 (summarised in *Figure 7.1*) provide convergent evidence for the association of the 'more youthful' structural and functional brain characteristics of 'maintainers' with superior cognitive and neural outcomes. Using multiple cohorts and varied methodology, 'maintainers' consistently showed superior cognitive performance at time of group definition, as well as over a number of prior and subsequent years. 'Maintainers' also had the lowest WMH burden at baseline scan and the most intact GM and WM after several years. This thesis therefore provides multi-modal evidence for 'brain

maintenance' as one mechanism that supports superior cognitive ageing, meaning the 'brain maintenance' model can be used as a framework for successful cognitive ageing and inform interventions to preserve cognitive abilities in later life.

Perhaps more interestingly, Chapters 4-6 robustly show that the STAC model is *not* supported by the evidence of this thesis. The STAC model proposes that older adults retain a *high level* of cognitive performance in the face of significant brain changes through 'scaffolding', a processing involving changes in brain function via engagement of additional neural resources (Park & Reuter-Lorenz, 2009). According to the STAC model, an 'adapter' profile, operationalised here as higher frontal RS connectivity and reduced GM volume in age-affected ROIs, should be a marker of an adaptive brain that protects cognitive functioning and maintains a relatively high level of cognitive ability. However, we found no instances of significantly better cognitive performance in 'adapters' compared to either 'decliners' or 'maintainers' across chapters, and instead 'adapters' were consistently observed to perform worse than both 'maintainers' and 'decliners' across a range of cognitive measures. These results clearly show that a STAC-based pattern of brain characteristics does not support 'superior' cognitive ageing.

The findings of Chapters 4-6 regarding the nature of 'decliners' are also inconsistent with the STAC model. Whilst a 'decliner' profile is not explicitly outlined in the STAC model, the model argues that cognition will be impaired in older adults who do not functional adapt to neural declines (e.g. have lower structure and function as with 'decliners'). However, our results showed in multiple datasets that 'decliners'

demonstrated better performance on some cognitive measures compared to 'adapters', although 'decliners' had poorer cognition and greater WMH burden relative to 'maintainers' in the Whitehall cohort (Chapter 4). The findings of these chapters show that the absence of higher RS in older adults with lower GM is associated with better cognitive outcomes than when higher RS is observed, inconsistent with the STAC framework.

In addition to these cognitive results, the brain imaging findings for 'adapters' and 'decliners' are also at odds with the STAC model. As STAC asserts that the capacity for compensatory increases in frontal function will eventually be overwhelmed by the extent of age-related change, this predicts that 'adapters' will ultimately develop a 'decliner' profile, and expects 'decliners' to have a greater extent of age-related change than 'adapters'. However, the results of Chapter 6, where 'adapters' were shown to have the poorest brain outcomes, are inconsistent with this assertion.

Basis of the 'adapter' and 'decliner' functional characteristics on RS-fMRI is also particularly appropriate to assess STAC-related increased brain function. 'Scaffolding' reflects the strengthening and formation of functional connections in the brain according to STAC, and RS captures the functional connectivity of different brain regions, rather than relative changes in the level of regional brain activity as measured in task-fMRI. The STAC authors also suggest RS may be particularly useful to investigate actual changes in brain mechanisms rather than differences in task-related strategies (Reuter-Lorenz & Park, 2014). However, our findings show increased frontal RS connectivity is not associated with a high level of cognitive

performance, contradicting the STAC model. It is possible that only the extrinsic challenge of a cognitive task elicits increased frontal function that supports superior cognition in later life, accounting for positive associations between increased task-related frontal activity and cognition (e.g. Cabeza et al., 2002; Davis et al., 2008; Grady et al., 2005; Gutchess et al., 2005; Spreng et al., 2010; Eyler et al., 2011). However, this is also inconsistent with the STAC model, which argues that scaffolding is a lifelong response to both extrinsic (e.g. cognitive) and intrinsic (e.g. neural decline) challenge, and would negate the main premise of STAC that functional increases in older adults are a response to the intrinsic challenge of brain ageing.

As the results of Chapters 4-6 demonstrate that higher frontal function is not protective of cognitive function, there must be an alternative interpretation for increased frontal function in 'adapters'. The results of this thesis are more consistent with longitudinal evidence that increasing frontal activation co-occurs with declines in cognition and brain structure (e.g. Goh et al., 2013; Hakun et al., 2015; Pudas et al., 2018), whilst the poorer long-term outcomes of 'adapters' resembles the inverted-U of increased brain activation in MCI, compared to healthy older adults, prior to reduced activation in AD (e.g. Dickerson et al., 2005; Kircher et al., 2007; Zamboni et al., 2013). Although not associated with a high level of cognitive performance, it is possible that higher RS observed in 'adapters' reflects *attempted* compensation for deterioration in brain structure, which may still have some benefit to cognition (Hakun et al., 2015; Pudas et al., 2018). However, according to the STAC model, even attempted compensation would be better for cognitive performance than no compensation, predicting 'adapters' would still demonstrate better

cognitive performance than ‘decliners’, inconsistent with our findings. Instead the relatively good outcomes in ‘decliners’ are more consistent with a ‘dedifferentiation’ interpretation of increased frontal RS in ‘adapters’, where *detrimental* increases in brain function result from reduced regional specification of function due to declining brain structure and function with age (e.g. Li et al., 2001; Maillet & Rajah, 2013). These results highlight the danger of assuming higher frontal function is compensatory, as the STAC model does, and advise caution in using a STAC framework to guide interventions to preserve cognition in later life. Importantly, whilst these results show ‘scaffolding’ does not support superior cognitive ageing, the evidence against the STAC model does not rule out the existence of individual differences in the neural basis of superior cognitive ageing, as different functional metrics, e.g. task-based fMRI, may be differently associated with cognitive superior performance.

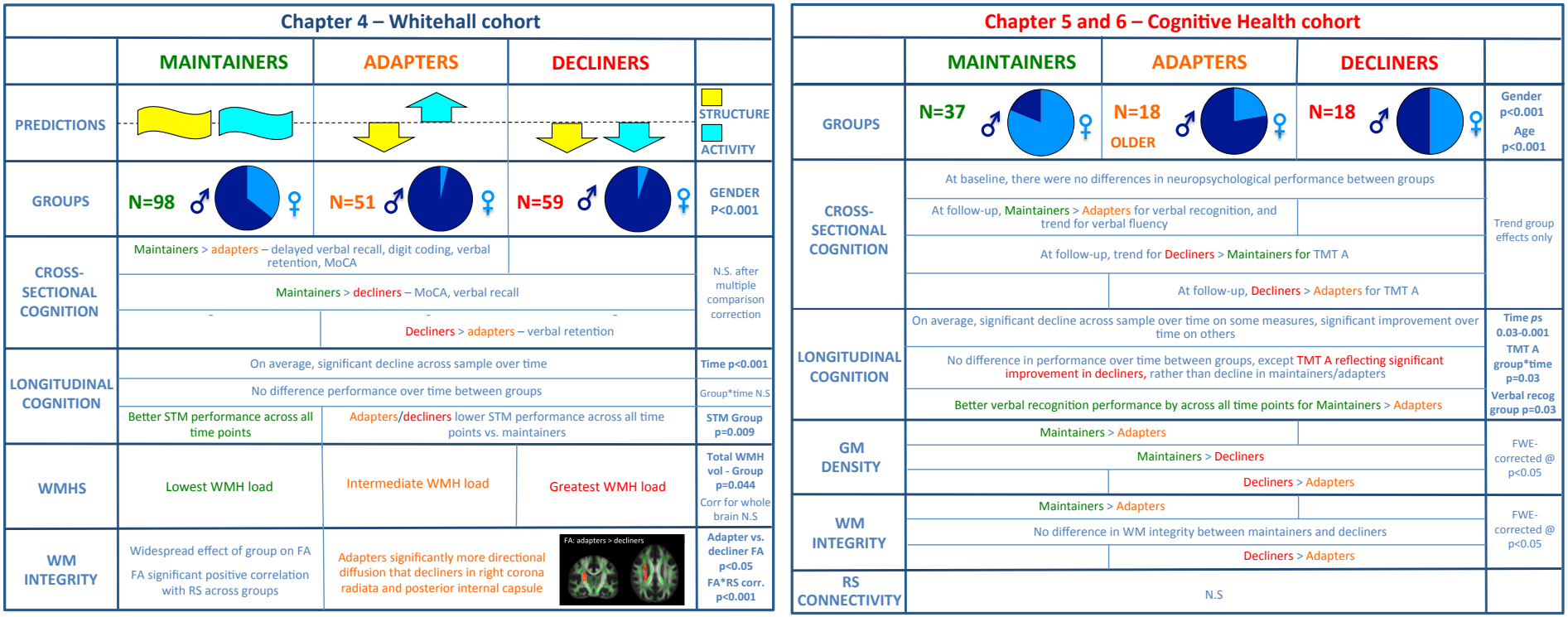


***Figure 7.1*. Overview of findings from Chapter 4, 5 and 6**

7.2. Risk and resilience

As the objective of this thesis was to investigate risk and protective factors related to cognitive variability in ageing to ultimately inform biomarkers and interventions to maximise cognition in later life, in this section I will discuss the findings of this thesis in the context of risk and resilience.

7.2.1 Risk

As discussed in Chapter 2, whilst possession of an APOE-ε4 allele increases risk of AD (Corder et al., 1993), not all ε4-carriers will develop AD. Evidence for ε4-related cognitive deficits relating to prodromal AD pathology in a subset of ε4-carriers reflects a robust effect on cognition in this subset to produce a significant group-level effect. This has not yet been capitalised on to refine cognitive markers that can cheaply identify currently healthy ε4-carriers showing the early consequences of incipient AD pathology. Furthermore, the effect(s) of APOE on CNS functions that may result in an ε4 cognitive phenotype, e.g. neuronal maintenance and repair, may also reflect a 'susceptibility' factor that contributes to increased risk of AD (Greenwood et al., 2005a) by interacting with amyloid pathways to promote or exacerbate the impact of amyloid deposition in ε4-carriers (Liu et al., 2013; Verghese et al., 2011). Greater evidence for an APOE-ε4 cognitive phenotype, and the related altered CNS function, can inform interventions to ameliorate increased AD risk in ε4-carriers.

In Chapter 3, I described that SMI is associated with increased risk of AD, but alone SMI is not sufficient to assess future risk of diagnosis. The SMI stage provides an

optimal period for intervention with disease modifying drugs for those in whom SMI is driven by preclinical pathology, before overt cognitive impairment has occurred. The MRI evidence presented in Chapter 3 supports the potential for structural MRI biomarkers in SMI to inform clinical decision-making and provide enriched samples for preclinical AD trials. Future work can identify the combination of imaging markers and other risk factors for clinical progression of SMI, e.g. family history of dementia and high education, that most precisely indicate increased risk of conversion from SMI to MCI/AD.

The results of Chapter 4-6 show that higher frontal RS does not support superior cognition in older adults, so rather than a STAC profile being a goal for interventions (e.g. Eyler et al., 2011; Park & Reuter-Lornez, 2009; Reuter-Lorenz & Park, 2014), increased frontal RS and lower GM may instead provide a neural marker to identify those at risk of poor cognitive and brain outcomes who may require intervention. Whether higher RS in 'adapters' represents attempted compensation or dedifferentiation should be explored to inform the nature these interventions will take. Further understanding of the changes in the brain that lead to higher frontal RS in older adults will also contribute to development of such interventions.

7.2.2 Resilience

Whilst Chapter 2 showed that APOE and cognition research has focused on the effect of the ε4 allele, greater understanding of the cognitive consequences of possessing a protective ε2 allele is needed. APOE-ε2 may protect cognition in later life by delaying deposition or lessening the impact of amyloid pathology, or by

promoting synaptic integrity throughout life (Suri et al., 2013). Whether APOE-ε2 is associated with specific or global effects on cognition remains to be seen. Another opportunity to investigate APOE-related resilience is the oldest ε4-carriers, who have shown superior cognitive performance compared to age-matched non-carriers. Understanding the factors that make these individuals resilient to, or at least postpone, the influence of their increased genetic risk for AD will inform interventions to ameliorate the increased risk of ε4 carriers more generally. Big data resources, such as the MRC Dementias Platform UK (DPUK; www.dementiasplatform.uk), provide novel opportunities to investigate these rare populations.

Protective factors may also contribute to the occurrence of SMI by promoting resilience to the negative impact of early AD pathology in some older adults. Some factors associated with increased risk of clinical progression of SMI, e.g. high education (e.g. Van Oijen et al., 2007; Chary et al., 2013), are also features of 'cognitive reserve' (e.g. Stern, 2012; Barulli & Stern, 2013) that may allow some individuals to cope with a greater burden of pathology before passing the threshold for cognitive impairment. SMI therefore provides a population in whom to study factors that may protect against impact of pathology and inform interventions to delay the onset of AD (e.g. Liu et al., 2012).

As Chapters 4 to 6 identified 'brain maintenance' as supporting superior cognition in later life, interventions should promote this profile of cognitive ageing to sustain cognitive abilities in later life. To inform these interventions, further research is

required to establish whether older adults who maintain a more youthful brain experience a slower rate of age-related decline (e.g. Cook et al., 2017), or have greater 'brain reserve', starting out with a bigger brain volume that can cope with age-related decline for longer (Satz et al., 2011; Barulli & Stern, 2013). Identification of the specific lifestyle and health factors that are associated with greater brain maintenance in old age will also inform interventions to promote this brain profile. As activities in midlife have been shown to have consequences for the brain in later life (e.g. Topiwala et al., 2017), lifespan and longitudinal studies will be important to determine when in the lifespan these factors are most important for later brain health.

7.3. Future directions

In the final part of this chapter, I will propose some future directions for research stimulated by the results of this thesis.

7.3.1 Sensitive cognitive measures

As shown in Chapter 2, sensitive cognitive measures are invaluable to unmask subtle variation in cognitive abilities between individuals. Use of sensitive cognitive measures in studies of superior cognitive ageing can address the limited sensitivity of neuropsychological measures and probe for subtle difference in specific cognitive functions across groups of high-functioning older adults. Sensitive measures of executive functions, particularly inhibition of irrelevant information and top-down attentional control, may be especially relevant to how some older adults preserve cognitive abilities over time, as declines in these functions are implicated in more general age-related cognitive decline (Hasher & Zacks, 1988; Zanto & Gazzaley,

2014). Sensitive cognitive measures may also provide additional means to identify cases of SMI driven by early AD pathology. Increased clinical progression of informant-corroborated SMI (Mark & Sitskoorn, 2013) suggests that valid but subtle cognitive impairments are missed by standard neuropsychological measures, which may contribute to the inconsistent association of objective cognitive impairment with subjective concerns. Cognitive measures that test domains affected in preclinical AD, e.g. spatial navigation (Allison et al., 2016), may unmask subtle objective cognitive deficits in those with normal scores on neuropsychological tests.

7.3.2 Multivariate MRI analysis

Multivariate imaging analysis techniques provide novel ways to study the neural basis of superior cognitive ageing, in comparison to previous studies that have primarily focused on specific brain regions involved in cognitive ageing. Multivariate techniques use information from the whole brain to uncover inherent patterns in the brain, and can provide more sensitive information than single brain regions (e.g. Westman et al., 2011). Techniques that use whole-brain information to estimate 'brain age' (Cole & Franke, 2017) would be useful to investigate 'maintainer', 'adapter' and 'decliner' groups, to explore whether maintainers have a 'younger' brain age. Discrepancies between chronological and brain age may also serve as a risk marker in those with 'older' brains, and provide an opportunity to identify protective factors associated with 'younger' brain. Furthermore, data-driven multivariate methods can identify multiple latent subgroups (e.g. Eavani et al., 2016) without *a priori* predictions of group characteristics, and can combine multiple imaging modalities (e.g. Groves et al., 2012) to look for covariance across measures

of brain structure and function. In relation to this thesis, such approaches could utilise the white matter differences observed between 'maintainers', 'adapters' and 'decliners' in Chapter 4 and 6 to inform group identification, and may be able to identify more than the three groups proposed here based on existing models of neurocognitive ageing.

7.3.3 Oldest-old

The oldest-old not only provide an opportunity to understand resilience to APOE-ε4 related AD-risk (see *7.2.2. Protection*), but also provide an ideal model of superior cognitive ageing as individuals have been shown to retain unusually good cognitive function into their 80s and beyond (e.g. den Dunnen et al., 2008). Some evidence suggests that cognitively high performing oldest-old do not show the same degree of compensatory function as in younger-old adults (Daffner et al., 2011), consistent with our findings that higher frontal brain activation may reflect deterioration rather than a protective characteristic. Extremely long-lived individuals with exceptional memory performance for their age also show relatively little age-related cortical atrophy and AD pathology (e.g. Gefen et al., 2015; Harrison et al., 2012), in line with our findings that brain maintenance is associated with superior cognitive performance. Investigating the 'maintainer', 'adapter' and 'decliner' profiles in the oldest-old will provide insight into whether the neural mechanisms supporting superior cognition represents a continuum (as suggested in Chapter 6) or whether, at least in some older adults, maintaining a more youthful brain represent an alternative trajectory that supports exceptional cognition into advanced old age.

7.4. Conclusions

The aim of this thesis was to improve our understanding of risk and protective factors associated with variability in cognitive ageing. The research presented in this thesis on APOE genotype and SMI illustrates the multiple mechanisms that may contribute to cognitive variability, and promotes the value of cognitive measures and neuroimaging markers for unmasking subgroups within a heterogeneous population, necessary to inform who to target with interventions and what form these interventions will take. Applying insight gained from APOE and SMI to the study of superior cognitive ageing, I investigated whether individual differences in the brain mechanisms supporting superior cognition in later life could be identified based on brain structure and function alone. Importantly, I reported consistent findings in different datasets that robustly do not support STAC as a mechanism for superior cognitive ageing, but support brain maintenance as a neural basis of superior cognitive ability in later life. Higher RS connectivity may still serve a 'compensatory' function related to poorer grey and white matter integrity, but does not underpin preservation of a high level of cognitive performance in old age. Use of sensitive cognitive and imaging techniques, as well as unique populations such as the oldest-old, can build on the results of this thesis to provide additional information to inform markers and interventions to help to maximise cognitive ability in later life.

Appendix 1.1. Methods for investigating variability in cognitive ageing

Introduction to magnetic resonance imaging (MRI)

Magnetic resonance imaging (MRI) is a flexible, non-invasive tool that allows in-vivo imaging of living tissue. Images are acquired by using magnetic fields to manipulate protons in water, the most abundant molecule in brain tissue. In the presence of a strong external magnetic field (B_0), the protons, which are usually in random orientations, become aligned with the magnetic field, resulting in net magnetisation parallel to the B_0 (longitudinal magnetisation). Additional magnetic fields, called radiofrequency pulses, are applied to tip the protons out of alignment with the B_0, into the transverse plane (transverse magnetisation). The subsequent realignment of the protons back to the magnetic field B_0 provide the basis of the MRI signal measured by the scanner using a 'receive coil'. A third set of magnetic fields, called gradients, are also applied to make protons in different locations experience slightly different magnetic fields, allowing localisation of signals received at the 'receive coil'. Different parameters of the applied magnetic fields give rise to different MRI modalities, which can provide information about varied aspects of brain health. Therefore, by imaging the brain with MRI we can measure gross anatomy, brain activity, structural and functional connectivity, and pathology. A detailed background of MRI physics can be found in Jezzard & Clare (2001).

MRI has transformed the study of human cognitive ageing, providing a link changes in the living brain with changes in cognition with age. MRI has elucidated the spatiotemporal nature of structural changes in the brain with age, and demonstrated increases and decreases in brain activation in older adults (Grady, 2012; Raz & Rodrigue, 2006). Perhaps the most interesting insight to brain ageing gained from MRI is the remarkable variability revealed in brain structure and function in older adults (Campbell et al., 2013; Fjell et al., 2009; Raz et al., 2005; Raz et al., 2010). In the next sections, I will provide a brief overview of different methods of structural and functional imaging.

Structural MRI

Structural MRI provides information about the anatomy of the brain, including tissue densities, pathology and overall gross anatomy. Different types of structural images are acquired by manipulating the repetition time (TR), time between successive excitations, and the echo time (TE), time between excitation and acquisition.

T1-weighted imaging

T1-weighted images are commonly used structural images that provide information about the gross anatomy of the brain. Images are acquired by exploiting the T1 relaxation time, the time taken for excited protons to realign with the B_0 magnetic field, which varies between tissue types (GM, WM, CSF). Acquiring images with a short TR (and TE) gives rise to the T1-weighted image contrast, where CSF appears dark (as CSF naturally has a long T1), WM appears bright (short T1) and GM appears grey (intermediate T1). T1-weighted images are normally analysed to extract estimates of GM tissue densities. Images can be segmented into tissue types (GM, WM, CSF) or specific cortical and subcortical regions-of-interest (ROIs), and the volume within these regions can be quantified based on the image signal intensity. Voxel-based morphometry (VBM) can also be used to explore local differences in GM density between groups or covariant with a parameter of interest (e.g. cognitive scores).

T2/FLAIR imaging

T2-weighted and FLAIR images are typically acquired to look at pathology, such as white matter hyperintensities. T2-weighted images are acquired by exploiting the T2 relaxation time, how fast the magnetisation in the transverse plane decays, which again varies by tissue type. Using a long TE (and long TR), the contrast in T2-weighted images makes CSF appears bright (due to long T2 in CSF), and GM/WM appears grey. A FLAIR (FLuid Attenuation Inversion Recovery) image is a T2-weighted image with the fluid (CSF) signal suppressed, so it appears black in images. Traditionally, WMHs have been quantified based on T2/FLAIR images using visual rating scales, requiring manual inspection of images, but tools to automatically segment WMHs and calculate the total volume speed up this process.

Diffusion-weighted imaging

Microstructural properties of the brain's structural connections, such as fibre orientation, fibre density, degree of myelination, can be assessed using diffusion-weighted imaging. Diffusion imaging is based on the principle that water molecules, which diffuse freely in water (isotropic diffusion), are constrained in white matter by the fatty myelin surrounding the axon, so must diffuse along the direction in which the axon is orientated (anisotropic diffusion). In diffusion imaging, a series of images are acquired, each measuring the diffusion of water along a different orientation. Diffusion MRI sequences apply two additional magnetic fields, diffusion gradients, and if diffusion has occurred along the specified orientation, there will be attenuation of signal measured after the second gradient is applied. Several images with no diffusion weighting (b=0) are also acquired as a reference, to calculate the amount of signal loss, and therefore the amount of diffusion, for each diffusion-weighted image.

To obtain microstructural information from diffusion images, typically a diffusion tensor model is fit at each voxel of the brain, often visualised as an ellipsoid. The orientation and length of the long axis of the ellipsoid estimates the direction of the fibre and amount of diffusion in that direction, whilst the ellipsoid's width captures how restricted diffusion perpendicular to the fibre is. From these estimates, parameters that capture aspects of axonal integrity can be calculated, including fractional anisotropy (FA), which captures the degree of diffusivity (how directional diffusion is along the principle fibre orientation), mean diffusivity (MD), which represents the average diffusion over all directions, and radial diffusivity (RD), which is the average amount of diffusion perpendicular to the principle fibre orientation. In WM, FA values are high, whilst MD and RD values are low. Therefore, decline in WM integrity is associated with decreases in FA and increases in MD and RD.

Functional MRI

Functional MRI measures the brain's neuronal activity indirectly via the BOLD (blood oxygen level dependent) signal, based on changes in blood oxygenation in response

to neuronal activity. Oversupply of oxygenated blood in response to neuronal firing decreases the ratio of deoxygenated haemoglobin, which disturbs the local magnetic field at active brain regions, thus increasing the MRI signal. In contrast to 3D structural images that cover the whole brain in the X-, Y-, and Z-axes, fMRI images are 4-dimensional (4D), meaning a series of whole-brain images are acquired consecutively. Each voxel of the 4D image contains a time-varying signal, which allows brain function over time to be analysed.

Task-based fMRI

In task-based fMRI, brain activation is recorded during the presentation of stimuli, which the participant may respond to. Based on the sequence of stimuli presented, a predicted response can be modeled (representing the expected signal at a voxel if it is responding to the stimuli) and compared to the actual BOLD response at each voxel using the general linear model (GLM). Task-fMRI analysis is univariate, meaning the model is fit at each voxel separately. Statistical maps are produced to represent significant activation in response to task conditions, which are thresholded to correct for multiple comparisons across the many voxels of the brain.

Resting-state fMRI

Resting-state fMRI (rs-fMRI) is acquired in the same way as task-fMRI, except the participant is not engaged in any task. rs-fMRI reflects spontaneous fluctuations in the BOLD signal, which occurs as temporally coordinated coherent activation in spatially distributed functionally diverse brain regions. Resting-state data is analysed in a multivariate way, taking into account the time-varying signal across all brain voxels. The temporal correlation of fluctuating signals is used to estimate functional connectivity. Sets of large-scale temporally correlated brain regions form resting-state networks (RSNs), which may support core cognitive processes (Cole et al., 2010). In this thesis, rs-MRI analysis has been conducted using independent component analysis (ICA), which decomposes resting-state signal into spatially independent spatial maps and associated time courses. ICA is performed at the group level to derive RSNs based on the entire sample. A technique called dual regression is used to obtain an ‘estimate’ of group-level RSNs for each subject.

Appendix 1.2. Overview of data used in this thesis

Chapter 3 - Subjective Memory Impairment and use of MRI for identifying Alzheimer's disease risk: review and case report

For the clinical case reported in Chapter 3, data primarily came from the Oxford Project to Investigate Memory and Ageing (OPTIMA) and Deep and Frequent Phenotyping (DFP) feasibility study.

OPTIMA was a longitudinal, clinico-pathological cohort of cognitively impaired and cognitive healthy older adults established in 1988, to 'advance our understanding of the causes, treatment and prevention of dementia'. Data used here came from the Longitudinal Early AD (LEAD) cohort within OPTIMA, established in 2009, where participants completed repeated structural and functional MRI and cognitive testing over 3 years.

The DFP feasibility study was conducted to establish the feasibility and acceptability of an intensive biomarker study to combine established and novel biomarkers for measurement of change in preclinical AD. Participants diagnosed with early AD underwent repeated clinical and cognitive assessment, MRI, MEG and PET imaging, as well as collection of urine, blood and CSF markers, at one of six UK sites. In the first year of my DPhil, I was heavily involved in data collection at the Oxford site.

Other patient data came from a study by Zamboni et al. (2013) and medical notes, whilst control MRI scans were obtained from the Oxford Parkinson's Disease Centre (OPDC), Filippini et al. (2012) and Zamboni et al. (2013).

Appendix Table 1.A. MRI sequence details for Chapter 3 Clinical Case					
	Patient				Controls
	2009	2012	2014	2015	
Sequence	MPRAGE	MPRAGE	MPRAGE	MPRAGE	MPRAGE
TR	2040ms	2040ms	2000ms	2000ms	2040ms
TE	4.7ms	4.68ms	1.99ms	1.99ms	4.7ms
TI	900ms	900ms	880ms	880ms	900ms
Flip angle	8°	8°	8°	8°	8°
Voxel dim, mm^3	1.0x1.0x1.0	1.0x1.0x1.0	1.0x1.0x1.0	1.0x1.0x1.0	1.0x1.0x1.0
Field of view	192mm	200mm	256mm	256mm	192mm
Acquisition time	6 mins	6mins	5mins	5mins	6 mins

Chapter 4 – Individual differences in neural mechanisms of superior cognitive ageing

Data for Chapter 4 primarily came from the Whitehall-II imaging sub-study. The Whitehall-II longitudinal cohort was established at UCL in 1985 with the aim of investigating the effect of social circumstances on health, and consists of 10,308 British civil servants. In the Whitehall-II imaging sub-study, 800 volunteers were randomly recruited from the 6035 participants that completed Phase 11 clinical examination in 2012-2013. Participants in the Whitehall-II imaging sub-study underwent a multi-modal MRI scanning session, detailed clinical and neuropsychological assessment, and provided blood and mucosal samples. The Whitehall-II imaging sub-study protocol is descripted in full in (Filippini et al., 2014). The old and young sample used to define age-affected ROIs were originally collected for a study investigating the effect of APOE on the brain (Filippini et al., 2011; Filippini et al., 2009).

During my DPhil, I was involved in collection of MRI and neuropsychological data for the Whitehall-II imaging sub-study.

Appendix Table 1.B. MRI sequence details for Chapter 4 Whitehall cohort				
	STRUCTURAL		**RESTING**	**DIFFUSION**
Sequence	Multi-echo T1	FLAIR	Multi-band, 6	Single shell
TR (ms)	2530ms	9000ms	1300ms	8900ms
TE (ms)	1.79ms/3.65ms /5.51ms/7.37ms	73.0ms	40ms	91.2ms
TI (ms)	1380ms	-	-	-
Flip angle	7°	150°	66°	-
Voxel dim, mm^3	1.0x1.0x1.0	0.9x0.9x3.0	2.0x2.0x2.0	2.0x2.0x2.0
Field of view (mm)	256mm	220mm	192mm	192mm
No. of volumes	1	1	460	-
Diffusion directions	-	-	-	60
B value (s/mm3)	-	-	-	1500
Acquisition time	6 mins	4 mins	10min	10mins

Chapter 5 and 6 – Longitudinal cognition and MRI in healthy older adults

Baseline data for Chapter 5 and 6 came from two studies conducted between 2012-2014, the Cognitive Health in Ageing computerised intervention study (MSD-IDREC-C1-2012-113) and the Cognitive Health in Ageing Exercise study (10/H0605/48).

In the computerised intervention study, participants completed a four-week mental-imagery based computerised cognitive training intervention, designed to investigate whether promoting positive affect (Blackwell et al., 2015) could increase cognitive function in older adults. Participants completed cognitive assessments pre- and post-training, as well as after a follow-up period, and also completed MRI & MEG scanning on completion of training. The main results of the intervention are reported in Murphy et al. (2015). In short, the intervention succeeded in boosting positive affect, but there were no transfers to cognition. The data used in this thesis were from the post-training cognitive and MRI assessment. I was a research assistant on this project, so was responsible for data collection and analysis.

In the exercise study, participants took part in a 12-week physical exercise programme to study the impact on cognition and brain structure and function in cognitively healthy older adults. Participants completed cognitive assessments and MRI scanning pre- and post-training, as well as after a follow-up period. The data used in this thesis were from the post-training cognitive assessment and pre-training MRI scan.

Participants that took part in either baseline study were invited to take part in the 'Longitudinal investigation of individual differences in the neural mechanisms of cognitive ageing" study (R47658/RE001). This study was conceived and data collected directly for this thesis. Data were primarily collected by me, with help from 3 research assistants/students.

Appendix Table 1.C. Chapter 5 & 6 Baseline T1 sequence details		
Baseline cohort	**CHA**	**Exercise**
Sequence	MPRAGE	Multi-echo
TR (ms)	2040ms	2530ms
TE (ms)	4.7ms	1.79ms/3.65ms/ 5.51ms/7.37ms
TI (ms)	900ms	1380ms
Flip angle	8°	7°
Voxel dim, mm^3	1.0x1.0x1.0	1.0x1.0x1.0
Field of view (mm)	192mm	256mm
Acquisition time	6 mins	6min 30sec
Scanner	Siemens Trio	Siemens Verio

Appendix Table 1.D. Chapter 5 & 6 Baseline resting-state sequence details		
Baseline Resting-state	**CHA**	**Exercise**
Sequence	EPI	Multi-band, 6
TR (ms)	2000ms	1300ms
TE (ms)	28ms	40ms
Flip angle	89°	66°
Voxel dim, mm^3	3.0x3.0x3.5	2.0x2.0x2.0
No. of volumes	300	460
Acquisition time	10mins	10mins
Scanner	Siemens Trio	Siemens Verio

Appendix Table 1.E. Chapter 6 Follow-up MRI sequence details			
	STRUCTURAL	**RESTING**	**DIFFUSION**
Sequence	MPRAGE	Multi-band 8	Single shell
TR (ms)	1900ms	730ms	3000ms
TE (ms)	3.97ms	34.6ms	80ms
TI (ms)	904ms	-	-
Flip angle	8°	52°	80°/180°
Voxel dim, mm^3	1.0x1.0x1.0	2.0x2.0x2.0	1.5x1.5x1.5
Field of view (mm)	192mm	192mm	204mm
No. of volumes	1	825	-
Diffusion directions	-	-	64
B value (s/mm3)	-	-	1500
Acquisition time	5 mins 30sec	10min	3min + 3min
Scanner	Siemens Prisma		

Summary of neuropsychological measures used

Here, the neuropsychological measures used in this thesis are briefly described.

Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005): The MoCA is a cognitive screening tool assessing a range of cognitive abilities, including executive function, 3D drawing, clock drawing, verbal immediate and delayed recall, serial subtraction, verbal abstraction, verbal fluency (see below), object naming and orientation. The maximum score is 30.

Verbal Fluency (Nasreddine et al., 2005): Participants are required to say as many words as possible beginning with the letter 'S' in 60 seconds. No maximum score.

Category Fluency (Hsieh et al., 2013): Participants are required to say as many words as possible from a particular category (animals) in 60 seconds. No maximum score.

Trail Making Test (TMT; Lezak et al., 2004): This test of speed and executive functions consists of two parts, A) connecting 25 numbered dots in ascending order, and B) connecting alternating numbers and letters in ascending order, using pencil and paper as fast and as accurately as possible. Scored as time in seconds to complete each task, therefore lower values represent better performance. The difference between trails B and A can be calculated to reflect the cost of the switching component in part B.

Rey-Osterrieth Complex Figure (RCF; Meyers & Meyers, 1995): This task requires participants to copy a complex geometric design, and then draw it again from memory immediately after copying, and again after a delay. Immediate and delayed recall scores both have a maximum of 36, with participants drawing points for each element of the drawing that is correct. Participants finally complete a recognition test, where they are required to correctly identify which sub-elements of geometrics figures were part of the copied figure, and which were not. The maximum recognition score is 12, representing 12 true positive and 0 false positive responses (also called discrimination index).

Hopkins Verbal Learning Test (HVLT; Brandt & Benedict, 2001): Participants learn a list of 12 words over three trials. Immediate recall score: total items corrected recalled across the three trials; maximum score 36. Learning score: the greater of items recalled on trial 2 or 3 minus items recalled on trial 1. Minimum: 0, maximum: 12. After a delay, participants must recall as many items as they can remember. Delayed recall score: total items correctly recalled after the delay; maximum score 12. Retention: number of items correctly recalled after the delay as a percentage of the greater of items immediately recalled on trial 2 or 3. Participants also complete a recognition test, where they must correctly identify which words were on the learned list, and which were not. The maximum recognition score is 12, representing 12 true positive and 0 false positive responses (also called discrimination index).

Digit span (Wechsler, 2008): In this test of short-term and working memory, participants must recall a series of numbers of increasing length in the forwards,

backwards and sequential (smallest to biggest) orders. Maximum score for each is 16.

Digit coding (Wechsler, 2008): Participants are given nine symbols each paired with a number (1-9) and must add as many symbols as possible that corresponds to a grid of numbers in two minutes. Maximum score is 135.

Test of Premorbid Function (TOPF, Wechsler, 2009*)*: Participants must read aloud a list of 70 written words of increasing complexity, and score a point for correct pronunciation. Raw scores are converted into estimated full-scale IQ. Maximum raw score is 70.

Reasoning – Alice Heim test (Heim, 1970): Participants must complete 65 verbal and mathematical reasoning items in 10 minutes. Maximum raw score is 65.

Immediate free recall (see Singh-Manoux et al., 2003): Participants are presented with a list of 20 words and must immediate recall as many as possible in writing, in 2 minutes. Maximum raw score is 20.

Vocabulary – Mill Hill (Raven, 1958): Participants are must choose the correct definition of a word (33 words in total) from 6 choices. Maximum raw score is 33.

Mini-Mental State Examination (MMSE; Folstein et al., 1975): A cognitive screening tool, consisting of measures of orientation, language, verbal recall and attention. Maximum score is 30.

Appendix 2. Definition of cognitive domains for Tables 2.1 and 2.2

Appendix Table 2.A. Definition of cognitive measures by domain	
Episodic Memory	WMS general memory index; WMS delay index; DRS memory; CAMCOG memory; verbal & non-verbal memory composites.
Verbal Episodic Memory	Rey Auditory Verbal Learning Test; CERAD word list learning; CERAD delayed word recall; WMS logical memory; California Verbal Learning Test; WMS verbal paired associates; Buschke selective reminding; Elderly verbal learning test; Short story memory test; various verbal immediate recall, delayed recall and recognition measures.
Non-Verbal Episodic Memory	Benton Visual Retention Test; Rey-Osterrieth Complex Figure Test recall and recognition; CERAD constructional praxis recall; WMS face recognition; WMS family pictures; WMS visual paired associates; Digit-symbol recall; Memory-in-reality test; Thurstone's picture memory; Fuld object memory test; CANTAB paired associates; Global-local memory test; various immediate and delayed visual reproduction, and picture recall and recognition measures.
Semantic Memory	WAIS general knowledge; animal naming test; fact recall; semantic memory composites.
Working Memory	WMS letter-number sequencing; Digit Span Backwards; Spatial Span Backwards; Operation Span; WMS working memory subtests; WMS visual memory span; CANTAB spatial working memory; Digit ordering test; Alpha span; WAIS arithmetic; working memory composites.
Executive Function	Trail Making Test B; Wisconsin Card Sorting Test; Stroop test; Tower of Hanoi; Rapid Visual Information Processing; Colour trails test B; Delis-Kaplan Executive Function System; D-KEF switching; Colour Word Inference Test; Figural fluency; Visual elevator test; Opposites; Figures of Speech; Set shifting; Symbol Letter Modalities Test*; Symbol Digit Modalities Test*; Digit Symbol Substitution*; WAIS symbol coding*.
Attention	Digit Span Forwards; Spatial Span Forwards; Paced Auditory Serial Addition; WMS attention index; DRS attention; attention composites.
Speed of Processing	Controlled Oral Word Association Test‡; Verbal fluency‡; CASI fluency‡; Trail Making Test A; Colour trails test A; WAIS symbol search; WAIS symbol coding*; Symbol Letter Modalities Test*; Symbol Digit Modalities Test*; Digit Symbol Substitution*; Random letter test; Alphabet coding test; design fluency^; speed composites.
Visuospatial Processing	WAIS block design; Constructional praxis; MMSE praxis; Clocks test; Line judgement; Rosen drawing; various figure copy; WMS picture completion; CASI visual construction; design fluency^; visuospatial

	composites.
Language	Controlled Oral Word Association Test‡; Verbal fluency‡; CASI fluency‡; Boston Naming Test; WAIS vocabulary; WAIS comprehension; Shipley vocabulary test; Lexical decision making; Auditory comprehension; Mill Hill Synonyms; Token test; WRAT reading; Spot-the-word lexical decision making
Intelligence	WAIS information/abstraction; WAIS similarities; Matrix reasoning; Moray House test; Raven's matrices; WAIS full-scale IQ; WASI estimated IQ: Figure Logic; Abstract reasoning; DRS conceptualization; National Adult Reading Test; Wechsler test of adult reading; Adult naming test; Heim intelligence test; CASI abstraction/judgement; WTAR-estimated IQ.
Global Cognition	MMSE; DRS total; Armed Forces Qualification Test; MoCA; global cognition composite.
Other	Cognitive asymmetry; reaction times; mirror learning; finger tapping; pegboard test; priming; achievement test; DRS initiation/preservation; composite of selected subdomains.

Abbreviations: CASI - Cognitive Abilities Screening Instrument; CERAD – Consortium to Establish a Registry for Alzheimer's Disease; D-KEF- Delis-Kaplan Executive Function; DRS – Dementia Rating Scale; MMSE – Mini-Mental State Examination; MoCA - Montreal Cognitive Assessment; WAIS – Wechsler Adult Intelligence Scale; WASI – Wechsler Abbreviated Scale of Intelligence; WMS – Wechsler Memory Scale; WRAT – Wide Range Achievement Test; WTAR – Wechsler Test of Adult Reading. *Symbols*: *test comes under speed of processing and executive functions; ^test comes under speed of processing and visuospatial processing; ‡test comes under speed of processing and language.

Appendix 3. Detailed methods and supplementary results for SMI and MRI

Supplementary Methods

Data

Patient cognitive scores from 1994-2009 were obtained from medical notes. Subsequent cognitive and MRI scores were acquired in a series of research studies: 2010-2013 – Oxford Project to Investigate Memory and Ageing (OPTIMA); 2012 – Zamboni et al. (2013); 2014-2015 – Deep and Frequent Phenotyping (DFP) pilot study. Control MRI scans were obtained from the Oxford Parkinson's Disease Centre (OPDC), Filippini et al. (2012) and Zamboni et al. (2013). Age- and education-matched normative cognitive data were obtained from Brandt & Benedict (2001), Crowe et al. (2010) and Crum et al. (1993).

MRI analysis

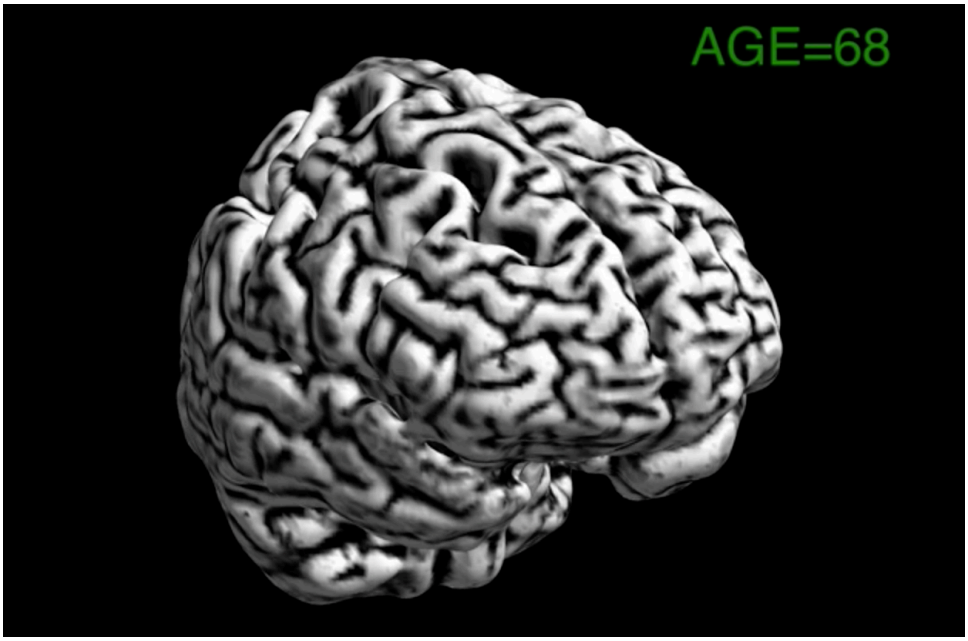
Four T1 structural MRI scans of the patient's brain, acquired between 2009 and 2015, were compared with cross-sectional structural scans from 27 elderly female controls (aged 66-76; mean=71.1 years), all with MMSE scores ≥28 (mean=29.6). Details of MRI sequences are included in *Appendix 1.2*. Written informed consent was obtained from all participants. Imaging data analysis was carried out using FSL tools (FMRIB's Software Library, http://fsl.fmrib.ox.ac.uk/; Smith et al., 2004). Structural scans were pre-processed using an in-house tool (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/fsl_anat). For *Figure 3.1*, the patient's four structural scans were aligned to a common space, firstly using affine registration to the middle time point (2012 scan) with 6 degrees-of-freedom (DOF), then registered to the MNI152 1mm isotropic standard brain with 12 DOF, using FMRIB's Linear Image Registration Tool (FLIRT; Jenkinson et al., 2002). For *Figure 3.2*, T1 images brain extracted using BET (Brain Extraction Tool; Smith, 2002) and brain tissues were segmented using FMRIB's Automated Segmentation Tool (FAST; Zhang et al., 2001) to create partial volume estimates (PVE) for GM, WM and CSF. GM volume was extracted within masks of the four cerebral lobes, based on the MNI Structural Atlas

(http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases), as well as hippocampal masks segmented using FIRST (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FIRST), an automated model-based tool for segmentation of subcortical brain structures.

Cognition

Full longitudinal scores are detailed in *Appendix Table 3.A*. There were two further time points 2011/01 and 2012/02 not included in the table, where only the MMSE was conducted. Scores were 26/30 and 27/30, respectively, at these time points.

Supplementary results



Appendix Figure 3.A. **Screenshot from 3D movie illustrating the progression of cortical and hippocampal atrophy in early Alzheimer's disease (from age 68 to 74).**

Serial T1-weighted MRI scans taken in a female since diagnosis of Alzheimer's disease aged 68 unmistakably illustrate progressive *in-vivo* hippocampal atrophy over 6 years, which paralleled the progression of cognitive decline.

Year of visit	1994/01	2003/03	2003/08	2008/03	2008/10	2009/03	2009/10*	2010/07^	2012/07	2013/11	2014/12	2015/01	2015/03
Age at visit, years	52	61	62	66	67	67	68	68	70	72	73	73	73
Setting of acquisition	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Research	Research	Research	Research	Research	Research	Research
Neuropsychology													
MMSE	NT	**30/30**	NT	**29/30**	NT	**26/30**	**26/30**	**24/30**	**26/30**	**26/30**	**22/30**	NT	NT
HVLT – immediate	NT	**22/36**	NT	**23/36**	NT	**21/36**	NT	**7/36**	**15/36**	**13/36**	**11/36**	**5/36**	**12/36**
HVLT - delay	NT	**11/12**	NT	NT	NT	NT	NT	**1/12**	**0/12**	**0/12**	**0/12**	**0/12**	**0/12**
HVLT – recognition	NT	NT	NT	**12/12**	NT	**11/12**	NT	**4/12**	**5/12**	**3/12**	**3/12**	**2/12**	**4/12**
CLOX 1	NT	**14/15**	NT	**15/15**	NT	**15/15**	NT	**15/15**	**15/15**	**15/15**	**15/15**	NT	NT
CLOX 2	NT	**15/15**	NT	**15/15**	NT	**15/15**	NT	**15/15**	**15/15**	**15/15**	**15/15**	NT	NT
MoCA	NT	NT	NT	NT	NT	NT	**23/30**	NT	**24/30**	**23/30**	NT	NT	NT
Graded naming test	**29/30**	NT	**29/30**	NT	**>99th per.**	NT	NT	NT	**28/30**	**29/30**	NT	NT	NT
WAIS verbal IQ	**126**	NT	NT	NT	**118**	NT	NT	NT	NT	NT	NT	NT	NT
WAIS perform. IQ	**115**	NT	NT	NT	**114**	NT	NT	NT	NT	NT	NT	NT	NT
WAIS full scale IQ	**125**	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT
WAIS digit span	**15**	NT	**15**	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT
WAIS vocabulary	**16**	NT	**16**	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT
WAIS similarities	**14**	NT	**14**	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT
WAIS picture comp.	**11**	NT	**12**	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT
WAIS block design	**13**	NT	**12**	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT
WAIS digit symbol	**12**	NT	**11**	NT	**98th per.**	NT	NT	NT	NT	NT	NT	NT	NT
Forward digit span	**9**	NT	**8**	NT	**7**	NT	**7**	NT	NT	NT	NT	NT	NT
Backwards digit span	**6**	NT	**6**	NT	**5**	NT	**4**	NT	NT	NT	NT	NT	NT
Paragraph recall imm.	**10.75**	NT	**+0.39**	NT	**16th per.**	NT	NT	NT	NT	NT	NT	NT	NT
Paragraph recall delay	**7.25**	NT	**-0.35**	NT	**10th per.**	NT	NT	NT	NT	NT	NT	NT	NT
BVRT – correct	**7**	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT
BVRT – errors	**7**	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT
Complex figure – copy	**32/36**	NT	**36/36**	NT	NR	NT	NT	NT	NT	NT	NT	NT	NT
Complex figure – delay	**12/36**	NT	**20/36**	NT	NR	NT	NT	NT	NT	NT	NT	NT	NT
List learning, trials 1-5	NT	NT	**+1.5**	NT	**10th per.**	NT	NT	NT	NT	NT	NT	NT	NT
List learning, delay	NT	NT	**+1.0**	NT	**2-5th per.**	NT	NT	NT	NT	NT	NT	NT	NT
Phonological fluency	NT	NT	**+1.07**	NT	**>99th per.**	NT	NR	NT	NR	NR	NT	NT	NT
Semantic fluency	NT	NT	**+3.91**	NT	**99th per.**	NT	**30**	NT	NT	NT	NT	NT	NT
Trail making A	NT	NT	**50-75th p**	NT	**75th per.**	NT	NT	NT	NT	NT	NT	NT	NT
Trail making B	NT	NT	**75-90th p.**	NT	**75th per.**	NT	NT	NT	NT	NT	NT	NT	NT
Stroop	NT	NT	**+0.98**	NT	**84th per.**	NT	NT	NT	NT	NT	NT	NT	NT
Clinical measures													
HADS – anxiety	NT	NT	**5**	NT	**8**	NT	NT	NT	NT	NT	NT	NT	NT
HADS – depression	NT	NT	**4**	NT	**4**	NT	NT	NT	NT	NT	NT	NT	NT
GDS	NT	NT	NT	NT	NT	NT	**3**	**3**	**2**	**3**	**0**	NT	NT
NPI	NT	NT	NT	NT	NT	NT	**0**	**0**	**1**	**2**	**0**	NT	NT
CDR	NT	NT	NT	NT	NT	NT	**0.5**	**0.5**	NR	NR	**1**	NT	NT
BADLs	NT	NT	NT	NT	NT	NT	**2**	**0**	**0**	**2/7**	**6**	NT	NT
Neuroimaging													
Cortical volumes													
Frontal lobe	NT	NT	NT	NT	NT	NT	**93190.5**	NT	**86866.7**	NT	**70182.9**	NR	**67411.8**
Temporal lobe	NT	NT	NT	NT	NT	NT	**65755.9**	NT	**58787.1**	NT	**47663.9**	NR	**47655.9**
Parietal lobe	NT	NT	NT	NT	NT	NT	**59290.7**	NT	**56791.8**	NT	**52563.2**	NR	**52824.8**
Occipital lobe	NT	NT	NT	NT	NT	NT	**51843.3**	NT	**49860.9**	NT	**47168.2**	NR	**46682.6**
Subcortical volumes													
R hippocampus	NT	NT	NT	NT	NT	NT	**2530.0**	NT	**2216.8**	NT	**1946.0**	NR	**1845.0**
L hippocampus	NT	NT	NT	NT	NT	NT	**2601.0**	NT	**2274.3**	NT	**2000.0**	NR	**1935.0**

Year of visit: YYYY/MM format; * indicates MCI diagnosis given; ^ indicates probable AD diagnosis given. *Neuropsychology and clinical measures*: +/- values are Z-scores; *N*th values are percentiles; all other values are raw scores. *Abbreviations*: NT - not tested; NR - not reported (measures were administered but scores were not obtainable); MMSE – Mini-Mental State Examination; HVLT – Hopkins Verbal Learning Test; MoCA – Montreal Cognitive Assessment; WAIS – Wechsler Adult Intelligence Scale; BVRT – Benton Visual Retention Test; HADS – Hospital Anxiety and Depression Scale; GDS – Geriatric Depression Scale; NPI – NeuroPsychiatric Inventory; CDR – Clinical Dementia Rating; BADLs – Bristol Activities of Daily Living; R – right; L – left.

Appendix Table 3.A. **Longitudinal neuropsychometric and neuroimaging measures for a clinical case of persistent subjective memory impairment**

Appendix 4. Supplementary methods and results for Chapter 4

Supplementary Methods – ROI definition:

Sample

27 healthy community-dwelling older adults aged 50 to 78 and 27 healthy young adults aged 20 to 35 (demographics shown in *Table 4.1*). Data were originally collected for a study investigating the effect of APOE on the brain (Filippini et al., 2009; Filippini et al., 2011). All participants were right-handed and had no current or history of neurological or psychiatric disorders, memory complaints, head injury, substance abuse (including alcohol), hypertension or corticosteroid therapy. All older adults scored over 95 on the Addenbrooke's Cognitive Examination – Revised (ACE-R; Mioshi et al., 2006). The sample in Filippini et al. (2012) was smaller, as participants were sub-selected to ensure a 'normal' APOE distribution (Menzel et al., 1983). In our expanded sample, there was no significant difference in the proportion of APOE-ε4 carriers between age groups (see *Table 4.1*).

MRI acquisition

Participants were scanned on the 3T Siemens Trio System (Siemens, Erlangen, Germany) at the Oxford Centre for Magnetic Resonance Imaging (OCMR), using a 12-channel head coil. *Resting-state fMRI:* Functional imaging was performed using a gradient echo EPI sequence, during which participants were instructed to lie in dimmed light with their eyes open, think of nothing in particular and not fall asleep. *Structural MRI:* A 3D high-resolution T1-weighted image was acquired using an MPRAGE sequence.

Resting-state fMRI processing

Pre-processing was carried out as for the classification sample, except spatial smoothing with a Gaussian kernel of full-width at half maximum (FWHM) of 5mm was applied before FIX, rather than after, due to use of different training data for FIX denoising. Due to differences in bias between old and young participants relating to

differing sensitivity to the head coil (Filippini et al., 2012), each individual fMRI image in the ROI sample was bias corrected using a bias estimate derived from the resting-state data. Bias-corrected images were fed into a group-level ICA, where individual participant scans were temporally concatenated into a single 4D file and decomposed into 30 components. Resulting components were visually inspected to identify the frontal network and artefactual components, of which 5 were identified. These six components were then used as input to a dual regression analysis (following Griffanti et al., 2016a), where first, the group components are entered in a linear regression to estimate the associated time course in each individual subject, and second, this time course is used to estimate subject-specific spatial maps. Voxel-wise age group statistical comparisons were performed on the subject-specific spatial maps using non-parametric permutation testing (Winkler et al., 2014) with cluster-based thresholding (clusters determined by Z>2.3) and a family-wise error (FWE) corrected cluster significance threshold of $p<0.05$ applied to suprathreshold clusters.

Structural MRI processing

Whole-brain structural data were analysed using a voxel-based morphometry (VBM) approach (Douaud et al., 2007). Briefly, structural images were brain extracted and segmented by tissue type. The resulting GM partial volume estimates (PVE) were aligned to standard space using non-linear registration (FNIRT), averaged, flipped along the x-axis and re-averaged to create a study-specific GM template. GM PVEs were then non-linearly re-registered to the study-specific template, and modulated by the Jacobian to correct for local expansion and contraction resulting from the non-linear spatial transformation. Modulated GM images were then spatially smoothed using an isotropic Gaussian kernel of 5mm. A voxel-wise GLM was applied using non-parametric permutation testing, with cluster-based thresholding (clusters determined by Z>2.3), and a FWE corrected cluster significance threshold of p<0.05 applied to supratheshold clusters.

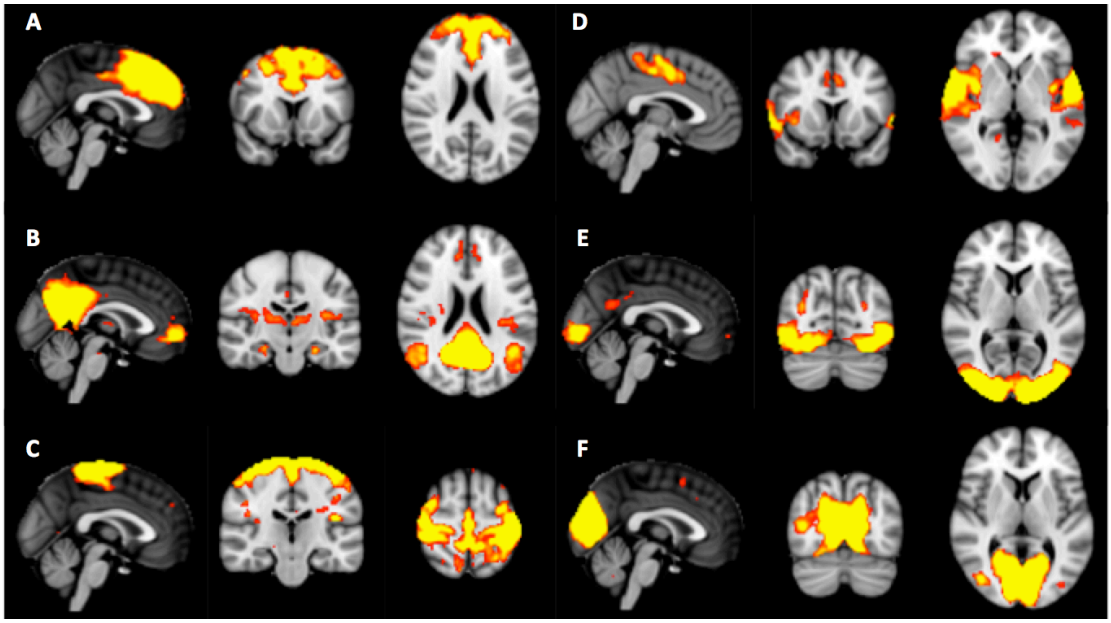
Supplementary results – ROI definition

Age effect on structural MRI

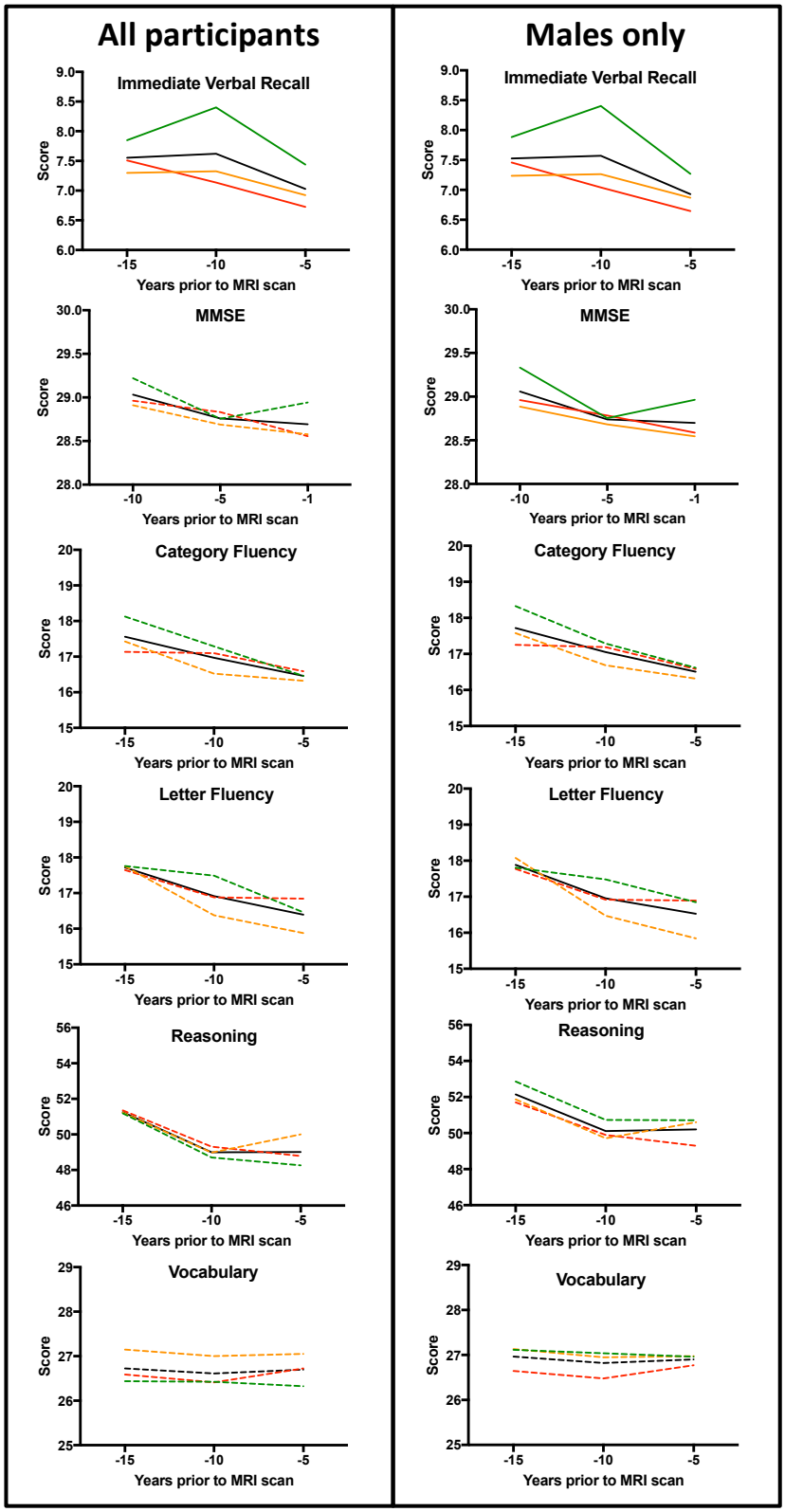
Older adults showed widespread reduction in GM density relative to younger adults, replicating the findings of Filippini et al. (2012). Reduced GM volume in older adults was found in distributed range of regions, including anterior and posterior cingulate, precuneus, middle temporal gyrus, insula, inferior, middle and superior frontal gyri, pre-and post-central gyrus, lateral occipital cortex, thalamus, caudate and cerebellum (see *Figure 4.2*).

Age effect on resting-state fMRI

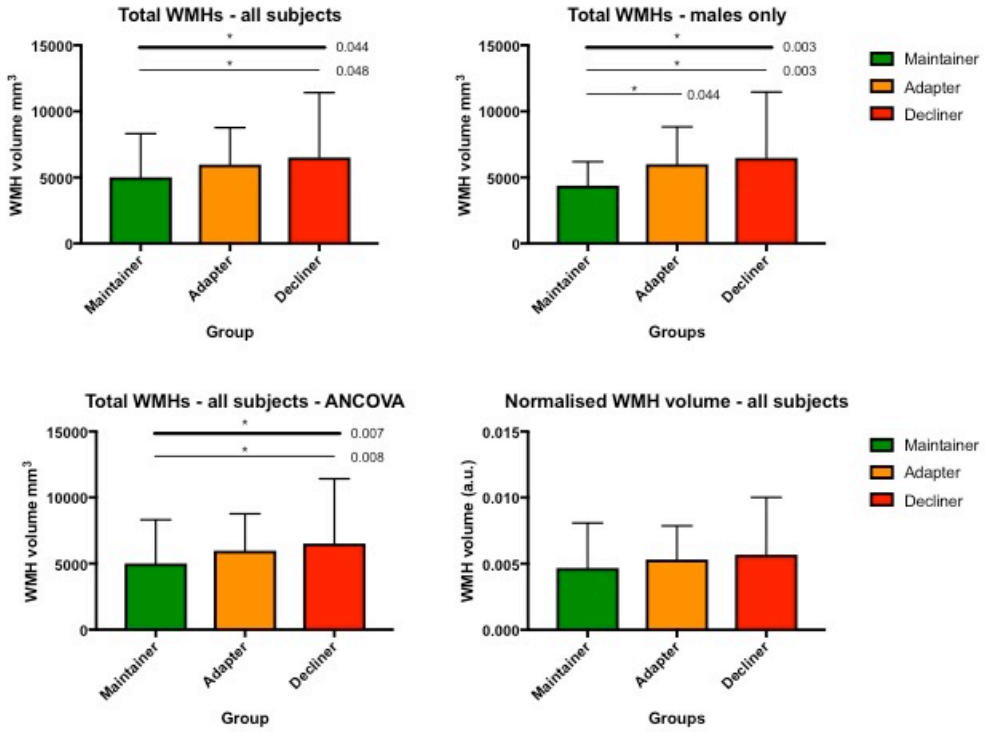
In total, 6 components were identified as RSNs (see *Appendix Figure 4.A*) including frontal, default mode network, sensorimotor, auditory, lateral visual and medial visual networks. Significantly increased temporal correlation was identified with the frontal RSN of older adults showed significantly compared to younger adults, replicating Filippini et al. (2012). The regions of significant difference included prefrontal cortex, superior, middle and inferior frontal gyri, precuneus, insula, thalamus, central operculum, intracalcarine sulcus and occipital fusiform regions (see *Figure 4.2*).



Appendix Figure 4.A. **Resting-state networks identified in group-ICA of old and young participants.** Identified RSNs included frontal (A), default mode (B), sensorimotor (C), auditory (D), lateral visual (E) and medial visual (F) networks.



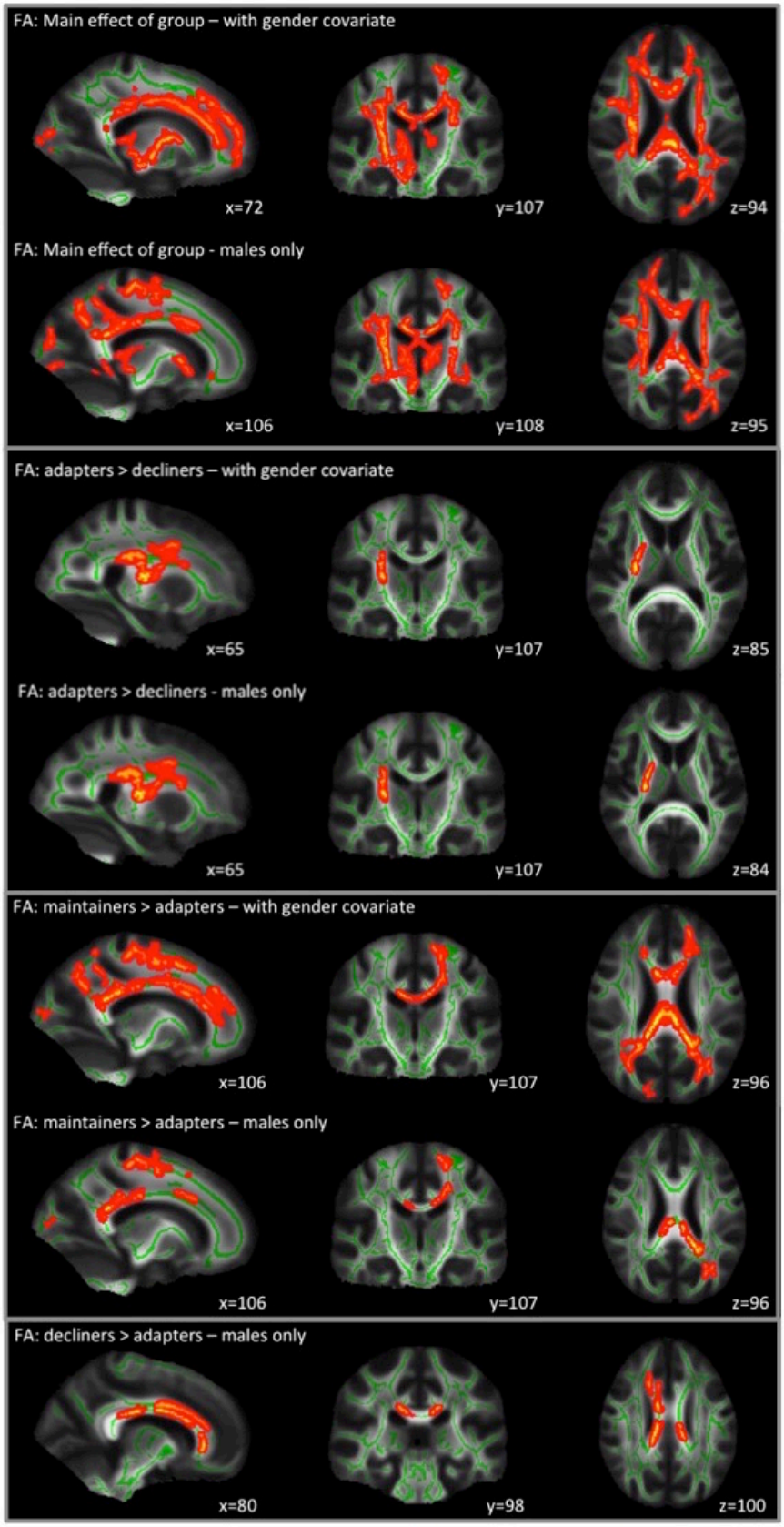
Appendix Figure 4.B. **Longitudinal neuropsychological performance for all subjects vs. males only.** Green - maintainers, orange - adapters, red – decliners, black – mean of all three groups; solid black lines indicate significant main effect of time; solid coloured lines indicates significant main effect of group.



Appendix Figure 4.C. White matter hyperintensity load by group.

Results are shown from one-way ANOVA of total WMH volume for all participants, controlling for gender (ANCOVA) and with males only, as well as for normalised WMH volume with all participants.

Appendix Table 4.A. **Demographical information for groups, shown for full sample and males only**				
Full sample	**Maintainers (N=98)**	**Adapters (N=51)**	**Decliners (N=59)**	***p***
Age, years	68.6 (4.7)	70.3 (5.0)	69.0 (5.7)	0.17
Education, years	14.4 (3.2)	14.9 (3.2)	15.3 (3.2)	0.24
Sex, % female	35.7%	3.9%	5.4%	<0.001
APOE, % ε4-carriers	20.9%	19.1%	34.0%	0.14
TOPF-estimated IQ	115.5 (7.6)	116.2 (7.6)	115.5 (6.2)	0.84
Males only	**Maintainers (N=64)**	**Adapters (N=49)**	**Decliners (N=56)**	***p***
Age, years	68.8 (4.9)	70.3 (4.9)	68.8 (5.7)	0.21
Education, years	14.7 (3.5)	14.8 (3.2)	15.5 (3.1)	0.39
APOE, % ε4-carriers	20.0%	22.4%	35.3%	0.17
TOPF-estimated IQ	115.6 (7.1)	116.1 (7.7)	115.6 (6.4)	0.93
Values represent mean (SD) unless otherwise stated. Abbreviations: APOE – apolipoprotein E; p – p-value; TOPF – Test of Premorbid Function, IQ – intelligent quotient.				



***Appendix Figure 4.D*. Results of TBSS analysis comparing FA between groups, controlling for gender and with males only. Coordinates in anatomical space.**

Appendix Table 4.B. **Cross-sectional neuropsychological performance between groups**																							
	All participants														**Males only**								
	Mean (SD)			**ANOVA all subs**			**Post-hoc**			**ANCOVA**			**Post-hoc**			**Mean (SD)**			**ANOVA**			**Post-hoc**		
Measure	M	A	D	F	*p*	η_p^2	M vs. A	M vs. D	A vs. D	F	*p*	η_p^2	M vs. A	M vs. D	A vs. D	M	A	D	F	*p*	η_p^2	M vs. A	M vs. D	A vs. D
MoCA	28.3 (1.3)	27.8 (1.2)	27.9 (1.2)	3.99	0.02	0.04	*t*	*t*	*ns*	3.34	0.04	0.03	*t*	*t*	*ns*	28.4 (1.2)	27.9 (1.2)	27.8 (1.2)	4.17	0.02	0.05	*t*	*	*ns*
Category fluency	23.7 (5.3)	22.0 (5.8)	22.9 (5.3)	1.67	0.19	0.02	*ns*	*ns*	*ns*	2.31	0.10	0.02	*ns*	*ns*	*ns*	24.1 (5.1)	22.3 (5.7)	22.8 (5.4)	1.83	0.16	0.02	*ns*	*ns*	*ns*
Letter fluency	16.3 (4.0)	15.5 (3.9)	16.5 (4.3)	0.82	0.44	0.01	*ns*	*ns*	*ns*	0.75	0.48	<0.01	*ns*	*ns*	*ns*	16.0 (3.9)	15.6 (4.0)	16.4 (4.0)	0.57	0.57	0.01	*ns*	*ns*	*ns*
TMT A	27.5 (6.8)	29.5 (8.4)	27.7 (9.3)	1.07	0.35	0.01	*ns*	*ns*	*ns*	1.29	0.28	0.01	*ns*	*ns*	*ns*	27.3 (7.5)	29.2 (8.4)	27.7 (9.6)	0.72	0.49	0.01	*ns*	*ns*	*ns*
TMT B	58.7 (22.3)	62.0 (25.6)	56.8 (21.2)	0.71	0.49	0.01	*ns*	*ns*	*ns*	0.82	0.44	0.01	*ns*	*ns*	*ns*	58.8 (22.9)	60.3 (23.6)	56.4 (21.7)	0.40	0.67	0.01	*ns*	*ns*	*ns*
RCF copy	32.0 (3.1)	31.3 (3.4)	31.5 (3.5)	1.04	0.35	0.01	*ns*	*ns*	*ns*	1.14	0.32	0.01	*ns*	*ns*	*ns*	32.1 (3.2)	31.4 (3.4)	31.4 (3.5)	0.90	0.41	0.01	*ns*	*ns*	*ns*
RCF delay	15.7 (5.9)	17.2 (6.4)	16.8 (5.2)	1.27	0.28	<0.01	*ns*	*ns*	*ns*	0.40	0.67	<0.01	*ns*	*ns*	*ns*	16.3 (5.7)	17.5 (6.2)	16.8 (5.3)	0.66	0.52	0.01	*ns*	*ns*	*ns*
HVLT total	29.7 (3.7)	28.3 (4.3)	28.3 (3.5)	3.29	0.04	0.03	*ns*	*t*	*ns*	2.35	0.098	0.02	*ns*	*ns*	*ns*	29.4 (3.9)	28.4 (4.3)	28.3 (3.6)	1.48	0.23	0.02	*ns*	*ns*	*ns*
HVLT delay	10.3 (1.7)	9.5 (2.2)	10.2 (1.4)	3.36	0.04	0.03	*	*ns*	*ns*	3.38	0.04	0.03	*	*ns*	*ns*	10.3 (1.8)	9.5 (2.2)	10.2 (1.4)	2.47	0.09	0.03	*ns*	*ns*	*ns*
HVLT retention	91.4 (10.7)	86.7 (15.5)	92.3 (9.4)	3.28	0.04	0.03	*t*	*ns*	*	3.67	0.03	0.04	*t*	*ns*	*	91.6 (11.4)	87.1 (15.7)	92.0 (9.5)	2.51	0.09	0.03	*ns*	*ns*	*ns*
BNT	57.9 (2.8)	58.0 (2.4)	58.2 (1.9)	0.20	0.82	<0.01	*ns*	*ns*	*ns*	0.23	0.80	<0.01	*ns*	*ns*	*ns*	58.3 (2.1)	58.0 (2.4)	58.2 (1.9)	0.32	0.73	<0.01	*ns*	*ns*	*ns*
Digit forward	11.1 (2.2)	11.3 (2.5)	11.5 (2.2)	0.50	0.61	0.01	*ns*	*ns*	*ns*	0.07	0.94	<0.01	*ns*	*ns*	*ns*	11.5 (2.1)	11.3 (2.5)	11.5 (2.3)	0.07	0.94	<0.01	*ns*	*ns*	*ns*
Digit backwards	9.9 (2.3)	9.9 (2.6)	10.6 (2.9)	1.70	0.19	0.02	*ns*	*ns*	*ns*	1.42	0.25	<0.01	*ns*	*ns*	*ns*	10.1 (2.2)	10.0 (2.6)	10.6 (2.9)	0.91	0.40	0.01	*ns*	*ns*	*ns*
Digit sequential	10.6 (2.4)	10.4 (2.4)	10.7 (2.5)	0.31	0.74	<0.01	*ns*	*ns*	*ns*	0.41	0.67	<0.01	*ns*	*ns*	*ns*	10.8 (2.1)	10.4 (2.5)	10.6 (2.5)	0.40	0.67	0.01	*ns*	*ns*	*ns*
Digit coding	67.3 (12.8)	61.8 (13.0)	64.6 (12.7)	3.19	0.04	0.03	*	*ns*	*ns*	2.91	0.06	0.03	*t*	*ns*	*ns*	66.4 (11.8)	62.3 (12.9)	65.4 (12.6)	1.54	0.22	0.02	*ns*	*ns*	*ns*

Abbreviations: M – maintainer; A – adapter; D – decliner; F – F statistic; p – p statistic; η_p^2 - partial eta squared; SD – standard deviation; ANOVA – analysis of variance; MoCA – Montreal Cognitive Assessment; TMT – Trail Making Test; RCF – Rey Ostereith Complex Figure Test; HVLT – Hopkins Verbal Learning Test; BNT – Boston Naming Test;; ns – non-significant >0.1; t – trend to significant <0.1, >0.05; * significant at p<0.05.

Appendix 5. Supplementary methods and results for Chapter 5

Supplementary Methods

Pre-processing of Cognitive Health in Ageing (CHA) and Exercise images was carried out as described in Chapter 5 (see *5.2.3.1 MRI pre-processing*). For the Exercise cohort, an alternative non-saturation reference image was supplied to use in motion correction and registration of resting-state images, due to the lower contrast of multi-band sequences. Spatial smoothing with a Gaussian kernel of 6mm was also applied after FIX denoising, due to the pre-processing applied to the training data used in FIX. For the CHA cohort, the default median volume from the 4D functional image was used for motion correction and registration. Spatial smoothing was applied with a 5mm Gaussian kernel before FIX denoising, due to the pre-processing applied to the training data used in FIX.

Supplementary Results

Baseline cognition - cognitive change from pre-to-post training cognitive assessments

As the post-training cognitive data were used from the baseline studies, cognitive change from pre-to-post intervention was checked to ensure change was similar across participants/cohorts *Appendix Figure 5.A* shows the pre-post training change scores across participants. The average change for almost all measures is close to 0, indicting little mean change pre-and post training. The mean change for the total sample is very similar to that for CHA and exercise groups separately.

Repeated measures ANOVA of pre and post training cognitive scores revealed significant improvement at post-training on verbal fluency [$F(1,77)=13.40$, $p<0.001$, $\eta^2=0.15$], category fluency [$F(1,77)=5.28$, $p=0.02$, $\eta^2=0.06$], TMT A [$F(1,77)=5.35$, $p=0.02$, $\eta^2=0.07$], TMT B [$F(1,77)=5.03$, $p=0.03$, $\eta^2=0.06$], digit span backwards [$F(1,77)=8.44$, $p=0.005$, $\eta^2=0.10$], consistent with practice effects. At post-training, scores were significantly worse for HVLT immediate recall [$F(1,77)=15.88$, $p<0.001$,

η^2=0.17], and HVLT delay recall [F(1,77)=10.68, p=0.002, η^2=0.12], which may reflect version effects.

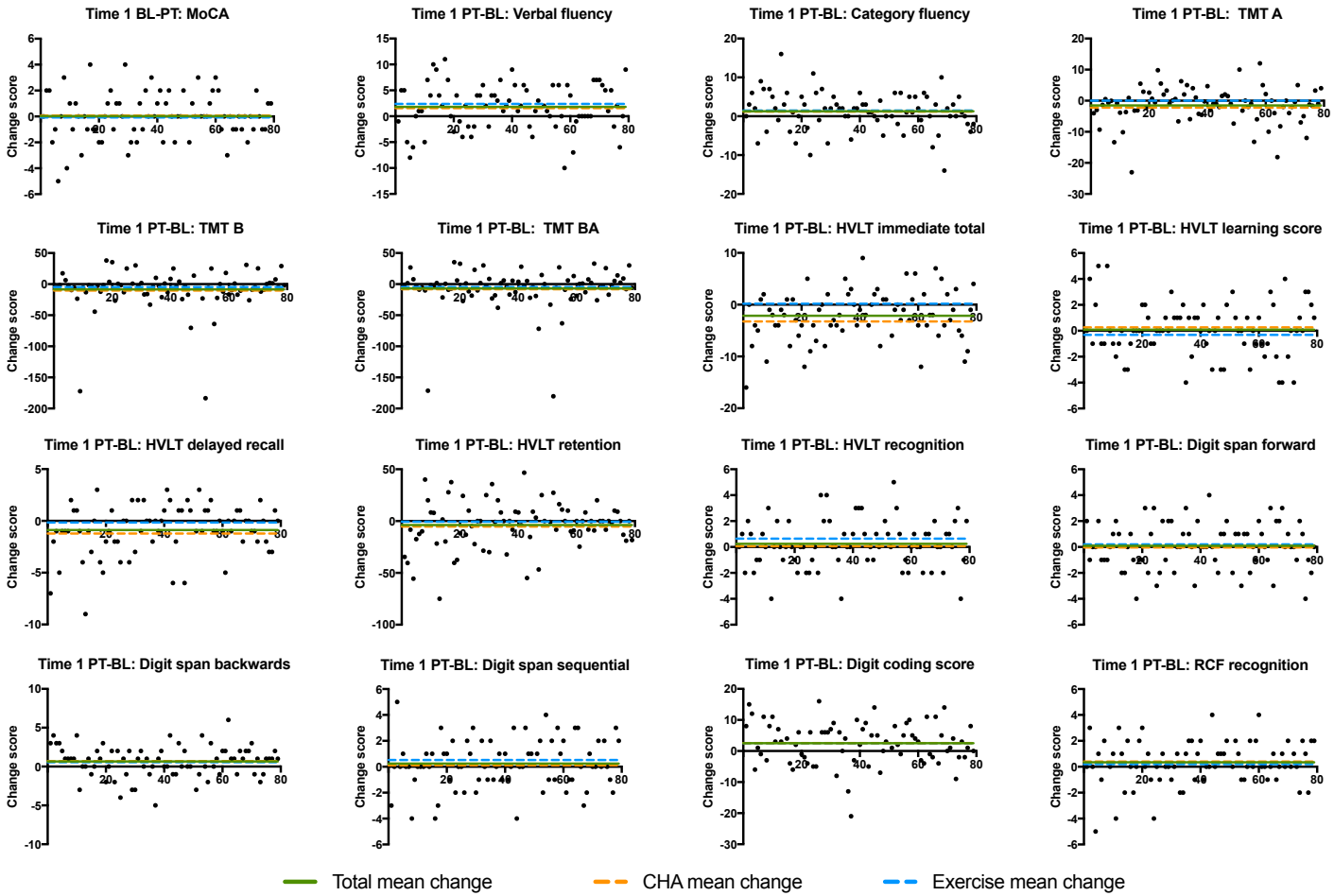
Demographics for final N=73

After excluding the 2 participants that fell on the median, the demographics for the total sample were largely unchanged. Differences between the CHA and exercise baseline cohorts were also largely unchanged, although the difference in estimated-IQ was no longer significant [p=0.06] (details reported in *Appendix Table 5.A*).

Appendix Table 5.A. **Demographics of N=73 sample, also shown by baseline cohort.**

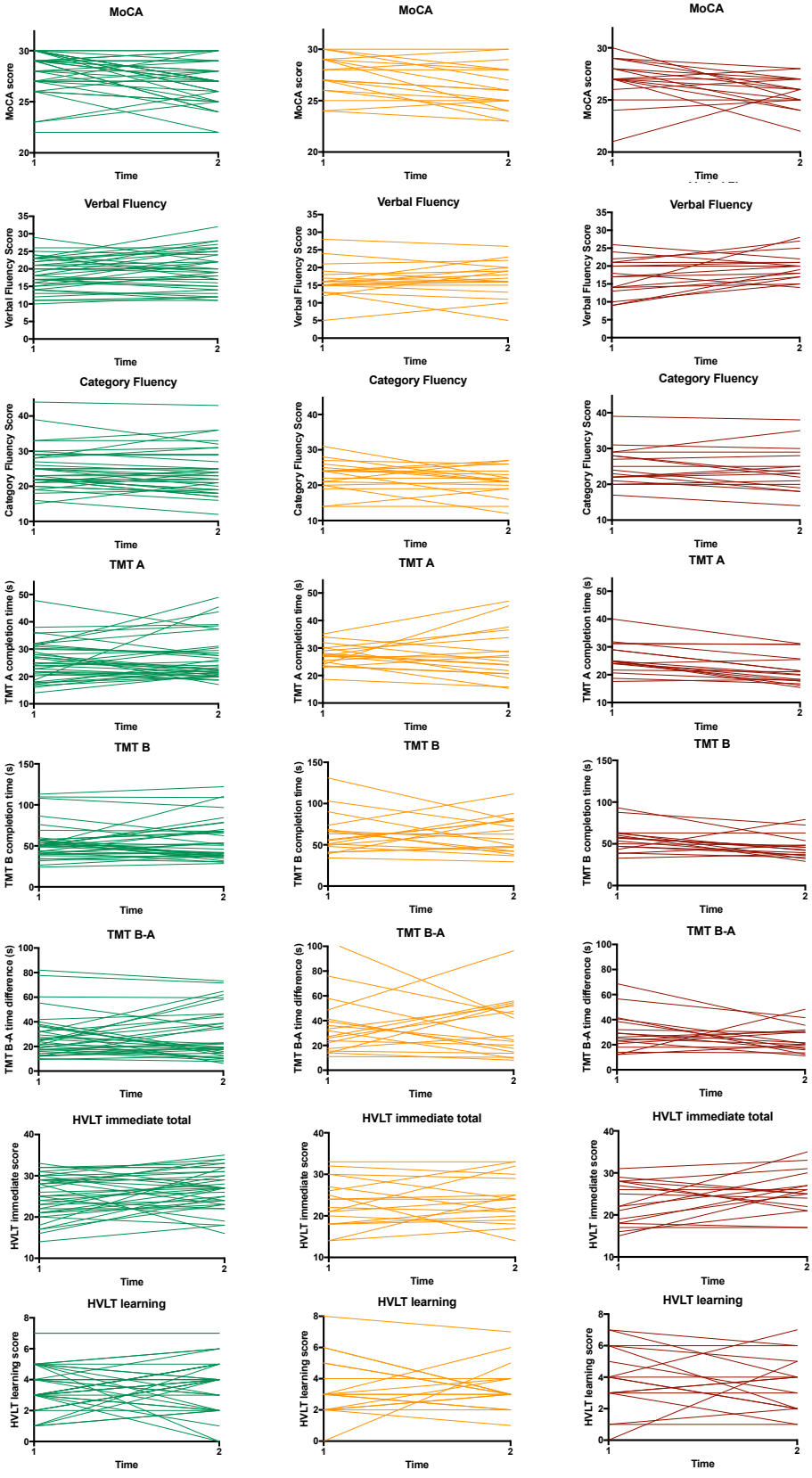
	Total sample (N=73)	CHA baseline (N=47)	Exercise baseline (N=26)	*p*
Follow-up period, yrs	4.0 (0.4)	3.9 (0.3)	4.3 (0.3)	**<0.001**
Age at baseline	67.5 (6.3)	67.3 (6.5)	67.8 (5.9)	0.74
Age at follow-up	72.0 (6.3)	71.7 (6.5)	72.4 (6.1)	0.64
MoCA at baseline	27.6 (2.1)	27.4 (2.2)	28.0 (1.8)	0.27
MoCA at follow-up	26.4 (2.1)	26.6 (2.1)	26.2 (2.0)	0.53
Years of education	15.8 (3.6)	16.5 (3.6)	14.4 (3.2)	**0.02**
Females, N (%)	43 (58.9%)	28 (59.6%)	15 (57.7%)	0.88
APOE*, ε4-carriers (%)	20 (28.2%)	13 (28.3%)	7 (28.0%)	0.98
TOPF-estimated IQ	113.5 (7.4)	114.7 (6.6)	111.3 (8.4)	0.06

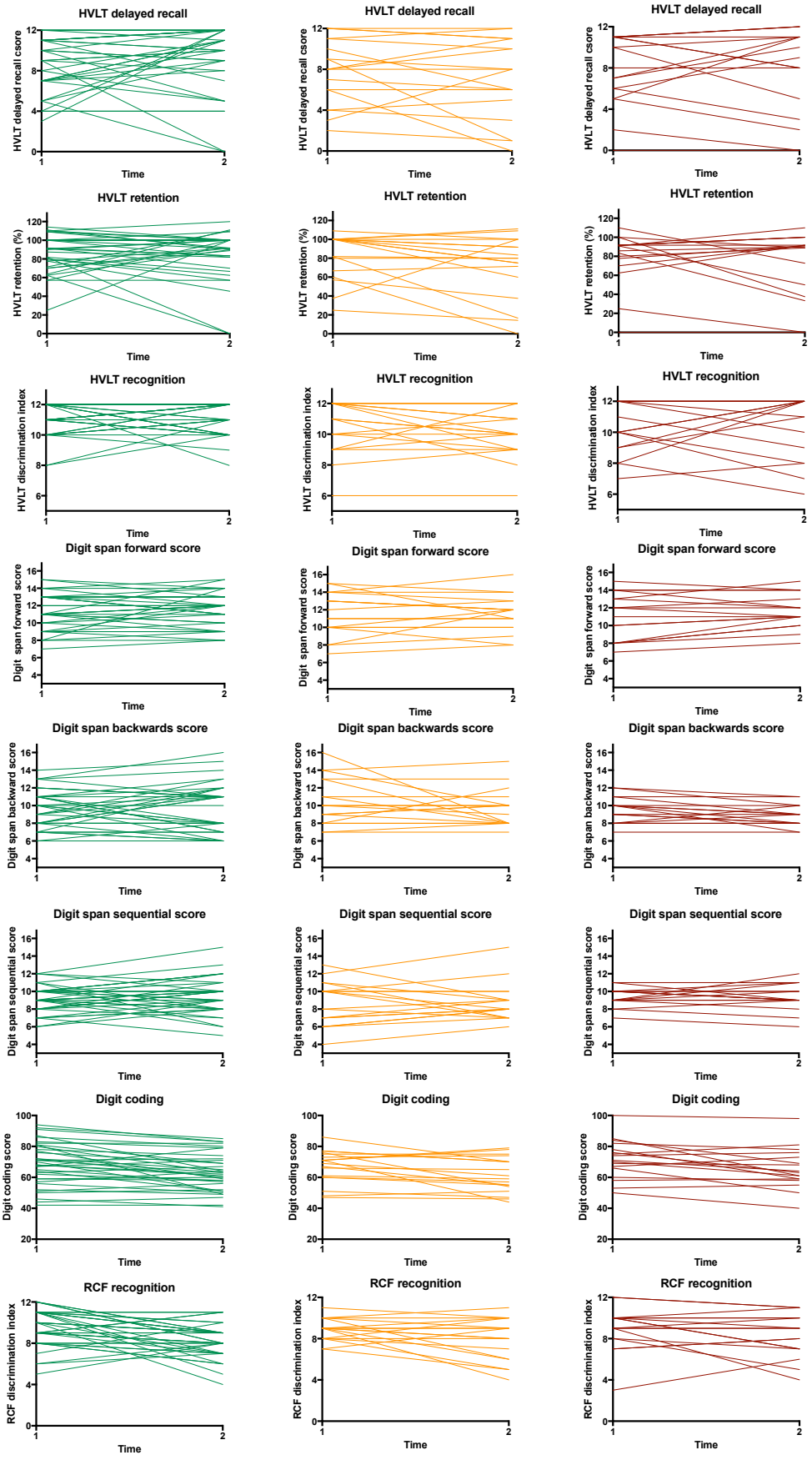
Values represent mean (SD) unless otherwise stated. *Abbreviations*: CHA – cognitive health in Ageing; MoCA – Montreal Cognitive Assessment; APOE - apolipoprotein E; TOPF – Test of Premorbid Function; IQ – intelligence quotient. *APOE genotype unavailable for 2 participants (1 CHA, 1 exercise).



Appendix Figure 5.A. **Cognitive change scores for baseline cohorts. Change calculated between pre- and post-intervention.** Each dot represents a subject. The mean change for all participants is shown as a solid green line, the mean change for CHA participants only is shown as a dashed orange line, and the mean change for Exercise participants only is shown as a dashed blue line. PT – post-training (intervention), BL – baseline, RCF – Rey Osterreith Complex Figure, TMT – trail making test, HVLT – Hopkins Verbal Learning Test.

Appendix Figure 5.B. **Spaghetti plots of longitudinal cognitive performance for each participant, shown by maintainers, adapters and decliners.**




HVLT delayed recall
HVLT delayed recall csore
Time
HVLT retention
HVLT retention (%)
HVLT recognition
HVLT discrimination index
Digit span forward score
Digit span backwards score
Digit span backward score
Digit span sequential score
Digit coding
Digit coding score
RCF recognition
RCF discrimination index

Appendix 6. Supplementary results for Chapter 6

Supplementary Results

Appendix Table 6.A. **Demographics for participants scanned and not scanned at follow-up**

	Scanned N=64	Not scanned N=15	*p*
Follow-up period, yrs	3.9 (0.3)	4.3 (0.4)	**0.001**
Age at baseline, yrs	67.4 (6.2)	68.6 (7.0)	0.51
Age at follow-up, yrs	71.8 (6.3)	73.6 (7.1)	0.33
MoCA at baseline	27.7 (2.1)	27.3 (2.1)	0.46
MoCA at follow-up	26.5 (2.2)	25.9 (2.0)	0.33
Years of education	15.7 (3.6)	16.3 (3.9)	0.52
Females, N (%)	36 (56.3%)	10 (66.7%)	0.46
APOE*, ε4-carriers (%)	17 (27.4%)	4 (28.6%)	0.93
TOPF-estimated IQ	113.7 (7.1)	113.8 (8.2)	0.95

Values represent mean (SD) unless otherwise stated. *Abbreviations*: MoCA – Montreal Cognitive Assessment, APOE – apolipoprotein E, TOPF – Test of Premorbid Function, IQ – intelligent quotient. * APOE genotype missing for 3 participants (2 scanned, 1 not scanned).

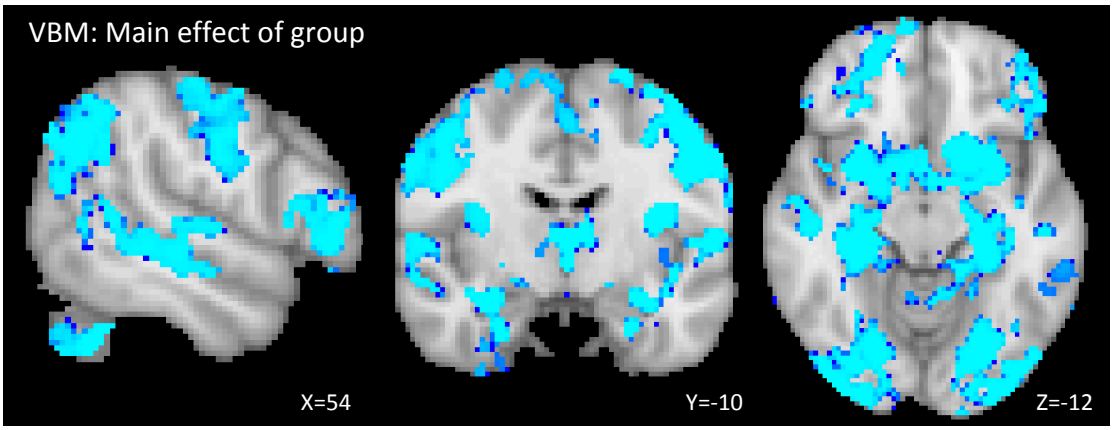
Appendix Table 6.B. **Demographics of total sample, also shown by baseline cohort.**

	Total sample (N=62)	CHA baseline (N=39)	Exercise baseline (N=23)	*p*
Follow-up period, yrs	4.0 (0.3)	3.8 (0.3)	4.2 (0.2)	**<0.001**
Age at baseline, yrs	67.5 (6.4)	67.4 (6.8)	67.7 (5.6)	0.86
Age at follow-up, yrs	71.9 (6.4)	71.7 (6.8)	72.2 (5.8)	0.76
MoCA at baseline	27.8 (2.1)	27.7 (2.1)	28.0 (1.9)	0.55
MoCA at follow-up	26.6 (2.1)	26.7 (2.1)	26.3 (2.1)	0.43
Years of education	15.7 (3.6)	16.5 (3.7)	14.2 (3.0)	**0.01**
Females, N (%)	36 (58.1%)	24 (61.5%)	12 (52.2%)	0.47
APOE*, ε4-carriers (%)	16 (25.8%)	10 (21.3%)	6 (26.1%)	0.93
TOPF-estimated IQ	113.5 (7.2)	114.8 (5.8)	111.4 (8.9)	0.12

Values represent mean (SD) unless otherwise stated. *Abbreviations*: CHA – cognitive health in Ageing; MoCA – Montreal Cognitive Assessment; APOE - apolipoprotein E; TOPF – Test of Premorbid Function; IQ – intelligence quotient. *APOE genotype unavailable for 2 participants (1 CHA, 1 exercise).

VBM – Main effect of group

Whole-brain GM analysis with VBM revealed a widespread effect of group membership on GM density (*Appendix Figure 6.A*), affecting superior and inferior frontal gryus, precentral, postcetnral gyrus, precuneus, lateral occipital cortex, angular gyrus, occipital pole, middle temporal gyrus, and subcortical structures including hippocampus, amygdala, caudate and accumbens.

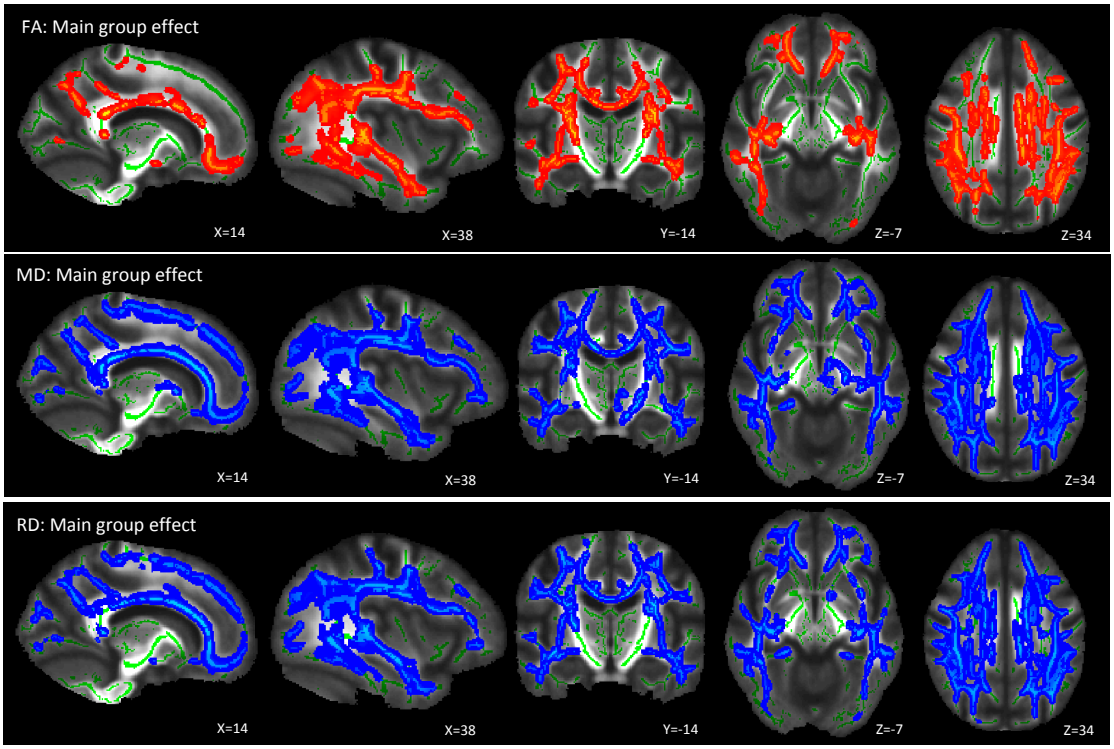


Appendix Figure 6.A. Regions of grey matter volume affected by 'group'.

Results are FWE-corrected at p<0.05. Coordinates are in MNI space.

TBSS – Main effect of group

Whole-brain WM analysis with TBSS revealed a widespread effect of group membership on FA, MD and RD.



Appendix Figure 6.B. **Regions of fractional anisotropy (FA), mean diffusivity (MD) and radial diffusivity (RD) affected by 'group' in TBSS analysis. Results are FWE-corrected at p<0.05. Coordinates are in MNI space.**

Resting-state – description of identified networks

RSN 1 – DMN, particularly the anterior prefrontal portions

RSN 2 – Precuneus, resembling the precuneal portion of the posterior DMN

RSN 3 – Superior parietal, resembling the parietal portion of the posterior DMN

RSNs 4-5 Right and Left frontoparietal networks

RSN 6 – Intraparietal sulcus, resembling the Dorsal Attentional Network

RSN 7 – Temporal and parietal regions, resembling the Central Executive Network

RSN 8 – Prefrontal, resembling the Executive Control Network

RSN 9 - Prefrontal and middle temporal regions

RSNs 10-12 - Visual networks

RSNs 13-15 - Sensorimotor networks, located in pre- and post-central gyrus

RSN 16 - Auditory, Heschl's gyrus

RSN 17 – Cerebellum

RSN 18 – Superior parietal, primarily located on the supramarginal gyrus

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